Dopamine D3 Receptor Heteromerization

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The dopamine (DA) D3 receptor (D3R) plays a pivotal role in the control of several functions, including motor activity, rewarding and motivating behavior and several aspects of cognitive functions. Recently, it has been reported that the D3R is also involved in the regulation of neuronal development, in promoting structural plasticity and in triggering key intracellular events with neuroprotective potential. A new role for D3R-dependent neurotransmission has thus been proposed both in preserving DA neuron homeostasis in physiological conditions and in preventing pathological alterations that may lead to neurodegeneration. Interestingly, there is evidence that nicotinic acetylcholine receptors (nAChR) located on DA neurons also provide neurotrophic support to DA neurons, an effect requiring functional D3R and suggesting the existence of a positive cross-talk between these receptor systems. Increasing evidence suggests that, as with the majority of G protein-coupled receptors (GPCR), the D3R directly interacts with other receptors to form new receptor heteromers with unique functional and pharmacological properties. Among them, we recently identified a receptor heteromer containing the nAChR and the D3R as the molecular effector of nicotine-mediated neurotrophic effects.

Keywords: dopamine ; neuroprotection ; neuroplasticity ; heteromer ; GPCR

1. Introduction

Dopamine (DA), one of the main neurotransmitters in the central nervous system (CNS), controls several physiological functions related to locomotor activity, learning and memory, cognition, attention, affective behavior, motivation and reward and endocrine regulation. DA also modulates a variety of functions in the periphery, including catecholamine release, cardiovascular function, renal function, vascular tone, hormone secretion and gastrointestinal motility [1].

DA exerts its effects by binding to and activating specific G protein-coupled receptors (GPCR) that represent the largest superfamily of cell surface receptors targeted by different classes of drugs. In mammals, five subtypes of DA receptors have been identified, labeled D1 through D5. These receptors are classified into two families based on structural, pharmacological and signaling properties. The D1-like family consists of D1 and D5 receptor subtypes (D1R and D5R), while the D2-like family comprises the D2, D3 and D4 receptors (D2R, D3R and D4R). Each receptor displays unique properties, including affinity to DA, and shows a peculiar neuronal distribution [1]. Interestingly, increasing evidence suggests that DA receptors can diversify and amplify their repertoire of signaling by forming homo- and hetero-dimers, a property typically shared by the GPCR family [2] that greatly increases their heterogeneity.

The relevance of DA is such that dysfunctions of DA transmission and receptor signaling are implicated in many neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD), schizophrenia, psychosis, Tourette Syndrome (TS) and depression, and in neurodegenerative diseases, including Parkinson's disease (PD), Huntington disease (HD) and multiple sclerosis (MS) [3]. Moreover, aberrant DA transmission underlies drug addiction [4]. On this line, modulation of DA transmission can control the symptoms of many diseases and DA receptors are important targets for drug discovery.

The D3R is expressed on DA neurons, both at the somatodendritic level and at synaptic terminals, in the substantia nigra (SN) and ventral tegmental area (VTA), as well as in the ventral striatum [5][6][7]. D3R are also found in the islands of Calleja and cerebellum [6][7] and, at low density, in medium spiny neurons (MSN) of the ventral [8] and dorsal striatum [7][9][10][11]. Activation of D3R modulates a variety of functions, including rewarding and motivating behavior [12], some features of cognitive functions [13] and locomotor activity [14]. Pre-synaptic D3R have been classically considered autoreceptors inhibiting both DA neuron firing and DA release [9][15][16]. Interestingly, D3R is characterized by high affinity for DA (420-fold higher than that of D2R); moreover, unlike D2R, small changes in the number or function of D3R severely affect synaptic transmission, a characteristic suggesting that this receptor could play a relevant role as a modulator of physiological dopaminergic function [13]. Moreover, there is substantial evidence that the D3R exerts neurotrophic, neuroprotective and

neurorestorative effects on DA neurons. On this basis, a new and essential role for D3R-mediated neurotransmission has been suggested, both in preserving DA neuron homeostasis in physiological conditions and in counteracting neuronal alterations prodromal to neurodegeneration [17][18][19][20][21][22][23].

