# Potential of olfactory neuroepithelial cells as a model to study schizophrenia: A focus on GPCRs (Review)

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**Abstract.** Schizophrenia (SZ) is a multifactorial disorder characterized by volume reduction in gray and white matter, oxidative stress, neuroinflammation, altered neurotransmission, as well as molecular deficiencies such as punctual mutation in Disrupted-in-Schizophrenia 1 protein. In this regard, it is essential to understand the underlying molecular disturbances to determine the pathophysiological mechanisms of the disease. The signaling pathways activated by G protein-coupled receptors (GPCRs) are key molecular signaling pathways altered in SZ. Convenient models need to be designed and validated to study these processes and mechanisms at the cellular level. Cultured olfactory stem cells are used to investigate neural molecular and cellular alterations related to the pathophysiology of SZ. Multipotent human olfactory stem cells are undifferentiated and express GPCRs involved in numerous physiological functions such as proliferation, differentiation and bioenergetics. The use of olfactory stem cells obtained from patients with SZ may identify alterations in GPCR signaling that underlie dysfunctional processes in both undifferentiated and specialized neurons or derived neuroglia. The present review aimed to analyze the role of GPCRs and their signaling in the pathophysiology of SZ. Culture of olfactory epithelial cells constitutes a suitable model to study SZ and other psychiatric disorders at the cellular level.

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## 1. Introduction

Schizophrenia (SZ) is a multifactorial disease with an unspecified origin. Although genetic, environmental, psychosocial and other factors might be involved in its etiology, the

precise pathophysiological mechanisms of its development remain unclear. SZ diagnosis is primarily based on symptoms classified as positive (hallucinations, delirium, disorganized speech, psychomotor disturbances), negative (affective flattening, alogia, avolition, asociality and anhedonia) or cognitive (memory and executive function deficits) (1,2).

SZ symptoms, specifically cognitive symptoms, are associated with the molecular structure of dopaminergic and serotonergic topology and brain networks (3).

A key objective in the study of neuropsychiatric disorders is to elucidate the pathophysiological processes occurring in the brain to improve understanding of the disease and diagnostic and therapeutic options available. The delicate nature of the brain complicates study, and although postmortem studies have yielded insight, there is need for suitable models to overcome ethical and methodological limitations to obtain brain samples. In recent years, *in vitro* models have emerged, such as the culture of induced pluripotent stem cells (iPSCs) (4) and induced neuronal (iN) cells (5), which allow reprogramming of cells into neural and glial cell lines (6). An alternative is the use of human olfactory neuroepithelial (hONE) cells: Primary neurons and glial cells can be taken via epithelial cells in the nasal cavity of living patients with a minimally invasive technique. The heterogeneous samples include stem cells with multipotent and regenerative capacities that can be differentiated into neuronal and glial cells for use *in vitro* and *ex vivo* (6,7). Neuropsychiatric disorders including SZ (8-12), Alzheimer's disease (13,14) and other mood and anxiety disorders (15) are associated with anosmia, and it has been shown that the olfactory epithelial cells of patients with these illnesses have cellular and molecular alterations, such as amyloid-β and paired helical filament-tau aggregates, alterations to the cell cycle and phosphatidylinositol signaling pathways, membrane phospholipid alterations, dysregulated neurodevelopmental pathways, dysregulated mitochondrial function, oxidative stress (16-25). Since the hONE cells of the olfactory bulb are connected to the olfactory cortex, neurobiological alterations in the limbic regions may be reflected in the hONE cells, suggesting these may serve as an appropriate model for the study of neuropsychiatric disorders.

In patients with SZ or SZ-like animal models, dysfunctions have been observed in intracellular mechanisms activated by key hormones, modulators and transmitters such as dopamine, glutamate, serotonin, acetylcholine (ACh), ATP, melatonin, endocannabinoids and oxytocin (26-28). These modulators exert action by binding to G protein-coupled receptors (GPCRs) and triggering complex downstream intracellular signaling cascades. In the physiology of the central nervous system (CNS), the GPCR family of receptors is involved in key cellular functions such as proliferation, differentiation, migration and neurotransmission both in undifferentiated and mature neurodevelopmental stages (29-31). Genomic and proteomic studies have demonstrated the association of SZ with alterations in expression of GPCRs and enzymes activated by them, such as phospholipase Cb (32-34). In addition, drugs (such as aripiprazole, azepine, chlorpromazine) used in the treatment of this psychiatric disorder target GPCRs. To the best of our knowledge, however, there are few studies of the functionality of these receptors and the actions of these drugs at the cellular level (6,35). One possibility to study these is the use of cells cultivated from patients.

The present study conducted a literature review on PubMed and Google Scholar, selecting articles associated with GPCRs and their connection to SZ, as well as GPCRs in stem cells and their relevance to SZ. The following search strategies were used: Schizophrenia AND olfactory epithelial cells AND GPCR; GPCR AND schizophrenia and schizophrenia AND stem cells.

## 2. Olfactory epithelial cells in in vitro study of SZ

To comply with the bioethical and anatomical restrictions around directly obtaining CNS tissue from patients with mental disorders or neurodegenerative diseases, several experimental approaches have been developed to study human neurons and neuroglial physiological processes at the cellular level (36-39). Cell models have been characterized, such as olfactory epithelial SCs, iP cells and monocytes induced to resemble neurons (6,21). In particular, SCs of the olfactory epithelium express different types of GPCR and may be a suitable model to study the function of these receptors at the cellular level and their alteration in SZ; alterations in neurodevelopment, stress response and gene/protein expression regulatory pathways have been found in patients with SZ through the use of cells in culture obtained from olfactory epithelium (40). Most of the currently validated cellular models take advantage of the specific characteristics of SCs, such as their self-renewal capacity and their differentiation potency (41,42). These characteristics are also useful to establish cryopreserved biobanks of neural SCs at different stages of development. These cells are multipotent and have been differentiated into neurons (43) and neuroglia (44), making the study of GPCRs at different stages of development in different cell types possible.

Studies have observed disease-associated pathological traits in both neural SCs and their differentiated progeny, such as alterations in microtubule organization (45), making these models suitable to investigate cellular and subcellular mechanisms underlying the pathophysiology of psychiatric disorder. Human olfactory neural stem cells obtained by the nasal cavity exfoliation procedure described by Benitez-King *et al* (37) have revealed cellular and subcellular alterations in patients with SZ, bipolar disorder and Alzheimer's disease (46) and in cannabis users (Fig. 1) (47,48). Specifically regarding GPCRs and their signaling, one study reported abnormal 3'-5'-cyclic adenosine monophosphate (cAMP) accumulation in patient-derived hONE cells (49). Another study reported melatonin $MT_1$ and $MT_2$ receptors and their involvement in the modulation of axonogenesis, associated with increased levels of phosphorylated (p)GSK3β (Fig. 1) (27); axonogenesis is impaired and melatonin receptor and pGSK3β levels are lower in cells derived from patients with SZ compared with those from healthy subjects (27). In olfactory cells of patients with SZ, trimethylation of histone H3 lysine and H3 lysine 27 alters expression of genes related to glutamate decarboxylase 1 and other pathways associated with SZ (50). Neural epithelial SCs from living patients obtained via non-invasive exfoliation allows observation of the pathophysiological mechanisms and structural and molecular changes in SZ (7,51,52). Moreover, this model presents an opportunity to obtain cells from a

