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REVIEW ARTICLE

Class A and C GPCR Dimers in Neurodegenerative Diseases

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Abstract: Neurodegenerative diseases affect over 30 million people worldwide with an ascending trend. Most individuals suffering from these irreversible brain damages belong to the elderly population, with onset between 50 and 60 years. Although the pathophysiology of such diseases is partially known, it remains unclear upon which point a disease turns degenerative. Moreover, current therapeutics can treat some of the symptoms but often have severe side effects and become less effective in long-term treatment. For many neurodegenerative diseases, the involvement of G protein-coupled receptors (GPCRs), which are key players of neuronal transmission and plasticity, has become clearer and holds great promise in elucidating their biological mechanism. With this review, we introduce and summarize class A and class C GPCRs, known to form heterodimers or oligomers to increase their signalling repertoire. Additionally, the examples discussed here were shown to display relevant alterations in brain signalling and had already been associated with the pathophysiology of certain neurodegenerative diseases. Lastly, we classified the heterodimers into two categories of crosstalk, positive or negative, for which there is known evidence.

Keywords: G protein-coupled receptors, dimers, class A, class C, neurodegenerative diseases, brain.

1. INTRODUCTION

1.1. Scope of Review

Neurodegenerative diseases, characterized by progressive neuronal dysfunction, toxicity and death [1], are prevalent among the worldwide elderly population [2]. These diseases cause irreversible damage to all types of brain functions and it is estimated that over 30 million individuals suffer from them worldwide [3, 4]. Parkinson's disease (PD), Alzheimer's disease (AD), Vascular dementia (VaD), Frontotemporal dementia (FTD), and Huntington's disease (HD) are the most prevailing ones [5, 6]. Among those, AD and PD have an earlier average onset between 50 and 60 years [5, 7, 8].

Impaired cognitive function, memory loss and negative personality are common traits associated with people suffering from AD [9-11]. The accumulation of amyloid β (Aβ) in amyloid plaques and hyperphosphorylated aggregates of the microtubule-associated protein tau in neurofibrillary tangles, which slowly progress from the frontal and temporal lobes to other areas of the neocortex are the pathological features observed in AD patients [9].

PD is predominantly characterized by motor impairments such as bradykinesia, rigidity, tremor and gait disorder [12]. Also non-motor impairments like cognitive impairment and neuropsychiatric symptoms are observed among PD patients [12]. The pathology of PD has been well-studied over the years. The loss of dopaminergic neurons in the substantia nigra is the major feature observed in PD patients, but also the deposition of Lewy bodies and abnormal aggregates of the α-synuclein protein in several brain regions, such as the substantia nigra and temporal cortex, have been described to play a role in PD [12].

In contrast to AD, VaD has a variable onset age and is the second most common cause of dementia [5]. Disturbance in the frontal executive function and multiple cerebral pathologies, including arteriosclerosis and various forms of arteritis, aneurysms or vessel occlusion, are the characteristic of VaD [13, 14]. Under the age of 65, FTD is known to be the major reason for dementia [5, 15]. FTD patients display neuropsychiatric symptoms and cognitive, motor and behavioural impairments, as well as the abnormal deposition of the three major proteins tau, transactive response DNA-binding protein 43 (TDP-43) and fused in sarcoma (FUS) protein in the brain [16].

As for PD, HD symptoms can be divided into motor and non-motor symptoms such as chorea, bradykinesia, impaired coordination, rigidity, which are motor symptoms, whereas

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depression and slowed cognitive function are described as non-motor symptoms [17]. The root cause of HD is genetic, unlike the other diseases described here. HD is caused by a CAG trinucleotide repeat expansion in the *Huntingtin (Htt)* gene [5, 17]. In unaffected individuals, the CAG repeats vary from 6 to 35 nucleotides, while > 36 repeats are present in HD patients [18]. The number of repeats inversely correlates with the age of onset [5, 18]. Consequently, Huntingtin protein (HTT) is deposited in the brain, typically not only in the cerebral cortex, but also in other regions such as striatum, hippocampus, and cerebellum [19].

Some of the structural and biological determinants of neurodegenerative diseases have already been revealed [20-24]. However, the turning point of when a pathological condition becomes chronic and leads to neurodegeneration remains elusive for most of the diseases. In this review, we focus on G protein-coupled receptor (GPCRs) heterodimers, which are known to play significant roles in the brain [25-29].

1.2. G Protein-coupled Receptors

1.2.1. General Mode of Action

GPCRs are the mediators of almost all (patho)physiological responses in the human body and comprise the largest family of membrane proteins [30, 31]. GPCRs share a common architecture of seven transmembrane helices (7TM), connected through 3 intra-and extracellular loops (ICL1-3, ECL1-3) with an extracellular N-terminus and intracellular C-terminus [32, 33]. Around 800 genes encode for GPCRs in the human genome [34, 35] and about 370 of them are non-sensory GPCRs, ~90% of each expressed in the brain [1, 5]. They play important roles in regulating mood, appetite, pain, vision, immune responses, cognition, and synaptic transmissions [5, 30, 33]. Most of these functions are mediated *via* endocrine and neurological pathways [1, 5, 29, 35].

In the brain, neurotransmitters signal *via* GPCRs to modulate the activity of muscles and neurons [36, 37]. Dopamine, serotonin, noradrenaline and other derivatives of amino acids and amines, but also oligopeptides like oxytocin or endorphins as well as purines constitute some of known GPCRs ligands [38-45]. Furthermore, an individual small-molecule neurotransmitter might target a dozen different GPCRs. Neurons expressing certain types of receptors are then formed as entire systems. The five main transmission systems are: noradrenaline, dopamine, histamine, serotonin, and the acetylcholine system [46-50]. Strong imbalances or disruption of these systems have been associated with many mental disorders and neurological conditions such as depression, schizophrenia, attention deficit hyperactivity disorder (ADHD), anxiety, memory loss, pain perception as well as dramatic changes in weight and addictions, aside from neurodegenerative diseases [51-59]. Some studies were also able to connect malfunctioning of the dopaminergic system to multiple sclerosis (MS) [60]. Genetics may also play a role [61].

Vertebrate GPCRs were classified through the GRAFS (Glutamate, Rhodophsin, Adhesion, Frizzled/Taste, Smoothened families) system that uses a phylogenetic tree of approximately 800 human GPCR sequences to assign the receptors to a specific family [62-65]. Another system, the A-F system, classifies GPCRs by their amino acid sequences and functional similarities (*e.g.* fingerprints of the characteristic 7TM domains) [65-67]. Here, GPCRs are categorized into six classes: Class A—rhodopsin-like receptors, Class B—secretin family, Class C—metabotropic glutamate receptors, Class D—fungal mating pheromone receptors (non-vertebrate receptors), Class E—cAMP receptors (non-vertebrate receptors, and Class F—frizzled (FZD) and smoothened (SMO) receptors [68, 69]. The difference between the GRAFS system and the A-F system is the further division of class B from the A-F system into the secretin and adhesion family in the first system based on preliminary findings that these two families evolved distinctly from each other [65].

From these, classes A and C receptor families comprise the relevant members involved in neurodegenerative diseases and neurological pathologies. These receptors also show a higher amount of relevant data regarding alternative signalling pathways through the formation of GPCR dimers.

1.2.2. Dimerization

For a long time, it was believed that the functional entity of GPCRs was monomeric: an extracellular signal, such as the binding of a ligand, would lead to conformational rearrangements within the protein so that the signal was further transmitted intracellularly *via* heterotrimeric G proteins, arrestin proteins and different downstream signalling cascades [70, 71]. This concept was then extended by findings that the receptors can also function as homo- and/or heterodimers or even higher-order oligomers with relevant biological value [72-74]. It was also reported that GPCRs can also form heterodimers with ionotropic receptors and receptor tyrosine kinases and henceforth modulate their function [76]. In addition, adaptor proteins were described to interact with receptor protomers, modulating their interactions [76]. Consequently, GPCR signalling is not only determined by conformational changes induced by ligand-binding, but also by interaction with other proteins [77], which diversifies and fine-tunes their signalling, rendering it a highly dynamic nature [77-80].

For instance, it was reported that the physiological consequences of GPCR-dimerization result in the modulation of downstream signalling, trafficking, and regulation as well as negative and positive cooperativity on ligand-binding [72, 80, 81]. Furthermore, allosteric dimerization between a monomer and another GPCR can influence ligand recognition by modulation of the orthosteric and allosteric binding sites. This can influence G protein-coupling and selectivity and may cause switching from G protein- to β-arrestin-coupling [80, 82]. Additionally, dimerization may lead to the appearance of novel allosteric sites that can again alter different pharmacological properties [82]. However, the structural basis behind such interactions is not fully understood yet.

While class C GPCRs function as dimers only, there is also evidence for the existence of homodimers, heterodimers, and/or higher-order oligomers in other GPCR classes through a variety of reports describing biophysical studies: single-molecule fluorescence-based approaches, X-ray crystallography, nuclear magnetic resonance (NMR) spectroscopy, and cryogenic electron microscopy (cryo-EM) - as well as compu-

tational studies [83-89]. Furthermore, the knowledge about GPCR-dimers involved in pathological conditions increased in the last few years [72]. Such an impact has been reported for asthma, cardiac failure, preeclampsia, schizophrenia and PD [72]. Several studies have shown that GPCR heterodimers elicit a significant role in various diseases at different stages by regulating the pathological condition towards its progression, or modulating selective downstream signalling cascades [72]. It was already hypothesized that learning and memory occur at a molecular level by the reorganization of homo- and heterodimers in the postsynaptic membrane [76]. According to the authors Borroto-Escuela and Fuxe, disbalances of homo- and heterodimers are linked to diseases and targeting heterodimers represents a novel strategy for the treatment of brain disorders [76, 90].

The understanding of the pharmacological and functional properties of GPCR classes A and C dimers can be crucial for the treatment of mental disorders and neurological conditions due to evidence suggesting that these macromolecular structures may play an important role. The large number of GPCRs and their ability to form different complexes, suggests the existence of a high number of possible GPCR heterodimers in the CNS. This also indicates that heterodimers constitute a unique signalling as such that different neurons with different heterodimers may respond differently to the same ligand [91]. Here, we review the latest advances in obtaining and understanding GPCR dimers (classes A and C) structure and function and, consequently, their role in neurodegenerative diseases. Listing of these complexes can be found in Table **1**. Until now, 56 dimers were identified as expressed in the brain. Out of these, 48 were from class A-class A dimers, 3 from class C-class C dimers and 5 were class A-class C dimers (Fig. **1**).

2. CLASS A G PROTEIN-COUPLED RECEPTORS

2.1. Class A Receptors in the Brain

The family of class A GPCRs, also referred to as rhodopsin receptors, consists of a very large and diverse group of receptors. They mediate signalling processes in all kinds of physiological actions such as cell communication, the senses of sight, smell and taste, sensory perception, chemotaxis and neurotransmission [71, 92]. In those processes, there is the involvement of a wide array of different ligands including light, peptides, lipids, proteins and small molecules such as biogenic amines, nucleotides and ions [71, 93]. The activation mechanism of class A GPCRs is the prime example for studying how monomeric GPCRs transduce extracellular signals into intracellular ones. All members of class A GPCRs share a sequence identity of more than 20% in their TM domains, so they are expected to have evolved from a common ancestor [94]. Hence, the growing number of structure-function studies and the increase in resolved crystal structures suggest that there are common structural and functional motifs responsible for the activation of this family of GPCRs [71, 95, 96]. In order to make the localization of such structural and functional motifs easy to compare between the different GPCR families, all GPCR residues are usually numbered according to the Ballesteros & Weinstein nomenclature [97]. Hereby, the first digit identifies the TM helix and the second digit identifies the position of the residues in relation to the most conserved residue in the TM helix, which is assigned the index number 50 (numbers decrease towards the N-terminus and increase towards the C-terminus) [71, 97]. As already summarized by Moreira [71] and Zhou *et al*. [98], the most important motifs are: (i) the interaction of the cytoplasmic "ionic lock" on TM3 with the consensus "(D/E)R(Y/M)" (3.49-3.51) with D/E (6.30) on TM6, which is disrupted when the receptor is activated [99-108]; (ii) the hydrophobic arginine cage around the conserved arginine (R3.50) of the DRY motif, which restrains its conformation in inactive state of the receptor consisting of two hydrophobic amino acids (such as L, V, I or M) on TM3 and TM6 (3.46, 6.37) [109-111]; (iii) the NPxxYxF motif on TM7, responsible for interaction of a tyrosine (7.53) on TM7 with the phenylalanine (7.60) on HX8 together with the side chain and backbone of an arginine on TM2 (2.40) *via* a water molecule [102, 112-123]; (iv) the Rotamer Toggle Switch, a coordinated change upon ligand coupling of aromatic residues in TM6 around a very conserved tryptophan (6.48) that leads to disruption of the ionic lock [110, 115, 124, 125]; (v) the CWxP motif, the cluster around the conserved tryptophan on TM6, which is part of the Rotamer Toggle Switch and also undergoes a conformational rearrangement upon activation from pointing towards TM7 in the inactive state to pointing towards TM5 in the active state [113, 120-128]; (vi) the PIF motif [97, 102, 129, 130], and (vii) the Na^+-pocket [114, 120, 128, 131-137]. It is well established that the outward movement of TM6 upon ligand binding is another common feature of class A GPCR activation. However, at the residue level, the changes that trigger such a movement can be individual for each receptor subfamily as it requires a global rearrangement of residue contacts and water-mediated interactions [98, 108, 138, 139].

2.1.1. 5-Hydroxytryptamine Receptors

Serotonin, also called 5-hydroxytryptamine (5-HT), is an important neurotransmitter responsible for anxiety, aggressive behaviour, stress, blood pressure regulation, peristaltic movements, heart rate, and the coagulation system [140-142]. 5-HT activates the largest subfamily of class A GPCRs [143]. This family comprises many members: 5-HT_{1A}R, 5-HT_{1B}R, 5-HT_{1D}R, 5-$HT_{1\varepsilon}$R, 5-HT_{1F}R, 5-HT_{2A}R, 5-HT_{2B}R, 5-HT_{2C}R, 5-HT_4R, 5-HT_{5A}R, 5-HT_{5b}R, 5-HT_6R, 5-HT_7R [144]. Many of them, such as 5-HT_{1A}R, 5-HT_{1D}R, 5-HT_{1E}R are drug targets of numerous disorders [145]. Currently, alterations in the serotoninergic neurotransmission and disturbances in the level of 5-HT have been described to be associated with migraine, epilepsy, PD, MS, ALS, ADHD and autism spectrum disorder (ASD) [140, 141, 146-150]. Especially for migraine, disturbances in the serotoninergic system are the hallmark of this disorder, which affects 11% of adults worldwide [140]. Chronically low 5-HT disposition due to malfunction of its biosynthesis leads to the development of migraine [140].

2.1.2. Adenosine Receptors

Adenosine receptors (AR) are another family of class A GPCRs that are activated by their endogenous ligand, adenosine [151]. The four members, A_1R, A_{2A}R, A_{2B}R, A_3R, have been considered potential targets for several disorders such as PD, schizophrenia, analgesia, ischemia and cancer [151, 152]. Some studies also reported the effects of adenosine on neuronal protection and neuronal viability as well as in

Table 1. GPCR Dimers and potential roles in neurodegenerative diseases.

Heterodimer	GPCR Class	Clinical Relevance	Crosstalk	References
DRD_1-DRD_2	Class A	PD Schizophrenia Autism Addiction Depression	Positive crosstalk	[461, 462, 464, 478, 486-488, 492, 495-497, 499, 501, 910, 911]
DRD_1-DRD_3	Class A	PD	Positive crosstalk	[477, 504-510]
DRD_2-DRD_3	Class A	PD Schizophrenia Autism ADHD	Positive crosstalk	[484, 513-517, 910]
DRD_2-DRD_4	Class A	PD	Positive crosstalk	[476, 521, 522]
DRD_5-DRD_2	Class A	Depression	Positive crosstalk	[493, 523]
A_1R-DRD_1	Class A	PD Schizophrenia Addiction	Negative crosstalk	[459, 524, 525, 527, 529-532, 565, 912-914]
$A_{2A}R$-DRD_2	Class A	PD Schizophrenia Addiction	Negative crosstalk	[72, 461, 529, 533-542, 915-918]
$A_{2A}R$-DRD_3	Class A	Schizophrenia	Negative crosstalk	[552]
DRD_1-H_3R	Class A	ADHD Schizophrenia Addiction	Positive crosstalk	[554-557]
DRD_2-H_3R	Class A	PD	Negative crosstalk	[558, 559]
DRD_2-SST_5R	Class A	Depression	Positive crosstalk	[561-563, 919]
DRD_2-NTS_1R	Class A	PD Schizophrenia	Negative crosstalk	[564-569]
DRD_2-TAA_1R	Class A	Schizophrenia	Negative crosstalk	[313, 324, 570-572]
DRD_2-OTR	Class A	Anxiety Autism	Positive crosstalk	[573, 574, 910]
DRD_2-GHS-R_{1a}	Class A	Eating disorders	Negative crosstalk	[582, 920, 921]
A_1R-$A_{2A}R$	Class A	Drug tolerance	Negative crosstalk	[458, 560, 583, 585-588]
A_1R-5-HT_2AR	Class A	Schizophrenia Anxiety	Negative crosstalk	[591, 592]
$A_{2A}R$-H_3R	Class A	PD	Negative crosstalk	[593, 922]
MOR-DOR	Class A	Chronic pain	Positive crosstalk	[601, 605-614, 923, 924]
MOR-KOR	Class A	Chronic pain	Positive crosstalk	[602, 604, 615]
MOR-$\alpha_{2A}R$	Class A	Addiction	Negative crosstalk	[604, 616-619, 925-928]
MOR-GPR139	Class A	Chronic pain	Negative crosstalk	[604, 623]
MOR-$V_{1B}R$	Class A	Chronic pain Morphine tolerance	Positive crosstalk	[604, 624]
MOR-GAL_1R	Class A	Chronic pain Addiction	Positive crosstalk	[604, 625, 626]
MOR-CB_1R	Class A	Chronic pain	Negative crosstalk	[604, 627, 629-633]
MOR-CCKBR	Class A	Chronic pain	Negative crosstalk	[604, 616]
MOR-CCR5	Class A	Chronic pain	Negative crosstalk	[636, 637]

(Table 1) contd….

Heterodimer	GPCR Class	Clinical Relevance	Crosstalk	References
MOR-DRD_1	Class A	PD Addiction	Negative crosstalk	[639]
MOR-DRD_2	Class A	Addiction	Negative crosstalk	[640-643]
5-HT_{1A}r-5-HT_{2A}r	Class A	Depression	Negative crosstalk	[646-649]
5-HT_{2A}-5-HT_{2B}	Class A	Addiction Depression	Negative crosstalk	[651, 652, 655]
5-HT_{2A}r-5-HT_{2C}r	Class A	Addiction Depression	Negative crosstalk	[651, 652, 655, 929, 930]
5-HT_{1A}r-5-HT_7r	Class A	Depression Anxiety Schizophrenia Addiction	Negative crosstalk	[656, 657, 659, 660]
5-HT_{1A}R-DRD_2	Class A	Schizophrenia	Positive crosstalk	[648, 661-665]
5-HT_{2A}R-DRD_2	Class A	Schizophrenia Autism	Positive crosstalk	[565, 662, 663, 666, 910]
5-HT_{1A}R-GAL_1R	Class A	Depression	Negative crosstalk	[668, 670, 672, 674, 675]
5-HT_{2A}R-OTR	Class A	Anxiety Autism Depression	Negative crosstalk	[676, 910]
5-HT_{2C}R-OTR	Class A	Depression	Negative crosstalk	[681]
5-HT_{2C}R-MT_2R	Class A	Depression Anxiety	Positive crosstalk	[682-687]
5-HT_{1A}r-MOR	Class A	Chronic pain	Positive crosstalk	[688]
CB_1R-CB_2R	Class A	AD PD	Positive crosstalk	[687, 698-700]
CB_1R-DRD_1	Class A	PD	Positive crosstalk	[707-710]
CB_1R-DRD_2	Class A	PD Schizophrenia Addiction Autism	Negative crosstalk	[704, 713-716, 718-720, 722, 910, 931]
CB_1R-A_{2A}R	Class A	Depression	Negative crosstalk	[723, 724, 726]
CB_1R-5-HT_{2A}R	Class A	Addiction Anxiety	Positive crosstalk	[731, 738]
GAL_1R-GAL_2R	Class A	Depression Anxiety	Positive crosstalk	[740, 741]
AT_1R-AT_2R	Class A	PD	Positive crosstalk	[742-744]
$mGlu_1$R-$mGlu_5$R	Class C	PD AD Schizophrenia Autism	Unknow	[35, 826]
$mGlu_2$R - $mGlu_4$R	Class C	PD AD Schizophrenia	Negative crosstalk	[824, 825, 932]
$GABA_{B1}$R- $GABA_{B2}$R	Class C	Nonspecific neurological diseases	Positive crosstalk	[806-811, 933]
DRD_1-$mGlu_5$R	Class A and C	PD	Positive crosstalk	[831]
A_1R-$mGlu_1$R	Class A and C	Schizophrenia	Negative crosstalk	[834-836]

(Table 1) contd….

