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Polypharmacology of dopamine receptor ligands

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ABSTRACT

Most neurological diseases have a multifactorial nature and the number of molecular mechanisms discovered as underpinning these diseases is continuously evolving. The old concept of developing selective agents for a single target does not fit with the medical need of most neurological diseases. The development of designed multiple ligands holds great promises and appears as the next step in drug development for the treatment of these multifactorial diseases. Dopamine and its five receptor subtypes are intimately involved in numerous neurological disorders. Dopamine receptor ligands display a high degree of cross interactions with many other targets including G-protein coupled receptors, transporters, enzymes and ion channels. For brain disorders like Parkinson's disease, schizophrenia and depression the dopaminergic system, being intertwined with many other signaling systems, plays a key role in pathogenesis and therapy. The concept of designed multiple ligands and polypharmacology, which perfectly meets the therapeutic needs for these brain disorders, is herein discussed as a general ligand-based concept while focusing on dopaminergic agents and receptor subtypes in particular.

Contents

Abbreviations: ACh, acetylcholine; AC, adenylyl cyclase; APO, apomorphine; PD, Parkinson's disease; CNS, central nervous system; COMT, catecholamine *O*-methyl transferase; DML, designed multiple ligands; L-DOPA, L-3,4-dihydroxyphenylalanine; LID, L-DOPA induced dyskinesia; DAT, dopamine reuptake transporter; EPS, extrapyramidal symptoms; GABA, γ-aminobutyric acid; IBS, imidazole binding site; MAO, monoamine oxidase; NET, norepinephrine reuptake transporter; SERT, serotonin reuptake transporter; THPB, tetrahydroprotoberberine.

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1. Introduction

Dopamine (**1**, Fig. 1) belongs to the class of catecholamine-based neurotransmitters, which only in the sixties was recognized as an independent neurotransmitter itself (Carlsson et al., 1958). Dopamine is also the precursor of epinephrine and norepinephrine. Tyrosine is the starting product for the synthesis of catecholamines, which can be absorbed by the cells from the extracellular space, or built up by phenylalanine hydroxylation. Tyrosine hydroxylation to L-3,4-dihydroxyphenylalanine (L-DOPA) followed by decarboxylation concludes the biosynthetic pathway to dopamine. This process takes place in various central and peripheral tissues and is the target of different therapeutic approaches. In patients with Parkinson's disease (PD) treated with L-DOPA, the biosynthesis of dopamine needs to be inhibited at the peripheral level, to reduce the unwanted side effects of peripheral increase of dopamine concentrations. Further reactions for biogenic amines involve a β-hydroxylation to norepinephrine and a following methylation to epinephrine (Broadley, 2010). Catabolic pathways, which contribute to down-regulation of dopamine signaling, involve degradation by monoamine oxidase A (MAO-A) and to less extend by monoamine oxidase B (MAO-B) or catecholamine O-methyl transferase (COMT) (Huotari et al., 2002; Youdim et al., 2006). As therapeutical approach inhibition of these pathways may increase dopamine level in human brain, while co-administration of COMT inhibitors enhances L-DOPA plasma availability by preventing peripherally decarboxylation of L-DOPA (Alavijeh et al., 2005; Youdim et al., 2006).

The dopamine receptor subtypes are widely expressed in various brain regions and peripheral tissues, although with different densities. The following description will focus on central tissues. The dopaminergic signaling pathways mainly arise from three different, but very close tissues in the mesencephalon and the diencephalon. The most relevant one is the substantia nigra, located in the mesencephalon, projecting to the corpus striatum by the nigrostriatal pathway. Degeneration of dopaminergic cells in this part of the brain and a following lack of dopaminergic signaling causes rigor, tremor, bradykinesia and postural instability which are the cardinal symptoms of PD (Blandini and Armentero, 2014). The mesolimbic pathway stems from the area tegmentalis ventralis, which is connected to nucleus accumbens and limbic cortex. This pathway plays a key role in the control of emotions and in reward. Therefore, a dysregulation of the dopaminergic signaling in these areas is highly relevant in brain diseases such as schizophrenia, and is also involved in the symptoms of drug addiction (Egerton et al., 2009). The tubero-infundibular system mediates many of the side effects elicited by drugs targeting the dopaminergic receptors. In normal

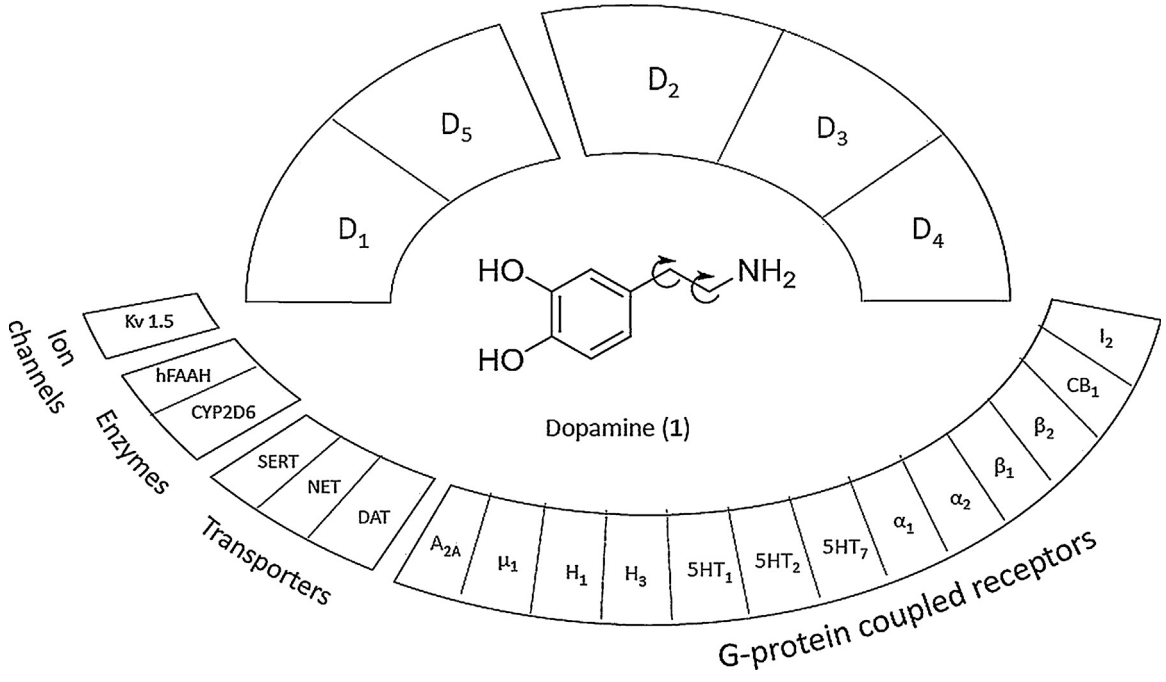

Fig. 1. Main targets of dopamine receptor ligands in multitargeting approaches, i.e. G-protein coupled receptors, enzymes, transporters and ion channels.