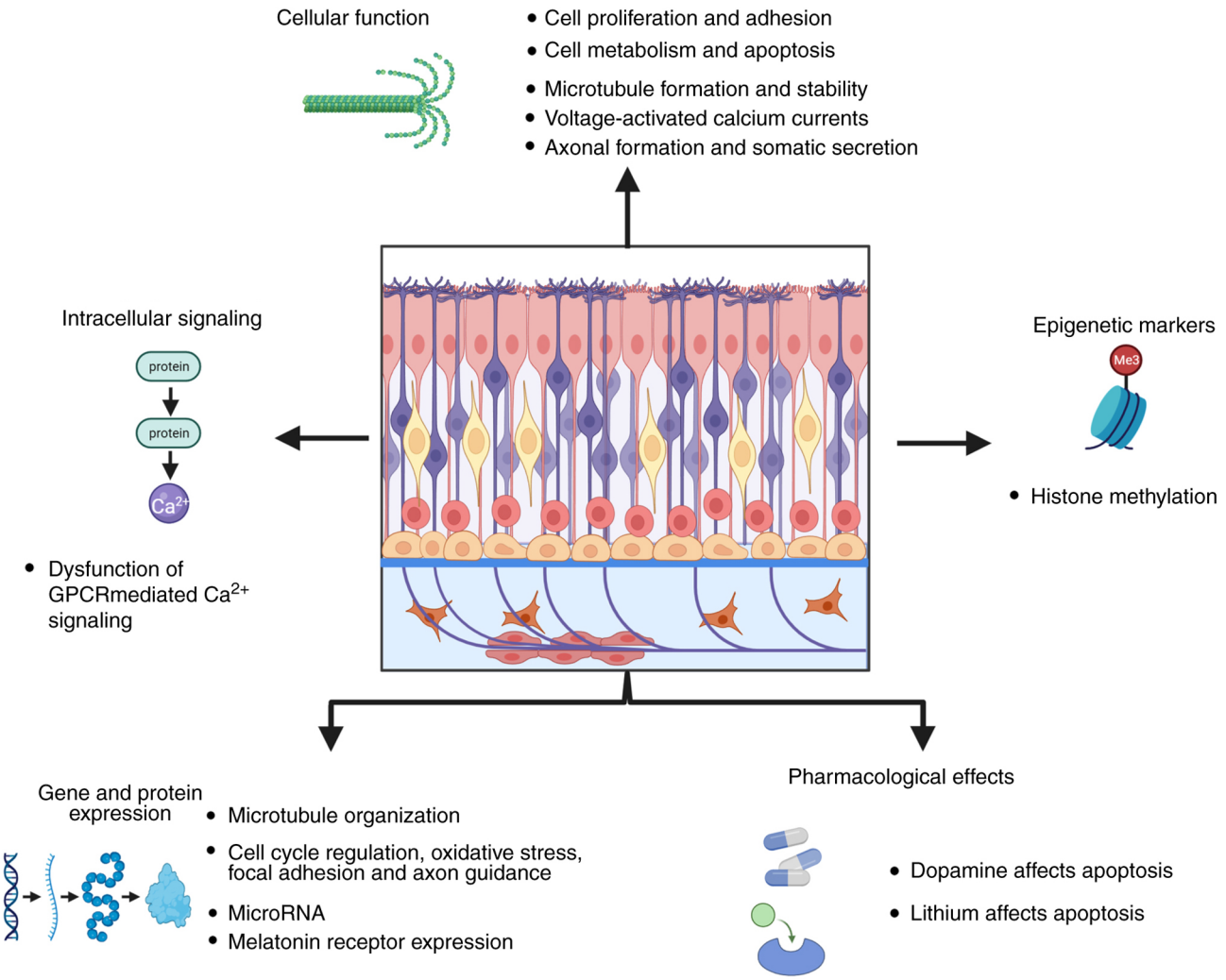


Figure 1. Olfactory neuroepithelial cells as a model to study schizophrenia at the cellular level. Mechanisms associated with schizophrenia at the cellular and molecular level, such as GPCR cellular signaling pathways, cellular functions, epigenetic markers, gene and protein expression; it also shows that neuroepithelial olfactory cells can be used as a pharmacological model. GPCR, G protein-coupled receptor.

single patient at different stages of disease, including naive stages and during treatment. Numerous *in vitro* models for the study of SZ have been developed and standardized using other human biospecimens such as postmortem brains and genetically engineered cells due to their accessibility and reliability (37,40,53,54).

*Advantages and limitations of olfactory neuroepithelial cell models*. The initial sample to develop iPSC and iN stem cells can be easily collected since, usually, peripheral cells are used. Meanwhile, the collection of hONE cells has moderate ease with a minimally invasive technique that a qualified professional should perform (6,55). hONE cells are ready for use ~4 weeks after collection, while iPSC require a longer waiting time (6). Additionally, costs to obtain hONE cells are lower than that for iPSCs and iN cells. hONE cells are neural tissue and do not require genomic reprogramming. Both hONE cells and iPSC have moderate or high proliferative capacity while iN cells do not possess this capacity (5,56). As iPSC and iN cells are induced models, it is difficult to determine the degree of phenotypical similarity with brain cells, while in hONE cells neurobiological properties are preserved (6). hONE cells are cultured from living patients, which allows the comparison of cells obtained at different stages of the illness and treatment.

*GPCR involvement in SZ-related pathways using ONE cells*. hONE cells are a relatively new model to study GPCR expression and function. hONE cultures have multipotent SC features and express functional purinergic P2 receptors (both ionotropic P2X and metabotropic P2Y receptors) (57). The activation of the purinergic pathway in these cells elicits transient increase in the intracellular calcium ($Ca^{2+}$) concentration, mainly by the participation of the P2Y receptors; the calcium increase induces exocytotic processes in these cells (57).

Moreover, other functional GPCRs are expressed in human olfactory neural SCs, such as dopaminergic, serotoninergic and adrenergic receptors (ARs). These cells express markers of multipotency (Fig. 2A) and elicit an increase in intracellular $Ca^{2+}$ concentrations in response to ligand binding (Fig. 2B). These characteristics contribute to a viable, minimally invasive model for neuronal culture sample from live patients with SZ to study the GPCR signaling pathways involved in this pathology.