Heterodimer	GPCR Class	Clinical Relevance	Crosstalk	References
5-HT_{2A}R-$mGlu_2$R	Class A and C	Schizophrenia Autism	Negative crosstalk	[838, 839, 841, 910, 934, 935]
MOR-$mGlu_5$R	Class A and C	Chronic pain Addiction	Negative crosstalk	[846, 847]
A_{2A}R-CB_1R-DRD_2	Class A	Schizophrenia	Negative crosstalk	[533, 704, 721, 722, 726, 848, 857-864]
A_{2A}R-DRD_2-$mGlu_5$R	Class A and C	PD Schizophrenia Addiction Autism	Negative crosstalk	[865, 866, 868, 910]

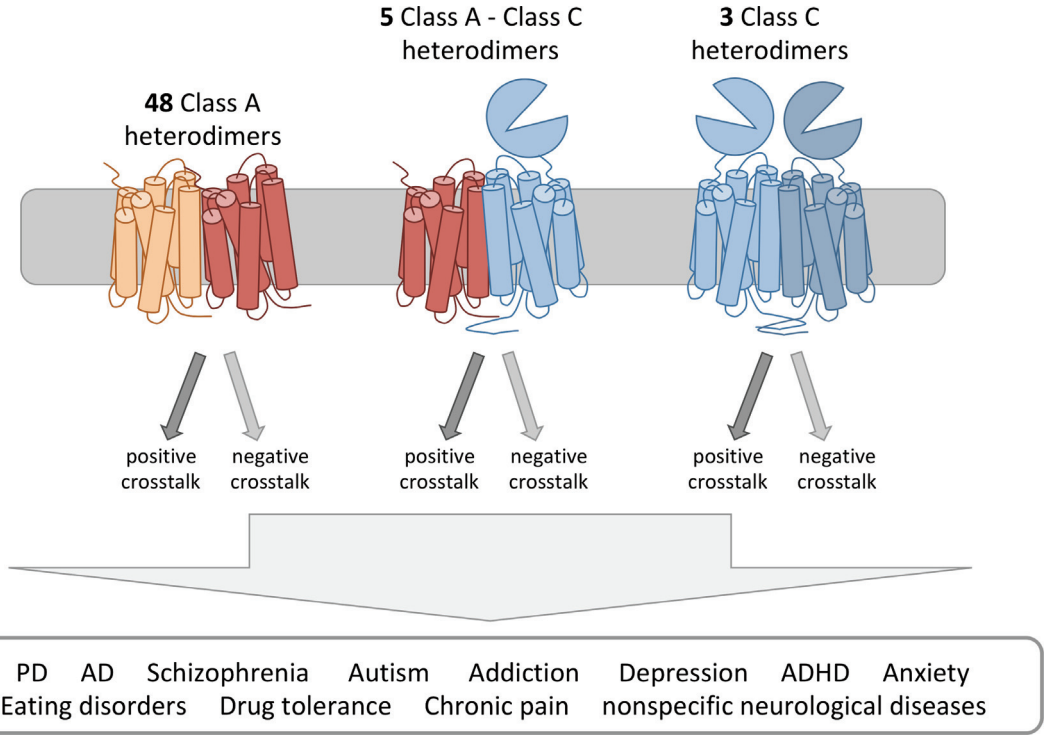

Fig. (1). Overview of neurodegenerative-relevant GPCR heterodimers of classes A and C. In the next sections, we describe brain-relevant class A GPCRs and known heterodimers followed by class C. A few examples of interclass heterodimers, comprising class A and class C as well as receptor mosaics will also be listed. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

inflammatory processes [153]. Combined effects may lead to considerations for ARs and possible roles in Lesch-Nyhan syndrome, Creutzfeldt-Jakob disease, Huntington's disease, PD and AD and multiple sclerosis, as well as the brain damage associated with stroke [152, 153].

2.1.3. Adrenoceptors

The noradrenergic system in the brain has the global function of neuronal modulation, controlling vigilance, attention, the sleep-wake cycle and to some extent also in learning and memory processes [154-157]. In addition, depression, anxiety and sensory information processing, such as pain or touch, mediated through the sympathetic nervous system, are processes regulated by noradrenaline and the neurohormone epinephrine through the noradrenergic system [154, 156-158]. All these ligands bind to the nine members of the adrenoceptor family, all expressed in the brain: α_{1A}AR, α_{1B}AR, α_{1D}AR, α_{2A}AR, α_{2B}AR, α_{2C}AR, β_1-AR, β_2-AR and the β_3-AR [71, 158, 159]. The adrenoceptors are further classified into three subgroups: the α1 group, which comprises α_{1A}AR, α_{1B}AR and α_{1D}AR since they couple to G_q; the α2 group containing α_{2A}AR, α_{2B}AR and α_{2C}AR, in which all couple to G_i and the β group which consists of the β_1-AR, β_2-AR and the β_3-AR, all able to couple to G_s. However, β_2-AR and β_3-AR also couple to G_i [160]. Disruption in the noradrenergic system was reported to be connected to a number of neurological diseases such as AD, epilepsy, ADHS, PD, depression, schizophrenia, and posttraumatic stress disorder [154].

2.1.4. Cannabinoid Receptors

The two cannabinoid receptors CB_1R and CB_2R together with their endogenous ligands, anandamide, 2-arachidonoylglycerol and other endocannabinoids, were discovered in the late 80s and resulted in a major effort in understanding

the mechanisms and physiological roles of the endocannabinoid system (ECS) [144, 161]. The ECS regulates a variety of physiological processes such as appetite, mood, memory and pain sensation [162]. This complex system is also believed to play a neuroprotective role during traumatic brain injury, and may be part of a natural compensatory repair mechanism, relevant also during neurodegeneration [163-166]. The modulation of this new neuronal network has been proposed to target many neurological conditions, including epilepsy, cognitive deficits and neurodegenerative diseases [163, 167, 168]. While CB_1R is mainly expressed in the brain, CB_2R can be found in diverse parts of the immune system and partially in the brain [169-171]. Interestingly, CB_1R is a promiscuous protein, able to couple to different G proteins, activate signalling pathways mediated by β-arrestins and signal from intracellular compartments, adding another level of complexity to this system [161, 172, 173]. Therefore, CB_1R has an impact in brain disorders including basal ganglia disorders such as AD, MS and HD [168, 174].

The expression pattern of CB_2R, contrasting to CB_1R, is more defined and increased in microglia and macrophages of the central nervous system (CNS) [171, 175]. The CB_2R is mainly associated with inflammation, and due to its selective localization, it is a promising target for AD and other basal ganglia disorders [168, 176-178].

2.1.5. Cholecystokinin Receptors

Cholecystokinin (CCK) is a gastrin-like peptide found in the brain and the gastrointestinal tract [179]. CCK triggers the signalling cascade by activating two GPCRs, CCK_1R/CCKAR and CCK_2R/CCKBR, also found in similar regions of the human body [144, 180]. The CCK_2R has been associated with the neurobiology of anxiety and panic attacks since the 90s [181]. The CCK_1R is mainly known as a physiologic mediator of pancreatic enzyme secretion and smooth muscle contraction of the gallbladder and stomach [182]. Yet, at minor levels, CCK_1R is also present in different regions of the brain, where it mediates the anorectic action of CCK [183-185]. Besides this function, CCK_1R also facilitates dopamine neurotransmission, regulates hypothalamic neurotransmitters, increases the excitability of the cortex and regulates endocrine secretions [182]. For instance, there is accumulating evidence that about 70% of PD patients have experienced diverse non-motor symptoms, most commonly gastrointestinal problems, before the onset of motor dysfunctions [186, 187]. Such findings suggest that neuropeptides derived from the gastrointestinal tract may be related to the onset of PD. This is further supported by the fact that CCK and several other neuropeptides are expressed in dopaminergic neurons of the substantia nigra, and galanin or opioid neuropeptides are also released from the hypothalamic neurons [186, 188, 189]. In PD patients or experimental models, significant changes in brain neuropeptides have already been observed [186].

2.1.6. Dopamine Receptors

The dopamine receptor family consists of five receptors (DRD_1-DRD_5) [190] which are divided into two subclasses (D1-like and D2-like) based on their coupling to G proteins. DRD_1 and DRD_5 couple to $G_{S,\ olf}$ and belong to the D1-like class, while DRD_2, DRD_3 and DRD_4 couple to $G_{i/o}$ and belong to the D2-like class [190-193]. Additionally, for DRD_2 two splicing variants exist, DRD_{2long} and the 29 amino acids shorter DRD_{2short} [190]. While DRD_{2long} is mostly located in the intracellular part, DRD_{2short} is primarily found at the plasma membrane [194]. DRs are associated with many pathological conditions and mental disorders, most prominently PD, schizophrenia, Tourette's syndrome, depression, bipolar disorder, hypertension, gastroparesis and nausea, as well as others [190, 193, 194].

2.1.7. Galanin Receptors

The neuropeptide galanin is widely found in the human brain and gastrointestinal tract and couples to three GPCRs: GAL_1R, GAL_2R and GAL_3R [195]. In the past, several physiological effects were attributed to galanin signalling including smooth muscle contraction, inhibition of insulin release and stimulation of growth hormone release [196-198]. However, it was revealed that the galanin-like immunoreactivity in the CNS and peripheral nervous system (PNS) leads to the regulation of numerous biological processes such as learning and memory, neurogenesis and neuroprotection, seizure activity, pain threshold, neurotransmitter and hormone release and many more [198-209]. Consequently, the role of galanin in mood disorders has attracted a lot of interest [198, 202, 210]. Neurological disorders have also been linked to galanin signalling such as AD, epilepsy, depression, eating disorders and addiction [205, 211].

2.1.8. Histamine Receptors

The histamine receptor (HR) family comprises four members, H_1R, H_2R, H_3R, H_4R [212]. Histamine itself is known to be involved in local immune responses as well as regulating functions in the gastrointestinal tract [213]. For a long time, it has been considered as a local hormone, as it lacks the endocrine glands to secrete it, but it has now been recognized as neurotransmitter [213, 214]. The HRs exert diverse functions in the brain. Whereas H_1R promotes wakefulness, nociception, endocrine homeostasis and appetite, the role of H_2R has not been established yet, since most known ligands are unable to cross the blood-brain barrier in sufficient concentrations [212, 215-219]. The H_3R is described as an "autoreceptor" with constitutive activity and decreases the release of histamine, acetylcholine, serotonin and norepinephrine [212, 220]. Lastly, H_4R is not located in the brain, but rather in basophils and in the bone marrow [212]. Especially H_1R and H_3R orchestrate disparate behaviours and homoeostatic functions [218]. Recent evidence suggested that aberrant neuronal histamine signalling may also be a key factor in degenerative diseases such as PD, AD, sleep disturbance and MS, as well as in addictive behaviours [218, 221-223]. Moreover, the concentration of metabolites of histamine was shown to be increased in the cerebrospinal fluid of schizophrenia patients compared to normal patients [224, 225]. In addition, a decrease in the binding sites of H_1R was observed in schizophrenia patients [224, 225].

2.1.9. Opioid Receptors

The oldest and most potent drugs used for the treatment of moderate-severe acute and chronic pain are opioids [226, 227]. Actions of opioids are mediated through opioid receptors (ORs), widely distributed across the skin, digestive tract, spinal cord and in the brain [70, 228-230]. There are four major classes of receptors: delta receptor (DOR), kappa re-

ceptor (KOR), mu receptor (MOR) and the NOP receptor [229, 231, 232]. ORs are activated by their endogenous opioid ligands that are released by neurons such as dynorphins, enkephalins, endorphins, endomorphins and nociceptin, but also by exogenous opiate drugs [233-239]. Since the ORs are all coupled to G_i proteins, their activation characteristically inhibits neuronal firing as well as neurotransmitter and hormone release [233, 240-243]. The opioid system plays an important role in hedonic homeostasis, mood and well-being, including a large number of sensory, motivational, emotional and cognitive functions and addictive behaviours [233, 244]. The ORs are also known to regulate peripheral functions, including endocrine, gastrointestinal, immune and respiratory functions and responses to stress [244]. Due to its main role in the control of pain, the opioid system is also associated with multiple adaptations in the nervous, endocrine and immune system which can lead to the development of pathologic, chronic pain [240, 245, 246]. In addition, ORs may play a pivotal role in the development of AD, since ORs are known to regulate the neurotransmitters acetylcholine, GABA, glutamate, norepinephrine and serotonin that have been implicated in the pathogenesis of AD [233].

2.1.10. Somatostatin Receptors

The peptide somatostatin (SST) consists of two bioactive forms, SST-14 and SST-28, produced in neuroendocrine cells in the periphery and in the brain that modulate cell secretion and proliferation as well as neurotransmission [247-250]. Five GPCRs, SST_1R, SST_2R, SST_3R, SST_4R and SST_5R mediate the actions of SST which are variably expressed in the brain [248, 250, 251]. SST_2R, SST_3R, SST_4R and SST_5R undergo rapid endocytosis, induced by the binding of agonists, while SST_1R does not internalize but is rather up-regulated when continuously exposed to agonists [252, 253]. The types of active SST isoforms, SST-14 and SST-28 vary in their distribution: SST-14 is more predominant in the CNS, whereas SST-28 is more abundant in peripheral organs [254, 255]. Both bind to the SSTR in nanomolar affinity. However, SST_5R has a higher affinity for SST-28 over SST-14, while for the other SSTRs the contrary is true [256]. In the cortex, SST is a protein marker of inhibitory interneurons, as SST is expressed mainly in a subset of GABAergic neurons [254]. SST and SSTRs contribute to cortical processing and in the striatum SST-positive interneurons are able to co-release glutamate and GABA [254]. This co-release generates excitation-inhibition sequences in postsynaptic neurons, which is interpreted as the glutamatergic response and persists for a shorter time than a usual inhibitory response would [254, 257, 258]. The involvement of SSTR in neurodegenerative and neuropsychiatric disorders such as AD, OD, HD, bipolar disorder, schizophrenia and major depressive disorder (MDD) has been linked to a decrease in the amount of expressed SST [254].

2.1.11. Vasopressin and Oxytocin Receptors

Arginine-vasopressin, also known as antidiuretic hormone (ADH), and oxytocin (OT) are hormones derived from neurohypophysis. These are similar nonapeptides that differ only at residues 3 and 8 [259]. ADH is essential for cardiovascular homeostasis (water body balance), key for shock states [259, 260]. OT is also known as the "quick birth" hormone because it facilitates reproduction in vertebrates at several levels due to its uterine-contracting properties. This hormone is the one that responds to sexual activity and during labour where oxytocin controls the highly potent uterotonic activity, induces milk production and additionally induces the first onset of maternal behaviour [259-263]. The actions of ADH are mediated by tissue specific GPCRs and are known as V1 vascular ($V_{1A}R$), V2 renal (V_2R) and V3 pituitary ($V_{1B}R$, previously known as V_3R) [264-266]. The $V_{1A}R$ has been shown to be ubiquitously expressed in the brain [259] and therefore plays a role in many physiological functions including cell contraction and proliferation, platelet aggregation, liver glycogenolysis, vascular smooth muscle, aldosterone secretion by the adrenals and subserve neurotransmitter-like actions of ADH in the CNS [267-271]. Species-typical social behaviours (*e.g.*, affiliative behaviour) in rodents and humans may be associated with the pattern of $V_{1A}R$ expression in the brain [272-275]. The $V_{1B}R$ mediates the release of ADH and beta-endorphin from the anterior pituitary through the mobilization of intracellular calcium by phosphatidylinositol hydrolysis [259, 276]. However, the receptor was also found in other organs including the adrenals, the brain and the pancreas [277-279]. In 2002, SSR149415, a $V_{1B}R$-antagonist, was developed with antidepressant- and anxiolytic-like properties [259, 280]. Since then, it has been hypothesized that $V_{1B}R$ may play an important role in major depressive disorder (MDD) and chronic stress. In addition it has been shown that a small subset of MDD patients displays an impaired hypothalamus-pituitary-adrenal (HPA) axis function, which was also present in patients with treatment-resistant depression or severe depression [281-290]. This led to the assumption that $V_{1B}R$-antagonists would improve the treatments of such conditions, and several selective and potent antagonists have been developed and their potential as antidepressants has been verified in animal models [290].

The main endocrine function of ADH, the facilitation of water reabsorption in the kidney through inhibition of the diuresis, is mediated by the V_2R [259]. The deployment of ADH analogous (dDADH, desmopressin) as selective V_2R-agonists has been successful for the treatment of central diabetes insipidus, patients suffering from hemophilia A and Von Willebrand's disease, the most frequent congenital bleeding disorders [291-296]. In summary, the key function of the V_2R is to regulate fluid homeostasis [297].

The last member of this family, the oxytocin receptor (OTR), is activated by the neurotransmitter oxytocin (OT) which regulates emotional, parental, affiliative and sexual behavioural functions, including mother-infant bonding [259, 298]. The OTR is expressed in the brain and body, especially in reproductive organs [298]. Also, the number of receptors varies in different periods of life such as birth and postpartum [298, 299]. In the brain, OT induces the suppression of GABAergic neurons [300, 301]. It has also been reported that OT has an anti-inflammatory effect, observable in wound healing and pain relief [302, 303]. Besides this function, anti-depressant effects have been described for OT [304, 305]. OT might also have anti-anxiety effects mediated by the HPA axis [306]. Recently, increased methylation levels in the OTR have been linked to obsessive-compulsive disorder (OCD) [307]. Another study demonstrated that substantial loss of hypothalamic oxytocin-producing neurons occurs in amyotrophic lateral sclerosis [308].

2.1.12. Trace Amine-associated Receptors

Trace amine-associated receptors (TAARs) were discovered in 2001 [309, 310] and are activated by a diverse group of aminergic compounds. In mammalian, the nine TAAR members are divided into two sub-families: $TAA_{1\text{-}4}R$ and $TAA_{5\text{-}9}R$ [311, 312]. In humans, there are six functional TAAR genes (TAA_1R, TAA_2R, TAA_5R, TAA_6R, TAA_8R and TAA_9R) and three pseudogenes (TAA_3R, TAA_4R and TAA_7R) [312]. TAA_1R is the most well-characterized member and a potential target for psychiatric disorders, such as schizophrenia [313] and drug abuse [314], as well as for metabolic disorders [315]. The endogenous trace amines p-tyramine, β-phenylethylamine, tryptamine and octopamine bind to TAARs [309, 316, 317], essentially to TAA_1R and TAA_4R, and they induce effects in CNS. For example, phenylethylamine acts as a postsynaptic neuromodulator of dopamine and noradrenaline neurotransmission [318]. Tryptamine potentiates neural responses to dopamine and causes an increased response to norepinephrine in cortical neurons [319]. Octopamine increases depressive and excitatory responses to norepinephrine in the rat cerebral cortex [320]. 3-Iodothyronamine may have a pro-learning anti-amnesia effect [319]. With the exception of TAA_1R, all TAARs have been detected in olfactory sensory neurons [321]. TAA_1R is coupled to G_s protein [309, 310], recruits the β-arrestin-2 cascade [322, 323] and increases the opening of inwardly rectifying K^+-channels that have the characteristics of G protein-coupled inwardly-rectifying potassium channels (GirK) channels [324, 325]. All the other TAARs within the olfactory epithelium are coupled to G_{olf} to regulate cAMP accumulation [326]. TAA_5R is also coupled to G_s cascade [327], $G_{q/11}$ cascade and $G_{12/13}$ dependent MAP kinase pathways [328]. In contrast, TAA_8R is G_i-coupled [329]. The signal transduction events of TAA_6R and TAA_9R are still unknown.

2.1.13. Neurotensin Receptors

The central and peripheral effects of tridecapeptide neurotensin (NT) are mediated through interaction with three identified neurotensin receptors: NTS_1, NTS_2 and NTS_3 (Sortilin 1) [330]. Whereas NTS_1 and NTS_2 receptors have seven transmembrane helices and are G protein-coupled, the Sortilin 1 receptor is a single transmembrane domain receptor [330]. NTS_1R is found in the brain and intestine of rats and humans [331]. In the brain, the NTS_1R is mainly found in neurons of the diagonal band of Broca, medial septal nucleus, nucleus basalis magnocellularis, suprachiasmatic nucleus, supramammillary area, substantia nigra and ventral tegmental area, as well as in the small dorsal root ganglion neurons of the spinal cord [332, 333]. NTS_2R is mostly expressed in brain [334-336] and mainly localized in the olfactory system, the cerebral and cerebellar cortices, the hippocampal formation and selective hypothalamic nuclei of the mouse [337] and rat [338] brain. NTS_1R are G_q-coupled [330, 339, 340], but some other studies demonstrated that NTS_1R are also $G_{i/o}$ and G_s-coupled [330, 341-343]. In contrast, signal transduction of NTS_2R receptors is still unclear. The role of neurotensin and its receptors is related to analgesic effects, which could be an alternative to opioids [344-346].

