Abnormalities of Dopamine D_3 Receptor Signaling in the Diseased Brain

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ABSTRACT: Dopamine D_3 receptors (D_3R) modulate neuronal activity in several brain regions including cortex, striatum, cerebellum, and hippocampus. A growing body of evidence suggests that aberrant D_3R signaling contributes to multiple brain diseases, such as Parkinson's disease, essential tremor, schizophrenia, and addiction. In line with these findings, D_3R has emerged as a potential target in the treatment of neurological disorders. However, the mechanisms underlying neuronal D_3R signaling are poorly understood, either in healthy or diseased brain. Here, I review the molecular mechanisms involved in D_3R signaling via monomeric D_3R and heteromeric receptor complexes (e.g., D_3R-D_1R, D_3R-D_2R, D_3R-$A_{2a}R$, and D_3R-D_3nf). I focus on D_3R signaling pathways that, according to recent reports, contribute to pathological brain states. In particular, I describe evidence on both quantitative (e.g., increased number or affinity) and qualitative (e.g., switched signaling) changes in D_3R that has been associated with brain dysfunction. I conclude with a description of basic mechanisms that modulate D_3R signaling such as desensitization, as disruption of these mechanisms may underlie pathological changes in D_3R signaling. Because several lines of evidence support the idea that imbalances in D_3R signaling alter neural function, a better understanding of downstream D_3R pathways is likely to reveal novel therapeutic strategies toward dopamine-related brain disorders.

KEYWORDS: Dopamine D_3 receptor, signaling, binding, affinity, heteromers, Parkinson's disease, essential tremor, schizophrenia, addiction

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Introduction

In the 1950s, after the role of dopamine (DA) as a signaling molecule in the brain was demonstrated,[1] it was reported that DA levels dramatically decrease in Parkinson's disease (PD).[2] Shortly after that, the DA precursor L-DOPA (L-3,4-dihydroxyphenylalanine) was started to be used to increase DA concentration in the brain of patients with PD.[2] The temporary relief of PD symptoms by L-DOPA indicated that loss of DA signaling is the pathognomonic feature of PD. Evidence from animal models and humans has shown that, in addition to PD, DA signaling also plays a central role in several brain disorders including schizophrenia, essential tremor, attention deficit hyperactivity disorder, depression, and addiction. This plethora of DA-associated diseases closely matches with the function of the DA system in multiple brain functions such as motor coordination, emotions, memory, reward mechanisms, and neuroendocrine regulation.

The brain DA system is constituted by DA-containing nuclei (i.e., substance nigra pars compacta, ventral tegmental area, and arcuate nucleus) and by the target areas (i.e., cortex, basal ganglia, thalamus, limbic structures, and pituitary gland).[1] On target areas, DA acts through five DA receptors, which belong to the superfamily of seven-transmembrane G protein–coupled receptors (GPCRs). Based on structural, biochemical, and pharmacologic criteria, DA receptors have been grouped into two main families: the D_1 (D_1 and D_5 subtypes) and D_2 (D_2, D_3, and D_4 subtypes) families.[3] Structurally, the major difference between D_3 receptor (D_3R) and D_1 family receptors is located in the third intracellular loop and carboxyl terminal tail: D_3R has a long third loop and short carboxyl terminus, whereas D_1 and D_5 receptors display opposite features showing short third intracellular loops and long carboxyl terminal tails. Compared with D_2 and D_4 receptors, D_3R has a distinctive third intracellular loop.[3]

A growing body of evidence suggests that aberrant D_3R signaling contributes to several brain disorders. Consequently, D_3R has emerged as a potential therapeutic target in the treatment of major neurological disorders such as schizophrenia,[4] PD,[5] and addiction. However, the mechanisms underlying D_3R signaling are poorly understood, either in healthy or diseased brain. Here, I review recent reports on the molecular mechanisms involved in D_3R signaling via monomeric D_3R and heteromeric receptor complexes. Then, I illustrate examples of qualitative and quantitative changes in D_3R signaling that may contribute to several brain diseases. I conclude with a description of potential targets for the modulation of D_3R signaling. Unraveling the unknown downstream signaling pathways activated by D_3R in both the healthy and the diseased brain is likely to reveal new therapeutic strategies toward DA-associated disorders.