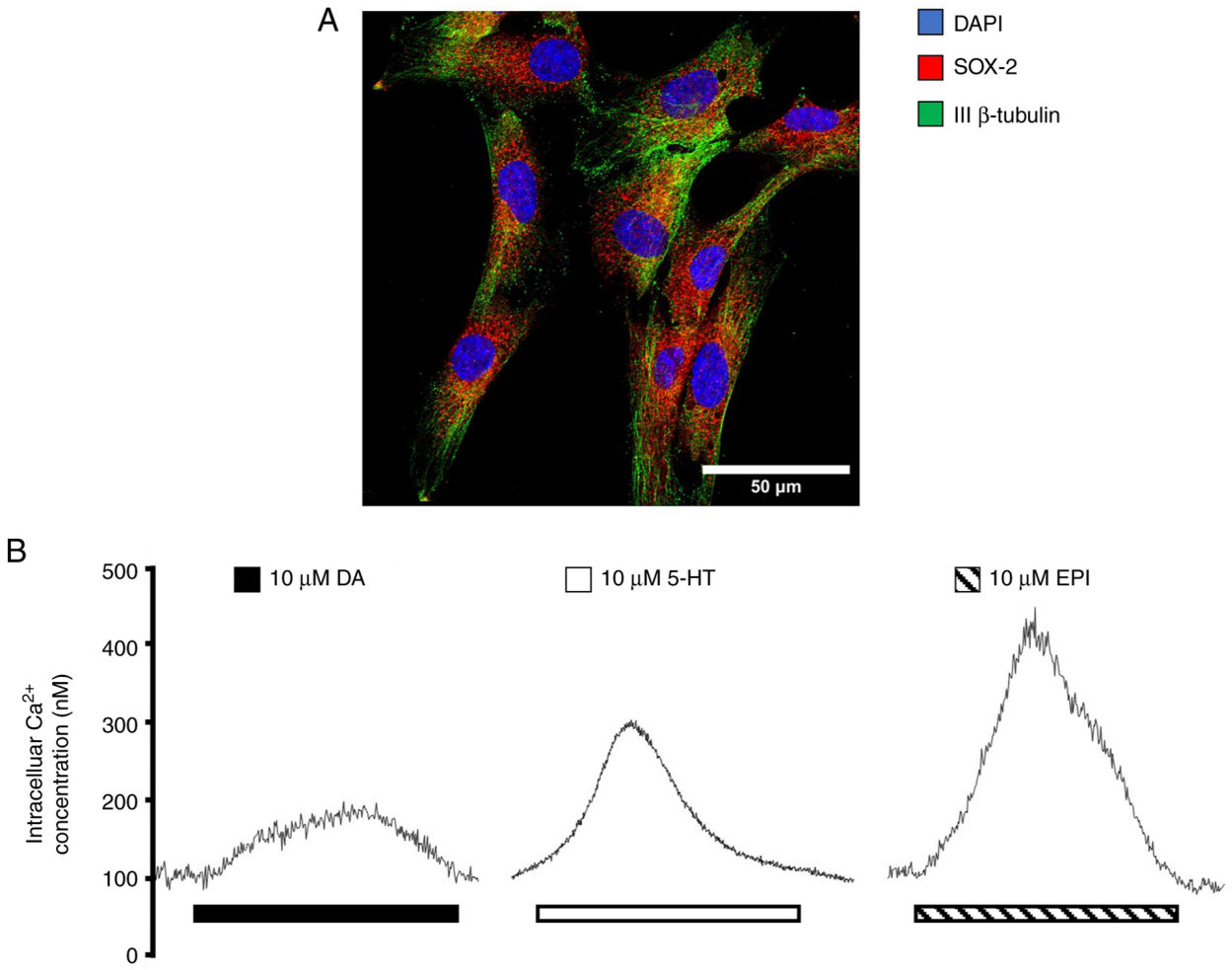


Figure 2. Characterization of stem cells obtained from olfactory epithelium by detection of specific protein markers and functional evaluation. (A) Confocal image of an olfactory epithelial stem cell expressing SOX-2 (red) and neuron-specific human III β-tubulin (green). Nuclei are stained with DAPI (blue). (B) Intracellular $Ca^{2+}$ concentration measurements illustrating the functionality of human olfactory epithelial stem cells. Stimulation with DA, 5-HT and or EPI increases intracellular $Ca^{2+}$ concentration (unpublished material). DA, dopamine; 5-HT, serotonin; EPI, epinephrine.

## 3. Dysregulated calcium signaling in SZ

$Ca^{2+}$ is a primary second messenger that regulates a myriad of cellular processes depending on its intracellular concentration, duration of stimulus and even global or local concentration changes (58).

The $Ca^{2+}$ signaling system in neurons is responsible for the regulation of multiple neural functions, including exocytosis, neuronal excitability, control of brain rhythms, information processing and changes in synaptic plasticity involved in learning and memory (59). Dysregulation of the $Ca^{2+}$ signaling pathway is implicated in the development of neural diseases, including SZ and bipolar disorder (59,60). Alterations in this system include the hypofunction of N-methyl-d-aspartate receptors (NMDAR) in early developmental stages, including complex transcriptional and compensatory events, resulting in a phenotypical switch in GABAergic neurons, altering γ rhythms (59). Even though the decreased activity of the NMDAR reduces $Ca^{2+}$ flow, the overall effect causes an increase in intracellular $Ca^{2+}$ in large neuronal populations (61,62). This is caused by the loss of inhibitory regulation in excitatory pathways from GABAergic interneurons (62,63). These pathways then increase intracellular $Ca^{2+}$ by activating non-NMDA channels, including GPCRs (64). Furthermore, in the cerebral cortex of patients with SZ, elevated levels of calcium/calmodulin-dependent protein kinase II (CAMKIIIβ) have been observed (65); this enzyme promotes $Ca^{2+}$-dependent neurotransmitter release (66,67) and this mechanism could be involved in the excessive dopamine release observed in animals dosed with amphetamine (68,69). Altered $Ca^{2+}$ signaling in SZ could cause the reduced dendritic extension and branching observed in prefrontal cortical neurons (70,71), since an optimal balance is required to maintain dendritic trees and altered $Ca^{2+}$ concentration can cause dendritic deformations (72-74). An increase in $Ca^{2+}$ activates cell apoptosis and may be associated with decreased neuronal cell number in cortical and subcortical regions observed in patients with SZ (75-80). Additionally, patients with SZ present an abnormal increase in neurons in the cortical white matter (81), and this may be caused by $Ca^{2+}$ dysregulation affecting neuronal migration (82,83). To the best of our knowledge, however, the participation of GPCRs in $Ca^{2+}$ signaling has not been investigated in hONE cells.

## 4. Role of GPCRs in cellular signaling in SZ

SZ clinical onset usually happens in early adulthood. It occurs in ~1% of the human population and in the US it is estimated to

Table I. GPCR alterations identified in animal models, *ex vivo* assays and patients with SZ.

| GPCR | Associated signaling | Implications in SZ | (Refs.) |
|---|---|---|---|
| Type $D_1$ ($D_1$ and $D_5$) | $G\alpha_q/G_s$ | Elevated mRNA levels of $D_1$ receptors in the temporal and parietal cortex | (93) |
| Type $D_2$ ($D_{2-4}$) | $G\alpha_i/G_o$ | Overexpression in the striatum leads to deficits in inhibitory neurotransmission and dopamine sensitivity in the prefrontal cortex | (92) |
| Adrenergic ($\alpha_1$, $\beta_{1-3}$)<br>Adrenergic ($\alpha_2$, $\beta_2$, $\beta_3$) | $G\alpha_q/G_s$<br>$G\alpha_i$ | Positive symptoms are exacerbated by selective and indirect norepinephrine receptor agonists, while antagonists decrease symptoms | (295) |
| Muscarinic ($M_1$, $M_3$, $M_5$)<br>Muscarinic ($M_2$, $M_4$) | $G\alpha_q/G_{11}$<br>$G\alpha_i/G_o$ | Transcriptional and proteomic alterations in $M_1$ and $M_4$ receptors in the hippocampus and prefrontal, frontal and cingulate cortex | (296,297) |
| mGlu (mGluR1, mGluR5) | $G\alpha_q/G_s$ | Overexpression of mGluR1 in the prefrontal cortex of patients | (152) |
| mGlu (mGluR2-4 and 6-8) | $G\alpha_i/G_o$ | mGluR2/3 may serve a role in working memory associated with NMDA receptor hypofunction | (82,298) |
| Serotonergic (5-$HT_1$, 5-$HT_5$) | $G\alpha_i/G_o$ | Decreased binding of 5HT to the 5-$HT_{1A}$ receptor in the amygdala of patients | (299) |
| Serotonergic (5-$HT_2$) | $G\alpha_q$ | Alterations in frontal cortical 5-$HT_{2A}$ receptor binding and decreased receptor density in the brain of patients | (300) |
| Serotonergic (5-$HT_4$, 5-$HT_6$, 5-$HT_7$) | $G\alpha_s$ | 5-$HT_7$ in the human brain and reduced mRNA levels in the prefrontal cortex of patients | (301) |
| $GABA_B$ metabotropic (GBR2) | $G\alpha_i/G_{\beta\gamma}$ | $GABA_BR1$ (6p21.3) and $GABA_BR2$ (5q34) gene loci are SZ susceptibility loci | (302) |

GPCR, G protein-coupled receptor; SZ, schizophrenia; D, dopamine; mGluR, glutamate metabotropic receptor; NMDA, N-methyl-d-aspartate; 5-HT, serotonin; GBR, GABA metabotropic receptor.

decrease lifespan by 28.5 years (84). Patients with SZ present brain structural alterations as well as dysfunction in several neurotransmission systems (dopaminergic, glutamatergic, GABAergic, ACh and serotonergic signaling), in addition to inflammation and oxidative stress. Patients also present loss of cerebral gray matter and abnormal distribution of neurons in the prefrontal cortex (PFC) (85-87). Patients with SZ present structural alterations in heavily myelinated brain tracts that comprise mostly white matter, which suggests that impaired brain connectivity and an overall dysfunction of the axo-myelin unit is a key mechanism underlying the pathophysiology of SZ (88). SZ has a complex genetic background and development depends on environmental factors (89,90). GPCRs play a key role in the development, progression and treatment of SZ (Table I).