2.1.14. Angiotensin Receptors

The actions of angiotensin II, which is an important peptide hormone in the renin-angiotensin-aldosterone system (RAAS), are mediated through angiotensin receptors AT_1R and AT_2R [347-349]. The RAAS system involves different peptides and proteins with opposing effects in order to function [350]. On one hand, vasoconstrictive, pro-inflammatory and pro-proliferative are mediated by angiotensin II, AT_1R and angiotensin-converting enzyme (ACE), while on the other hand, cardio-protective effects are mediated by Ang(1-7), AT_2R and ACE2 [350]. However, angiotensin II displays ubiquitous actions by activation of different pathways by the binding to AT_1R and AT_2R in order to initiate the RAAS system or to further get cleaved into shorter peptides such as Ang IV, Ang(1-7) and almandine [350-353]. Besides, angiotensin II, angiotensin I and angiotensin III are endogenous ligands of ATRs [347]. The AT_1R is clinically relevant as it is targeted by a large class of sartans, AT_1R blockers [347]. The AT_1R is mainly expressed in the brain, heart, blood vessels, lungs and kidneys [354, 355] and is known to bind to $G_{q/11}$, $G_{i/o}$ proteins, G_{12} and G_{13} proteins as well as tyrosine kinases [350, 356]. Functions involving AT_1R are cardiac hypertrophy, vasoconstriction, aldosterone synthesis and secretion, increased vasopressin secretion, decreased renal blood flow and renin inhibition, central and peripheral sympathetic nervous system activity and osmocontrol [357]. In the brain, AT_1R antagonists were shown to reduce fear memory recall in mice [358, 359].

AT_2R was shown in *in vitro* and *in vivo* studies to counterbalance the effect of AT_1R, however, this is still speculative [349, 350, 352, 360-362]. AT_2R are highly expressed in fetus and neonates and induce fetal tissue development, and so, although controversially, it is assumed they are involved in vascular growth [363, 364]. However, some studies could show that AT_2R was upregulated after vascular injury, cardiac failure, myocardial infarction or wound healing, suggesting that this possibly reflects the re-activation of this fetal genetic programme [349, 352, 365, 366]. The expression of AT_2R in humans is therefore developmentally regulated. In adults, AT_2R is expressed in lower density in the adrenal medulla, brain and reproductive tissues [363, 364]. AT_2R expression in the cerebellum has been associated with inhibition of cell growth differentiation, neuronal regeneration and ventricular hypertrophy [367]. Also, it was suggested that AT_2R-mediated effects in other tissues require the local conversion of angiotensin II to II [368-370]. The downstream signalling transduction of the AT_2R is poorly understood. It is known that the receptors possess important structural motifs which are typical for class A GPCR activation; however, several modalities can result in AT_2R activation [371-388].

The existence of AT_3R and AT_4R was also proven, but only AT_4R remained to be relevant [389, 390]. AT_4R was shown to be the mammalian selective receptor for angiotensin IV (Ang3.8) as well as a receptor for insulin-regulated membrane aminopeptidase [391-394]. It has been proposed that the AT_4R may be relevant in the regulation of the extracellular matrix of the CNS and modulation of oxytocin release [391, 395-399].

2.1.15. Growth Hormone Secretagogue Receptors

The Growth Hormone Secretagogue Receptor (GHS-R) is a GPCR that binds growth hormone secretagogues (GHSs), like ghrelin. GHS-R is G_q and G_s-coupled and the binding of ghrelin or synthetic peptidyl and non-peptidyl

ghrelin mimetic agents leads to increased intracellular calcium content [400, 401]. GHS-R and its ligand ghrelin have special influence on food intake, gut motility, sleep, memory, behaviour, lipid and glucose metabolism, and cardiovascular effects [402]. GHS-R is expressed by growth hormone-releasing hormone (GHRH) neurons in the pituitary [403], but also in hypothalamus, pancreas, adipose tissue, immune cells and cardiovascular system [404, 405]. GHS-R has two isoforms, GHS-R_{1a} and GHS-R_{1b}, but only $GHSR_{1a}$ transduces ghrelin signalling by binding the active form of ghrelin [406]. GHS-R_{1a} agonist and antagonist revealed to have benefits in cancer, cachexia [407-409], aging related cognitive decline [410, 411], obesity [412] and diabetes [413-415].

2.1.16. Melatonin Receptors

The melatonin receptors MT_1R and MT_2R are expressed in several areas in the human body such as brain, retina, cardiovascular system, organs or skin are activated by their endogenous ligand melatonin [416-420]. An additional MT_3R has been identified in birds and amphibians [420]. MT_3R was later identified in humans as a cytoplasmic enzyme, involved in the detoxification by reduction of quinones and also bound with low affinity to melatonin [421, 422]. Melatonin is a hormone mainly produced in a circadian rhythm in the pineal gland, with low levels during the day and high levels at night [418, 423-425]. This circadian secretion was found to be regulated by the suprachiasmatic nucleus (SCN) in a negative feedback-loop by melatonin binding to MT_1R and MT_2R, which then decreases SCN firing [426]. Melatonin is mainly known as a sleep promoter and regulator of circadian rhythms. Still, more effects such as antioxidants, reproduction-stimulation, analgesic and suppression of tumours have been attributed to it [420, 427].

It has been identified that the sleep-promoting effects of melatonin are mainly regulated by MT_1R [428]. MT_1R was also shown to be involved in adaptation to the light/dark-circle, phase-shifting activity and prolactin secretion [420, 428]. MT_1R and also MT_2R exert their signals by binding to $G_{i/o}$ proteins [429]. However, they are also able to bind to other G proteins such as G_q and soluble guanylate cyclases [418, 428-430]. In contrast to MT_1R, MT_2R was shown to regulate a variety of functions in the body. It is known that melatonin inhibits through MT_2R the Ca^{2+}-dependent release of dopamine in the retina [431] as well as light-dependent phagocytosis and photopigment disc shedding [432]. MT_2R was also shown to be expressed in a higher amount on differentiating osteoblasts [433].

In many studies, melatonin improved the treatment of PD, AD, alcoholism, depression or traumatic brain injuries [416, 434, 435]. For instance, addictive behaviours have been associated with an increased MTR-related cAMP concentration in the mesolimbic dopaminergic system [420]. Mostly, melatonin is used as a treatment for different types of insomnia, jet lag or shift work due to its sleep-promoting function [426]. MT_1R and MT_2R were also found to exist as homo- and heterodimers *in vivo* and *in vitro* [419, 436-438]. In mice rod photoreceptors, *in vivo* melatonin mediated the light sensitivity by formation of heterodimers, which led to heterodimer-specific activation of phospholipase C and protein kinase C [438]. This effect was abolished in MT_1R KO mice, MT_2R KO mice and in mice overexpressing a non-functional mutant of MT_2R that also interfered with the formation of functional heterodimers [438].

2.1.17. Orphan Class A Receptors

The orphan receptor GPR139 was first discovered in 2002 [439], further curated in full-length in 2005 and classified into the class A GPCR family, right next to its closest relative, GPR142 [440-442]. As GPR139 is still considered an orphan receptor, a precise function remains to be determined. However, some reports suggest a role for GPR139 in locomotor activity, metabolism, alcohol addiction and hyperalgesia and phenylketonuria [443]. Lastly, genetic analysis has linked GPR139 to depression, schizophrenia and ADHD [443-448].

2.2. Class A Receptor Heterodimers

While class C GPCRs are obligate dimers, for a long time it was not clear if class A GPCR was able to dimerize, and what was the importance of such macromolecular structures. However, as GPCRs exhibit a high tendency to aggregate, some authors raised the question: What are the criteria for a minimal functional unit? [449, 450]. Indeed, for example, it was found for the 5-HT_4R that two monomers were associated with one G protein [451]. In this case, one 5-HT_4R was enough to simulate the G protein, but positive receptor cross-talk was observed upon co-activation, leading to the conclusion that 5-HT_4R would rather function as homodimers [450]. This was also the case for the DRD_2. In a study by Han *et al.* 2009 [452] it was shown that the maximal activity of the DRD_2 was achieved upon agonist-binding to one monomer but was modulated by the constitutive activity of the second monomer, indicating asymmetric functional interaction [450]. Hence, the minimal functional unit of class A receptors, which can either be a monomer or a homodimer, appears to be receptor-dependent [73]. In addition to these findings, heterodimers have been intensively studied using cotransfected cells in biochemical, biophysical and pharmacological experiments with wildtype or often also using mutant receptors [453-455].

Since the family of class A GPCRs comprises many receptor subfamilies such as dopamine, adenosine or serotonin receptors that mediate diverse functions in the human body transduced by only one endogenous ligand, it becomes patent that heterodimerization is indeed also required for this GPCR class [456, 457]. Many prominent examples have been intensively studied, such as the A_1R-$A_{2A}R$ complex, which is able to couple to G_i at low concentrations of adenosine and to G_s at high concentrations [458-460]. Another example is the DRD_1-DRD_2, which couples to G_q, whereas as monomers, the DRD_1 and DRD_2 couple to G_s or G_i, respectively [461-464]. Lastly, the finding that opioid receptors are also able to form heterodimers resolved many questions about atypical behaviour of targeting drugs, which apparently were selective for such heterodimers [465-472].

However, the idea of dimerization/oligomerization of GPCRs for neurotransmitters was already formulated by Fuxe *et al.* in the 80s [457, 473-475]. Since then and until 2014 the number of protein-protein interactions between GPCRs was found to be 537, according to Borroto-Escuela *et al*., indicating that class A GPCR dimers are an important and relevant discovery [476].

2.2.1. Dopamine - Dopamine Receptor Heterodimers

The five members of the dopamine receptor family are known to form dimers among their family and with other class A GPCRs [477-480]. Besides homodimers DRD_2-DRD_2 [78, 481], DRD_3-DRD_3 [482], DRD_4-DRD_4 [480], also many heterodimer combinations were identified such as DRD_5-DRD_2 [483], DRD_1-DRD_2 [478], DRD_1-DRD_3 [477] or DRD_2-DRD_3 [484]. More combinations were reviewed in Schiedel *et al.* [80], displaying the dopamine signalling heterogeneity [479, 485].

DRD_1 and DRD_2 receptors are mainly expressed in the dorsal (caudate-putamen) and ventral striatum (nucleus accumbens, NAc) areas [486]. DRD_1-DRD_2 was discovered using co-immunoprecipitation (Co-IP) and confocal Förster-Resonance-Energy-Transfer (FRET) experiments performed in brain tissues [464, 478, 487] and later by protein complementation studies [488]. More recent studies demonstrated the existence of the heterodimer in the dorsal striatum and NAc of mammalian species, including mouse, rat, nonhuman primate, and human, with a higher extent in the ventral than in the dorsal striatum [489-491]. In 2020, a study showed that the heterodimer is also found in cortical brain regions, such as piriform, medial prefrontal, and orbitofrontal, and claustrum, amygdala, and lateral habenula [492]. Many studies using signalling assays were able to show that the heterodimer formation might induce a change in the pattern of G protein-coupling (Fig. **2A**) [461, 487, 491, 493]. Monomeric DRD_1 couples to G_s and DRD_2 to $G_{i/o}$, but DRD_1-DRD_2 was found to be associated with $G_{q/11}$ and activate the phospholipase C cascade in the striatum [464]. However, in order to conduct such actions and subsequent intracellular Ca^{2+} release, the specific DRD_1 agonist SKF83959 had to bind to both receptors: it acted as a full agonist at DRD_1 and high-affinity partial agonist for a pertussis toxin-resistant at DRD_2 [464]. Furthermore, the intracellular calcium increase was associated with an increase in striatal calcium/calmodulin kinase IIa (CaMKIIa) phosphorylation [494]. The DRD_1-DRD_2 was reported to be upregulated in individuals suffering from depression [495, 496], while it was diminished in schizophrenia patients (Fig. **2B**) [497]. In striatal neurons, the DRD_1-DRD_2 heterodimer activity resulted in rapid activation of cytosolic and nuclear CaMKII with an increase in brain-derived neurotrophic factor (BDNF) expression, which was the first evidence by then, linking dopamine receptors and endogenous GPCR heterodimers to neuronal maturation [462].

Regarding the potential interface of the DRD_1-DRD_2, a comprehensive study by O'Dowd *et al*. [498] showed that it involves a pair of adjacent glutamic acids in the C-terminus of the DRD_1 and a pair of adjacent arginine residues in ICL3 of the DRD_2, oppositely charged residues, able to form stable electrostatic interactions [461, 498]. When SKF83959, which apparently is an agonist to the DRD_1-DRD_2, was administered to rats, activation of the heterodimer generated aversion in conditioned place preference studies, while disruption of it was rather rewarding [461]. Schizophrenia is known to be associated with hyperdopaminergia in subcortical dopamine projections [461]. Compared to globus pallidus tissue from normal subjects, the number of agonist-detected high-affinity state DRD_1-DRD_2 was found to be increased in globus pallidus tissue of schizophrenia patients [461]. According to George et al., these findings possibly reflect the hyperdopaminergic state associated with schizophrenia, similarly to what was observed upon amphetamine administration [461, 486].

A recent study revealed that genetic variations of DRD_2 (Val96Ala, Pro310Ser, and Ser311Cys) affect the heterodimerization between DRD_1 and DRD_2 [478]. In addition, the Ser311Cys variant seems to be a risk factor in schizophrenia [499] and shows a better response to the schizophrenia treatment [500]. Once this DRD_2 variant forms less heterodimeric interactions with DRD_1 than DRD_2 native, targeting the DRD_1-DRD_2 heterodimer under excessive dopaminergic firing will result in antipsychotic actions, with minimal side effects [478]. Another recent study showed that DRD_1-DRD_2 heterodimers play a role in cocaine dependence [501] and repeated cocaine administration in rats increases DRD_1-DRD_2 heterodimer expression [491]. The cocaine-induced biochemical changes, such as accumulation of ΔFosB, phosphorylation of extracellular signal-regulated kinases (ERK), and phosphorylation of Thr34-DARPP-32 in NAc are blocked by heterodimer activation [501]. Similar to what happens with cocaine, heterodimer expression is also increased after chronic administration of Δ-tetrahydrocannabinol (THC) in rhesus monkeys [491]. Consequently, the DRD_1-DRD_2 heterodimer would also be a good pharmacological target in cannabis use disorder (CUD) and the THC-induced changes in dopamine signalling are also implicated in behavioural despair disorders [491, 492, 502, 503].

Another dopamine receptor heterodimer, DRD_1-DRD_3 was also found to be expressed in the ventromedial striatum by FRET and bioluminescence resonance energy transfer (BRET) techniques [477, 504-507]. One of the first studies about DRD_1-DRD_3 heterodimer's mechanism, reported in 2008 that DRD_3 activation amplified DRD_1-mediated AC signalling in the DRD_1-DRD_3 heterodimer (Fig. **2C**) [507]. However, in 2014, Ferré and co-workers reported that co-activation of both receptors had antagonistic effects at the level of the AC, due to DRD_3-mediated inhibition [504]. Therefore, co-activation of both receptors led to the canonical negative interaction at the level of AC signalling, the recruitment of β-arrestin-1 and selective activation of MAPK signalling, which was mediated by a G protein-independent mechanism (Fig. **2D**) [504, 505]. Furthermore, this positive crosstalk through β-arrestin-1 recruitment and MAPK signalling, induced by DRD_3 and DRD_1 agonists, respectively, was counteracted by DRD_1 and DRD_3 antagonists. Moreover, the DRD_1-DRD_3 heterodimer was implicated in L-DOPA-induced dyskinesia [504, 508-510]. Some studies reported that DRD_1 super-sensitivity during L-Dopa induced dyskinesia was accompanied by DRD_3 up-regulation [508-510], and mice with DRD_3 knockout displayed reduced L-Dopa-induced dyskinesia [510, 511]. *In vitro* studies performed by Cortés and colleagues using transfected human embryonic kidney 293 (HEK293) cells [504] and *in vivo* studies conducted by Bishop and colleagues (using hemi-parkinsonian rats) [509] demonstrated that DRD_1-DRD_3 heterodimers influenced the cooperative effect of both receptors in L-Dopa-induced dyskinesia. The co-activation with the DRD_1 and DRD_3 agonists SKF38393 and PD128907, respectively, generated an exacerbated dyskinetic effect, and an increase of downstream signalling of ERK phosphorylation, which is specific to dyskinesia as general locomotor effects or pERK were not observed in non-responders [509].

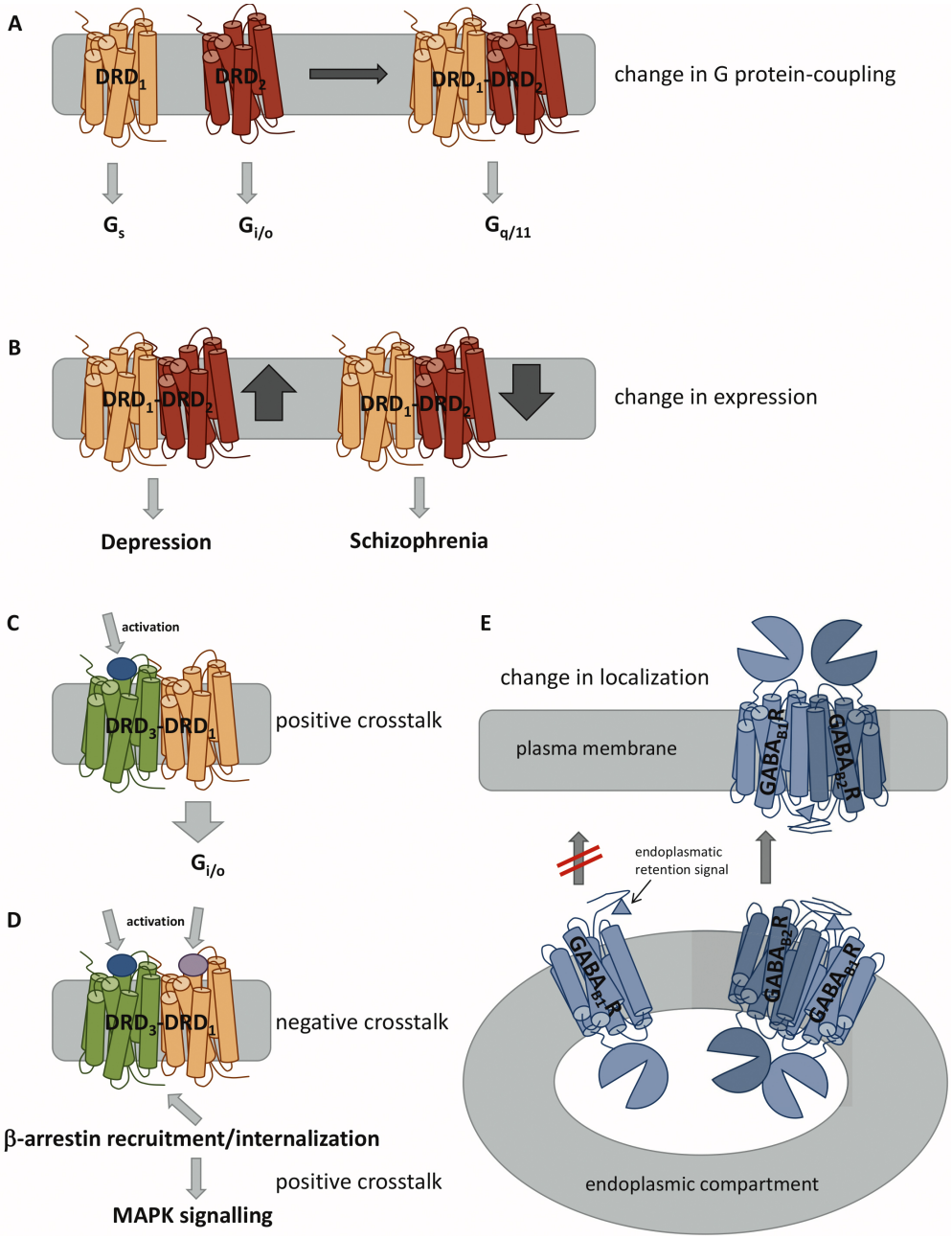

Fig. (2). Possible modulations upon GPCR dimer formation. (**A**) Heterodimerization can induce a change of G protein-coupling. (**B**) Different expression levels of heterodimers are associated with distinct diseases. (**C**) Activation of one receptor can promote signalling of the other receptor *via* positive crosstalk. (**D**) Activation of both receptors can lead to β-arrestin recruitment and internalization *via* negative crosstalk. This can lead to intracellular signalling *via* mitogen-activated protein kinase (MAPK). (**E**) Dimerization can be necessary for plasma membrane localization, *e.g.*, by masking an endoplasmic retention signal, which will prevent the transport to the plasma membrane as monomers. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

In 2001, evidence based on Co-IP studies at cultured cells pointed DRD_2 and DRD_3 heterodimerization [484]. DRD_2 and DRD_3 were found to colocalize on dopaminergic neurons as autoreceptors and at postsynaptic loci to dopaminergic projections in the globus pallidus, nucleus accumbens and in the frontal cortex on pyramidal cells and/or GABAergic interneurons [512, 513]. In a study by Maggio and colleagues, [514], it was shown that some antiparkinsonian agents (pramipexole and ropinirole) with a preference for DRD_3, displayed amplified potency at DRD_2-DRD_3 heterodimers. In COS-7 cells cotransfected with DRD_2 and DRD_3, together with a chimeric AC AC-V/VI, these same agents were able to suppress forskolin (FK)-stimulated cAMP production with higher potencies as compared to cells only transfected with DRD_2 or DRD_3 receptors and without exposure to the ligands [514, 515]. Furthermore, the binding of this heterodimer may be responsible for the antipsychotic actions of DRD_2 partial agonists and DRD_3 agonists, such as aripiprazole and N-desmethylclozapine [514, 516]. The characterization of the pharmacological properties of the

DRD_2-DRD_3 heterodimer by Novi and co-workers [516] showed that the agonist quinpirole potently suppresses FK-induced cAMP accumulation in recombinant cell lines transfected with DRD_2 receptors and AC-V/VI, while the partial agonists aripiprazole, S33592, bifeprunox, NDMC, and preclamol less strongly reduce FK-stimulated cAMP accumulation. On the other hand, all these compounds failed to modify FK-induced cAMP accumulation in cells transfected with DRD_3 and the chimeric DRD_3-insensitive AC-V/VI [516]. However, in cells transfected with DRD_2 and an excess of DRD_3, together with AC-V/VI, quinpirole diminished FK-induced cAMP accumulation with a potency and efficacy comparable to cells transfected solely with DRD_2, and the partial agonists were inactive [516]. These results suggest that an excess of DRD_3 receptors can modify the functional status of DRD_2 receptors, since partial agonists of DRD_2 are transformed into antagonists at the DRD_2-DRD_3 heterodimers [514, 517]. Thus, this could justify the low incidence of extrapyramidal side effects of the partial agonists, as the extent of the DRD_2-DRD_3 heterodimer formation is low in the dorsal striatum [514, 517]. Knowledge about the structure and action mechanism of this heterodimer provides insights into cellular processes associated with diseases such as schizophrenia, PD, and ADHD.