Monomeric and Heteromeric D_3R Signaling

Brain D_3R messenger RNA (mRNA) is detected early in development (e.g., in the embryonic days 10 and 11 of rodents)[6] and continually expressed during the postnatal

period.[7–10] In adult rats[11] and mice,[12] regions that affect emotional, cognitive, and endocrine functions express D_3R mRNA (e.g., nucleus accumbens, islands of Calleja, hippocampus, prefrontal cortex, hypothalamus, and striatum). Interestingly, in the mouse brain, the D_3R co-expressed with D_1R and D_2R with regional, sex, and age-dependent differences in the co-expression pattern.[12] In the human brain, D_3R mRNA has been detected in nucleus accumbens and in the islands of Calleja.[13] Although D_3R is widely expressed in the brain, elucidating D_3R signal transduction mechanisms has been challenging because D_3R and D_2R have similar pharmacologic profiles due to the high sequence identity and homology shared by these receptors (e.g., homology of 52% overall and of 75% in the transmembrane domain of rat sequences).[11] To specifically activate D_3R, many studies have been performed in heterologous expression systems. These experimental systems have revealed that D_3R can be linked to a wide array of intracellular signals via its coupling to multiple G protein α subunits, such as $G_{i\alpha 3}$,[14] G_o,[15,16] G_q,[17,18] and G_s.[19] Consistent with its ability to activate multiple G proteins, D_3R can modulate several downstream effectors including adenylyl cyclase, cyclin-dependent kinase 5 (CDK5), creatine kinase 1 (CK-1), protein kinase A (PKA), protein kinase B (PKB)/Akt, protein kinase C (PKC), phospholipase C (PLC), phospholipase D (PLD), protein phosphatase 2B (PP2B), and extracellular signal–regulated kinase (ERK).[14–16,18,20–27] Moreover, under particular conditions, D_3R can mediate both opposite and synergistic interactions with signaling pathways related to the production of cyclic adenosine monophosphate (cAMP).[21] Despite having similar sequences and pharmacologic profiles, D_3R and D_2R exhibit significant biochemical differences. For instance, D_2R activates ERK via a $G_{i\alpha}$-dependent pathway, whereas D_3R activates ERK by a mechanism that depends on $G_{\beta\gamma}$.[26]

In addition to the canonical signaling via monomeric GPCRs, several reports indicate that the interaction among GPCRs (forming dimers and higher-order entities) can influence GPCR signaling both quantitatively (i.e., heteromers exhibit increased affinity for the ligand) and qualitatively (i.e., heteromers use alternative signaling pathways).[28,29] In particular, D_3R functionally interacts with adenosine A_{2a} receptors ($A_{2a}R$),[30] D_1R,[31,32] D_2R,[33] and nicotinic acetylcholine receptors.[34] The D_3R-D_1R interaction increases the affinity of D_1R for its ligand after D_3R activation, whereas no change is observed in the D_3R affinity to its ligand.[31] The activation of $A_{2a}R$ in the D_3R-$A_{2a}R$ macromolecular complex reduces both the affinity of D_3R for DA and the D_3R-mediated inhibition of adenylate cyclase, whereas $A_{2a}R$ signaling is inhibited by D_3R activation.[30] Moreover, D_3R interacts with its own alternatively spliced variant, named D_3nf, as demonstrated by co-immunoprecipitation and colocalization experiments.[35–37] The expression of D_3nf reduces the ligand-binding capacity of D_3R, possibly due to D_3R-D_3nf mislocalization from the plasma membrane to intracellular compartments.[37]

The D_3R gene contains 6 exons and 5 introns and produces at least 7 distinct alternatively spliced variants including the full-length D_3R, a shorter receptor isoform (D_3S) lacking 21 amino acids within the third intracellular loop (IL_3), and the truncated isoform D_3nf lacking transmembrane-spanning domains 6 and 7 by a premature stop codon.[38] Interestingly, D_3R and D_3S bind DA with high affinity, whereas the 5 additional D_3R variants including D_3nf do not bind DA, but they may regulate receptor dimerization.[39] Overall, this evidence supports the idea that receptor-receptor interactions at neuronal surface modulate D_3R signaling.