2. D3 Receptor Heteromerization

As with the majority of GPCR, DA receptors were classically considered to operate as monomers that interact with G proteins to modulate specific effectors. However, in the last two decades, several GPCRs have been shown to directly interact with other receptors to form homodimers, heterodimers or high-order oligomers [24] and, among them, DA receptors appear to be highly promiscuous proteins able to form heterodimers. Dimerization can involve the extracellular loops, as in the case of the m3 muscarinic receptor dimers [25], the transmembrane helices, as was described for the β2-adrenergic receptor dimerization [26], and the intracellular loops, as in the case of the $GABA_B$ receptor dimerization [27], and both covalent [28] and non-covalent bonds can structurally stabilize heterodimers. Although the physiological function of heterodimers is not completely defined, it is well known that receptor heterodimerization may modify the ligand binding profile, the signaling transduction and the cellular trafficking of interacting receptors. The formation of receptor heterodimers may give rise to novel receptors units with unique pharmacological, signaling and trafficking properties that are different from those of their monomeric counterparts [29][30]. Intriguingly, heterodimers may be involved in cellular processes underlying several human disorders, not only in the CNS, but also in peripheral areas (for a review, see References [31][32]). Therefore, targeting specific GPCR heterodimers may represent a promising alternative to conventional drug development approaches.

The D3R may form heterodimers with other DA receptor subtypes, such as the D1R and the D2R [14][29][33] (Table 1). In particular, heterodimerization of D1R and D3R has been demonstrated in the striatum and nucleus accumbens (NAc) [33]. From a functional point of view, D1R-D3R heterodimerization increases the affinity of DA for the D1R and the potency of DA in activating AC via the D1R and impairs agonist-induced D1R internalization [14][33], suggesting that, within the D1R-D3R heterodimer, D1R-mediated transmission is likely potentiated by the D3R. Moreover, a synergistic cross-talk between D1R and D3R agonists in activating Erk1/2 signaling has also been described [34]. More recently, it has been reported that the simultaneous activation of D1R and D3R within the D1R-D3R heteromer results in G protein-independent, ß-arrestin-dependent Erk1/2 and Akt activation both in the NAc and in transfected cells [35]. The characteristics and localization of the D1R-D3R heterodimer in the striatum suggest that this complex could be the functional unit mediating the development of levodopa (L-DOPA)-induced dyskinesia in PD models [31][36][37][38][39], thus providing a unifying mechanism for D1R- [31][40][41] and D3R-mediated alterations in the development of these side effects of L-DOPA therapy.

Table 1. Heteromeric complexes containing the D3R.

Receptor Complex	Detection Method	Suggested Relevance
DA receptors		
D1R–D3R	FRET and BRET in transfected cell lines [14][33]	Parkinson's disease [14][33][41]
	CO-IP in transfected cell lines and rat striatum [33]	Addiction [35][41]
	PLA in rat and monkey striatum [42]	LID [33][35][41][42]
D2R–D3R	CO-IP in transfected cell lines [29]	Parkinson's disease [30][43]
		Schizophrenia [30]
Other GPCRs		
D3R–A2AR	FRET in transfected cell lines [44]	Parkinson's disease [44]
		Schizophrenia [44]
D3R–MT1R/MT2R	BRET in transfected cell lines [45]	Intraocular pressure [45]
	PLA in human non-pigmented ciliary body epithelial cells [45]	
Ion Channels		

Receptor Complex	Detection Method	Suggested Relevance
D3R-nAChR	BRET in transfected cell lines [20]	Parkinson's disease [19][20]
	PLA in mouse primary mesencephalic DA neurons and midbrain sections [20], and in hiPSC-derived DA neurons [19]	Addiction [20]

In the CNS, co-localization of D2R and D3R has been reported both in DA neuron synaptic terminals, and in post synaptic dopaminergic projections, mostly in the globus pallidus and NAc [6], and indication of physical interaction between these receptors has been provided [29][43]. Many drugs, including D2-like receptor agonists, show high potency and efficacy at the D2R-D3R heterodimer, suggesting that this receptor complex could potentially play a role in the pathophysiology and treatment of several brain diseases [43]. Beside its interaction with DA receptor subtypes, the D3R may also form complexes with other GPCRs (Table 1). Specifically, it has been reported that adenosine A2AR and D3R interact to form the A2AR-D3R heterodimer, in which the A2AR antagonistically modulates both the affinity and the signaling of the D3R [44]. Moreover, on the basis of pharmacological and functional studies, an interaction has been proposed for the neurotensin NTS2 receptor and D3R [46], and for the endothelin ETB receptor and D3R [47], even if the existence of these heterodimers has not been conclusively demonstrated. More recently, heterodimers containing the D3R and either the MT1 or MT2 melatonin receptors have been detected in both transfected cells and in human eye postmortem tissues, where they are thought to regulate intraocular pressure. This heterodimerization abolishes D3R-Gi coupling and signaling to the Erk1/2 pathway [45]. Beside GPCRs, other structurally and functionally different classes of receptors, as ion channel receptors, may interact with D3R [48] (Table 1). In particular, we recently reported a direct interaction of D3R with the nicotinic acetylcholine receptor (nAChR) [20].

Taken together, these findings indicate that the pharmacological and functional characteristics of the D3R may be specifically modulated in different brain areas or in pathological conditions by interactions with other membrane receptors.

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