DRD_4 is also expressed in the brain, but its expression is lower than other types of dopamine receptors [518, 519]. However, human DRD_4 has polymorphic variants [520] that are more abundant: $DRD_{4.2}$, $DRD_{4.4}$ and $DRD_{4.7}$ [476]. DRD_2 and DRD_4 receptors partially co-distribute in the dorsal striatum and appear to play a fundamental role in complex behaviours and motor function. In 2011, based on BRET and *in situ* proximity ligation assay (PLA) in cotransfected HEK293T cells showed the coupling between DRD_2 and DRD_4 [476]. Specifically, they showed that the long form of human DRD_2 (DRD_{2long}) was able to interact and form heterodimers with the three human DRD_4 isoforms, with the $DRD_{4.7}$ variant being the least effective [476]. Upon co-activation by the DRD_4 agonist PD168077, DRD_2 agonist-induced ERK phosphorylation was enhanced in cells co-expressing DRD_2 with $DRD_{4.2}$ and $DRD_{4.4}$, but not in cells co-expressing DRD_{2long} with $DRD_{4.7}$ [476]. The $DRD_{4.7}$ variant showed reduced ability to form a heterodimer with DRD_{2long}, as no additive effect was observed after combined treatment with DRD_2 and DRD_4 agonists (quinerolane and PD, respectively) on MAPK activity when these receptors were expressed together [476]. Furthermore, the short form of DRD_2 (DRD_{2short}) was reported to form heterodimer complexes with $DRD_{4.2}$ and $DRD_{4.4}$, while the $DRD_{4.7}$ failed to interact with DRD_{2short} in BRET studies, using cotransfected HEK293T cells [476]. So, the biochemical crosstalk between DRD_{2short} and cotransfected DRD_4 variants potentiates DRD_4-mediated MAPK activation and ERK phosphorylation by DRD_2 and not the inverse [521]. This biochemical crosstalk was not observed in striatal slices taken from gene knock-in mice carrying the human $DRD_{4.7}$, confirming that DRD_2 and $DRD_{4.7}$ do not form heterodimers [521]. Solely DRD_2-$DRD_{4.2}$ and DRD_2-$DRD_{4.4}$ heterodimers exist in the striatum and they may be a potential target for antiparkinsonian drugs [522].

Finally, O'Dowd and colleagues also demonstrated the existence of the DRD_5-DRD_2 heterodimer in HEK293T cells co-expressing both receptors, through FRET analyses [493]. The authors reported that co-activation of both receptors of the DRD_5-DRD_2 heterodimer resulted in the generation of a calcium signal [493]. DRD_5 was able to activate a strong calcium signal when it was expressed alone. These calcium signals resulting from activation of DRD_5 alone or within a heterodimer require $G_{q/11}$ and PLC activity and the presence of extracellular calcium [493]. However, DRD_5 and DRD_2 heterodimerization negatively modified the functional unit of calcium signalling, attenuating the ability of the DRD_5 receptor to trigger a calcium signal. DRD_5 and DRD_2 receptors have been shown to cooperate functionally to facilitate motor activity and striatal long-term depression [523].

2.2.2. Dopamine - Adenosine Receptor Heterodimers

Besides neuronal dopaminergic transmission regulation through different heterodimers compositions, dopamine can also be regulated by adenosine. According to George *et al.*, two mechanisms of adenosine receptor-mediated neuromodulation of dopamine exist in cells: (i) adenosine counteracts cyclic adenosine monophosphate (cAMP) levels, which are modulated by dopamine; (ii) adenosine-dopamine receptor dimers exert a different signal then when they are activated as monomers [461].

Co-expression of adenosine and dopamine receptors in different basal ganglia pathways and pathways that control motor behaviour, underlined that different heterodimers exist in neuronal subpopulations [461]. In 2000, Gines and co-workers showed the existence of A_1R-DRD_1 heterodimer, using Co-IP in cotransfected fibroblast cells and cortical neurons in culture [524]. The expression of the A_1R-DRD_1 heterodimer in the brain was demonstrated by Franco and co-workers using FRET and BRET techniques [525]. A_1R and DRD_1 were found to colocalize in soma and dendritic regions of cortical neurons [526, 527]. One of the first pieces of evidence found was that A_1R agonists can reduce oral dyskinesias induced by levodopa in rabbits [528]. Adenosine agonists inhibited the motor responses of dopamine in basal ganglia and vice-versa, suggesting their functional antagonist action [529]. While DRD_1 is predominantly coupled to G_s protein, which in turns stimulates AC, A_1R is coupled to $G_{i/o}$ protein, which has inhibitory effects [528]. A_1R antagonist 1, 3-dipropyl-8-cyclopentylxanthine leads to an increase in the DRD_1-induced cAMP response, which can be related to their regulation of G proteins having offsetting activities [530]. Thus, co-activation of A_1R-DRD_1 heterodimer induces a decrease in the affinity of DRD_1 for agonist and, consequently, decrease of the DRD_1-induced cAMP accumulation [524, 530]. Kalivas and co-workers demonstrated that A_1R-DRD_1 heterodimer can also be involved in the pathophysiology of addiction [531]. They reported that cocaine, a potent stimulant of the CNS, targets the A_1R-DRD_1 heterodimer in rat nucleus accumbens, inhibiting the physical interaction between A_1R and DRD_1 [531]. This evidence emphasizes the therapeutic relevance of this heterodimer for cocaine addiction. Moreover, a recent study demonstrated the existence of A_1R-DRD_1 heterodimers in the spinal motoneuron, using PLA experiments and that adenosine tonically inhibited DRD_1-mediated signalling in the spinal motoneuron [532]. Given the importance of controlling motoneuron excitability, the A_1R-DRD_1 heterodimer may also be a potential target for

the treatment of spinal cord injury, motor aging-associated disorders, and restless legs syndrome.

$A_{2A}R$-DRD_2 heterodimer was among the first heterodimers reported, involving two different neurotransmitters [461, 533, 534]. The existence of $A_{2A}R$-DRD_2 was proven by Co-IP, BRET and FRET analyses [535, 536]. Later on, PLA studies located the $A_{2A}R$-DRD_2 in the mice striatum [537, 538]. A functional association between $A_{2A}R$ and DRD_2 was also reported to exhibit a negative allosteric cooperativity in which the activation of the $A_{2A}R$ by CGS21680 ($A_{2A}R$ agonist) leads to a decrease of DRD_2 of dopamine binding affinity [533, 539-541]. Furthermore, the activation of $A_{2A}R$ was shown to decrease the coupling of DRD_2 to its $G_{i/o}$ protein and stimulation of DRD_2 was shown to decrease the coupling of $A_{2A}R$ to its G_s protein [534, 542]. The effect of the $A_{2A}R$-DRD_2 heterodimer on ligand binding of the monomers and G protein-coupling was also associated with cross-desensitization mechanisms, which function *via* agonist-induced coaggregation and co-internalization of both receptors [534]. The $A_{2A}R$-DRD_2 is also a promising candidate target for the treatment of PD, schizophrenia and addiction [529, 535, 542, 543]. For instance, the $A_{2A}R$-DRD_2 has been considered a potential target to reduce L-DOPA-induced dyskinesia in PD treatment [72, 544]. Behavioural and microdialysis experiments in mouse, rat, dog and human models suggested a mechanism that involves a co-expression of $A_{2A}R$-DRD_2 in striatopallidal GABAergic neurons and nucleus accumbens [545-548]. Consequently, selective and potent $A_{2A}R$ antagonists are able to reduce DRD_2-dependent signalling in these areas and enhance therapeutic effects, as was demonstrated in animal models of PD [540, 549-551].

Indications that DRD_3 can heterodimerize with $A_{2A}R$ emerged in 2005, based on confocal microscopy and FRET studies using transiently cotransfected HeLa cells [552]. Results from confocal microscopy showed that $A_{2A}R$ and DRD3 colocalize in the plasma membrane, and results from FRET experiments showed that $A_{2A}R$ and DRD_3 receptors could form heterodimers in the transiently cotransfected HeLa cells [552]. Also, saturation analysis of [^{3}H]dopamine binding in the $A_{2A}R$-DRD_3, a CHO cell line was generated, indicating that $A_{2A}R$ agonist CGS-21680 is able to significantly reduce the affinity of the high affinity binding state of the DRD_3 receptors for dopamine [552]. Moreover, A_{2A} and DRD_3 receptors seem to interact at the G protein coupling level since the CGS-21680 $A_{2A}R$ agonist fully counteracted the dopamine mediated strong inhibition of forskolin-induced cAMP accumulation. So, when both receptors are co-expressed in the same cells, the antagonistic interaction of $A_{2A}R$-DRD_3 is verified, that is, A_{2A} receptors antagonistically modulate both, the affinity and signalling of DRD_3 receptors [552]. Since DRD_3 is involved in the treatment of schizophrenia, the DRD_3-$A_{A2}R$ receptor interactions could provide an alternative antischizophrenic treatment.

2.2.3. Dopamine Receptor and Other GPCR Heterodimers

Besides the intensive relationship between dopamine and adenosine receptors, DRs may also form heterodimers with GPCRs from other families. For instance, H_3R is found in striatal medium spiny neuron that expresses post-synaptic DRD_1 and obtains histaminergic input from hypothalamic asynaptic varicosities [553]. The receptors were then shown to form DRD_1-H_3R heterodimers by BRET and binding assays in transiently transfected human embryonic cells [554], Co-IP experiments in rats [555] and PLA studies in mice striatum [556]. Upon DRD_1 and H_3R receptors activation by their respective agonists (SKF 38393 and (R)-α-methylhistamine (RAMH)), DRD_1 and H_3R lead to the coupling to the $G_{i/o}$ protein and MAPK cascades, respectively [554]. The unique biochemical function of this heterodimer is supported by the fact that, when each receptor is activated alone, DRD_1 leads to the coupling to the $G_{s/olf}$ protein, while H_3R does not signal through the MAPK pathway, and they are unable to induce ERK1/2 phosphorylation in mice with either receptor knockout [554, 555, 557]. In addition, DRD_1 and H_3R antagonists, such as SCH 23390 and thioperamide, can block the distinct signalling mediated by the heterodimer [554]. An antagonist of one of the receptor units in the DRD_1-H_3R heterodimer is able to induce conformational changes in the other receptor and block specific signals originating in the heterodimer [554]. One of the last studies on this heterodimer, performed in rats and mice, reported that cocaine inhibited the bidirectional cross antagonism and the inhibitory effect of the DRD_1 and H_3R signalling [556]. McCormick and co-workers reported that σ1R binds DRD_1-H_3R heterodimers in transfected cells and in mouse and rat striatum. Authors also postulated that cocaine, a σ1R agonist, modifies the structure and counteract the biochemical properties of the DRD_1-H_3R heterodimer, such as heterodimer signalling through G_i protein, the ability of H_3R activation to signal through MAPK, and the ability of H_3R ligands to inhibit the effects of DRD_1-mediated signalling, including cell death [556]. They also reported that blockade of H_3R-mediated inhibition of DRD_1 function in the σ1R-DRD_1-H_3R complexes plays a key role in the effects of cocaine [556]. So, σ1R-DRD_1-H_3R may be a new target for the treatment of cocaine abuse.

Besides the DRD_1, also DRD_2 was found to form a heterodimer with H_3R, which was discovered by Ferrada and co-workers in 2008 using BRET in cotransfected HEK293 cells [558]. Heterodimerization of DRD_2 and H_3R was also demonstrated *in vivo* by Moreno and co-workers, using Co-IP studies in rat striatal tissues [555]. DRD_2 and H_3R can colocalize in GABAergic striatal efferent neurons and in specific DRD_2-expressing GABAergic enkephalinergic neurons [559]. The study by Ferrada and co-workers reported the existence of behaviourally significant antagonistic postsynaptic interactions [560] between H_3R and DRD_2 receptors in reserpinized mouse model [558]. Whereby the stimulation of the H_3R significantly decreased the ability of agonists to bind to the DRD_2, while antagonists were unaffected [558]. Thus, this heterodimer may play a role in the function of the GABAergic enkephalinergic neuron [558]. Beyond Parkinson's disease, a therapeutic approach based on H_3R receptor-mediated negative modulation of DRD_2 receptor function may emerge and play a role in disorders involving the cortico-striatal-thalamo-cortical circuits, such as Huntington's disease, Tourette syndrome, obsessive-compulsive disorder, schizophrenia and addiction [558].

DRD_2 was also found to colocalize with SST_5R in transfected HEK293 cells, using FRET [561]. The heterodimerization of both receptors was promoted by application of an-

tidepressant drugs (desipramine and citalopram) [561]. The physical evidence of DRD_2-SST_5R heterodimer was then proven with PLA studies in the striata of mice and striatal neuronal cultures [562]. It was suggested that the DRD_2-SST5R may be a potential mediator of antidepressant effects since the heterodimerization of these receptors appeared to occur in native brain tissue and in primary striatal neuronal cultures [562]. Furthermore, prolactin is a neurotransmitter regulated by those two receptors and its excessive excretion was reported in cases of depression [563]. In addition, a study by Szafran-Pilch *et al.* suggested that the stimulation of DRD_2-SST_5R may enhance the inhibition of this prolactin [562]. Proceeding with the promiscuous DRD_2, another interaction partner was reported in a BRET study using transfected HEK293T cells: NTS1R [564]. Recently, Friedland *et al.* reported the existence of DRD_2-NTS1R heteroreceptor complexes in the accumbens core and shell, especially in the dorsal striatum, using PLA assays [565]. The NTS1R was shown to negatively modulate DRD_2 signalling through immediate receptor-receptor crosstalkbased on CRE luciferase gene assay, NTS1R activation generates a blockade of the DRD_2 induced inhibition of the AC-PKA-CREB pathway [566-568]. Also, the NTS1R agonist NT(8-13) reduces the $G_{\alpha q}$-mediated calcium signal in the DRD_2-NTS1R heterodimer compared to the NTS1R monomer, which can also be reversed by DRD_2 antagonists [565]. The heterodimer activation by CS148, an NTS1R agonist and also DRD_2 antagonist, increases the calcium response, depending on the effect of the monovalent ligands indicating an allosteric DRD_2-mediated modulation [565]. This provides the evidential basis for functional association of DRD_2 and NTS1R in brain areas that are closely linked to the pathophysiology of schizophrenia [565, 569].

Another partner for DRD_2 is the TAA_1R, a member of class A GPCRs, not yet well investigated. The DRD_2-TAA_1R heterodimer was found in dopaminergic innervated areas and provided a mechanism for dopamine neurotransmission modulation *via* TAA_1R [570, 571]. Different studies could show that TAA_1R may affect the DRD_2 function and firing rate of dopaminergic neurons [324, 570, 572]. The DRD_2- TAA_1R heterodimer exerts its effect through the cAMP pathway, and haloperidol was found to promote cAMP-mediated TAA_1R signalling [570]. With haloperidol as a known antipsychotic, the DRD_2- TAA_1R may have a role in the treatment of schizophrenia [313]. The DRD_2-OTR was identified in cotransfected HEK293 cells using PLA [573, 574]. Further studies on the DRD_2-OTR suggested the existence of allosteric reciprocal interactions endowed with the ability to enhance signalling of DRD_2-OTR. The heterodimer is excreted upon OT activation, facilitating DRD_2 signalling *via* allosteric receptor-receptor interactions [574]. It was also reported that the dysfunction of the DRD_2-OTR in the central amygdala might lead to anxiety development [574]. Therefore, restoration of its activity may be a new therapeutic approach to treat anxiety [574].

Another DRD_2 interaction partner represents the growth hormone secretagogue receptors (GHS-R), also known as Ghrelin receptors [575, 576]. GHS-R_{1a} is a transcript variant of GHS-R and encodes the functional protein, which defines a neuroendocrine pathway for growth hormone release [577]. GHS-R signals *via* $G_{\alpha q/11}$ cascade to mobilize calcium from intracellular stores [578] and plays a role in the regulation of feeding behaviour [579]. Similarly, DRD_2 is also known to control physiological functions like food consumption [580, 581]. Henceforth, it was very likely that a DRD_2-GHS-R_{1a} exists, which was eventually discovered by Smith and co-workers using immunofluorescence and time-resolved FRET experiments in hypothalamic neurons of rodents [582]. Within the DRD_2-GHS-R_{1a}, the apo-ghrelin (unliganded) GHS-R_{1a} was reported to modulate DRD_2 signalling from the normal $G_{\alpha i/o}$ subunit mediated inhibition of cAMP to $G_{\beta\gamma}$ subunit mediated PLC-IP3 cascade [582]. Also, in the absence of ghrelin, the endogenous ligand of GHS-R, dopamine and/or DRD_2 agonists were able to activate this biased $G_{\beta\gamma}$ subunit mediated PLC-IP3 signalling, suggesting that apo-GHS-R_{1a} acts as an allosteric modulator on DRD_2 [582]. In order to assess if the allosteric interaction between DRD_2 and GHS-R_{1a} could be pharmacologically targeted, the selective GHS-R_{1a} antagonist JMV2959 was applied in treated mice with the highly selective neutral GHS-R_{1a} antagonist JMV2959 prior to cabergoline treatment. It was shown that cabergoline-induced anorexia (selective DRD_2 agonist) was blocked upon binding to the DRD_2-GHS-R_{1a} [582]. Targeting heterodimers represents a therapeutic advantage for the treatment of eating disorders.

2.2.4. Adenosine - Adenosine Receptor Heterodimers

The endogenous purine nucleoside adenosine is obtained by the breakdown of adenosine triphosphate (ATP) and consists of ribose sugar and adenine attached by a glycosidic linkage [583]. The importance of ATP and its metabolites is further underlined as they are the main energetic molecules in living organisms. The actions of adenosine through the four specific ARs are found in every single mammalian cell [583]. The first heterodimer consisting of A_1R and $A_{2A}R$ was found in 2006 by a study using Co-IP, BRET and time-resolved FRET techniques from Ciruela *et al*. [458]. It was shown that A_1R-$A_{2A}R$ exists in striatal glutamate neurotransmission at the presynaptic level [458]. Interestingly, both monomers are known to couple to different G proteins, A_1R couples to $G_{i/o}$ whereas $A_{2A}R$ couples to G_s [584]. Ciruela and co-workers were able to demonstrate that depending on the concentration of adenosine, the regulation of glutamate release by cortical glutamatergic terminals would be opposite [458, 583]. A_1R-$A_{2A}R$ was shown to regulate the GABA uptake through adenosine in astrocytes. Hence, it was suggested that A_1R-$A_{2A}R$ acts as a sensor of adenosine concentration as consequent fine-tuning modulation of striatal glutamatergic neurotransmission, in a manner, that there is either A_1R or $A_{2A}R$-mediated signalling [583]. Elevated extracellular levels of adenosine activate the $A_{2A}R$ protomer in this complex, producing an antagonist allosteric receptor-receptor interaction inhibiting A_1R protomer signalling. Thus, activation of the $A_{2A}R$ in A_1R-$A_{2A}R$ heterodimers produces an increase in glutamate release, while the activation of A_1R leads to the opposite effect [458, 560, 585]. Upon G protein-coupling to the heterodimer, the long C-terminus of $A_{2A}R$ is the key region that determines the dominant $A_{2A}R$-mediated signalling [583, 586]. A_1R-$A_{2A}R$ heterodimers may exist in glutamate projections that regulate GABA striatal pallidal neurons, mediating motor inhibition. In the case of this heterodimer, $A_{2A}R$-induced glutamate release should neutralize movement inhibition, making it a therapeutic tar-

get for neurological diseases associated with motor activity [587]. Other studies determined caffeine as a new ligand for A_1R-$A_{2A}R$, which when chronically applied, led to strong tolerance to the psychomotor effects of caffeine mediated by A_1R-$A_{2A}R$ [588].