*Dopaminergic receptors*. The biological functions of the catecholaminergic neurotransmitter dopamine in the brain and periphery are mediated by dopamine receptors $D_{1-5}$. These functions include regulation of sleep, feeding, synaptic regulation, attention, cognitive function, hormonal regulation, affection, reward systems, voluntary movement, vision and smell (91).

Based on binding to G proteins, dopamine receptors are classified as class 1 ($D_1$ and $D_5$) or 2 ($D_2$, $D_3$ and $D_4$). $D_1$-type receptors are mainly associated with Gαq/Gs proteins and stimulate adenylyl cyclase (AC) activity, cAMP production and $Ca^{2+}$ release from intracellular stores. By contrast, $D_2$-type receptors bind with Gα i/o proteins to inhibit cAMP production (92,93). Dopamine receptors are the most studied molecular targets in numerous neurological and psychiatric disorders, such as SZ, Parkinson's disease, bipolar disorder, attention deficit hyperactivity disorder, Huntington's disease, and Tourette syndrome (94-96). The exacerbation of the psychotic effects of dopaminergic drugs in SZ may be due to excessive stimulation of supersensitive postsynaptic dopaminergic receptors, particularly $D_2$ receptors, which is the pharmacological target of antipsychotics (97).

Variation in dopamine levels and the symptoms of SZ are dependent on the associated brain region; increased release in the striatum is associated with positive symptoms (hallucinations and delusions) where the binding of the $D_2$ receptor predicts the response to treatment with antipsychotics. However, the occupation of $D_2$ receptors in the ventral region of the striatum is associated with negative symptoms such as passivity, apathy and social withdrawal (98). These conclusions are supported

by genetic research showing a clear association between the dopamine receptor $D_2$ gene and SZ (86,99). Although the majority of the currently authorized antipsychotic drugs block $D_2$-type dopamine receptors, clinical symptomology is not completely treated in most patients. However, they have effects on other receptors in the brain, such as dopamine, serotonin, histamine, norepinephrine and ACh receptors, resulting in other abnormality, such as the risk of extrapyramidal side effects (100). $D_2$ receptors are involved in postsynaptic activation and autoreceptor-mediated inhibition of dopamine release in the striatum and the $D_1$ receptor modulates actions of dopamine in the corticostriatal circuitry; alterations in dopamine $D_1$ receptors and key molecules in their signaling pathways have been found in the PFC of patients with SZ (101). Other studies have visualized expression in limbic and cortical areas of $D_3$ and $D_4$ dopamine receptors (102,103). Moreover, clozapine, a second generation antipsychotic drug, has a higher affinity for the $D_4$ receptor, which supports its participation in the pathophysiology of SZ (102). On the other hand, the distribution and low cerebral abundance of $D_3$ receptors, as well as their close homology with the $D_2$ receptor, indicate they may serve as pharmacological targets, especially since their implementation could avoid the adverse motor effects produced by the inhibition of the $D_2$ receptor (104).

*ARs*. ARs are divided into $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$, and $\beta_3$. The $\alpha_1$ receptors couple to protein Gq/phospholipase C signaling proteins and $\alpha_2$ couple to Gi proteins. The $\beta_1$ and $\beta_2$ adrenoceptors activate Gs/AC/cAMP/protein kinase a (PKA) and $\beta_3$ receptors couple to both Gs and Gi (105).

$\alpha_1$-ARs present three molecular subtypes ($\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$) that regulate the functions of the sympathetic nervous system by transducing signals after binding with cognate agonists, such as endogenous catecholamines norepinephrine and epinephrine (106). In the peripheral nervous system (PNS), $\alpha_1$-ARs participate in nervous regulation of the cardiovascular and other system functions (107).

The positive symptoms of SZ are exacerbated by selective and indirect AR agonists (ephedrine, clonidine and desipramine), while they are decreased by antagonists (yohimbine, propranolol and oxypertine) (85,108). Additionally, α-ARs are linked to cognitive deficit in SZ (109) and PFC impairment via PKC activation (85,110,111). In neocortical pyramidal cells, adrenergic arousal controls coupling between apical and somatic integration regions by the regulation of hyperpolarization-activated currents ($I_h$) and altering apical amplification (AA) (112). Higher levels of cAMP lead to excessive $I_h$, therefore increasing AA. Patients with SZ exhibit translocation in the disrupted in schizophrenia 1 (DISC1) gene and DISC1-regulated phosphodiesterase 4 (PDE4) activity; in the presence of high concentration of cAMP, this increases hydrolysis; however, but this process is altered in these patients (113,114). This area is key for spatial working memory (WM), in which $\alpha_{2A}$ receptors serve a key role by inhibiting the cAMP/PKA pathway, thus reducing the persistent firing by increasing the open state of hyperpolarization and cyclic nucleotide-gated channels (115,116). The effects of adrenergic signaling are subtype-specific and could be influenced by noradrenaline concentration and receptor affinity. The effect is mediated through the persistent firing of the $\alpha_{2A}$ receptors, and the use of an exogenous general β agonist does not alter the outcome. This phenomenon may be related to the upregulation of cAMP (117). In another study, the use of a $\beta_1$ antagonist improved WM and the activation of $\beta_2$ enhanced this effect, illustrating the complex modulation by adrenergic receptors (117-119).

Certain single nucleotide polymorphisms (SNPs) have been associated with SZ, including two SNPs in the promoter region of the $\alpha_{1A}$ receptor gene (120), as well as methylenetetrahydrofolate reductase (MTHFR) (121,122). A detection system has been proposed to measure levels of 5-MTHF in patients with MTHFR SNPs (123).

*Muscarinic receptors*. ACh is a crucial neurotransmitter that participates both in the CNS and PNS. There are two types of receptors activated by ACh, nicotinic ionotropic and muscarinic metabotropic receptors (mAChRs) (124). There are five types of muscarinic receptors that can be classified as those coupled to Gq/G11 ($M_1$, $_3$ and $_5$) and those coupled to Gi/o ($M_2$ and $_4$) (124-126). The $M_1$ receptor is the most prevalent receptor in the CNS, located in postsynaptic neurons and some peripheral tissues (126). Meanwhile, in the presynaptic neurons, the $M_2$ and $M_4$ receptors are expressed, while in the postsynaptic neurons, the $M_3$, $M_4$ and $M_5$ receptors are expressed, with the $M_3$ typically being the less abundant (126). Lower levels of $M_1$ and $M_4$ expression have been detected in the cortex (127,128), hippocampus (129) and striatum (130).