Multiple D_3R-associated pathways have been described in neurons.[22,27] Indeed, D_3R can modulate neural activity by acting on neurotransmitter receptors via PKA, as well as on ion channels via $G_{\alpha i/o}$, as demonstrated by electrophysiological and imaging studies in isolated neurons and brain slices from rodents.[17,40–42] These studies, however, did not clarify whether D_3R effects are mediated by monomeric-canonical pathways or by heteromeric receptors. In medium spiny neurons (MSNs) of the striatum, D_3R modulates Ca^{2+} channels via PLC and PP2B[43] and can also activate the Akt/mTOR/p70S6/4E-BP1 pathway,[44] which play a key role in protein synthesis, synaptic plasticity, and memory. Also, D_3R suppresses synaptic transmission by reducing $GABA_A$ receptor current via PKA-mediated endocytosis of $GABA_A$ receptors in the nucleus accumbens[40] and in CA1 pyramidal neurons from the hippocampus.[41] Actions of D_3R in the brain might be region specific[7] and may be quantitative and qualitatively modified under disease states, as discussed in the following sections.

D_3R Signaling in Brain Diseases

Essential tremor

A critical insight into the role of D_3R signaling in brain dysfunction was provided by studying the D_3R Ser9Gly polymorphism in patients with essential tremor, the most commonly inherited movement disorder. In essential tremor, a subtle change in the D_3R sequence (Ser9Gly polymorphism) increases D_3R coupling to both the inhibition of cAMP formation and the activation of the MAPK pathway (Figure 1A). The enhanced D_3R function, associated with the Gly-9 variant, was linked with the risk and age at onset for essential tremor.[45] Further supporting the primary role of the gain of function of D_3R in pathological DA signaling, the D_3R-Gly-9 variant has been associated with impulsive behavior in PD, the second most prevalent neurodegenerative disease. Thus, these data suggest that an enhanced D_3R signaling could impair reward-risk assessment in the mesolimbic system and contribute to the development of impulsive behavior, in carriers of this genotype. Overall, these data suggest that a gain of function in two D_3R signaling pathways significantly contributes to brain dysfunction. It is noteworthy that the association of the D_3R Ser9Gly polymorphism with essential