2.2.5. Adenosine Receptor and Other GPCR Heterodimers

The frequency of 'spontaneous' (non-electrically evoked) excitatory postsynaptic currents (EPSCs) in layer V pyramidal neurons increases after 5-HT_2A receptor activation [589] and leads to an increase in late components of EPSCs evoked by electrical stimulation [590]. Since A_1R and 5-HT_2AR receptors are both localized in the prefrontal cortex, a study on how A_1R receptor modulates 5-HT_2A-enhanced 'spontaneous' and electrically evoked excitatory postsynaptic currents in layer V pyramidal neurons in the medial prefrontal cortex was conducted by Aghajanian and co-workers [591]. They showed that A_1R agonist (N^6-cyclopentyladenosine) suppressed the frequency of EPSCs generated *via* 5-HT_2A receptor-induced glutamate release in the medial prefrontal cortex. As it did not generate large postsynaptic currents, the suppression mechanism was thought to be predominantly presynaptic [591]. Also, in 2009, Marek studied the effects of the A_1R receptor agonist N^6-cyclohexyladenosine on phenethylamine hallucinogen DOI-induced head shakes in order to examine a behaviour induced by activation of 5-HT_2A receptors in the rat prefrontal cortex [592]. The results showed that while N^6-cyclopentyladenosine suppressed head shakes, induced by activation of 5-HT_2A receptors with the DOI, an A_1R receptor antagonist (DPCPX) enhanced DOI-induced head shakes and blocked the suppressant action of an A_1R agonist on DOI-induced head shakes [592]. This mechanism of action of A_1R agonists on the 5-HT_2A receptor suggests a novel therapeutic approach for schizophrenia as well as psychosis and anxiety disorders [591, 592].

In 2018, an $A_{2A}R$-H_3R heterodimer was discovered for the first time in recombinant cell systems and in rat striatal nerve terminals, based on functional complementation and Co-IP assays in HEK293T cells [593]. $A_{2A}R$ and H_3R were found to be co-expressed in the cortico-striatal glutamatergic afferents and the GABAergic medium-sized spiny neurons that originate from the indirect pathway of the basal ganglia [593]. Therefore, both monomers can regulate the striatal GABAergic and glutamatergic transmission. It was reported that the co-activation of $A_{2A}R$ and H_3R leads to enhancement of $A_{2A}R$ signalling and decrease of H_3R functionality *via* their coupled G proteins [593]. As a protomer, H_3R is coupled to $G_{i/o}$ proteins and, consequently, inhibits AC activity. When RAMH, a H_3R agonist, activates the H_3R receptor, it leads to a decrease in cAMP formation. However, the expression of $A_{2A}R$ leads to an increase in the H_3R-mediated cAMP formation [593]. In addition, the endogenous ligand histamine cannot signal through the heterodimer, unlike the exogenous agonist RAMH, suggesting that RAMH can lead to conformational changes in the H_3R, allowing heterodimerization. On the other hand, the histamine-induced changes may not be sufficient to signal the heterodimer [593]. Based on binding studies with striatal membranes and histamine, it was demonstrated that H_3R activation by histamine increased the binding affinity of the $A_{2A}R$ for its agonist CGS-21680, while RAMH resulted in a decrease of the binding affinity, indicating that histamine and RAMH lock the H_3R in different conformational states that affect its interaction with the $A_{2A}R$ [593]. It is possible that the H_3R-$A_{2A}R$ heterodimer plays a role with key physiological implications.

2.2.6. Opioid - Opioid Receptor Heterodimers

As referred, the most effective analgesics in clinical pain management are opioids such as morphine, codeine, hydrocodone, oxycodone, fentanyl, and tramadol [594]. However, they are also commonly prescribed and frequently abused [595, 596]. Among the intricacy of opioid receptor pharmacology, opioid receptor heterodimers represent another important layer of signalling complexity and provide an opportunity for the development of analgesics with fewer side effects [597]. Dimerization was already reported for homodimers MOR-MOR [598] and heterodimers containing only opioid receptors such as MOR-DOR [599-601], MOR-KOR [602] and DOR-KOR heterodimer [603], were proven to exist both *in vitro* and *in vivo*. OR heterodimers are often expressed in limited and specific brain regions and are involved in adverse effects induced by chronic opioid therapy, underlining the importance to develop therapeutic strategies to target these heterodimers [109, 604].

Selective agonists and antagonists were developed to target MOR-DOR [605]. Devi and Rozenfeld reported that the MOR agonist Tyr-D-Ala-Gly-*N*-Me-Phe-Gly-ol (DAMGO) activates $G_{i/o}$-mediated signalling in MOR-expressing cells as well as β-arrestin-2-mediated signalling for changing the dynamics of ERK-mediated signalling in MOR-DOR heterodimer-expressing cells [606]. In MOR-DOR expressing cells, using a chimeric G protein-mediated calcium fluorescence assay, it was shown that the DOR selective agonist SNC80 induces intracellular Ca^{2+} release [607]. Another example is CYM51010, a selective MOR-DOR agonist, able to induce the recruitment of β-arrestin-2 and GTPγS binding, which could then be blocked by a MOR-DOR selective antibody (mAb) [608]. Here, the DOR was shown to have an antagonistic allosteric influence on MOR activity within the heterodimer [604]. The DOR peptide antagonist TIPPΨ was shown to enhance the binding of morphine to MOR, $G_{i/o}$ coupling and inhibition of cAMP levels [601]. Furthermore, the MOR-DOR may also have specific intracellular trafficking. According to studies by Milan-Lobo and Whistler, MOR and DOR are only able to dimerize when both are present in the plasma membrane [609]. Controversy, Hasbi *et al.* stated that MOR-DOR are located in the endoplasmic reticulum, where they recruit the G_{az} protein [610]. Another study by Décaillot *et al.* reported that the agonists DAMGO, Deltorphin (Delt) II, SNC80 and methadone could induce MOR-DOR endocytosis, but others such as DADPE were not able to do so [611]. In the same study, Décaillot and co-workers identified RTP4, a Golgi chaperone as an important regulator of MOR-DOR levels at the cell surface [611]. This was found to be in concordance with a study by He *et al.*, where the application of DOR-selective agonists Delt I, Delt II and SNC80 induced endocytosis and further procession of degradation of DOR and MOR, resulting in a reduced MOR surface expression in double-transfected HEK293 cells [612]. This effect was also achieved when DAMGO, a selective MOR agonist, was applied [612]. The effect was then only diminished when an interfering peptide D-Phe-Cys-Tyr-D-

Trp-Om-Thr-Pen-Thr-NH2 (CTOP) or the antagonist naloxone was added [612]. To perform a whole-brain dual receptor mapping study, RedMOR/ greenDOR double knock-in mice were generated. MOR and DOR were colocalized in subcortical neuronal networks, responsible for eating actions, sexual behaviours or response to aversive stimuli [613]. In 2018, Wang *et al.* found that the co-expression of MOR and DOR is restricted to small populations of spinal cord neurons and yet is rare in the parabrachial, amygdala and cortical regions of the brain for pain processing [614]. In another study Gomes *et al*. showed, using tail-flick assays in mice, that the CYM51010 ligand for the heterodimer MOR-DOR has analgesic activity identical to the one from morphine [608]. Also, CYM51010-induced analgesia was abrogated in MOR knockout mice and still persisted in morphine-tolerant mice [608]. The evidence of these heterodimers in CNS pain circuits suggests that MOR-DOR heterodimers cellular interactions are important for the development of novel opioid analgesics.

The MOR-KOR heterodimer was discovered in 2010 by Chakrabarti and co-workers [602]. The results of their study showed that MOR-KOR was more prevalent in the spinal cord of proestrus (with high estrogen receptor levels) vs. diestrus females and vs. males [602, 615]. It was then concluded that dynorphin would serve a potential female-specific KOR-ligand within the MOR-KOR. Furthermore, gender- and ovarian steroid-dependent recruitment of MOR-KOR was seen as a way to balance the actions of anti-nociceptive and pro-nociceptive functions of the dynorphin/KOR opioid system in the spinal cord. Lastly, various types of chronic pain states that are significantly more common in women than men, could be the result of the impaired formation of MOR-KOR and therefore, this holds promise for the development of a special ligand to target the MOR-KOR [604].

2.2.7. Opioid Receptor and Other GPCR Heterodimers

The main goal of studying OR heterodimers is to understand their existence and physiological function from the perspective of pain transmission. Once resolved, potent analgesics with fewer side effects could be developed. Studies by Vilardaga *et al.* and Yang *et al.* showed that a conformational antagonistic crosstalk exists between MOR and α_{2A}AR [616, 617]. FRET microscopy studies showed that MOR and α_{2A}AR communicate *via* a switch of conformations within the monomers that leads to inhibition of one monomer by the other [616]. Morphine binding to MOR within the MOR-α_{2A}AR was reported to induce a conformational change in the norepinephrine-bound α_{2A}AR, which then inhibits $G_{\alpha i}$ signalling and the downstream MAP kinase responses [616]. Hence, MOR activation mediates the rapid inactivation of its coupled partner α_{2A}AR. Already in the 90s it was reported that combined agonists acting on MOR and α_{2A}AR would act synergistically when co-administered into the spinal cord and would have an analgesic effect [618]. Furthermore, it was also reported that norepinephrine or clonidine, which are both agonists of α_{2A}AR, were able to reduce significantly the release of glutamate, substance P and calcitonin gene related peptides from spinal cord synapses [619, 620]. MOR and α_{2A}AR were both located in the superficial layers of the dorsal horn of the spinal cord, and in the rat spinal cord, α_{2A}AR was located on the terminals of capsaicin-sensitive, SP-containing primary afferent fibers in immunostaining studies [619]. Both receptors were reported to affect the nociceptive system and are particularly involved in the depression of neurotransmitter release in the spinal cord [621, 622]. However, the synergy of MOR and α_{2A}AR agonists in the MOR-α_{2A}AR in analgesia remains unclear [604].

In 2019, Wang and co-workers identified the MOR-GPR139 heterodimer in which the orphan GPR139 negatively regulates the opioid receptor function, signalling and trafficking [604, 623]. By using *C. elegans* as a model organism, it was shown that mammalian MOR was expressed in the nervous system of nematodes (tgMOR), and that application of morphine and fentanyl leads to a decrease in locomotion in nematodes expressing tgMOR [604, 623]. By applying a large-scale genetic screening and whole genome sequencing, Wang *et al.* identified the orphan receptor FRPR-13, the homolog of the human GPR139, as a negative regulator of MOR *in vivo* [604, 623]. The functional relationship between MOR and GPR139 was further investigated in MOR and GPR139 transfected HEK293 cells, where MOR activation was shown to cause an opening of G protein-coupled inwardly rectifying potassium channels (GIRKs). This leads to hyperpolarization of membrane potential, which can be inhibited by GPR139 expression [604, 623]. In addition, Wang *et al.* were able to show that MOR and GP139 could be co-immunoprecipitated. They also showed that when GPR139 was highly overexpressed, the cell surface expression of MOR was reduced, suggesting that GPR139 is able to regulate MOR trafficking to the plasma membrane or internalization [604]. Furthermore, GPR139 was found to bind directly to MOR *in vitro,* promote the recruitment of β-arrestin-2 and inhibit GIRK and G protein activation [604]. More evidence for MOR-GPR139 was generated in *in situ* hybridization experiments, where MOR and GPR139 are co-expressed in similar brain regions [604]. Wang *et al.* also provided electrophysiological evidence, where in cultured brain slices GPR139 deficiency reduced the basal firing rate and increased opioid sensitivity in neurons [604]. Lastly, Wang *et al.* investigated the relationship between MOR and GPR139 in *in vivo* animal studies in mice. GPR139 knockout (KO) mice had normal baseline learning, nociception, locomotor activities, and motor coordination but showed sensitivity to morphine-induced analgesia and reward effects [604, 623]. When JNJ-63533054, an GPR139-agonist, was administered, morphine-induced analgesia and rewards were inhibited in mice [604, 623]. Also, GPR139 KO mice did not show explicit opioid withdrawal reactions [604, 623]. Hence, GPR139 was identified as a novel anti-opioid system in the brain.

In 2018, Koshimizu and co-workers identified the MOR-V_{1B}R heterodimer [624]. The endogenous ligand of V_{1B}R, ADH (or also AVP) was reported to regulate morphine tolerance and sensitivity [604]. Koshimizu *et al.* revealed that in V_{1B}R KO mice, the nociceptive thresholds and morphine sensitivity are enhanced. Also, the development of analgesic tolerance to morphine was significantly delayed in these mice when V_{1B}R-subtype-selective antagonist SSR149415 was administrated [624]. Furthermore, application of SSR149415, a selective V_{1B}R-antagonist but not a V_{1A}R-antagonist, into the lateral ventricle of the mice also reduced

the development of morphine tolerance [604, 624]. In *in situ* hybridization experiments, Koshimizu *et al.* discovered that MOR and $V_{1B}R$ colocalized in the rostral ventromedial medulla [604, 624]. By using cotransfected HEK293 cells, a functional interaction between MOR and $V_{1B}R$ was observed as well as in single cells BRET analysis (close proximity of both receptors <10 nm) [604, 624]. In another experiment, using a radioligand binding assay and cyclic AMP assay, morphine binding to MOR was shown to be significantly influenced by MOR-$V_{1B}R$ formation [604, 624]. Also, ADH-enhanced morphine-induced super activation of the AC triggered by the MOR-$V_{1B}R$, was indicated to be dependent on β-arrestin-2 and ERK phosphorylation [604, 624]. Koshimizu and co-workers also discovered that a leucine-rich segment in the C-terminal tail of the $V_{1B}R$ is responsible for binding of β-arrestin-2, which when deleted through genome editing, increased morphine analgesia and reduced ADH-mediated AC super activation increased [604, 624]. Taking all findings together, it was suggested that the MOR-$V_{1B}R$ is indeed another mechanism to alter opioid receptor function such that morphine-induced analgesia could be potentiated, and morphine tolerance could be delayed.

The formation of a MOR-GAL_1R was identified by Moreno *et al.*, in transfected cells and in neurons in the rat ventral tegmental area (VTA) [625]. Previous *in vivo* studies showed that behavioural effects of MOR agonists were counteracted by galanin [604]. According to Moreno *et al.,* the MOR-GAL_1R mediates antagonist interactions between MOR- and GAL_1R-selective ligands and is a key player in the functioning of dopaminergic neurons [625]. In another study by Cai *et al.,* it was discovered that methadone potency for stimulating dopamine release and euphoria was reduced through MOR-GAL_1R heterodimers in the rat VTA [604, 626]. Such alterations of opioid receptor functions in opioid-induced rewarding were not observed for other opioids such as morphine and fentanyl [604, 626]. These data suggest that MOR-GAL_1R mediates dopaminergic effects of opioids and that pharmacological differences between methadone and other opioids may provide a way to dissect the euphoric from therapeutic effects of methadone-like compounds [604, 626]. Consequently, novel methadone-like compounds with reduced potency, able to activate MOR-GAL_1R may be a possibility to develop safer opioid analgesics [604, 626].

Early studies in 2001 identified MOR and CB_1R co-localization in lamina II neurons in the spinal cord [627]. Synergistic interactions between the opioid and the cannabinoid system in analgesia were already known, as the CB_1R is also present in the brain on primary sensory neurons in the DRGs, spinal cord, and some brain regions related to pain processing [604, 628, 629]. Rios *et al.* were able to show MOR-CB_1R heterodimers in transfected HEK293 cells using biophysical methods, such as BRET [630]. Additionally, they demonstrated that co-activation of MOR-CB_1R would lead to antagonistic allosteric interactions, which was determined by cross-inhibition of neurite outgrowth involving inhibition of the Src-STAT3 pathway [604, 630]. In 2016, Manduca *et al.* identified MOR-CB_1R heterodimers in rodents nucleus accumbens core (NAcC) and studied the importance of MOR-CB_1R heterodimers to control social behaviour in adolescent rodents [631]. They studied, in particular, the role of the endocannabinoid 2-arachidonoylglycerol (2-AG) in social play [631]. 2-AG is released in the brain of adolescent rats during social play [632] and 2-AG levels are high in the NAc of socially stimulated mice [633]. Systemic administration of the JZL184 (a 2-AG hydrolysis inhibitor) or morphine (MOR agonist) increased social play behaviour in adolescent rats [631]. However, these social play-enhancing effects were blocked by direct infusion of SR141716 (CB_1R antagonist) and naloxone (MOR antagonist) into the NAcC [631]. Neuronal plasticity and socioemotional behaviours could be modulated by MOR-CB_1R.

Already in the 90s it was discovered that the cholecystokinin octapeptide (CCK8) antagonises opioid analgesia [634]. Furthermore, using L-365, 260, a CCK_2R/CCKBR-selective antagonist, it was shown that CCK-8 inhibited opioid analgesia through CCKBR [635]. In 2018, Yang *et al.* identified the MOR-CCKBR heterodimer, which they believed may underlie the CCK8-antagonism of opioid analgesia [604, 616]. Co-localization studies using double-labelling immunofluorescence staining showed that MOR and CCKBR colocalize in neurons in spinal cord dorsal horn and DRGs. Using Co-IP and fluorescence lifetime-imaging-microscopy-based fluorescence resonance energy transfer (FLIM-FRET) assays, Yang *et al.* showed heterodimerization of MOR and CCKBR in HEK293 cells [604, 616]. They also validated that the TM3 of MOR plays a key role in the formation of MOR-CCKBR [604, 616]. The MOR-CCKBR functions include a decrease in MOR affinity for ligands and reduction of agonist-mediated phosphorylation of ERK1/2 in transfected HEK293 cells [604, 616]. In their study Yang and co-workers developed a cell-penetrating interfering peptide by adding the TAT sequence (RKKRRQRRR) to the C terminal of the entire TM3 (TM3MOR-TAT), which disrupted the MOR-CCKBR [604, 616]. In transfected cells TM3MOR-TAT was shown to enhance MOR signalling and in rats it prevented CCK8-induced antagonism against morphine analgesia, rendering TM3MOR-TAT as a promising target for increasing morphine analgesia without applying increasing amounts of morphine [604, 616].

Suzuki *et al.* demonstrated that MOR and CCR5 can also form heterodimers in the cell membrane of lymphocytes, using Co-IP and chemical crosslinking experiments [636]. In this study, the authors demonstrated that the MOR-CCR5 heterodimer is functional, since the co-activation of receptors with morphine (MOR agonist) and MIP-1beta (CCR5 agonist) suppresses the inhibitory effect of MIP-1beta and increases the stimulatory effect of morphine on CCR5 expression [636]. Also in 2002, based on behavioural test in rats' PAG (the brain area that is the focus of opioid analgesic actions), Szabo *et al.* found the ability of CCR5 receptors to desensitize MOR receptors [637]. They demonstrated that chemokine ligands for CCR5 (CCL5) can inactivate the normal neuronal signalling pathway involved in reducing the sensation of pain [637]. Thus, activation of MOR-CCR5 increased nociception.

In 2008, immunohistochemistry experiments by Juhasz *et al.* demonstrated that MOR and DRD_1 colocalized in neurons of the cortex and caudate nucleus and in living cells [638]. They showed within the cellular nuclear translocation pathway that MOR-DRD_1 formation resulted in a significantly enhanced surface expression of MOR [638]. Tao *et al.* per-

formed Co-IP, BRET and cross-antagonism assays and confirmed the existence of MOR-DRD_1 [639]. Furthermore, they showed that SCH23390, a DRD_1-selective antagonist, was able to inhibit the agonist-induced activation of MOR and downstream signalling in transfected cells and in striatal tissues from wild-type but not DRD_1 KO mice [639]. Similarly, to what has been described for heterodimers so far, antagonizing one monomer within the dimer also inhibits the signalling of the partnered monomer, although the latter was activated by its own ligand [639]. In addition, the MOR-DRD_1 was identified *in vivo* through biochemical and biophysical assays [639]. Here it was shown that by destruction of the dopaminergic projection from the ventral tegmental area to the striatum, dopamine release was abolished, and SCH23390 was still able to significantly inhibit agonist-induced MOR behavioural responses in rats [639]. Lastly, Tao *et al.* demonstrated that MOR or DRD_1 KO mice were not able to show locomotor sensitization to morphine because they were unable to form MOR-DRD_1 [639]. Hence, MOR-DRD_1 may be involved in the dopamine-independent expression of locomotor sensitization to opiates [639].

MOR and DRD_2 receptors are colocalized in the spinal cords of mice, confirmed by Co-IP assays [640]. In 2019, Stove and co-workers proved the existence of MOR-DRD_2 heterodimers using HEK293T and HeLa cells, both cotransfected, by Co-IP, BRET, FRET and functional complementation of split luciferase techniques [641]. MOR activation by its agonists (DAMGO and fentanyl) resulted in recruitment of β-arrestin to the receptor and, consequently, caused internalization of the receptor [642, 643]. This β-arrestin recruitment is associated with the unwanted effects of opioids [644, 645]. Based on time-lapse imaging technique, the effect of heterodimerization of MOR-DRD_{2long} on the internalization characteristics of MOR indicated a decrease in the internalization of MOR-YFP (MOR associated with Yellow fluorescent protein) with the co-expression of DRD_{2long}, when stimulated upon addition of DAMGO [641]. This suggests that the heterodimer may be a potential therapeutic target associated with diseases such as addiction.

