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Review

Advances and challenges in the search for D_2 and D_3 dopamine receptor-selective compounds

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ABSTRACT

Compounds that target D2-like dopamine receptors (DRs) are currently used as therapeutics for several neuropsychiatric disorders including schizophrenia (antagonists) and Parkinson's disease (agonists). However, as the D_2R and D_3R subtypes are highly homologous, creating compounds with sufficient subtype-selectivity as well as drug-like properties for therapeutic use has proved challenging. This review summarizes the progress that has been made in developing D_2R- or D_3R-selective antagonists and agonists, and also describes the experimental conditions that need to be considered when determining the selectivity of a given compound, as apparent selectivity can vary widely depending on assay conditions. Future advances in this field may take advantage of currently available structural data to target alternative secondary binding sites through creating bivalent or bitopic chemical structures. Alternatively, the use of high-throughput screening techniques to identify novel scaffolds that might bind to the D_2R or D_3R in areas other than the highly conserved orthosteric site, such as allosteric sites, followed by iterative medicinal chemistry will likely lead to exceptionally selective compounds in the future. More selective compounds will provide a better understanding of the normal and pathological functioning of each receptor subtype, as well as offer the potential for improved therapeutics.

1. Introduction

Dopamine receptors (DRs) belong to the G-protein coupled receptor (GPCR) super-family and are divided into two subcategories based on their structure, pharmacology, and signaling preferences. The D1-like receptors, consisting of the D_1R and D_5R, promote intracellular cAMP accumulation through activating Gs or Golf proteins [1]. In contrast, D2-like receptors, consisting of the D_2R, D_3R, and D_4R, activate Gi/o proteins to diminish cAMP levels as well as modulate select ion channels [1]. D_2Rs are also known to signal through G protein-independent pathways involving the recruitment of the scaffolding protein β-arrestin and downstream activation of glycogen synthase kinase-3 (GSK-3) [2,3]. Importantly, aberrant DR signaling is linked to the etiology and/or therapy of a number of neuropsychiatric disorders including Parkinson's disease and schizophrenia (Table 1) [1,2]. Most therapeutics that target these disorders are known to be selective for the D2-like receptor subfamily, however, these drugs, as well as related research tool compounds, lack complete selectivity and can modulate multiple members of this subfamily. This is particularly true for the structurally-related D_2R and D_3R subtypes where most clinically used compounds modulate both of these two receptors to varying degrees [4].

Since the ascertainment of the D_2R as the "antipsychotic receptor" (reviewed in [5]) and the subsequent cloning of the closely related D_3R [6] there has been a drive to understand the physiological and pharmacological differences between the D_2R and D_3R. The D_2R and D_3R share 78% amino acid homology within their transmembrane-spanning domains [7], and are nearly identical in their orthosteric binding sites where the majority of dopaminergic ligands bind [8,9]. Studies using mRNA in situ hybridization and receptor autoradiography [6,10–12] have localized the D_3R mainly to the "limbic" regions of the brain including the ventral striatum, with the highest densities in the Islands of Calleja and the olfactory bulb [13]. The D_2R has a significantly wider distribution throughout the brain, and displays expression levels several orders of magnitude higher than that of the D_3R [6,10], with the highest expression seen in the striatum (particularly the dorsal striatum), nucleus accumbens, and olfactory tubercle. The D_2R and D_3R appear to couple to similar signaling pathways including activation of Gi/o proteins to inhibit cAMP accumulation, Gβ/γ proteins to activate GIRK channels, and the recruitment of β-arrestin following agonist stimulation. Notably, however, when compared in parallel, the strength

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Table 1
Roles of dopamine receptor subtypes with regard to disease and therapeutics.