Genetic alterations in the muscarinic signaling pathway have been associated with SZ, including SNPs in the gene for the muscarinic acetylcholine receptor M1 (CHRM1) (131), as well as changes in methylation of the promoter of this gene, caused by the increase in microRNA (miRNA or miR) that regulates this gene (miR-107) (132). SNPs for CHRM4 (126,133) and CHRM5 (126,134) have also been linked with an increased risk of SZ.

The use of animal models has demonstrated the participation of the mAChRs in the pathogenesis of SZ. In $M_1$ knock-out (KO) mice, impaired WM and long-term potentiation are observed (126,135). In a double KO mice model for $M_1$ and $M_4$, impaired prepulse inhibition (PPI) is observed (126,136). $M_4$ KO mice models have been reported to present impaired PPI, abnormal social behavior, locomotor activity, sensorimotor gating, abnormal antipsychotic function, dopaminergic hyperexcitability and altered striatal dopamine release regulation (126,137-142). It has been observed that $M_5$ KO mice present changes in PPI and reduced striatal dopamine release (126,142-144).

Alterations in other participants of this signaling pathway affect SZ. Acetylcholinesterase inhibitors, the enzyme that hydrolyses ACh, decrease visual hallucinations (85,145,146). Additionally, choline acetyltransferase (ChAt), the enzyme that synthesizes Ach, has decreased activity in the nucleus accumbens and pontine tegmentum of patients with SZ, which is associated with cognitive performance. An SNP for ChAt is associated with SZ (147).

*Glutamatergic receptors*. Glutamate is the primary excitatory neurotransmitter in the CNS responsible for modulation of synaptic transmission and neuronal excitability.

This modulation is mediated by the activity of ionotropic and metabotropic glutamate receptors (mGluRs) (85,148,149). There are eight subtypes of mGluRs encoded by the glutamate metabotropic receptor 1 (GRM1)-8 genes and these receptors are be classified into three groups: Group I includes receptors coupled to a Gq/11 protein (mGluR1 and mGluR5) and group II (mGluR2 and mGluR3) and III (mGluR4, -6, -7 and -8) are coupled to Gi/Go protein (85,148,149). All receptor subtypes are expressed in neurons and glial cells, except mGluR6, which is primarily expressed in the retina (85,150).

Alterations in mGluR1 are associated with SZ. Patients with SZ may have deleterious GRM1 non-synonymous SNPs (85,151); in postmortem studies, patients with SZ have higher levels of mGluR1α in the PFC (85,152). The role of mGluR1 has been studied through KO mice. These animals have decreased hippocampal long-term potentiation leading to a deficit in associative learning (148,153,154) and activity-dependent synaptic plasticity (154). mGluR1 deficiency causes long-term depression in the cerebellum and motor learning impairment (148,155) and a decrease in PPI (148,156). Use of mGluR1 negative allosteric modulators is effective in the treatment of positive SZ symptom models (85,148,157).

mGluR5 may be involved in SZ as this receptor potentiates the NMDAR in brain regions of interest in SZ (158). In mGluR5KO mice, there is a deficit in PPI (148,159). Furthermore, a KO model of miR-50103p induces dendritic structural defects, glutamatergic transmission enhancement and sociability, memory and sensorimotor gating deficits, which are attenuated when restoring miR-50103p expression. These effects were attributed to the upregulation of mGluR5 since this miRNA negatively regulates the expression of the receptor. When using a negative allosteric modulator of mGluR5, similar effects were observed (160). In animal models of positive and negative symptoms, a positive allosteric modulator of mGluR5 effectively improves all types of SZ symptom (85,148,157). Furthermore, mGluR5-selective negative allosteric modulators in adult rats causes social interaction deficits, impaired WM, reduced instrumental learning, decreased overall response in 5-choice serial reaction time task (5-CSRT) and increased NMDAR antagonist side effects (158,161-165). Postsynaptic mGluR2/3 activation can augment NMDAR currents via Src kinase in pyramidal cells of the hippocampal CA1 (166) and in the PFC via PKC activity (167) and soluble N-ethylmaleimide-sensitive factor attachment protein receptor proteins (157,168).

Although the group II receptors have not been as extensively studied, they may serve as therapeutic targets. In animal models of SZ, the activation of mGluR2/3 decreases the psychomotor activity and neurochemical effects produced by psychostimulants (85,169). Agonists of mGluR2/3 decrease extracellular dopamine efflux in the substantia nigra, nucleus accumbens and dorsal striatum (157,170-173). The activation of mGluR2/3 functions as an autoregulator to decrease glutamate release, makes it a target for the development of agonists for treatment of SZ (157,174). Additionally, in preclinical trials, mGluR2/3 agonists (LY354740 and LY379268) decrease NMDAR antagonist-induced hyperlocomotion (175-178) and behavioral stereotypes (175,179) and behavioral and electrophysiological effects and head twitches induced by (+/-)1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) in mice (180) and improve SZ-like symptoms induced by prenatal stress and postnatal isolation (157,181,182). In negative symptom models, the agonists improve deficits in social interaction (183-185) and mobility attenuated by dizocilpine in the swimming test (157,178). For cognitive symptoms, mGluR2/3 agonists decrease deficits in discrete-trial delayed alternation task (175) and errors in the 5-CSRT (157,186). However, it has also been shown that agonists can impair cognitive symptoms. Impaired cognition by inhibiting hippocampal synaptic transmission (187) and exacerbated deficits in the 5-CSRT have been observed (157,188).

mGluR2 is associated with the serotonergic receptor 5-$HT_{2A}$R based on the behavioral, pharmacological, and biochemical results observed when antagonizing receptor signaling (157,189-191). The antipsychotic properties of mGluR2 have been attributed to the effects on the serotonin receptor and it has also been observed that 5-$HT_{2A}$R antagonism in mice with atypical antipsychotics decreases expression of GRM2 encoding mGlu2 through a decrease in histone deacetylase 2 (157,192).

The least explored receptors are those in group III. All receptors in this group have been studied in KO mice models (180,184-197). The administration of a group III agon ist (1S,3R,4S)-1-aminocyclo-pentane-1,3,4-tricarboxylic acid (ACTP-1) decreases hyperlocomotion induced by MK-801 and amphetamines and improves head twitches induced by DOI in mice (157,193). The mGluR4 is expressed throughout the brain but is most densely expressed in the cerebellum; KO mice can present impairments in cerebellar synaptic plasticity and motor learning of complicated tasks and altered spatial memory performance. These receptors are key in regulation of GABAergic absence seizures in the thalamocortical region (148,194-196). In positive symptom animal models, the administration of mGluR4 agonist (LSP1-2111 and LSP4-2022) improves psychosis symptoms (hyperlocomotion and head twitches) (157,197,198). mGluR4 agonists also improve deficits in social interaction and novel object recognition (157,198). mGluR6, which is primarily expressed in the retina, presents delayed response when retinal bipolar cells are stimulated with light in mGluR6 KO mice (148,199,200). There have been reports of photoreceptor and bipolar and retinal ganglion cell (RGC) dysfunction in SZ (201,202). RGC signaling deficit is associated with SZ, particularly in patients that experience visual hallucinations (202).