2.2.8. Serotonin - Serotonin Receptor Heterodimers

5-HT_{1A} and 5-HT_{2A} receptors, which have inhibitory actions *via* $G_{i/o}$ and excitatory actions *via* $G_{q/11}$, respectively, are the two major known 5-HT receptors in the brain [646]. The evidence that 5-HT_{1A} and 5-HT_{2A} receptors can form a heterodimer was given by Borroto-Escuela *et al.* in the dorsal hippocampus and the anterior cingulate cortex using *in situ* PLA assay and BRET saturation assay in cotransfected HEK293T cells [647]. Based on a 5-HT_{1A} radioligand binding assay, Borroto-Escuela *et al.* showed that TCB2 (5-HT_{2A} agonist) reduced the binding affinity of the 5-HT_{1A} agonist ipsapirone in membranes of the frontal lobe of the cortex [647]. However, this action seems to be blocked by ketanserin, a 5-HT_{2A} antagonist. These results suggest that 5-HT_{1A}-5-HT_{2A} heterodimers perform inhibitory interactions of the allosteric type, with a dominant effect of 5-HT_{2A} over 5-HT_{1A} protomer [647]. In 2018, another study with this heterodimer was performed to understand how antipsychotic drugs, such as clozapine, ketamine and haloperidol affect the formation of the heterodimer [648]. Clozapine and ketamine showed an impact on heterodimer formation, whereas ketamine exhibited high affinity only for 5-HT_{2A}, clozapine only had an effect on heterodimers in low dosage [648]. Since both receptors are known to be involved in depression [649], this heterodimer may play a role in this disease.

5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors are both $G_{q/11}$-coupled receptors, which mediate excitatory neurotransmission [650]. These receptors are co-expressed in GABAergic interneurons and in a subpopulation of pyramidal neurons of the prefrontal cortex (PFC) [651, 652] and in dopaminergic neurons of the ventral tegmental area [653, 654]. Using Co-IP and BRET techniques, Moutkine and co-workers demonstrated that 5-HT_{2A}-5-HT_{2B} and 5-HT_{2A}-5-HT_{2C} heterodimers can be formed when co-expressed in heterologous expression systems [655]. In 5-HT_{2C}-containing heterodimers, ligands bind and activate only the 5-HT_{2C} protomer. The same authors also demonstrated that 5-HT_{2A}-5-HT_{2B} and 5-HT_{2A}-5-HT_{2C} heterodimers exhibit an asymmetry in G_q-protein coupling, and that signalling from 5-HT_{2A} and 5-HT_{2B} protomers is blunted, as only the 5-HT_{2C} protomer is able to activate the G_q protein [655]. Thus, there is a dominance of 5-HT_{2C} on 5-HT_{2A} and 5-HT_{2B} receptor binding. Also, this dominant effect was validated *in vivo* (observed in neurons), which resulted in an exogenous expression of an inactive form of the 5-HT_{2C} receptor in the locus ceruleus associated with a decreased 5-HT_{2A}-dependent noradrenergic transmission [655]. As such, these heterodimers must be considered for depression and addiction conditions.

Heterodimerization between 5-HT_{1A} and 5-HT_7 receptors was demonstrated by Ponimaskin and colleagues using Co-IP and immunoblotting techniques and FRET assays in co-transfected neuroblastoma N1E-115 cells [656]. The 5-HT_{1A} receptor is $G_{i/o}$-coupled, which induces inhibition of AC and decrease in intracellular cAMP [657, 658], and the 5-HT_7 receptor is $G_{\beta\gamma}$-coupled, which activates K^+ channels and MAPK Erk2 [657]. 5-HT_{1A}-5-HT_7 heterodimerization decreases the 5-HT_{1A}-receptor-mediated activation of G_i protein without affecting 5-HT_7-receptor-mediated G_s protein activation. Also, authors discovered that 5-HT_{1A}-5-HT_7 heterodimers reduce the ability of 5-HT_{1A} receptors to activate GIRK channels, an effect mediated through the Gβγ subunits of inhibitory G proteins [657]. This phenomenon may result from 5-HT_7 interacting with and directly modulating 5-HT_{1A}. In addition, MAP kinases ERK1/2 phosphorylation is induced by 5-HT_{1A} agonists, and this signal is enhanced when 5-HT_7 receptors are co-expressed suggesting that heterodimerization favors activation of 5-HT_{1A}-receptor-mediated ERK signalling whereas it prevents 5-HT_{1A}-mediated activation of $G_{i/o}$-GIRK channel activity [657]. The differences in desensitization patterns between pre- and postsynaptic 5-HT_{1A} receptors can be explained by the differences in the relative concentration of 5-HT_{1A}-5-HT_7 heterodimers on presynaptic serotonergic neurons and postsynaptic neurons. Besides, a regulated and balanced ratio of homo- and heterodimerization on pre- and postsynaptic neurons may be involved in both the onset and the response to the treatment of neurological conditions, such as depression, anxiety, schizophrenia and drug abuse [659, 660].

2.2.9. Serotonin Receptor and Other GPCR Heterodimers

It is well established that the dopaminergic and the serotonin system play an important role in neurotransmission,

and thus their malfunctioning is suggested to be linked to the development of psychiatric disorders such as schizophrenia [648]. Łukasiewicz and co-workers identified in HEK293 cells the presence of 5-HT_{1A}R-DRD_2 heterodimers [661]. The heterodimerization was shown to be mainly enhanced by exposure of clozapine but also by other antipsychotics such as olanzapine, aripiprazole, and lurasidone [661]. Functional assays like cAMP and IP1 and ERK activation, indicated that the different antipsychotics exhibited diverse effects on the 5-HT_{1A}R-DRD_2 [661]. For instance, Łukasiewicz *et al*. demonstrated that clozapine and 8-OH-DPAT potentiated postsynaptic effects, especially ERK activation [661]. Furthermore, 5-HT_{1A}R activation by 8-OH-DPAT along with the DRD_2-blockade by clozapine led to a conformal change within the heterodimer and consequently changed their signalling *via* $G_{\alpha q/11}$-mediated activation of ERK1/2 [661]. In 2018, a study by Szlachta *et al.* investigated the role of well-known antipsychotic drugs, clozapine and haloperidol, in the formation of 5-HT_{1A}R-DRD_2 heterodimers in mouse cortex [648]. By using PLA, in *in vitro* and *ex vivo* experiments, co-localization of 5-HT_{1A}R and DRD_2 was confirmed [648]. Also, Szlacht and co-workers demonstrated that low-dose administration of clozapine increased the levels of 5-HT_{1A}R-DRD_2, while administration of haloperidol decreased their level in mouse cortices [648]. Different studies located the 5-HT_{1A}R-DRD_2 in the dorsal and ventral striatum using *in situ* PLA and FRET as well as in cellular models using BRET [662-664]. The 5-HT_{1A}R-DRD_2 has been developed as an important therapeutic target due to a well-documented serotonin-dopamine interaction and its relevance to schizophrenia [665].

A study by Albizu *et al.*, using radioligand-binding and inositol phosphate production assays, identified functional crosstalk between 5-HT_{2A}R and DRD_2 in the mouse brain and in HEK293 cells [663]. They were able to show that DRD_2 activation increases the hallucinogenic agonist affinity for 5-HT_{2A}R and decreases the 5-HT_{2A}R induced inositol phosphate production [663]. Albizu and co-workers demonstrated that the inhibition of MK-801-induced locomotor activity by DRD2 antagonist haloperidol requires the 5-HT_{2A}R expression [663]. MK-801, a potent and selective non-competitive NMDA receptor antagonist also known as dizocilpine, serves as a pharmacological model for schizophrenia in mice [666]. It was reported that MK-801 increases the locomotor activity of mice, a behaviour that is suppressed by the DR-antagonist haloperidol [667]. In Co-IP studies, Albizu *et al*. showed that 5-HT_{2A}R and DRD_2 are able to interact physically in HEK293 cells [663]. Lastly, they suggested that depending on the treatment combination, different actions could be achieved by application of DRD_2-ligands such as quinpirole or butaclamol and 5-HT_{2A}R-ligands such as DOI and ketanserin [663]. DRD_2 expression was shown to increase the efficacy of DOI to activate the 5-HT_{2A}R-induced phosphoinositol $G_{q/11}$ signalling pathway [663]. Only the hallucinogenic partial agonist DOI seemed to promote this effect on 5-HT_{2A}R signalling [663].

The 5-HT_{1A}R and GAL_1R are both known to couple to $G_{i/o}$ proteins and transduce their signals mainly by inhibitions of the AC, calcium channel activity and neurotransmitter release [657, 668, 669]. In 2010, Borroto-Escuela *et al.* discovered 5-HT_{1A}R-GAL_1R heterodimers in double-transfected mammalian cells with PLA and FRET techniques [668]. The presence of 5-HT_{1A}R-GAL_1R, induced either MAPK or AC signalling pathways, indicating an allosteric cross-inhibition mechanism in order to block the excessive activation of $G_{i/o}$ and an exaggerated inhibition of AC or stimulation of MAPK activity [668]. By using reporter gene assays, CRE-luciferase and SRE-luciferase assays, it was possible for Borroto-Escuela *et al.* to further assess possible antagonistic allosteric receptor-receptor interactions 5-HT_{1A}R-GAL_1R [668]. In the brain, previous biochemical, cardiovascular and behavioural work has given additional proof for the existence of antagonistic 5-HT_{1A}R-GAL_1R interactions [670-675].

Only recently, in 2019, Chruścicka *et al*. discovered the existence of 5-HT_{2A}R-OTR heterodimers *in vitro* in living cells using a flow cytometry-based FRET approach and confocal microscopy [676]. The 5-HT_{2A}R and OTR were found to be expressed in similar brain regions modulating central pathways critical for social and cognition-related behaviours [677-680]. Therefore, Chruścicka *et al.* applied the PLA technique *ex vivo* in order to observe the formation and location of the 5-HT_{2A}R-OTR, which were found in limbic regions such as hippocampus, cingulate cortex and nucleus accumbens [676]. These were identified as key regions associated with cognition and social-related behaviours [676]. Functional crosstalk was observed in 5-HT_{2A}R-OTR using cellular-based assays, when a reduction in potency and efficacy of oxytocin, carbetocin and WAY267464 (synthetic OTR-agonists) was observed on OTR-mediated $G_{\alpha q}$ signalling [676]. Likewise, 5HT-induced activation of 5-HT_{2A}R also revealed attenuation in $G_{\alpha q}$-mediated signalling. According to Chruścicka *et al.* co-trafficking of 5-HT_{2A}R and OTR within the cell was also demonstrated [676].

Chruścicka *et al.* pointed toward the existence of 5-HT_{2C}-OTR heterodimer, based on FRET and confocal microscopy *in vitro* in a heterologous cell expression system and further using PLA assays in the rat brain [681]. 5-HT_{2C}R and OTR co-expression resulted in an attenuation of OTR-mediated G_q-signalling and significant changes in receptor trafficking. This attenuation was specifically caused by 5-HT_{2C}R protomer activation [681]. It seems likely that 5-HT_{2A}R-OTR and 5-HT_{2C}-OTR heterodimers can be involved in the development of depression and other types of psychiatric diseases involving disturbances in social behaviours.

To date, a functional link between the serotoninergic and melatoninergic systems has only been sparsely reported. In a study by Prosser *et al.*, functional crosstalk between those two systems was reported, revealing that melatonin inhibits the ability of 5-HT to phase shift the suprachiasmatic circadian clock [682]. In addition, melatonin is synthetically derived from 5-HT, and therefore a close relationship is probable [683]. Furthermore, the clinically proven antidepressant agomelatine, the first *non*-monoaminergic therapeutic, was shown to act as an agonist at MT_1R and MT_2R, which are coupled to G_i proteins, while it is a neutral antagonist at the $G_{q/11}$-coupled 5-HT_{2C}R system [684, 685]. According to Racagni, the affinity of agomelatine was reported to be substantially lower at 5-HT_{2C}R compared to MT_1R and MT_2R *in vitro*, suggesting that it may exert its actions "synergistically" [686]. It was also discovered that 5-HT_{2C}R, MT_1R and

MT_2R are necessary for the expression of the antidepressant actions of agomelatine, which cannot be reproduced either by melatonin or by selective 5-$HT_{2C}R$ antagonists alone [683, 686]. However, Kamal *et al.* presented evidence that 5-$HT_{2C}R$ and MT_2R are able to form a heterodimer, by using Co-IP, BRET and pharmacological techniques in transfected cells and in human cortex and hippocampus [683]. The 5-$HT_{2C}R$-MT_2R was also discovered in the mouse brain [687]. The 5-$HT_{2C}R$-MT_2R was reported to be composed of G_i-coupled melatonin MT_2R and G_q-coupled serotonin 5-$HT_{2C}R$ [683, 687]. The activation of 5-$HT_{2C}R$-MT_2R was shown to amplify the activation of 5-HT-mediated G_q/phospholipase C response and trigger melatonin-induced unidirectional transactivation of the 5-$HT_{2C}R$ [683, 687]. According to Kamal *et al.*, agomelatine (antidepressant) has a distinctive profile on 5-$HT_{2C}R$-MT_2R. Whereas melatonin is able to activate both G_i and G_q pathways, agomelatine tends to activate the G_i/cAMP pathway and has an allosteric antagonistic effect on 5-HT-induced G_q pathway activation [683]. Lastly, a beneficial involvement of agomelatine in 5-$HT_{2C}R$-MT_2R heterodimer was suggested for the treatment of major depression and generalized anxiety disorder [683].

MOR and 5-HT_{1A} receptors are co-expressed in discrete areas of brain, such as, dorsal raphe nucleus, periaqueductal grey neuron, dorsal horn of the spinal cord, amygdala and primary afferent nociceptive fibers [688-690]. Also, both receptors are coupled to $G_{i/o}$ protein, which induces the inhibition of AC, the opening of K^+ channels, the closing of Ca^{2+} channels and the stimulation MAPK ERK1/2 pathways [691]. 5-HT_{1A}-MOR heterodimers were detected by Cussac *et al.* using Co-IP and by BRETmax determination in transiently cotransfected COS7, HEK293 or CHO-K1 cells [692]. To demonstrate the functional transactivation in GPCR heterodimers, they used receptor-G_α-protein fusions, consisting of the application of fusion proteins of protomers with a subtype of G_α protein, and that it is only activated by protomers if they are not in a free form [693]. As a result, by co-expressing the MOR and 5-HT_{1A}-$G_{\alpha o}$ fusion protein as well as MOR and 5-HT_{1A}-$G_{\alpha 15}$ fusion protein, they demonstrated that both receptors could induce transactivation of the G_α protein fused to its partner protomer in membrane preparations and in live cells, respectively [692]. In addition, MOR and 5-HT_{1A} receptors can co-exert control in the ERK1/2 pathway. However, the MOR receptor-induced EKR1/2 phosphorylation was selectively desensitized by prolonged stimulation and activation of 5-HT_{1A} receptor with 8-OH-DPAT agonist [692]. This heterodimer could have interesting therapeutic influences since MOR and 5-HT_{1A} are involved in pain control.

2.2.10. Cannabinoid - Cannabinoid Receptor Heterodimers

One of the most important inhibitory regulation mechanisms acting in the CNS is the cannabinoid system [694, 695]. The two cannabinoid receptors, CB_1R and CB_2R, share around 44% sequence similarity [696, 697]. Until 2012 it was not clear if cannabinoid receptors were able to form heterodimers, despite the fact that CB_1R and CB_2R have overlapping expression tissues and that they have been shown to regulate similar cellular processes [698]. Heteromerization of CB_1R and CB_2R was then demonstrated in a large study by Callén *et al*. [698]. In this study, the receptors were investigated using cotransfected cells and in a variety of brain tissues, including pineal gland, nucleus accumbens, and globus pallidus and BRET technique and *in situ* PLA [698]. Another study by Sierra and co-workers identified the first CB_1R-CB_2R heterodimers in pallidothalamic projection neurons in the monkey, using PLA [699]. Both, CB_1R and CB_2R are coupled to G_i proteins, which is particularly interesting as within the CB_1R-CB_2R heterodimer the CB_1R-antagonist AM251 was reported to block the effect of the CB_2R-agonist JWH133 and *vice versa*, the CB_2R-antagonist AM630 was reported to inhibit the effect of the CB_1R-agonist ACEA [698, 700]. Furthermore, agonist co-activation by ACEA and JWH133 of the CB_1R-CB_2R heterodimer was shown to lead to negative crosstalk in Akt phosphorylation and neurite outgrowth [698, 700]. Recently, a study by Narvarro *et al.* showed that CB_1R-CB_2R heterodimers are expressed in LPS/IFN-γ-activated microglia [701]. When compared to resting cells, it was visible that CB_2R became robustly coupled to G_i in activated cells if CB_1R and CB_2R were also present, suggesting a potentiation effect by CB_1R-CB_2R [701]. In addition, an upregulated expression of CB_1R-CB_2R was observed in primary microglia cultures from the hippocampus of mutant β-amyloid precursor protein ($APP_{Sw,\ Ind}$) mice, a transgenic AD model [701]. Lastly, Navarro and co-workers identified a correlation between the increased expression of CB_1R-CB_2R in the striatum of in 6-hydroxy-DA-lesioned rat model for PD and dyskinesias by chronic levodopa treatment [701].

2.2.11. Cannabinoid Receptor and Other GPCR Heterodimers

The cannabinoid and the dopaminergic system are known to display complex interactions within the basal ganglia [702-704]. The CB_1R was shown to be co-expressed with DRD_2 in the soma and dendrites of the ventral striatopallidal GABAergic neurons [705]. Meschler *et al.* also reported interactions between CB_1R and DRD_2 (and DRD_1) in the rat and monkey striatum [706].

CB_1R and DRD_1 receptors colocalize in the basal ganglia circuitry, sharing the same G protein transduction pathway and playing a main role in the control of motor activity in both systems [707, 708]. In 2011, Tersian and colleagues provided the first evidence for physiological crosstalk between CB_1R and DRD_1 receptors in the modulation of depression-like behaviour, social skills, and fear conditioning [709]. In this study, the authors revealed that conditional CB_1R knockout mice lacking CB_1Rs in neurons expressing DRD_1 exhibited significantly increased contextual and auditory-cued fear. This suggested that a specific reduction of endocannabinoid signalling in neurons that express simultaneously dopamine DRD_1 is indeed able to affect acute fear adaptation [709]. Serrani *et al.* studied the role of DRD_1 receptors in the behavioural responses induced by acute and repeated stimulation of cannabinoid CB_1R receptors, including the development of physical dependence, using female dopamine DRD_1 receptor-deficient mice and wild-type littermates treated with HU-210 (a synthetic cannabinoid agonist) [710]. The results of the study showed that the mutant mice, compared to wild-type females, exhibited an enhanced response to the acute motor and hypothermic effects of HU-210 [710]. Administration of SR141716A (CB_1R antagonist)

precipitated a cannabinoid withdrawal syndrome in HU-210 tolerant female mice. Furthermore, the severity of the cannabinoid withdrawal syndrome was potentiated in female mice with DRD_1 deficiency [710]. Therefore, there is involvement in DRD_1 in the acute effects induced by HU-210, as well as in the somatic expression of cannabinoid withdrawal, supporting the functional interaction between the cannabinoid and dopaminergic systems in the development of cannabinoid dependence [710].

Some studies pointed out that CB_1R and DRD_2 receptors are colocalized in the basal ganglia, mainly in the striatopallidal GABAergic neurons and in the cortico-striatal glutamate neurons [711-713]. The first author to provide evidence of CB_1R-DRD_2 heterodimerization was Kearn *et al.*, based on Co-IP studies in KEK293 cells [704]. Then, other studies confirmed this evidence in globus-pallidus and striatum of rodents and primates, using BRET, PLA and Co-IP assays [713-718]. In the study of Kearn *et al.,* it was demonstrated that stable expression of CB_1R and DRD_2 in HEK293 cells resulted in a pertussis toxin-insensitive component to CB_1R activation of ERK 1/2 and a stimulation of AC activity after simultaneous activation of both receptors by the agonists quinpirole (DR-agonist) and CP55940 (CB_1R-agonist) [704]. Furthermore, the study showed and confirmed previous results [719, 720] that DRD_2-activation together with the activation of CB_1R resulted in the complex coupling G_s instead of its preferred G-protein, $G_{i/o}$, which was observed in an increase in cAMP levels instead of a synergistic inhibition of AC activity [704, 719, 721, 722]. In addition, recent studies revealed that CB_1R-DRD_2 heterodimerization requires the bidirectional allosteric interaction of the two receptors, as the expected effect was not observed when only one receptor was activated [715, 716]. A recent study from Bagher *et al.* revealed that CB_1R-DRD_2 heterodimer formation in C57BL/6J mice is reduced when treated with the typical antipsychotic haloperidol [714]. In addition, the abundance of the heterodimer increased when treated with the nonselective cannabinoid receptor agonist (CP55, 940), whereas the atypical antipsychotic olanzapine treatment had no effect [714]. These results suggest that this heterodimer has an influence on dopamine and cannabinoid-related disorders.