Receptor subtype	Potential role in disease	Potential therapeutic
D_1R	Cognitive decline (aging/stress)	Agonist [118]
[a]Caudate-putamen, nucleus accumbens, substantia nigra, olfactory bulb, amygdala, frontal cortex	Obesity	Antagonist [119]
	Sexual disorders	Agonist [120]
	Hypertension	Partial agonist [121]
D_2R	Schizophrenia	Antagonist [18]
[a]Dorsal striatum, nucleus accumbens, olfactory tubercle	Parkinson's disease	Agonist [122]
	Huntington's disease	Partial agonist/stabilizer [123]
	Restless legs syndrome	Agonist [124]
	Depression	Agonist [125]
	Tourette's syndrome	Antagonist [20]
	ADHD	Agonist/antagonist [126]
	Type 2 diabetes	Agonist [127]
	Sexual disorders	Agonist [120]
	Hyperprolactinemia	Agonist [128]
	Cancers	Antagonist [22–24]
D_3R	Schizophrenia	Antagonist [38]
[a]Ventral striatum, islands of Calleja, olfactory bulb	Parkinson's disease	Agonist [98]
	Huntington's disease	Partial agonist/stabilizer [123]
	Restless legs syndrome	Agonist [124]
	Depression	Agonist [125]
	Tourette's syndrome	Antagonist [20]
	Substance use disorders	Antagonist [42]
	ADHD	Agonist/antagonist [126]
	Sexual disorders	Agonist [120]
D_4R	ADHD[b]	Agonist/antagonist [129]
[a]Low levels in frontal cortex, amygdala, hippocampus, hypothalamus, globus pallidus substantia nigra pars reticulate, thalamus	Schizophrenia	Agonist [130]
	Substance use disorders	Antagonist [131]
	Sexual disorders	Agonist [120]
D_5R	Cognitive decline (aging/stress)	Agonist [118]
[a]Low levels throughout cortex, substantia nigra, hypothalamus, hippocampus, dentate gyrus	Obesity	Antagonist [119]
	Sexual disorders	Agonist [120,132]
	Hypertension	Partial agonist [121]

[a] Primary areas of localization.
[b] Unclear role/genetic linkage.

or degree of D_3R signaling through these pathways appears to be less efficacious than that of the D_2R [14–17].

While it is generally agreed that blockade of D_2R-mediated signaling is the primary mechanism of action of all antipsychotics [18], these drugs also interact with the D_3R to varying degrees at therapeutic doses. In fact, most antipsychotics are known to interact with a broad array of GPCRs and these off-target activities are responsible for a number of observed side effects such as weight gain and metabolic syndrome [19]. Clearly, the identification of more D_2R-selective agents for the treatment of schizophrenia is highly desirable. Notably, the D_3R has also become a drug target in its own right for such diverse conditions as addiction (antagonists) and neuroprotection in Parkinson's disease (agonists). Thus, there is a desire to develop compounds that selectively target the D_2R or the D_3R with minimal subtype cross-reactivity, not only to ascertain the physiological and pathological functions governed by these individual subtypes, but also because such compounds will likely exhibit significant clinical utility.

Three primary approaches have been used to identify and develop D_2R or D_3R subtype-selective small molecules: 1) synthesis of structural analogs of known compounds to generate structure-activity relationship (SAR) information for determining how chemical structure can lead to increased subtype selectivity; 2) high-throughput screening of large (thousands to millions) compound libraries to identify novel chemical scaffolds with promising selectivity profiles, followed by chemical optimization; and 3) use of molecular (crystal) structures of the receptors, or corresponding homology models, to rationally design new compounds, or structure-based virtual (in silico) screening to identify unique chemical scaffolds. Each approach has benefits and pitfalls and some have been more successful than others – several groups have used a combination of these approaches. Taken together, these studies have resulted in novel compounds capable of targeting the D_2R and D_3R subtypes selectively. This review will discuss several of these compounds, focusing on those that show the highest selectivity. It will also highlight caution that is needed in interpretations of selectivity, and difficulties in determining if a given compound will be selective in all cases.

2. D_2R-selective antagonists

As noted above, selective antagonists of the D_2R can be useful for treating psychosis and schizophrenia, but can also be useful as therapeutics for other neuropsychiatric disorders such as Tourette's syndrome and Huntington's chorea [20,21], and some cancers such as glioblastomas [22–24]. However, despite the clear therapeutic indications, the successful development of truly selective D_2R antagonists has proven difficult. A few compounds have been developed using multiple approaches that show moderately high selectivity, and this pursuit remains an active area of investigation.

Robert Mach's group has developed several D_2R-preferring antagonists based on previously known structures. These include derivatives of the D2-like antagonist haloperidol and the Merck compound L741,626, which shows moderate D_2R selectivity [25–27] (Fig. 1). Using in vitro radioligand binding and in situ functional assays, the derivatives from Mach's group exhibit between 10 and 100-fold selectivity for the D_2R vs. the D_3R [25–27]. The most promising of these compounds displays over 100-fold D_2R vs. D_3R selectivity in radioligand binding assays [25]