The mGluR7 receptor is widely expressed but has a lower affinity to glutamate than other receptors and downregulates overstimulation by glutamate (148), as indicated by the epileptic phenotype observed in mGluR7 KO mice (148,203). mGluR7 KO mice exhibit worse short-term neural plasticity in the hippocampus (85,204,205), memory and learning deficits (204,206-209) and an altered fear (209) and anxiety response (20,85,148,204,210). In preclinical studies, mGluR7 negative allosteric modulators 6-(4-methoxyphenyl)-5-methyl-3-pyridin-4-ylisoxazolo[4,5-c] pyridin-4(5H)-one and (+)-6-(2,4-dimethylphenyl)-2-ethyl-6,7-dihydrobenzo[d]oxazol-4(5H)-one improves symptoms caused by MK-801 and DOI-induced head twitches (85,211-213), while an mGuR7 agonist (AMN082) produces the opposite effects (157,197).

mGluR8 is less expressed than mGluR4 and -7; it is primarily expressed presynaptically and widely throughout the brain (148,157). This receptor serves as an autoreceptor in the lateral prefrontal path of the dentate gyrus, therefore gating glutamatergic transmission into the hippocampus (157,214), which is why mGluR8 KO mice exhibit deficiency in hippocampal-mediated learning (157,215). Unlike the other group III receptors, mGluR8 agonist [(S)-3,4-DCP] does not affect NMDAR or amphetamine hyperactivity, suggesting that it might be an ineffective target for SZ treatment (157,216).

*Purinergic receptors*. P2Y metabotropic purinoceptors are a family of proteins divided into eight subtypes (P2Y1, 2, 4, 6 and 11-14) that can be activated by several nucleotides such as ATP, ADP, UTP, UDP and UDP-glucose (217). Activation of these receptors induces biological effects due to the subsequent activation of different effectors, including MAPK, ρ-associated protein kinase, phospholipase A2, nitric oxide and the transactivation of growth receptors (218). Several signaling pathways activated by ATP and other nucleotides via P2Y, participate in regulation of CNS development. Stimulation of the $P2Y_1$ receptor promotes adult neurogenesis (219,220). The P2Y receptors have been suggested to be involved in SZ. $P2Y_1$ receptor agonist (MRS2365) to the PFC in rats impairs WM and other behavioral responses that may be involved in conditions that increase ATP concentration, such as SZ (221). Perisomatic interneurons, which modulate γ oscillations, express $P2Y_1$Rs (222). These cells have been implicated in SZ and cognitive deficit (222) and γ oscillations and PPI alterations have been reported in SZ animal models (223,224).

The role of the purinergic signaling system in SZ has gained interest (225,226). Based on modulation of glutamatergic and dopaminergic systems by adenosine, it has been theorized that complications during the early stages of brain development lead to an excessive release of adenosine that induces brain changes. The dysfunctional activation of adenosine receptor $A_1$R decreases activity of dopamine, consequently increasing cytotoxicity through glutamate (227). Adenosine $A_{2A}$ receptor ($A_{2A}$R) KO mice showed that, in astrocytes, these receptors disrupt glutamate homeostasis, leading to psychomotor and cognitive impairment, which may be involved in the development of SZ (228). Moreover, $A_{2A}$Rs can form heterodimers with $D_2$ receptors. $A_{2A}$Rs are highly expressed in certain brain regions implicated in SZ and may modulate $D_2$ receptors. However, no difference in expression of these receptors is observed in male patients with SZ treated with antipsychotic medication compared with healthy controls by measuring a tracer through positron emission tomography (229).

*Wnt/FRIZZLED (FZD) receptors*. Wnts transduce signaling cascades to regulate SC differentiation in various types of tissues such as skin, muscle, colon and bone marrow; in addition, they promote cell proliferation and differentiation to regulate maintenance of the adult hippocampus and neuronal progenitors of the subventricular zone (230,231). A distinctive aspect of Wnt signaling is its ability to favor tissue growth while inducing cell proliferation, serving as a directional growth factor and preventing the formation of amorphous structures, an essential feature during tissue development and homeostasis in adults (232,233).

Neuroinflammation and immune dysfunction could be involved in the pathogenesis of SZ, supported by the higher incidence of autoimmune disease in patients with SZ. The inflammatory process is mediated by Wnt/β-catenin dysregulation, with the primary effector being NF-κB, stimulating production of inflammatory markers, including various cytokines, and favoring oxidative stress. Many of these processes promote psychotic symptoms. SZ is associated with a decrease in Wnt/β-catenin pathway activity, leading to an upregulation of PPARγ and downregulation of PPARα (234-236). The increase of PPARγ increases oxidative stress and inflammation (234). The Wnt/β-catenin pathway is involved in the pathogenesis of numerous neuropsychiatric disorders. There have been reports of myelin and oligodendrocyte dysfunction in SZ (88,237), indicating that the Wnt/β-catenin pathway could be altered in this illness. The levels of β-catenin are decreased in the hippocampal region of patients with SZ and downstream alterations in this pathway have been also observed (238).

Genome-wide SNP analysis has identified multiple SNPs associated with SZ, including the FZD1 gene at chromosome 7q21.13 (239), as well as FZD3 gene on the chromosome 8p21 (240-242). FZD3 SNPS are also implicated in methamphetamine psychosis (243). There is aberrant Wnt gene expression at multiple levels of the signaling pathway. Microarray analysis demonstrates that patients with SZ exhibit dysregulated mRNA expression of genes that attenuate β-catenin signaling and favor non-canonical signaling, while transcription factor nuclear factor of activated T cells 3, which is activated downstream by the non-canonical pathway, is upregulated (244).

*Cannabinoid receptors*. Cannabinoid receptor subtypes 1 and 2 ($CB_1$ and $CB_2$) are metabotropic receptors primarily coupled to Gi/o proteins. Activation of these receptors inhibits the enzymatic activity of AC), and decreases the intracellular levels of cAMP (245). These receptors couple to Gq/11 or Gs, inducing different responses (246). They are expressed in neuroglia, immune cells and neurons in the CNS (247). Furthermore, olfactory (248) and neural SCs (NSCs) express a functional endocannabinoid system (249).

$CB_2$ receptors are usually absent in neurons, although they are functionally active in SCs and, together with $CB_1$, modulate processes such as proliferation, cell cycle maintenance, and NSC differentiation via the PI3K/Akt pathway (250-253).

Excessive activation of the endocannabinoid system through $CB_1$ receptors of inhibitory GABAergic interneurons in the ventral tegmental area, basolateral amygdala and the medial PFC generates a hyperdopaminergic and hypoglutamatergic environment, causing SZ (254,255). Through *in vivo* and postmortem studies, it has been shown that gene, mRNA and protein levels of these receptors are decreased and dysregulated in multiple brain regions of patients with SZ (256-258). In animal models, chronic blockade of $CB_2$ receptors has been shown to induce anxiolytic action (259). Treatment with a selective $CB_2$ agonist reduces depressive-like behaviors (260). Maternal deprivation induces a significant increase in $CB_2$ receptor immunoreactivity in the hippocampus, suggesting participation of this receptor in psychiatric neurodevelopmental

Table II. Effect of different agonistic and antagonistic treatments targeting GPCRs in patients with schizophrenia.