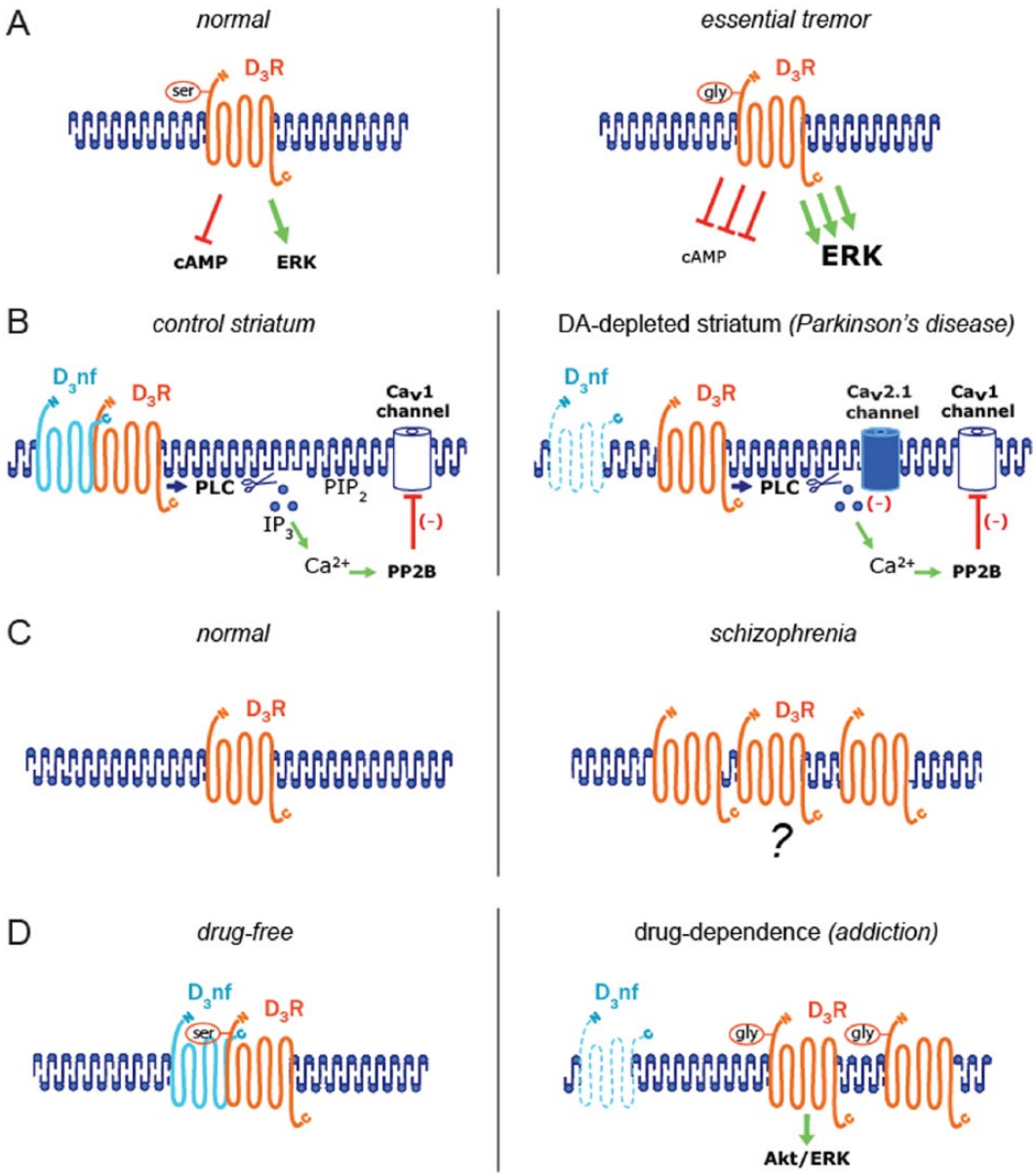

Figure 1. D_3R in brain diseases. Based on recent reports, all models show molecular D_3R changes/variants associated with specific pathological conditions. (A) The D_3R-Gly-9 variant has been linked with the risk and age at onset for essential tremor. Relative to the D_3R-Ser-9 variant, the D_3R-Gly-9 is more efficient in both the inhibition of cAMP formation and the activation of ERK. (B) Under normal DA levels (control striatum), D_3R interacts with D_3nf and modulates Ca_V1 (L-type) channels through a PLC/IP_3/Ca^{2+}/PP2B signaling pathway, whereas after chronic DA depletion (as seen in PD), D_3R-D_3nf interaction is reduced as a result of the D_3nf downregulation. Membrane redistribution of the "D_3nf-free" D_3R may situate it near the $Ca_V2.1$ channels, thus allowing channels to sense phosphatidylinositol-4,5-biphosphate depletion and reduce their opening after PLC activation by D_3R. (C) Some postmortem studies suggest that brain D_3R levels may be elevated in schizophrenia. (D) Long-lasting neuroadaptations following chronic drug use include an enhancement in both D_3R expression and D_3R-dependent signaling (Akt and ERK activation). Also, the functionally enhanced D_3R-Gly-9 variant has been associated with drug-dependence. D_3R indicates D_3 receptor; DA, dopamine; ERK, extracellular signal–regulated kinase; PLC, phospholipase C.

tremor has been found to be significant in American, French,[45] and Spanish[46] but not in Italian[47] or Asian[48] populations.

Parkinson's disease

Supporting the idea that a gain of function of D_3R can impair brain physiology, recent evidence suggests that D_3R activity is enhanced in PD,[43,49] a neurodegenerative disease characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta. Loss of dopaminergic neurons is accompanied by a dramatic reduction in DA levels in the striatum.[50–52] Several reports have shown that DA depletion induces compensatory mechanisms (e.g., an increase in the number and the affinity of receptors), similar to that observed after ligand depletion in other receptor-ligand systems.[53,54] For instance, positron emission tomography using [^{11}C]raclopride has shown an increased density of D_2-class receptors in the putamen nucleus in PD.[55] Also, biochemical, electrophysiological,

and behavioral data have shown that DA depletion increases the sensitivity (supersensitivity) of D_2-class receptors in animals models of PD (e.g., DA depletion induced by reserpine,[56] α-methyl-*p*-tyrosine,[57] 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP],[58] and 6-hydroxydopamine [6-OHDA]).[49,59,60] In the 6-OHDA model, electrophysiological recordings in striatal MSNs have shown that D_3R signaling contributes to the D_2-class supersensitivity,[43,49] thus suggesting that DA depletion may increase D_3R expression and activity.