The expression of CB_1R and $A_{2A}R$ in corticostriatal glutamatergic terminals suggests an interaction potential between those two receptors [723, 724]. Indeed, it has been demonstrated that the ability of WIN 55212-2, a CB_1R-agonist, to increase DARPP32 phosphorylation and inhibit motor activity requires the presence and the activation of $A_{2A}R$, which then functions as a heterodimer [725, 726]. The study of Carriba *et al.* also demonstrated, through Co-IP and BRET experiments in living cells and in rat striata, that CB_1R-$A_{2A}R$ heterodimers are functional since they were shown to mediate the cannabinoid-induced motor effects [723, 726]. Another study by Tebano *et al.* using SH-SY5Y neuroglioblastoma cells in biochemical and cellular signalling assays as well as behavioural tests using wildtype and $A_{2A}R$ KO mice indicated that striatal CB_1R activation-induced synaptic effects depend on $A_{2A}R$ activation [724]. Indeed, CB_1R-agonist WIN55, 212-2-induced motor depressant effects are inhibited by the $A_{2A}R$-antagonist ZM241385 [726]. Furthermore, Tebano and co-workers demonstrated that the blockade of $A_{2A}R$ reduces WIN55, 212-2-induced depression of synaptic transmission in corticostriatal slices and that the synaptic effects of WIN 55212-2 are reduced in slices from $A_{2A}R$ KO mice. According to Tebano *et al.,* this suggests the occurrence of a permissive role of $A_{2A}Rs$ towards CB_1R effects [726]. In addition, this permissive role of the $A_{2A}R$ was reported to occur in postsynaptic effects [726].

The main psychoactive compound in *Cannabis sativa*, THC, a ligand of cannabinoid receptors, is known to induce a variety of behavioural responses and undesirable effects such as dependence, anti-anxiety effects and memory impairments [727-731]. Different studies have shown that THC and other cannabinoid-induced behaviours are typically mediated by 5-$HT_{2A}R$ [732-734]. CB_1R, which typically couples to G_i and G_q 5-HT2AR, coupled to Gq, was found to be colocalized in brain structures involved in regulating emotions, learning, and memory, including the amygdala, cerebral cortex, and hippocampus [735-737]. For the first time in 2015, it was discovered that the anxiolytic and amnestic effects of THC, a CB_1R-agonist, require the presence of 5-$HT_{2A}R$ [731]. Behavioural studies in 5-$HT_{2A}R$ KO mice, BRET, cAMP and calcium signalling assays using cotransfected HEK293T cells and *in situ* PLA using mouse brain slices, determined a remarkable 5-$HT_{2A}R$-dependent dissociation in the beneficial antinociceptive effects of THC and its detrimental amnesic properties, mediated by CB_1R-5-$HT_{2A}R$ [731]. Furthermore, their study showed that CB_1R and 5-$HT_{2A}R$ are expressed and functional in specific brain regions involved in memory impairment [731]. Moreover, it was shown that in CB_1R-5-$HT_{2A}R$ co-stimulation of both receptors by agonists WIN 55212-2 and DOI reduces cell signalling, antagonist binding to one receptor (either rimonabant or MDL 100907) blocks signalling of the interacting receptor, and heterodimer formation leads to a switch in G-protein coupling for 5-$HT_{2A}R$ from G_q to G_i [731]. Heterodimerization was shown to be disrupted *in vivo* by ICV infusion of synthetic peptides with the sequence of TM5 and TM6 of CB_1R, leading to blunted amnesic and anxiolytic, but not antinociceptive, effects of THC selectively in wild-type mice [731]. Later Galindo *et al.* presented more evidence that CB_1R-5-$HT_{2A}R$ exists in *ex-vivo* primary cultures of human olfactory epithelial cells [738]. Furthermore, they observed a positive correlation between CB_1R-5-$HT_{2A}R$ heterodimer expression, and the amount of cannabis consumed. A negative correlation was observed between heterodimer expression levels and attention and working memory performance in cannabis users [738]. Galindo and co-workers also observed negative crosstalk between CB_1R and 5-$HT_{2A}R$ within the heterodimers in human olfactory epithelial cells when co-stimulated with WIN 55212-2 and DOI, which would lead to reduced activation of ERK1/2 signalling [738]. Furthermore, rimonabant and MDL 100907 blocked the effects induced by WIN 55212-2 and DOI, suggesting that CB_1R-5-$HT_{2A}R$ in control subjects and in cannabis users display bidirectional cross antagonism [738].

2.2.12. Diverse GPCR Heterodimers

Besides the more common families described above, other class A GPCRs can form heterodimers. One example is the GAL_1R-GAL_2R heterodimer, identified in HEK293T cells using BRET and in the midbrain raphe-dorsal hippocampal pathways of rodents using *in situ* PLA [739]. In this

study by Borroto-Escuela *et al.*, the hypothesis was formulated that the N-terminal galanin fragments preferring binding sites on galanin receptors are formed through the formation of GAL_1R-GAL_2R heterodimers. The galanin 1-15 fragment was shown to induce a disbalance in GAL_1R-GAL_2R signalling, where enhanced activation of $G_{i/o}$-mediated signalling *via* GAL_1R was observed, while no significant effects were induced by $G_{q/11}$-mediated signalling of GAL_2R [739]. By comparing the results of the study between the two galanin fragments, galanin (1-15) and galanin (1-29), it was suggested that the orthosteric agonist binding site of GAL_1R may have an increased affinity for the galanin (1-15) vs galanin (1-29), leading to its demonstrated increase in potency to inhibit CREB vs galanin (1-29) in CRE luciferase reporter gene assays [739]. Furthermore, Borroto-Escuela and co-workers demonstrated that NFAT reporter gene assays galanin (1-29) shows a higher efficacy than galanin (1-15) in increasing $G_{q/11}$-mediated signalling over GAL_2R of GAL_1R-GAL_2R heterodimers [739]. The reported galanin(1-15)-mediated disbalance may contribute to depression and anxiety-related behaviours [740, 741].

In 2020, Rivas-Santisteban *et al.* discovered the existence of AT_1R and AT_2R heterodimer expression in hemilesioned 6-OH-DA rat model of PD [742]. AT_1R and AT_2R, which are part of the angiotensin-peptide producing RAS, and their endogenous ligand angiotensin are important regulators of motor control, have been suggested to be promising targets for PD and related conditions such as levodopa (L-DOPA)-induced dyskinesias [742-744]. In their study, Rivas-Santisteban and co-workers demonstrated that co-activation of AT_1R and AT_2R by Ang II and CGP-42112A within the AT_1R-AT_2R heterodimer was known to reduce the downstream signalling of angiotensin II [742]. However, a cross-potentiation was observed, as the application of AT_1R-antagonist candesartan increased the effect of the selective AT_2R-agonist CGP-42112A [742]. Regarding their relevance for PD, it was demonstrated that microglial AT_1R-AT_2R heterodimers are upregulated in parkinsonian conditions and in L-DOPA-induced dyskinesias and their activation was observed to exert neuroprotective effects [742]. Lastly, Rivas-Santisteban *et al.* suggested that the opposite action of AT_1R and AT_2R by AT_1R-antagonist-mediated cross-potentiation of AT_2R actions and the upregulation of AT_1R-AT_2R heterodimers in microglia may be beneficial to treat PD through AT_2R by this heterodimer signalling mechanism [742].

3. CLASS C G PROTEIN-COUPLED RECEPTORS

3.1. Class C Receptors in the Brain

The class C receptor family in humans is composed of γ-aminobutyric acid B receptors ($GABA_{B1}R$ and $GABA_{B2}R$ receptors), calcium-sensing receptor (CaSR), metabotropic glutamate receptors ($mGlu_{1\text{-}8}R$), sweet and amino acid taste receptors and several orphan receptors (GPR156, GPR158, GPR179, GPRC5A, GPRC5B, GPRC5C, GPRC5D, GPRC6) [144, 443, 745]. Among them, CaSR, $GABA_BR$ and mGluR are highly expressed in the brain and represent an important class of drug targets for neurological diseases and calcium homeostasis [746-748].

mGluR and $GABA_BR$ receptors are particularly relevant as they constitute a comprehensive model for the allosteric regulation and cooperativity of receptor protomers, which can be tendentially transferred to other GPCR classes, such as class A receptors [89]. Even though their sequences and overcall structures differ significantly from other classes, some structural similarities have been reported between classes A and C receptors. The most significant similarities were found in the TM domains. In class A receptors, the "ionic lock" is defined by a salt bridge between a conserved Arg3.50 and Glu(Asp)6.30, while this motif occurs *via* Lys3.50 and Glu6.35 in class C [749].

Aside from the common architecture of GPCRs, the class C receptors possess an extracellular domain that contains a Venus flytrap (VFT) module and a cysteine rich domain (CRD, except in the $GABA_BR$) [748]. This exceptionally large extracellular domain contains the orthosteric binding site for ligands, while in the 7TM region only allosteric binding sites are found [748]. Moreover, the C-terminus is highly variable and plays a role in scaffolding and signalling protein coupling [745]. Another unique characteristic of the class C receptor family is the fact that they only function as homodimers (mGluR and CaSR) or heterodimers ($GABA_BR$) [748]. The structure of the VFT was first solved for the $mGlu_1R$ (PDB-id: 1EWV, 1EWT, 1EWK) [750] and it revealed that the VFT consists of a bilobed domain being separated by a cleft in which endogenous ligands are able to bind [750-752]. In the absence of a ligand, the VFT oscillates between an open and closed conformation [748]. Agonists interact with lobe 1 in the open form of the VFT and stabilize the closed conformation through additional contacts with lobe 2, while antagonists inhibit the VFT closure [748, 753]. Due to the necessary dimerization of class C receptors, the VFTs consequently interact with each other by forming constitutive dimers. Different studies found that a hydrophobic interaction between lobe 1 of each monomer is the driving force for VFT dimerization [754, 755]. An additional disulphide bond linking the two VFTs was reported to further stabilize the dimer [755-757]. The CRD, which is a segment of 80 amino acids, containing 9 conserved cysteines, connects the VFT and the 7TM domains [745, 748]. Crystallography data shows that the CRD physically separates the VFT and 7TM modules (PDB-id: 2E4U, 2E4V, 2E4W, 2E4X, 2E4Y, 2E4Z) [758]. Especially for mGluR, a conserved disulphide bond between the VFT and the CRD is necessary for receptor activation through allosteric interaction between VFT and 7TM [759]. CRD is also a mediator of receptor activation for CaSR [748, 760].

3.1.1. Calcium-sensing Receptor

CaSR is a unique receptor, highly sensitive to calcium ions (Ca^{2+}) and their concentration change in the extracellular space [748]. CaSR ensures calcium homeostasis and can consequently be activated by calcium itself without the cooperation of other ligands [746, 761]. Pathological conditions involving CaSR are hyperparathyroidism, osteoporosis and different forms of hypocalcemia [761-763]. CaSR is pharmacologically targeted by positive allosteric modulators (PAMs), *i.e.*, cinacalcet, evocalcet and etelcalcetide, for the treatment of secondary hyperparathyroidism and familial hypocalciuric hypercalcemia (FHH1). CaSR negative allosteric modulators (NAMs) act as calcilytics and are currently

in phase II clinical trials for the treatment of Autosomal-Dominant Hypocalcemia Type 1 (ADH1) [764, 765].

Although CaSR is mainly expressed in the parathyroid gland and in the renal tubules of the kidney, there is also a significant expression in the brain [766, 767]. Calcium is one of the most abundant second messengers in the brain [768]. In the extracellular space calcium levels are maintained constant (between 1.1 and 1.4 mM), whereas in resting neurons calcium levels are strictly maintained around 100 nM [769, 770]. Without a substantial calcium gradient, neuronal functions, such as gene transcription, synaptic transmission, memory encoding, apoptosis, and many others, may not be conducted [768, 769]. The inability to maintain required calcium levels has been brought into context with neurodegenerative diseases such as PD, AD, HD, where this neuronal calcium dysregulation contributes to motor and/or cognitive dysfunctions [769, 771-775].

3.1.2. γ-aminobutyric Acid B Receptors

γ-aminobutyric acid (GABA) is the major neurotransmitter for inhibitory signals in the mammalian CNS [748]. $GABA_BR$, which responds to GABA, regulates synaptic plasticity, learning, and memory in the dentate gyrus [1], mediating a slow and prolonged synaptic inhibition [776]. It only functions as obligate heterodimers of the two subtypes, $GABA_{B1}R$ and $GABA_{B2}R$ [777-782] with two distinct features: $GABA_{B1}R$ contains the GABA binding site [783], whereas $GABA_{B2}R$ activates the $G_{i/o}$ protein [784]. $GABA_B$ receptors are responsible for neuronal excitability and plasticity [748]. For instance, in a VaD rat hippocampus, a reduction was observed in $GABA_BR$ expression, resulting in spatial learning and memory deficits [1, 785]. However, under certain conditions, they may promote neuron survival such as metabolic stress, ischemia and apoptosis [748, 786-788]. Consequently, these receptors are considered promising targets for the treatment of many diseases, including spasticity, neuropathic pain, drug addiction, schizophrenia, anxiety, depression or epilepsy [789-792].

3.1.3. Metabotropic Glutamate Receptors

L-Glutamate is the major neurotransmitter for most of the excitatory synapses in the mammalian CNS [8]. As L-glutamate is the endogenous ligand for mGluR, they participate in the neuronal excitability and modulation of synaptic transmission in the CNS [793, 794]. The mGluR family comprises eight members, which are further classified based on their G protein coupling and sequence homology. The first group (Group I) consists of $mGlu_1R$ and $mGlu_5R$, which are coupled to G_q/G_{11} [1, 795]. The second group consists of $mGlu_2R$ and $mGlu_3R$ (Group II) and the third group (Group III) of $mGlu_4R$, $mGlu_6R$, $mGlu_7R$ and $mGlu_8R$, of which all are coupled to G_i/G_o [793, 795]. As such, mGlu receptors negatively regulated the adenylyl cyclase (AC) and were also reported to activate MAP kinase and PI-3-kinase pathways [793, 795]. The $mGlu_5R$ has been reported to be involved in several neurodegenerative disorders [793]. Since $mGlu_5R$ is highly expressed in astrocytes, glial cells and neurons of the forebrain and hippocampus, several lines of evidence suggest a significant role of $mGlu_5R$ in developmental and neurodegenerative disorders such as Down Syndrome and AD [796, 797].

Over the last years, several mGluR agonists, antagonists, PAMs and NAMs have been developed and studied *in vivo* animal models [1]. Comprehensive work from Chen *et al.* showed that LY341495 (Group I/II mGluR antagonist) was able to block amyloid β-enhanced long-term depression and improve synaptic plasticity [798]. In addition, the authors also showed that pre-treatment with $mGlu_{1/5}R$ agonist, DHPG, decreased amyloid β-enhanced long-term depression [798]. Another study by Renner *et al.* demonstrated that SIB1757, a non-competitive antagonist of $mGlu_5R$, prevented amyloid β oligomer-induced synaptic N-Methyl-D-aspartic acid receptor NMDAR reduction [799]. Moreover, Caraci and co-workers demonstrated that the $mGlu_2R$ PAM LY566332 amplified amyloid β-induced neurodegeneration, while treatment with the antagonist LY341495 of $mGlu_{2/3}R$ prevented this effect [800]. In a similar manner, the dual $mGlu_{2/3}R$ agonist LY379268 exhibited neuroprotection by a paracrine mechanism mediated by transforming growth factor-β1 [800]. Consequently, negative modulation of the $mGlu_5R$ could be a promising strategy for the treatment of PD and AD. Moreover, dual activation of Group II receptors, $mGlu_2R$ and $mGlu_3R$ could be a strategy for providing neuroprotection against amyloid β-induced toxicity [800].

3.2. Class C Receptor Heterodimers

In 1998, Marshall and colleagues discovered that heterodimerization formation was crucial for a functional $GABA_BR$ [76, 801]. Since then, the concept of GPCR dimerization has been widely accepted for class C receptors. The receptor-receptor cooperation has been found to be positive and negative and vital for signal transduction [89, 802-805]. Class C GPCRs act as obligate dimers, since the VFTs of the single receptors have to interact with each other [754-757]. Therefore, homo- and heterodimerization is a common event among class C GPCRs.

In a recombinant system, it was found that $GABA_{B1}R$ cannot reach the cell surface without the presence of $GABA_{B2}R$, as $GABA_{B1}R$ contains a C-terminal endoplasmic retention motif, only masked when the heterodimer is formed (Fig. **2E**) [806, 807]. Unexpectedly, all orthosteric agonists and antagonists rather bind to the VFT of the $GABA_{B1}R$. This coupling leads to the necessary conformational change in $GABA_{B1}R$, which crosstalks to $GABA_{B2}R$ leading to an active conformer able to bind to G protein and promoting functional physiological responses [808-811]. Also, additional GPCRs which can bind to $GABA_BR$ were identified: *e.g.*, $GABA_AR$, $mGlu_1R$, NMDA, IGF-1, and TrkBR. It also has been shown that these GPCRs are able to form multicomplexes such as tetramers [812, 813]. Such tetramers were described to exhibit negative cooperativity between the $GABA_BR$-heterodimers by decreasing the coupling efficiency towards G_i proteins [802, 814]. Despite the large therapeutic potential and the development of many PAMs and NAMs which could help investigate the relationship between the monomers of the $GABA_BR$, only Baclofen (Lioresal), a selective $GABA_BR$ agonist is available on the market [815, 816].

Furthermore, the well-known $GABA_BR$, the eight members of the mGluR family, are key modulators of glutamatergic synaptic transmission of excitatory and inhibitory responses in the brain [794, 817, 818]. The structure of the

mGluR contains special features such as a large cysteine enriched domain, which is linked to the transmembrane domain, and a large extracellular domain involving the VTF, where glutamate binds involving the VFT, which is also linked to the transmembrane domain, binding pocket to glutamate [76]. Many GPCRs are known to interact and regulate the mGluR subgroups, such as the neuronal Ca^{2+} binding protein 2 that forms a co-assembly and coupling with activated Ca^{2+}-activated K^{+}-channels; and the contactin-associated protein 1, which appear to be important for the function of $mGlu_5R$ to control memory formation in the hippocampus [76, 819-823].

For instance, the $mGlu_2R$-$mGlu_4R$ heterodimer was already discovered in 2005 by Doumazane and co-workers using a technique to study plasma membrane receptor complexes and FRET [824]. Later, Kammermeier and co-workers elucidated that $mGlu_2R$-$mGlu_4R$ complexes are functional in neurons, only using both, $mGlu_2R$ specific and $mGlu_4R$ specific agonists [825]. Each individual receptor has two NAM binding sites and one PAM binding site. The activation of each receptor by NAMs was able to reverse the signalling of this heterodimer. Moreover, only one PAM per complex was needed for full enhancement of heterodimer complex activity [824].

The $mGlu_1R$-$mGlu_5R$ heterodimer in mice, was identified by Pandya and co-workers in 2016 [826]. The $mGlu_1R$-$mGlu_5R$ was expressed in the cerebral cortex, hippocampus and hippocampal neurons using an interaction proteomics strategy and super resolution microscopy [826]. The exact receptor complex composition is still unclear, but there is the indication that scaffolding proteins, phosphatases and kinases are involved in the process [827]. In synaptic and extrasynaptic locations, $mGlu_1R$-$mGlu_5R$ also appears to be in balance with the corresponding homodimers $mGlu_1R$-$mGlu_1R$ and $mGlu_5R$-$mGlu_5R$ [828]. The $mGlu_1R$-$mGlu_5R$ heterodimer may be a potential therapeutic target in autism spectrum disorders [826].

Although class C GPCRs, and especially mGluRs, are functional as constitutive dimers, the importance of dimerization remains unclear [818]. A study by El Moustaine *et al.* also demonstrated that the dimer formation is not required for G protein coupling, but rather for agonist activation and for limiting the agonist activity of PAMs [810, 818]. This asymmetrical activation is also consistent with the asymmetric functioning reported for class A GPCR dimers [452, 829, 830].

4. HETERODIMERS CLASS A-CLASS C

GPCR heterodimers of the same classes such as class A - class A or class C - class C appear to be physiologically conclusive as they have the same activation mechanism despite the different ligands and G protein-coupling state. Also, their physiological functions appear coherently, notwithstanding that the partnered proteins often belong to different families. However, the existence of GPCR heterodimers of different classes such as class A - class C heterodimers, which will be described here, add another perspective to the complexity of GPCR signalling.