| Drug | Typical GPCR-associated signaling | Atypical GPCR-associated signaling |
|---|---|---|
| Aripiprazole | Dopamine Antagonist (√√√) $D_2$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ↓$IK^+$; (√√) $D_3$ $G_i$ ↓ cAMP; (√) $D_4$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ↓$IK^+$ | Serotonin Antagonist (√√√) $5HT_{1a}$ $G_s$ cAMP; (√√√) $5HT_{2a}$ $Ca^{2+}$ PLC; (Ö) $5HT_{2c}$ $Ca^{2+}$ PLC; (√) $5HT_7$ $G_s$↑cAMP<br>Adrenergic Antagonist (√√) a1 $G_q$ $IP_3/Ca^{2+}$<br>Histamine Antagonist (√) $H_1$ $G_q$ $IP_3/Ca^{2+}$ |
| Azepine | Dopamine Antagonist (ÖÖÖ) $D_2$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ↓$IK^+$; (√) $D_3$ $G_i$ ¯cAMP | Serotonin Antagonist (√√√√) $5HT_{2a}$ $Ca^{2+}$ PLC; (√√) $5HT_{1a}$ Gs ↑cAMP; (√√) $5HT_{1b}$ $G_i$ ↓cAMP; (√√) $5HT_{2c}$ $Ca^{2+}$ PLC; (√) $5HT_6$ $G_s$ ↑cAMP; (√) $5HT_7$ $G_s$ ↑Camp |
| Chlorpromazine | Dopamine Antagonist (√√√) $D_1$ $G_s$ ↑cAMP; (√√) $D_5$ $G_s$ ↑cAMP; (Ö) $D_2$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ¯$IK^+$; (√) $D_3$ $G_i$ ↓cAMP | Serotonin Antagonist (√√√) 5HT1a $G_s$ ↑cAMP; (√√√) $5HT_{2a}$ $Ca^{2+}$ PLC<br>Adrenergic Antagonist (√√) a1 $G_q$ $IP_3/Ca^{2+}$; (√√) a2 $G_i$ ↓cAMP<br>Histamine Antagonist (√) $H_1$ $G_q$ $IP_3/Ca^{2+}$<br>Muscarinic Antagonist (√) $M_1$ $G_q$ $IP_3/Ca^{2+}$; (√) $M_2$ $G_i$ ↓cAMP ¯$IK^+$ |
| Clozapine | Dopamine Antagonist (√√√) $D_1$ $G_s$ cAMP; (√√) $D_4$ $G_i$ ↑ cAMP ;(Ö) $D_2$ $G_i$ ↓ cAMP ↓ $Ca^{2+}$ ↓$IK^+$; (√) $D_3$ $G_i$ ↓ cAMP | Serotonin Antagonist (√√√) $5HT_{2a}$ $Ca^{2+}$ PLC<br>Adrenergic Antagonist (√√) a1 $G_q$ $IP_3/Ca^{2+}$<br>Muscarinic Antagonist (√√) $M_1$ $G_q$ $IP_3/Ca^{2+}$; (√) $M_2$ $G_i$ ↓cAMP ¯$IK^+$; (√) $M_3$ $G_q$ $IP_3/Ca^{2+}$<br>Muscarinic Agonist (√) $M_4$ $G_i$ ↓cAMP ↓$IK^+$ |
| Fluphenazine | Dopamine Antagonist (√√√) $D_2$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ↓$IK^+$ | Muscarinic Antagonist (√√) $M_1$ $G_q$ $IP_3/Ca^{2+}$<br>Adrenergic Antagonist (√√) a1 $G_q$ $IP_3/Ca^{2+}$<br>Histamine Antagonist (√) $H_1$ $G_q$ $IP_3/Ca^{2+}$ |
| Haloperidol | Dopamine Antagonist (√√√) $D_1$ $G_s$ ↑ cAMP; (√√) $D_2$ $G_i$ ↓cAMP ¯$Ca^{2+}$ ↓$IK^+$ | Muscarinic Antagonist (√) $M_1$ $G_q$ $IP_3/Ca^{2+}$<br>Adrenergic Antagonist (√) a1 $G_q$ $IP_3/Ca^{2+}$ |
| Olanzapine | Dopamine Antagonist (√√√) $D_1$ $G_s$ ↑ cAMP; (√√) $D_5$ $G_s$ ↑ cAMP; (√√) $D_2$ $G_i$ ↓cAMP ¯$Ca^{2+}$ ↓$IK^+$; (√) $D_3$ $G_i$ ↓cAMP | Serotonin Antagonist (√√√) $5HT_{2a}$ $Ca^{2+}$ PLC; (√√√) $5HT_{2c}$ $Ca^{2+}$ PLC<br>Adrenergic Antagonist (√√) a1 $G_q$ $IP_3/Ca^{2+}$<br>Muscarinic Antagonist (√√) $M_1$ $G_q$ $IP_3/Ca^{2+}$; (√) $M_2$ $G_i$ ↓ cAMP ↓$IK^+$; (√) $M_3$ $G_q$ $IP_3/Ca^{2+}$; (√) $M_4$ $G_i$ ↓cAMP ¯$IK^+$; (√) $M_5$ $G_q$ $IP_3/Ca^{2+}$<br>Histamine Antagonist (√) $H_1$ $G_q$ $IP_3/Ca^{2+}$ |
| Quetiapine | Dopamine Antagonist (√√) $D_1$ $G_s$ ↑ cAMP; (√√) $D_2$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ↓$IK^+$ | Serotonin Antagonist (√√√) $5HT_2$ $Ca^{2+}$ PLC; (√√√) $5HT_1$ $G_i$ ↓cAMP ¯$IK^+$<br>Histamine Antagonist (√) $H_1$ $G_q$ $IP_3/Ca^{2+}$<br>Adrenergic Antagonist (√√) a1 $G_q$ $IP_3/Ca^{2+}$; (√) a2 Gi ↓ cAMP |
| Perphenazine | Dopamine Antagonist (√√) $D_2$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ↓$IK^+$ | Adrenergic Antagonist (√√) a1 $G_q$ $IP_3/Ca^{2+}$ |
| Risperidone | Dopamine Antagonist (√√) $D_2$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ¯$IK^+$; (√) $D_3$ $G_i$ ↓ cAMP | Serotonin Antagonist (√√√) $5HT_2$ $Ca^{2+}$ PLC<br>Adrenergic Antagonist (√√) a1 $G_q$ $IP_3/Ca^{2+}$<br>Histamine Antagonist (√) $H_1$ $G_q$ $IP_3/Ca^{2+}$<br>Muscarinic Antagonist (√√) $M_1$ $G_q$ $IP_3/Ca^{2+}$; (√√) $M_2$ Gi ↓cAMP ¯$IK^+$ |
| Thioridazine | Dopamine Antagonist (√√) $D_2$ $G_i$ ¯cAMP ↓$Ca^{2+}$ ↓$IK^+$ | Adrenergic Antagonist (√√) a1 $G_q$ $IP_3/Ca^{2+}$ |
| Trifluoperazine | Dopamine Antagonist (√√) $D_2$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ↓$IK^+$ | Adrenergic Antagonist (√√) a1 $G_q$ $IP_3/Ca^{2+}$ |

Table II. Continued.

| Drug | Typical GPCR-associated signaling | Atypical GPCR-associated signaling |
|---|---|---|
| Ziprasidone | Dopamine Antagonist (√√) $D_2$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ↓$IK^+$; (√) $D_3$ $G_i$ ↓cAMP | Serotonin Antagonist (√√√) $5HT_{2a}$ $Ca^{2+}$ PLC; (√√) $5HT_{2c}$ $Ca^{2+}$ PLC; (√√) $5HT_{1d}$ $G_i$ ↓cAMP ↓$Ca^{2+}$ ↓$IK^+$<br>Adrenergic Antagonist (√) a1 $G_q$ $IP_3$/$Ca^{2+}$<br>Histamine Antagonist (√) $H_1$ $G_q$ $IP_3$/$Ca^{2+}$ |

(√√√) High effect; (√√) Moderate effect; (√) Mild effect; ↓ decreased effect; ↑ increased effect. The information of this table was taken from (2,292,303). GPCR, G protein-coupled receptor; IK, potassium current; 5-HT, serotonin; PLC, phospholipase C; $IP_3$, inositol 1,4,5-trisphosphate; Gi, G inhibitory; Gs, G stimulatory.

diseases such as SZ (261). Polymorphisms in the genes for cannabinoid receptors and the endocannabinoid system are associated with SZ (28) and quality of the response to antipsychotics (262).