The enhancement of D_3R signaling by DA depletion may be reflecting changes in pharmacologic parameters (potency, affinity, and receptor number). At present, however, there is no consensus on which pharmacologic parameter is mainly affected.[10,11,61–64] Although unilateral lesion of the substantia nigra with 6-OHDA increases the potency of the selective D_3R agonist 7-OH-DPAT in striatum[65] and cerebellum,[66] pharmacologic depletion of catecholamines increases the affinity of putative D_3 sites with no increase in the total number of sites in striatum.[67] An alternative mechanism underlying the enhancement of D_3R signaling following DA depletion may rely on a reduced interaction of D_3R with its regulatory splice variant D_3nf. Indeed, D_3nf protein levels were found to be reduced in striatal homogenates from 6-OHDA lesioned rats.[43] In line with a reduction in D_3R-D_3nf interaction after DA depletion, the D_3R/D_3nf mRNA ratio increases when D_3R is pharmacologically blocked (i.e., mimicking "hypodopaminergic" states).[68]

According to recent reports, qualitative changes in D_3R signaling may also contribute to the pathophysiology of PD. In particular, a switch in D_3R signaling has been described in striatal MSNs and striatonigral terminals of hemiparkinsonian rats,[43,69] a PD model based on the 6-OHDA–mediated lesion of substantia nigra pars compacta in one hemisphere. In striatal MSNs, while physiological D_3R signaling inhibits Ca_V1 (L-type) Ca^{2+} channels by PP2B activation, D_3R additionally modulates $Ca_V2.1$ (P/Q-type) channels via the hydrolysis of phosphatidylinositol-4,5-biphosphate (PIP_2) after DA depletion (Figure 1B). This $Ca_V2.1$ modulation by the D_3R-PIP_2 pathway is not detected in neurons from control animals, thus suggesting that this pathway is induced by DA depletion.[43] Because $Ca_V2.1$ channels mediate γ-aminobutyric acid (GABA) release from the terminals of striatal neurons, the PIP_2-dependent D_3R signaling may reduce GABA release and affect synaptic transmission between striatal neurons after DA depletion.

In striatonigral terminals, the switch in D_3R signaling is related to the D_3R-D_1R interaction.[69] Although D_3R activation potentiates both the stimulation of GABA release and the production of cAMP by D_1R in terminals from the control (nonlesioned) hemisphere, D_3R inhibited both D_1R actions in terminals from the denervated hemisphere.[69] Overall, data from MSNs and striatonigral terminals support the notion that DA depletion switches D_3R signaling in basal ganglia.

L-DOPA, the gold standard treatment for PD, reduces parkinsonian symptoms but in later stages induces dyskinesia, a side effect characterized by hyperkinetic involuntary movements.[70] Notably, L-DOPA increases D_3R expression in the caudate/putamen nuclei and striatonigral MSNs.[62,63,71–73] Recent evidence indicates that D_3R plays a major role in L-DOPA–induced dyskinesia, which can be reduced by blocking D_3R[73–75] and D_1R[75] in parkinsonian models. Interestingly, in MPTP parkinsonian primates, a partial block of D_3R (using a partial agonist for D_3R) reduces dyskinesia without affecting the therapeutic effects of L-DOPA, whereas no recovery of motor disturbances is observed if D_3R is entirely blocked.[74] These data emphasize that D_3R mediates different actions, participating in both dyskinesia and motor recovery following L-DOPA treatment, thus highlighting the importance of fine-tuning D_3R signals in PD-diseased brain.

Schizophrenia

Dopamine signaling is the main target in schizophrenia, a mental disorder characterized by hallucinations, bizarre delusions, and negative symptoms such as lack of motivation, reduction in spontaneous speech, and social withdrawal. Indeed, first-generation antipsychotics (e.g., haloperidol and chlorpromazine) bind to D_2-class receptors.[76,77] Since its cloning in 1990, D_3R emerged as a potential target for antipsychotics.[11,78] Although it is controversial whether D_3R levels are affected in schizophrenia,[79] postmortem studies suggest that D_3R levels may be elevated in people with schizophrenia who are off antipsychotics (Figure 1C).[4] In contrast, the parietal cortex of postmortem tissue from long-term hospitalized patients with chronic schizophrenia expresses low D_3R levels.[80] These data suggest that long-term antipsychotic medication may modify brain D_3R expression in schizophrenia. Interestingly, low D_3R mRNA levels in patients with schizophrenia have been associated with an enhanced D_3nf-specific splicing of D_3R pre-mRNA.[81]