In 2020, Sebastianutto *et al.* discovered the DRD_1-$mGlu_5R$ heterodimer using BRET and bimolecular fluorescence complementation (BiFC) techniques at the plasma membrane in HEK293 cells, primary hippocampal neurons and in 6-OHDA lesion in mice and rats, which were used as PD models [831]. The dopaminergic and glutamatergic systems are known to signal to the striatum where their crucial inputs control action selection and behavioural plasticity [832, 833]. Hence, these basal-ganglia circuits represent an important target of L-DOPA-based therapy in PD [831]. Sebastianutto and co-workers demonstrated that the DRD_1-$mGlu_5R$ synergistically activates PLC signalling and intracellular calcium release in response to either glutamate or dopamine [831]. In addition, PLC signalling was seen to be responsible for a considerable proportion of striatal ERK1/2 activation in PD-model rodents which were treated with DRD_1-agonists SKF38393 or quinpirole [831]. Moreover, in the PD-model rodents, DRD_1-$mGlu_5R$ complexes were found to be strongly upregulated in the dopamine-denervated striatum [831]. DRD_1-$mGlu_5R$-dependant PLC signalling was also linked to enhanced activation of extracellular signal-regulated kinases in striatal neurons, leading to dyskinesia in animals treated with L-DOPA or DRD_1-agonists SKF38393 or quinpirole [831]. It was concluded that DRD_1 appeared to engage in preferential crosstalk with $mGlu_5R$- and G_q-related signalling components in dopamine-denervated striatal neurons [831].

Another example, A_1R-$mGlu_1R$, was discovered by Ciruela *et al.* in 2001 using Co-IP, immunohistochemistry and ligand-binding experiments in HEK293 and rat cerebellum synaptosomes [834]. Furthermore, they showed that activation of A_1R and $mGlu_1R$ would lead to a synergistic neuroprotection effect, since preincubation with quisqualic acid ($mGlu_1R$-agonist) and adenosine was much more effective than pre-treatment with any of the compounds used in their study. Later, more studies based on an analysis of non-neuronal cells using Co-IP and FRET by Kamikubo *et al.* supported the existence of A_1R-$mGlu_1R$ [835]. In a previous study, it was described that, in cerebellar Purkinje cells, the activation of A_1R attenuates neuronal responses to glutamate, as mediated by $mGlu_1R$ [835, 836]. The $mGlu_1R$ is also known to regulate responses such as long-term depression of postsynaptic response to glutamate, which is a cellular basis for cerebellar motor learning [835]. Furthermore, Kamikubo and co-workers demonstrated that the activation of $mGlu_1R$ through glutamate inhibits A_1R signalling, which was measured in elevated cAMP signalling, since the A_1R is known to couple $G_{i/o}$-proteins [835, 837]. Kamikubo *et al.* concluded from their findings that $mGlu_1R$-mediated inhibition of A_1R signalling, which should activate PKA and CREB may play a role in $mGlu_1R$-dependent cerebellar long-term depression and motor learning [835].

In 2008, González-Maeso *et al.* identified a physical and functional interaction between 5-$HT_{2A}R$ and $mGlu_2R$ in cortical pyramidal neurons using Co-IP, BRET and FRET in HEK293 cells and brain cortices from mice and humans [838, 839]. Competition binding experiments showed that the $mGlu_2R$-agonist LY379268 was able to increase the affinity of hallucinogenic drugs such as DOI, DOM or for the 5-$HT_{2A}R$-binding site [839]. However, it was also shown that the 5-$HT_{2A}R$-agonist DOI decreased the affinity for $mGlu_2R$-agonists LY379268, DCG-IV, and L-CCG-I [839]. Hence, within the 5-$HT_{2A}R$-$mGlu_2R$, unique cellular responses are

mediated when targeted by hallucinogenic drugs and activation of $mGlu_2R$ was shown to abolish hallucinogen-specific signalling and behavioural responses. González-Maeso *et al.* further supported those findings by showing that hallucinogens, including mescaline, psilocybin, and lysergic acid diethylamide (LSD) which profoundly affect perception, cognition, and mood and are known to activate $5\text{-}HT_{2A}R$, but not all excerpt hallucinogenic behaviours [840]. It was shown that hallucinogenic and non-hallucinogenic $5\text{-}HT_{2A}R$-agonists both regulate signalling in the same $5\text{-}HT_{2A}R$-expressing cortical neurons. However, different agonists were found to either regulate phospholipase C *via* coupling to $G_{q/11}$ proteins and/or bind to $G_{i/o}$ proteins and Src [840]. Fribourg *et al.* demonstrated that the signalling of the endogenous ligand on the associated protomer is suppressed or potentiated by an agonist or an inverse agonist of one protomer, respectively [841]. Therefore, the $5\text{-}HT_{2A}R\text{-}mGlu_2R$ heterodimer establishes an optimal $G_{i/o}\text{-}G_q$ balance in response to serotonergic and glutamatergic drugs binding. The hallucinogenic agonists LY341495 ($mGlu_2R$ inverse agonist) and DOI ($5\text{-}HT_{2A}R$ receptor agonist) promote a decrease in $G_{i/o}$ and a strong increase in G_q. The opposite happens with the antipsychotics LY379268 ($mGlu_2R$ receptor agonist) and clozapine (inverse $5\text{-}HT_{2A}R$ receptor agonist), which produce the opposite effect on $G_{i/o}\text{-}G_q$ balance. Lastly, González-Maeso and co-workers identified that $mGlu_2R$ interacts *via* TM4 and TM5 with $5\text{-}HT_{2A}R$ [839].

In 2009, Schröder *et al.* identified the $MOR\text{-}mGlu_5R$ heterodimer using Co-IP in HEK293 cells [842]. It was long hypothesized that opioid analgesia and tolerance could be modulated by metabotropic glutamate receptors [842-845]. Studies by Gabra *et al.* and Lee *et al.* were able to show that the $mGlu_5R$-antagonist MPEP inhibits hyperalgesia, nociceptive behaviour and inflammation. Moreover, when co-administered with morphine, the morphine-induced antinociception development was suppressed [846, 847]. The treatment of the cotransfected MOR and $mGlu_5R$ cells with DAMGO, a selective MOR-agonist, showed that co-expression of $mGlu_5R$ had no significant effect on the agonist binding sites and functional coupling of the MOR towards DAMGO, as DAMGO-induced inhibition of intracellular cAMP level was still observed [842]. However, when MPEP was co-administered, DAMGO-induced MOR phosphorylation, internalization, and desensitization were decreased, whereas non-selective competitive $mGlu_5R$-antagonists or -agonists had no effects [842]. According to Schröder *et al.,* this allosteric modulation of $mGlu_5R$ on MOR displayed a mechanistic basis as to how the $MOR\text{-}mGlu_5R$ functions, further supported by DAMGO-induced co-internalization of MOR and $mGlu_5R$ and the increase of MPEP bindings sites and a change of binding affinity of $mGlu_5R$ after the co-expression of MOR [842].

5. HETERORECEPTOR MOSAICS

The term "receptor mosaics" stands for assemblies of more than two receptors and was already introduced in the 80s to underline the role of topology in the highly dynamic life cycles of GPCRs [848-851]. Such mosaics may be the result of engrams of short-term memory, which are stored as a state of a molecular circuit. They further suggested that these mosaics may be the representations of engrams of ultra-short memory in transient receptor mosaic formed in kiss-and-run encounters [850, 852-854]. There are now many indications that heteroreceptor mosaics exist in nerve cells and throughout the brain [850, 853, 855].

The $A_{2A}R\text{-}CB_1R\text{-}DRD_2$ mosaic is one of the few examples where more than two receptors exhibit protein-protein interactions [533, 726, 856]. It also underlines the relevance of adenosine, dopamine and cannabinoid signalling and their pivotal contribution to various signalling mechanisms. The $A_{2A}R\text{-}CB_1R\text{-}DRD_2$ heterooligomer was identified for the first time in 2008 [857] using a method combining BiFC and BRET techniques [858-864]. In 2009, the $A_{2A}R\text{-}DRD_2\text{-}mGlu_5R$ was discovered in HEK293 cells, using BiFC and BRET approaches [865]. In addition to adenosine and dopamine transmission, glutamate transmission also plays an important role in the function of striatal GABAergic efferent neurons originating in the nucleus accumbens. In 2001, Popli *et al.* discovered the $DRD_2\text{-}mGlu_5R$ heterodimer and its association with $A_{2A}R$ receptor [866]. Authors used 6-OH-DA-lesioned rats as PD models to conduct behavioural and microdialysis experiments. In 6-OH-DA rats, the selective $mGlu_5R$-agonist (RS)-2-Cholro-5-Hydroxyphenylglycine (CHPG) was shown to inhibit the contralateral turning induced by quinpirole, a DR-agonist and less pronounced by the DR-agonist SKF 38393 [866]. The effect of CHPG on quinpirole-induced turning was significantly potentiated by CGS 21680, an $A_{2A}R$-agonist and attenuated by SCH 58261, an $A_{2A}R$-antagonist [866]. CHPG was shown to reduce the affinity of the high-affinity state of DRD_2 for quinpirole and this effect was again enhanced by CGS 21680 in rat striatal membranes [866]. $A_{2A}R$ and $mGlu_5R$ agonists (CGS 21680 and CHPG, respectively) synergistically increase ventral pallidal extracellular level of GABA in the nucleus accumbens promoting potential stability of the inhibitory dopaminergic DRD_2 effects on the striatopallidal GABA pathway [867]. In PD, where the dopaminergic nerve terminals are degenerated, the DRD_2 on the glutamate nerve terminals can no longer appropriately inhibit glutamate release. Here, $A_{2A}R$ and $mGlu_5R$ antagonists could be successful to inhibit parkinsonian symptoms considering their increasing dominance, since the inhibitory DRD_2 lose their function [868]. Consequently, extracellular levels of adenosine and glutamate may increase, leading to a higher probability of formation of $A_{2A}R\text{-}DRD_2$, $DRD_2\text{-}mGlu_5R$ and $A_{2A}R\text{-}DRD_2\text{-}mGlu_5R$ that leads to further inhibition of PD symptoms. Lastly, $A_{2A}R\text{-}CB_1R\text{-}DRD_2$ and $A_{2A}R\text{-}DRD_2\text{-}mGlu_5R$ mosaics have recently been demonstrated in living cells using fluorescent techniques [861, 865].

6. GPCR INTERACTING PROTEINS

Besides the binding of GPCRs to G proteins, β-arrestins and kinases, there exists a large number of GPCR interacting proteins (GIPs) [823, 869-872]. GIPs can be other cytoplasmic or transmembrane proteins such as heat-shock proteins, PSD-95/Discs-large/ZO-1 (PDZ) domain-containing proteins or GPCR-associated sorting proteins (GASPs) [873-875], among many others. They excerpt multiple effects on GPCRs: interact with GPCRs in a more receptor-selective manner and can additionally mediate downstream signalling directly through binding to GPCRs, organize GPCR signalling through G proteins, promote receptor trafficking or an-

chor the receptors in certain subcellular areas [823, 869, 872, 876]. In contrast to GPCRs, GIPs are capable of clustering various proteins and coordinating different types of signals such as positive and negative feedback signals, graded or digital signals, and transient or oscillatory signalling [823, 877, 878].

In terms of GPCR dimerization, it is known that the receptors influence each other through protein-protein interactions (PPIs) and subsequent conformational rearrangements upon the dimerization event. These can also influence the affinity for the binding of G proteins, and alterations in ligand binding affinity, among many other effects [72, 80-82]. It also raised the question, how could dimerization affect the coupling to GIPs [871]? For instance, it was reported that MT_1R directly and constitutively bind to G_i proteins and RGS20, forming the MT_1R homodimers-RGS20-G_i protein complex [879]. Regulators of G-protein signalling (RGS) proteins bind to the activated form of G_α proteins and accelerate their GTPase activity [880, 881]. By using BRET probed inserted at multiple sites of the complex and by homology modelling experiments, Maurice *et al.* suggested a model, where the G_i protein can bind to one MT_1R, while the RGS20 binds to the other MT_1R [879]. Similar observations were made for MT_1R/MT_2R-RGS20-G_i protein-complex, which was previously not known to bind to RGS20 [879]. Hence, it was concluded that the formation of asymmetric quaternary complexes involving GIP-binding and non-GIP-binding receptors may lead to sensitivity for GIPs, which is only present upon formation of such complexes [871, 879]. Another example was recently discovered involving mGluRs, known to be obligate dimers. The constitutive active $mGluR_1$ and $mGluR_5$, in the absence of glutamate, were reported to form an interaction with Homer1a. This protein, part of the scaffolding protein family Homer, lacks dimerization capacity [882-885]. Usually, $mGlu_{1/5}R$ dimers are functionally physically linked to NMDA receptors *via* scaffolding proteins, which are then disrupted through the binding of Homer1a [882, 886, 887]. The $mGlu_{1/5}R$-Homer1a-complex has been associated with several functions in synaptic plasticity of the visual system, in rewarded synapses, in chronically overactivated synaptic networks and sleep cycle [882].

Hence, the binding of GIPs to GPCR dimers adds another level of signalling complexity towards downstream signalling and indicates that its fine-tuning can also be context-dependent [886, 888].

SUMMARY AND CONCLUDING REMARKS

It has been widely accepted by now that GPCRs are able to couple to other GPCRs to alter their partner's signalling and/or their own, which furthermore diversifies and fine-tunes their physiological responses. Many studies have demonstrated that the nature of crosstalk within the heterodimer or oligomer can be either positive or negative. Hence, when GPCRs form a heterodimer, it was shown that this leads to the enhancement of each other's natural signalling pathways or inhibition of downstream signalling of either one receptor or both. Among all heterodimers described in this review, there was a clear balance between examples, which promoted either positive or negative crosstalk. In addition, there are still more options of alternate signalling by heterodimers to be investigated. Especially, when it comes to formation of oligomers, the signalling repertoire is even further increased.

The concept of GPCR dimers, which carry out physiological and pathophysiological actions in the brain, adds a new dimension to molecular signalling in the nervous system.

To be able to target both monomers within the dimer at the same time, new concepts in drug design have been explored. Already in 1982, the concept of bivalent ligand was discovered and introduced for opioid heteromers by Philip Portoghese [889, 890]. Many have been developed over the years [891, 892] to target other disease-relevant dimers. By definition, bivalent ligands consist of two distinct pharmacophores that are connected by a linker/spacer; hence they are able to target two GPCRs simultaneously [893]. They can be further classified into either homobivalent ligands with two identical pharmacophores or heterobivalent ligands with two different pharmacophores [891].

The advantage of targeting both monomers of the dimer simultaneously provides insight into enhanced physiological responses and may help to understand the dynamic interactions of the two proteins, as usually, either one of them is targeted by their ligands resulting in positive or negative crosstalk. Moreover, bivalent ligands can be designed to either consisting of two agonists, two antagonists or cross-overs which make them a helpful tool to understand the dynamics of dimerization and subsequent downstream signalling [891]. Considering the recent developments of bivalent ligands, most of them target class A heteromers, including opioid receptors, dopamine receptors, serotonin receptors and cannabinoid receptors [891]. However, one ligand was developed for a heterodimer between class A and class C, MQ-22a, which targets the DRD_2-$mGlu_5R$ heteromer [894]. Interestingly, an allosteric modulator 3-[(2-methyl-4-thiazolyl)ethynyl]pyridine (MTEP) was chosen for $mGlu_5R$, while for DRD2 ligands targeting the orthosteric binding pocket were selected, the DRD_2- and DRD_4-agonist 5-hydroxy-2-(dipropylamino)tetralin (DPAT) and the DRD_2-antagonist 1, 4-disubstituted aromatic piperazine (DAP) [894]. Consequently, also the level of binding property of the selected pharmacophores provides an additional chemical space to be explored in terms of dimerization dynamics as it has been shown for monomers that the physiological response also varies if ligands bind either to orthosteric or to the allosteric binding pockets [895-897]. Other bivalent ligands were also proposed to induce dimerization, as shown for the gastrin-releasing peptide receptor GRPR within 20-30Å [898].

Together with the growing numbers of GPCR crystal structures available and the improvement in computational techniques such as homology modelling, ligand docking and molecular dynamics, bivalent ligands are additional pharmacological tools for investigating the dimerization process and dynamics. Still, there is room for improvement as none of the bivalent ligands has made it to clinical trials yet, mostly due to their large size (> 700 kDa) and consequent unfavourable pharmaco-chemical properties, selectivity profiles and lacking *in vivo* studies [891].

Aside from bivalent ligands, nanobodies, which are mostly derived from antibody fragments from the heavy chain-

only antibodies of camelids, have emerged as promising alternatives due to their high target specificity [899, 900]. Like bivalent ligands, nanobodies were also discovered in the 1980s but their utility was for long not recognized [901]. Nanobodies can be fused to fluorescent tags, radioisotopes or other biosensors to monitor cellular processes in living cells [900]. More recently, fluorescently labelled conformation-specific nanobodies were utilized to monitor the activation of GPCRs upon ligand binding or rapid state transformation in living cells [900, 902-905]. In another more recent study. nanobodies were used to modulate the activity of $mGlu_4R$ in the brain but not Glu_4R heteromers with other GluRs, indicating that therapy of PD or pain could be improved through subtype-selective and blood-brain barrier permeable nanobodies [899]. While only biparatopic nanobody targeting different binding sites of the chemokine receptor CXCR2 entered phase 1 studies as potential new therapeutic for inflammation [906, 907], nanobodies specifically targeting GPCR dimers (homo- and heterodimers) will be for sure a promising new therapeutic approach. Ernumab, a monoclonal antibody, was recently approved for preventive treatment of chronic migraine as it binds to the calcitonin gene-related peptide receptor dimers [906, 908, 909].

All in all, future studies should be directed to identifying the dimer interface to design and develop interface-interfering molecules, able specifically disrupt the dimer. This strategy will help determine the functional role of the dimer as well as the allosteric receptor-receptor interaction within the dimer.

Herein, we provided a collection of neurodegenerative-relevant GPCR heterodimers of classes A and C, which appear to be promiscuous in their signalling. A detailed structural and functional characterization of these macromolecular machineries will be key to the development of new and improved drugs to treat neurodegenerative diseases.

LIST OF ABBREVIATIONS

5-HT	=	5-hydroxytryptamine
ACE	=	Angiotensin-Converting Enzyme
AD	=	Alzheimer's Disease
ADH	=	Antidiuretic Hormone
ADH1	=	Autosomal-Dominant Hypocalcemia Type 1
ADHD	=	Attention Deficit Hyperactivity Disorder
ALS	=	Amyotrophic Lateral Sclerosis
ASD	=	Autism Spectrum Disorder
AR	=	Adenosine Receptors
Aβ	=	Amyloid β
BDNF	=	Brain-Derived Neurotrophic Factor
BiFC	=	Bimolecular Fluorescence Complementation
BRET	=	Bioluminescence Resonance Energy Transfer
CaMKIIa	=	Calcium/Calmodulin Kinase IIa
cAMP	=	Cyclic Adenosine Monophosphate
CaSR	=	Calcium-Sensing Receptor
CCK	=	Cholecystokinin
CCK8	=	Cholecystokinin Octapeptide
CCL5	=	Chemokine Ligands for CCR5
Cryo-EM	=	Cryogenic Electron Microscopy
CNS	=	Central Nervous System
Co-IP	=	co-immunoprecipitation
CUD	=	Cannabis Use Disorder
DOR	=	Delta Receptor
ECS	=	Endocannabinoid System
ERK	=	Extracellular Signal-regulated Kinases
EPSCs	=	Excitatory Postsynaptic Currents
FHH1	=	Familial Hypocalciuric Hypercalcemia
FRET	=	Förster-Resonance-Energy-Transfer
FK	=	Forskolin
FTD	=	Frontotemporal Dementia
FUS	=	Fused in Sarcoma
FZD	=	Class F-frizzled
GABA	=	γ-aminobutyric Acid
GASPs	=	GPCR-associated Sorting Proteins
GHS-R	=	Growth Hormone Secretagogue Receptor
GHRH	=	Growth Hormone-Releasing Hormone
GIPs	=	GPCR Interacting Proteins
GIRKs	=	G Protein-Coupled Inwardly Rectifying Potassium Channels
GPCR	=	G Protein-Coupled Receptor
HD	=	Huntington's Disease
HEK293	=	Transfected Human Embryonic Kidney 293
HR	=	Histamine Receptor
HTT	=	Huntingtin
KO	=	Knockout
KOR	=	Kappa Receptor
LSD	=	Lysergic Acid Diethylamide
MAPK	=	Mitogen-activated Protein Kinase
MDD	=	Major Depressive Disorder
MS	=	Multiple Sclerosis
MOR	=	Mu Receptor
NAcC	=	Nucleus Accumbens Core
NAMs	=	Negative Allosteric Modulators
NMR	=	Nuclear Magnetic Resonance
NT	=	Neurotensin
OCD	=	Obsessive-compulsive Disorder
OT	=	Oxytocin
OTR	=	Oxytocin Receptor

OR = Opioid Receptor
PAMs = Positive Allosteric Modulators
PD = Parkinson's Disease
PFC = Prefrontal Cortex
PNS = Peripheral Nervous System
PPIs = Protein-Protein Interactions
RAAS = Renin-Angiotensin-Aldosterone System
RAMH = (R)-α-Methylhistamine
RGS = Regulators of G-protein Signalling
SCN = Suprachiasmatic Nucleus
SMO = Smoothened
SST = Somatostatin
TAARs = Trace Amine-Associated Receptors
THC = Δ-Tetrahydrocannabinol
TDP-43 = DNA-Binding Protein 43
VaD = Vascular Dementia
VFT = Venus Flytrap
VTA = Ventral Tegmental Area

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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