*Sphingosine-1-phosphate (S1P) receptors*. S1P is produced in all cell types during the catabolic degradation of membrane glycosphingolipids and sphingomyelin, which results in sphingosine that is phosphorylated by sphingosine kinase (SphK) to S1P, a bioactive signaling molecule that serves as a ligand for GPCRs of the Gi/o, G12/13, and Gq types (263). Various hormones, cytokines and growth factors can activate the SphK/S1P signaling pathway, modulating cell proliferation, migration and survival. The SphK/S1P pathway has been associated with stem/progenitor cells and tissue self-renewal in the vascular, immune, muscular and nervous systems (264-267).

In the pathogenesis of SZ, there are alterations in myelin, white matter integrity and metabolism of lipids. Recent targeted mass spectrometry-based analysis found that postmortem samples of the corpus callosum of patients with SZ have lower levels of S1P (268). Furthermore, one study divided patients with SZ into those that present an upregulation of S1PR1 and those that have levels comparable to controls (269). This may be used as a biomarker since S1PR1 can be detected through positron emission tomography (269).

*Neuropeptide Y (NPY) receptors*. NPY is a 36-amino acid peptide produced by GABAergic interneurons that is widely expressed in the CNS and PNS during development and adulthood. The Y receptors are a family of proteins divided into five subtypes ($Y_1$, $Y_2$, $Y_4$, $Y_5$, and $Y_6$) that are activated by the NPY family of hormones, which consists of three native peptide ligands (NPY, pancreatic polypeptide and peptide YY). All NPY receptors are involved in the Gi signaling cascade; upon activation, the α subunit decreases cAMP production and the b/g subunit activates various kinase cascades. This ligand-receptor interaction can lead to decreased $Ca^{2+}$ channel activity and increased G-protein-coupled inward rectifying potassium currents (270,271).

NPY serves an important role in the regulation of learning, memory, feeding and endocrine secretion (272). NPY is found in the olfactory neuroepithelium, where it stimulates proliferation of olfactory SCs (273). Additionally, NPY regulates the response of olfactory receptors, apoptosis and cell regeneration (274) and protects sensory neurons from death due to excessive GluR activation by decreasing $Ca^{2+}$ entry into the presynaptic nerve terminal via PKA- and p38K-associated signaling (275).

NPY participates in adult neurogenesis in the hippocampal dentate gyrus, caudal subventricular zone and subcallosal zone (276). *In vivo*, by fusing NPY vectors with a brain transport peptide (apolipoprotein B), proliferation of neural precursor cells in the subgranular zone of the hippocampus increases substantially without neuronal differentiation (277). Furthermore, NPY promotes the proliferation of olfactory and hippocampal SCs (272,273,278).

NPY gene and mRNA expression is decreased in PFC of patients with SZ (279,280); these prefrontal deficits depend on regional supply of brain-derived neurotrophic factor through a miRNA-regulated mechanism (279). Additionally, activation of the $Y_2$ subtype of NPY receptor regulates central dopamine signaling, which is closely related to the pathophysiology of psychotic symptoms (281,282).

*Chemokine receptors*. Chemokines are a family of small cytokines (CXC, CC or β-chemokines, C, and CX3C), that regulate chemotaxis, hematopoiesis, angiogenesis, survival, proliferation, migration and degranulation of leukocytes by coupling with their respective GPCRs (283). Chemokine receptors are divided into four subtypes according to their activating chemokine ligands (284). Chemokines are key regulators of SCs in specific tissues (268,285) and can mediate migration of multipotent SCs (286). CXCR4 modulates growth factor signaling and is expressed *in vitro* in adult human and murine NSCs and cells from the embryonic murine subventricular zone (287).

In addition to chemotactic functions, it has been observed that chemokines participate in neuromodulation, neurotransmission and neurogenesis, exert a pleiotropic effect and exacerbate inflammation, which is why their dysregulation is associated with neurobiological processes associated with mental illnesses such as SZ (284,288). A systematic review demonstrated an association between chemokines and neuroinflammation and the pathogenesis of SZ, highlighting that there is a genetic association of SZ with polymorphisms

of chemokine receptor genes, blood levels of CXCL8/IL-8, CCL2/(monocyte chemoattractant protein 1, chemokine (C-C motif) ligands 4 (CCL4)/macrophage inflammatory protein 1β (MIP-1β), and CCL11/eotaxin-1 are increased and chemokine expression and their receptors are changed in brain regions and peripheral immune cells of patients with SZ and animal models have revealed molecular mechanisms associated with deregulation of the CX3CL1-CX3CR1 and CXCL12-CXCR4 axes, demonstrating that deregulation of chemokine expression may contribute to the neurobiological processes that cause SZ (284).

## 5. GPCRs as therapeutic targets in SZ

Management of patients with SZ consists of pharmacotherapy and/or psychotherapy and its principal goal is to improve quality of life and limiting side effects of treatment to maintain adherence to the treatment. The primary pharmacological therapy used in SZ is based on total or partial antagonists of the dopamine $D_2$ receptor, however, few patients fully recover or exhibit reversed negative symptoms (Table II). Moreover, the cognitive impairments of SZ are usually resistant to current antipsychotic treatment (289).

GPCRs play an important role in the treatment of SZ because they transmit the extracellular signal into cells by activating the signaling cascade coupled to G proteins. Advances in pharmacology have made it possible to identify drugs that can modify the interaction of GPCRs related to dopaminergic and serotonergic activity in the treatment and management of SZ (290,291). Understanding the role of GPCRs in the signal transduction of SZ is fundamental for the discovery of pharmacological targets. The basis of pharmacological treatment for SZ requires a complete understanding of GPCR-mediated signaling, transducers and associated second messengers. Structural plasticity of GPCR proteins underlying physiological regulation with pharmacological implications in clinical use has been summarized previously (292).

Considering SZ pathophysiology and ineffective antipsychotic therapy with severe side effects and poor adherence to the therapeutic regimen that diminishes quality of life and undermines the beneficial effects of the drugs, novel treatments directed at the whole symptomatology as well as specific symptoms are needed. There are numerous clinical studies of GPCR targets, including those directed at general, positive, negative and cognitive symptoms (30,293,294).

## 6. Conclusion

The present review demonstrated that GPCR alterations can be associated with the pathophysiology of psychiatric disorders and neurodegenerative diseases, such as SZ. GPCRs are a therapeutic target of antipsychotics used in the treatment of SZ. To the best of our knowledge, however, experimental evidence regarding the functionality of these receptors in patients is scarce. Knowledge of GPCR signaling in human multipotent SCs and their progeny differentiated in neurons or neuroglia could widen the study of the pathophysiology of SZ and other diseases such as diabetes, myocardial infarction, stroke, Parkinson's disease, Alzheimer's disease and multiple sclerosis.

Some of the limitations of hONE as a model of study in SZ include lack of information about GPCRs functionality in hONE cells; also, since these cells are undifferentiated, they may have a distinct expression of channels and receptors than their differentiated progeny, and the results obtained in the undifferentiated cells should be corroborated in conventional SZ models based on differentiated dopaminergic and serotoninergic neurons.

Models such as patient-derived iPSCs, transdifferentiated neurons, olfactory sensory neurons and cerebral organoids can provide understanding of SZ and facilitate the development of treatment. Particularly, the culture and cryopreservation of olfactory SCs have been characterized and used to identify several dysfunctional processes at a cellular level; this has been proposed as a model to understand the pathophysiology of neuropsychiatric disorders and detect biomarkers for diagnosis. This model could be useful to study the functionality of GPCR in SZ. GPCRs and their associated signaling pathways are possible therapeutic targets for SZ, although further research using experimental and bioinformatic tools is needed.

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## Availability of data and materials

Not applicable.

## Authors' contributions

ZASF, BSRM, EFS, BS and HSC conceived the study. HS, LMM, MVT, EC, AAG, GOLR, RA and JA edited the manuscript. All authors wrote the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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