Addiction

Chronic drug use induces long-lasting neuroadaptations which has been associated with dopaminergic abnormalities. Although studies of D_3R expression in human cocaine-dependent subjects have had conflicting results,[39] the use of the D_3R-preferring radioligand [^{11}C](+)PHNO has shown higher number of available D_3R in the substantia nigra, hypothalamus, and amygdala of cocaine addicts, compared with healthy controls[82] (Figure 1D). Notably, substantia nigra D_3R levels correlated with years of cocaine use.[82] Consistent with the idea that chronic cocaine exposure leads to adaptive increases in D_3R expression, a 6-fold increase in D_3R mRNA levels was found in the nucleus accumbens of cocaine overdose victims, as compared with age-matched and drug-free control subjects.[83] Similarly, an increased [^{11}C](+)PHNO binding, reflecting

higher D_3R levels, has also been observed in the substantia nigra of methamphetamine users,[84] as well as in hypothalamus of alcohol-dependent patients.[85] According to the heightened D_3R signaling in drug users, the functionally enhanced D_3R-Gly-9 variant was associated with the development of early-onset heroin dependence in Chinese population (Figure 1D).[86]

Studies in vitro and in animal models support the idea that drug use induces D_3R signaling abnormalities. In vitro, cocaine increases dendritic arborization and soma area in cultured dopaminergic neurons from mouse via D_3R-dependent activation of ERK and Akt.[87] In rats, it has been suggested that D_3R play an important role in mediating nicotine's effects on the brain.[88] In both adolescents and adult rats, nicotine upregulates D_3R but reduces D_3nf mRNA levels in the nucleus accumbens, thus increasing the D_3R/D_3nf ratio (Figure 1D).[88] It has also been proposed that D_3R and its alternatively spliced isoform D_3nf may play a role in cocaine addiction (a risk factor for schizophrenia) and behavioral sensitization (the progressive and long-lasting augmentation of certain behaviors following repetitive stimulant drug administration).[39] Supporting this idea, D_3R has been found to enhance the reinforcing effect of cocaine,[89] and blockade of D_3Rs inhibits cocaine's rewarding effects and relapse to drug-seeking behavior in rats.[90] A cornerstone study demonstrated the crucial role of D_3R signaling in the motivation to take drug induced by drug-related cues.[91] In this study, rats were trained to self-administer cocaine by a lever pressing. Next, progressively, a light stimulus was associated with cocaine self-administration. Light stimulus, which then becomes the conditioned stimulus, gains reinforcing properties and finally maintains drug-seeking behavior even without drug delivery. Remarkably, the selective D_3R partial agonist BP897 dose-dependently reduced cue-induced cocaine-seeking behavior in rats trained under this schedule of reinforcement.[91]

Overall, multiple lines of evidence support the idea that D_3R plays a central role in addiction, thus driving a need to develop novel pharmacologic agents targeting this receptor. Since 2005, 110 patents or patent applications have been published on original compounds with D_3R selectivity.[79] In contrast to the initial lack of D_3R-selective drugs, a list of compounds with relative high selectivity for D_3R currently includes the following: BP 897, SB-277011A, S33084, ABT-925, GSK598809, and F17141.[79] In particular, GSK598809 has proven to transiently alleviate craving in smokers after overnight abstinence, thus providing the first clinical evidence for a usefulness of D_3R antagonist for the treatment of addiction.[92]

Emerging perspectives for improving the treatment of brain disorders focus on the understanding of pathophysiology mechanisms to identify disease pathways, which will finally facilitate the selection of therapeutic targets.[93] In DA-related brain diseases, quantitative and qualitative changes in D_3R signaling may be reflecting direct effects on basic mechanisms that control D_3R activity at the cell surface, such as desensitization and internalization. A better understanding of these basic mechanisms in both the healthy and the diseased brain is likely to reveal new molecular targets for therapeutic.

Modulation of D_3R Signaling

Dopamine receptors are modulated by several mechanisms, such as homologous and heterologous desensitization, a reversible reduction in signal transduction after acute activation. Experimental and theoretical data suggest that D_3R desensitization (tolerance) can develop after its structural rearrangement following agonist binding, and that the magnitude of the second D_3R response can be reduced by 60% compared with the first response.[94] Also, D_3R can be desensitized following phosphorylation by both PKC[95] and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII).[96] Both PKC and CaMKII phosphorylate the 229-serine residue at the IL_3, a region that exhibits high divergence between D_2R and D_3R, and may play a crucial role in the unique signaling signatures of each receptor subtype.[97] Downregulation of D_3R signaling by CaMKII depends on intracellular Ca^{2+} levels and, therefore, is associated with neuronal activity.[96] Importantly, the CaMKII-mediated inhibition of D_3R is not observed after DA depletion.[69]

