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Current drug treatments targeting dopamine D3 receptor

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ABSTRACT

Dopamine receptors (DR) have been extensively studied, but only in recent years they became object of investigation to elucidate the specific role of different subtypes (D1R, D2R, D3R, D4R, D5R) in neural transmission and circuitry. D1-like receptors (D1R and D5R) and D2-like receptors (D2R, D2R and D4R) differ in signal transduction, binding profile, localization in the central nervous system and physiological effects. D3R is involved in a number of pathological conditions, including schizophrenia, Parkinson's disease, addiction, anxiety, depression and glaucoma. Development of selective D3R ligands has been so far challenging, due to the high sequence identity and homology shared by D2R and D3R. As a consequence, despite a rational design of selective DR ligands has been carried out, none of currently available medicines selectively target a given D2-like receptor subtype. The availability of the D3R ligand [^{11}C]-(+)-PHNO for positron emission tomography studies in animal models as well as in humans, allows researchers to estimate the expression of D3R in vivo; displacement of [^{11}C]-(+)-PHNO binding by concurrent drug treatments is used to estimate the in vivo occupancy of D3R. Here we provide an overview of studies indicating D3R as a target for pharmacological therapy, and a review of market approved drugs endowed with significant affinity at D3R that are used to treat disorders where D3R plays a relevant role.

1. Introduction

Dopamine (DA) activity in the central nervous system (CNS) is mediated by five G protein-coupled receptors grouped in two classes, the D1-like receptors (D1R and D5R) and the D2-like receptors (D2R, DR and D4R), which differ in their signal transduction, binding profile and physiological effects (Seeman & Van Tol, 1994; Beaulieu & Gainetdinov, 2011). D1-like receptors are principally coupled to stimulatory G_s-proteins and enhance the activity of adenylyl cyclase, whereas D2-like receptors are primarily coupled to inhibitory G_i-proteins and suppress the activity of adenylyl cyclase (Beaulieu & Gainetdinov, 2011). D2-like receptors represent the most relevant class in the pathophysiology of neurological and psychiatric disorders. However, while the role of the D2R subtype has been extensively studied in several neuropsychiatric diseases such as schizophrenia, Parkinson's disease (PD) and addiction, the role of D3R and D4R is still under investigation. The primary sequence of D3R is close to that of the D2R and, to a lesser extent, of D4R. Human D2R and D3R are highly homologous (Sibley & Monsma, 1992), sharing 78% of sequence identity in the transmembrane domains, including the binding site (Shi & Javitch, 2002). This sequence identity has introduced difficulties in the design of selective ligands. The initial lack of selective pharmacological tools delayed the elucidation of the role of D3R and raised even questions about the physiological significance of the D3R. From the beginning, attention has been attracted to the restricted distribution of the D3R in the brain. Indeed, the D3R subtype shows a distinct distribution with high levels in the limbic system, including the islands of Calleja, the nucleus accumbens and the olfactory tubercles, brain areas critically involved in the regulation of motivation, reward and cognitive functions (Levesque et al., 1992; Landwehrmeyer et al., 1993). Available evidence indicates that D3R functions, at least in part, as an autoreceptor (i.e. a presynaptic receptor), with inhibitory effects on DA impulse flow and DA release (Gobert et al., 1995; Tepper et al., 1997). It has been shown that D3R-null mice ($D3R^{-/-}$) have extracellular levels of DA twice as high as their wild-type (WT) littermates, consistent with the presynaptic location mentioned above, where D3R would inhibit DA release (Koeltzow et al., 1998; Joseph et al., 2002).

As mentioned above, D3R activates Gαi/o proteins to inhibit cAMP production and decrease protein kinase A (PKA) activity (Robinson & Caron, 1997; Missale et al., 1998), but D3R also regulates other intracellular pathways, including the extracellular signal regulated kinase 1/2 and Akt cascades through G protein-dependent and/or independent

Abbreviations: 5-HT, 5-hydroxytryptamine; 7-OH-DPAT, 7-hydroxy-N,N-di-n-propyl-2-aminotetralin; [^{11}C]-(+)-PHNO, [^{11}C]-(+)-propyl-hexahydro-naphtho-oxazin; AH, aqueous humor; BDNF, Brain-Derived Neurotrophic Factor; CNS, central nervous system; DA, dopamine; DR, dopamine receptor; $D2_LR$, dopamine receptor 2 long form splice variant; $D2_SR$, dopamine receptor 2 short form splice variant; $D3R^{-/-}$, dopamine receptor 3 null mice; EMA, European Medicines Agency; FDA, Food and Drug Administration; IOP, intraocular pressure; L-DOPA, L-3,4-dihydroxyphenylalanine; LID, L-DOPA-induced dyskinesia; NOR, novel object recognition; PD, Parkinson's disease; PET, positron emission tomography; WT, wild type; SAR, structure activity relationship; SUD, Substance Use Disorder.

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mechanism, this latter involves β-arrestin (Cussac et al., 1999; Collo et al., 2008, 2012). The ability of ligands to differentially affect signaling through these pathways, referred to as biased agonism or functional selectivity, may be therapeutically exploitable. Recently, ligands that are devoid of D2R-mediated Gαi/o protein signaling, but behave as partial agonists for D2R/β-arrestin interactions, have been found to exert a number of effects in preclinical models of schizophrenia-like behavior while causing lower catalepsy (Park et al., 2016). To the best of our knowledge, biased agonism of D3R selective antipsychotics has not yet been documented, but we may predict that, as reported for D2R, it could support fewer side effects and greater therapeutic efficacy for treating conditions such as schizophrenia.

As the majority of G protein-coupled receptors, D3R forms both homo- and heteromers (recently reviewed by Maggio et al., 2015). Heteromers have been reported with D2R (Scarselli et al., 2001), D1R (Fiorentini et al., 2008; Marcellino et al., 2008), and also with the adenosine receptor A2AR (Torvinen et al., 2005). DR heteromers exhibit pharmacological and cell signaling properties distinct from their constituent receptors (Lee et al., 2004). Binding to D2R–D3R heteromers may account, at least in part, for the antipsychotic effect of aripiprazole and N-desmethylclozapine (Novi et al., 2007). In fact, while these two compounds behave as partial agonists at D2R, they behave as antagonists at the D2R–D3R heteromers. On the other hand, activation of D1R–D3R heteromers is putatively involved in L-DOPA-induced dyskinesia in Parkinson's disease (Ferré et al., 2010). The D1R–D3R heteromers display higher affinity for DA compared to D1R alone, which results in an increase of G protein signaling and cAMP accumulation. Functional selectivity/biased agonism may be also related to the formation of homo- and heteromers. In this respect, it has been shown that heterodimerization of D3R with D1R abolishes agonist-induced D1R internalization induced by D1R agonists while enables internalization of the D1R/D3R complex in response to the paired D1R and D3R stimulation, a β-arrestin-dependent mechanism (Fiorentini et al., 2008). Most of the evidence supporting the formation of GPCR dimers and oligomers comes from heterologous systems, therefore the existence of such signaling complexes in the native context as well as their biological significance have been questioned (Lambert & Javitch, 2014; Frederick et al., 2015), being extremely difficult to dissociate downstream crosstalk from the actual physical interaction of two receptors in a signaling complex (Han et al., 2009; Urizar et al., 2011; Frederick et al., 2015).