Although D_3R undergoes limited agonist-induced internalization,[98] D_1R-D_3R heterodimers can be internalized in response to the paired stimulation of both D_1R and D_3R via a β-arrestin–dependent mechanism in human embryonic kidney 293 cells.[32] Also, a recent report showed that PKC-mediated phosphorylation of D_3R can induce clathrin-mediated D_3R endocytosis and lysosomal D_3R degradation.[95] Similarly, via caveolin/clathrin-mediated D_3R internalization, dysbindin-1 reduces the magnitude and potency of DA-induced cAMP production and phosphorylation of ERK1/2 and Akt.[99] Notably, dysbindin-1 is a candidate gene for schizophrenia. Palmitoylation is another posttranslational modification that can regulate D_3R activity. Compared with D_2R, D_3R undergoes a more extensive palmitoylation on its cysteine residues at the carboxyl terminus tail and, importantly, palmitoylation was found to be essential for cell surface expression, PKC-mediated endocytosis, agonist affinity, and agonist-induced tolerance of D_3R.[100] Also, DA receptor–interacting proteins, such as AIP1 (ALG-2 interacting protein 1) could be substantial in D_3R stability and trafficking.[101]

Concluding Remarks and Perspectives

In the past few years, great progress has been made in understanding D_3R signaling in heterologous systems. Although neural D_3R signaling is incompletely understood, a growing body of evidence indicates that changes in D_3R-induced pathways contribute to several neurological disorders. Future studies may delineate the relative contribution of monomeric-canonical versus heteomeric D_3R signaling to pathological brain states. Another intriguing aspect that remains to be clarified is whether

sex-specific differences influence D_3R signaling in the diseased brain, as suggested by the association of the Gly allele of the D_3R Ser9Gly polymorphism with schizophrenia in female but not male patients.[102,103]

According to several reports, changes in both D_3R signaling and DA levels are common factors in PD and schizophrenia. Similarly, quantitative and qualitative changes in D_3R signaling develop after DA depletion in the 6-OHDA hemiparkinsonian model.[43,69] However, it remains to be clarified whether the altered D_3R signaling is reflecting an adaptive mechanism to compensate changes in DA levels. Some properties of D_3R strongly suggest that D_3R is the main detector of changes in extracellular DA concentration and, consequently, D_3R signaling may be mainly affected by pathological changes in DA levels, as those observed in PD and schizophrenia. In particular, presynaptic and postsynaptic sites can contain D_3R,[104,105] which exhibits high affinity for DA (~25 nM).[11,97,106] Considering basal extracellular (5-10 nM) and synaptic (50 nM) concentrations of DA,[107–110] a fraction of D_3R may be constitutively activated, thus playing a crucial role in both tonic and phasic DA signaling.[67] Interestingly, the occupancy of D_3R by DA is not completely abolished by catecholamine depletion using reserpine,[67,111] suggesting that even under severe reduction in DA level, D_3R is partially activated and able to perceive changes in DA concentration. Thus, a tempting but simplified model for PD may rely on an enhancement in striatal D_3R signaling as part of an adaptive mechanism to compensate the dramatic reduction in DA levels.

Although there is a clear role of D_3R signaling in drug-seeking behaviors and relapse in animal models, it is uncertain whether these findings translate to humans. Studies in humans could evaluate the significance of D_3R signaling in neurological diseases. However, direct evidence of molecular mechanisms in the human brain has been elusive, primarily due to methodological limitations. Notably, novel approaches allow the study of functional responses, including receptor signaling, in postmortem human tissue.[112,113] Using these novel approaches directly in human brain tissue, future studies will help to identify mechanisms that underlie pathological D_3R signaling, either induced by quantitative or qualitative changes.

In summary, many brain disorders are characterized by perturbations in D_3R signaling. A better understanding of how D_3R activity can be regulated may uncover causal factors and may even suggest novel treatments for DA-related diseases. In particular, elucidating the mechanisms that control expression, desensitization, and alternative splicing of D_3R may identify novel opportunities to modulate D_3R signaling.

Author Contributions

GAP: Wrote the first draft of the manuscript, developed the structure and arguments for the paper, made critical revisions, reviewed and approved the final manuscript.

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