Pharmacological, genetic and human *post-mortem* studies have demonstrated the central role of D3R in the pathophysiology and treatment of schizophrenia, drug addiction, PD and depressive disorders, as discussed below. Addiction still represents the main research field with potential clinical application for D3R ligands. However, recent data have underscored the potential use of D3R ligands in diseases not previously taken into account, such as glaucoma. A number of D3R selective compounds have been developed and further helped the study of D3R location and function. A patent survey published in 2013 reports more than 110 submitted patent applications concerning D3R selective ligands (Sokoloff et al., 2013); however none of them has yet reached clinical approval, mainly because they did not fulfill requirements of pharmacokinetics and/or safety. On the other hand, thanks to current experimental tools, some approved drugs, used since long time and believed to act through D2R binding, have been reviewed and are now considered to act, at least in part, through D3R. Here, we first review the relevance of D3R in several patho-physiological conditions; thereafter, we discuss the determinants of D3R selectivity and the assessment of D3R occupancy in vivo through positron emission tomography (PET) studies; finally, we summarize the data supporting D3R-related clinical benefits for already market approved drugs. DA and DR exert several relevant functions also at the periphery, particularly at the level of the cardiovascular system and the kidney, involved in regulation of blood pressure, sodium balance, and renal and adrenal functions (for reviews see Missale et al., 1998; Choi et al., 2015; Zhang & Harris, 2015). A number of recent papers have investigated the D2R like receptors in the kidney in animal models. However, except DA itself, which can be used to treat shock, no drugs acting at D3R are yet approved with indications for cardiovascular or renal diseases. Therefore, the role of D3R at the periphery will not be further discussed here. We conclude that, based on currently available data, efforts in drug research and development are warranted to obtain novel selective D3R ligands endowed with adequate safety profile for clinical use in humans.

2. Diseases involving D3 receptor transmission

2.1. Schizophrenia

Schizophrenia is a disease affecting about 1% of population worldwide, characterized by abnormalities of behavior and thinking with inability to understand reality. The first-line pharmacological treatment for schizophrenia is represented by antipsychotics. Since long time, antipsychotics were considered D2R antagonists (Kapur & Mamo, 2003), and later on reconsidered as D2R-like antagonist, to indicate their poorly selective binding at D2R, D3R and D4R. None of the antipsychotic currently available act as selective ligand for D3R (Schotte et al., 1996; McCormick et al., 2010); for example, in vivo human PET studies have shown that clozapine, olanzapine and risperidone poorly occupy D3R in the brain of patients with schizophrenia (Graff-Guerrero et al., 2009a; Mizrahi et al., 2011). In contrast with human studies, a number of D3R selective ligands have recently become available for animal studies, where they have been tested, together with genetic deletion, to sort out the role of D3R in schizophrenia. Available drug treatments are effective in improving positive symptoms (delusions, hallucinations), but show limited activity on negative symptoms (anhedonia, social withdrawal, lack of motivation) and on cognitive dysfunction. It has been suggested that blockade of D3R may impact cognitive impairment, but preclinical data are somehow conflicting; indeed, $D3R^{-/-}$ show a better performance than WT in a step-through passive-avoidance paradigm (Micale et al., 2010), while treatment with the D3R selective antagonist SB277011 does not improve the performance in the Morris water maze test (Tanyeri et al., 2015). On the other hand, while overexpression of D3R in striatum does not induce cognitive deficits, it disrupts motivation, suggesting that changes in D3R may be involved in the negative symptoms of schizophrenia (Simpson et al., 2014). Most antipsychotics, either first or second generation, do not display selectivity for D3R over D2R, but few compounds, including aripiprazole, blonanserin and cariprazine, show some D3R selectivity (Table 1). Asenapine has higher affinity at D3R compared to D2R, but displays higher affinity at some 5-hydroxytryptamine (5-HT) receptor subtypes (Shahid et al., 2009). The therapeutic potential of antipsychotics in relation to their interaction with D3R is discussed below.

2.2. Parkinson's disease (PD)

PD is a common degenerative disorder of the aging brain, affecting about 0.3% of the entire population and about 1% of the population older than 60. Clinically, PD is characterized by the triad of tremor at rest, slowness of voluntary movements and rigidity. The main biochemical abnormality in PD is the profound deficit in brain DA levels, primarily, but not exclusively, attributed to the loss in the substantia nigra of dopaminergic neurons projecting to the striatum. Current pharmacological treatment for PD aims at restoring dopaminergic transmission. The L-DOPA therapy remains the gold standard for the symptomatic treatment of PD (Poewe et al., 2010). The therapeutic response to L-DOPA typically consists of two components: the short-duration response, an improvement in motor disability lasting a few hours following the administration of a single dose; the long-duration response, a sustained benefit deriving from prolonged administration lasting many hours or days after discontinuation of treatment.