

Dopaminergic System: Selected Advances and Emerging Potential Therapeutic Targets

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ABSTRACT

Studies on different physiological and pathophysiological properties of the dopaminergic system have led to novel evidences and theories that suggest the possible targeting of such system in a variety of pathologies and disorders. Herein, we illustrate the applications and the therapeutic importance that such findings and advances might have. We hope that the content of this work will guide researches devoted to dopaminergic aspects that combine neurosciences with pharmacology.

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1. OVERVIEW

Dopamine (DA) represents an important neurotransmitter not only due to the physiological functions it governs but also because the diverse roles it has been shown to play within some diseases' mechanisms [1]. Indeed, in the mammalian central nervous system, dopamine represents the most ubiquitous catecholamine neurotransmitter [2].

Dopaminergic receptors (DRs) classification went through different steps. The initially identified D1 and D2 subtypes [3] DRs have been recently classified, based on molecular biological data, into five different subtypes [3]. Thus, DRs are divided into two families classified as D1-like family (that includes D1 and D5 DRs) and D2-like family (that includes D2, D3 and D4 DRs) [4-6]. We notice that invertebrate neurons also express D1 and D2-like receptors [7], in addition, D2 and D1 like receptors are co-expressed on the same invertebrate neurons but probably govern different functions [6] thus, provides a model for laboratory's study to further our understanding of this system.

DRs are G protein coupled receptors (GPCRs). While D1-like receptors are usually coupled to protein Gs [3, 5], D2-like receptors are generally coupled to Go or Gi proteins [5]. After DR stimuli, dopamine is released then it binds to DRs and depending on the receptor subtype two possible pathways exist. D1-like receptors activate downstream adenylyl cyclase, D2-like receptor group inhibit adenylyl cyclase thus, modulate the production of cAMP that activates protein kinase A [8-10] and the extracellular signal-regulated kinase [11,12] that has been associated with many functions and properties such as behavioral responses to psychostimulants [13], apoptosis and cellular differentiation [10].

2. DISTRIBUTION AND PHYSIOLOGY

Generally speaking dopaminergic (DA) neurons form the nigrostriatal dopamine system that includes the substantia nigra and the locus ceruleus [14]. Other authors indicated that dopamine, which is synthesized from tyrosine, is stored in vesicles of dopaminergic neurons that are mainly found in the substantia nigra (SN) and ventral tegmental area (VTA) of the brain [15, 16]. The anatomic distribution of the dopaminergic neurons shows that in the basal ganglia and mesolimbic areas of the brain dopamine is a major neurotransmitter [17-23] and within the mesocorticolimbic system, dopaminergic neurons, that project to the olfactory tubercle, the amygdala, the prefrontal cortex and the shell of the nucleus accumbens [24], begin in the ventral tegmental area (VTA) [25]. It has also been suggested that the subtype D4R of the DRs is expressed in the photoreceptors [26]. Therefore, shows the complex distribution that suggests the diverse functions this system controls.

Dopaminergic system has been linked to a variety of physiological functions. Indeed, dopamine is involved in the control of a variety of functions such as endocrine regulation, locomotion, emotion [2, 17-23] and food intake [2]. It is also believed to play a role in short-term memory and attention [27-31]. Both the normal development and the neuronal activity in the prefrontal cortex (PFC) appear to involve dopaminergic afferents from the mesencephalon [32]. This activity was confirmed by the presence of dopamine in the developing PFC of the 17-day embryo [33]. Furthermore, in primates while during adolescence increased dopamine concentrations have been reported in cortical and subcortical tissue compared to childhood and adulthood [34, 35], D1 and D2 receptors densities appear to decline from adolescence to adulthood [36-38]. In addition, in the adult forebrain dopaminergic projections have important roles in the neurogenesis [39] and during rat retinal ontogenesis dopamine exist in an early stage [40, 41] thus, reflects the importance dopaminergic system has during the neurodevelopment.

On the other hand, the fact that tissue plasminogen activator (tPA) can act as a modulator of neurotransmission and synaptic plasticity by influencing dopaminergic and glutamatergic functions [42] shows the role dopamine can play in synaptic plasticity. Dopaminergic system is also implicated in the decision making process [43].

3. SELECTED THERAPEUTICS AND PHARMACOLOGICAL POSSIBILITIES

Based on the biological properties and the pharmacological observations, diverse emerging possibilities and applications came out and described how dopaminergic system already constitutes a target for some diseases and a potential target for other pathologies. As instance, administering dopamine D2 agonists could target D2 sensitization and attenuate relapse [44]. On the other hand, dopamine has a protective effect in the retina [5] supposing a possible therapeutic application of the dopaminergic agonists. In psychiatry, the links between both the pleasure [45, 46] and the anti-stress effect [47] on one side with the dopamine on the other side may constitute a starting point to new psychiatric drugs. DRs stimulation leads to an increased feelings of wellbeing [48] and stress reduction [49] supposing also a possible targeting of the dopaminergic system in some psychiatric and psychological diseases. It has also been reported that individuals with lack of D2 receptors have an important risk to develop eating bingeing, pathological gambling, sex addiction, ADHD, and antisocial behavior [50-62] and authors suggested a possible link between the heightened DA efficacy and adolescents' risk-taking and emotional lability [63].

In addition, hyperactivity of the dopaminergic system was involved in the positive symptoms of schizophrenia [64-66] and it has been reported that cognitive deficits in schizophrenia may be aggravated by the dopaminergic impairments [67]. On the other hand, positive symptoms in schizophrenia may be controlled by the use of D2 blockers via increasing the activity of GABA systems [68] and many authors suggested that D1 agonists and D2 antagonists can increase NMDAR- and GABA-R-activated synaptic conductances and thus, be useful in the treatment of schizophrenic symptoms [2, 69]. Herein, we mention that Reward Deficiency Syndrome (RDS) treatments was proposed as a multi-approach that includes slow acting and less powerful dopamine agonists and natural dopaminergic repletion therapy in addition to exercise and an appropriate diet [70]. Importantly, D1-like receptors agonists have been proposed as an antihypertension treatment [71].

For the neurodegenerative diseases both neurite outgrowth and an increased high-affinity DA uptake has been reported as the results of the GDNF-promoted survival and differentiation of DA neurons [72-75] highlighting link between the DA and the neurite outgrowth for which many publications pointed out the dopamine D5 receptor as playing a role in it. Indeed, dopamine has the ability to promote or inhibit neurite outgrowth [76-78] therefore, a detailed description of the diverse DRs remains important to clarify the role of dopamine during development and regeneration [6]. Importantly, D5 receptors that are localized in the substantia nigra-pars compacta, hypothalamus, striatum, cerebral cortex, nucleus accumbens and olfactory tubercle [79], have been linked to neurogrowth functions. In fact, D1-like receptors (D1 and D5) likely

mediate growth cone collapsing behavior via the link they have with the cytoskeleton in the Lymnaea neurons [78]. D1-like receptors is also associated with an antiapoptotic effect in early postnatal retinas [80] and both dopamine and a D1-agonist have a protective effect of the retinal neurons via the inhibition of the glutamate-induced activation of nitric oxide synthase [81]. More important, D1/D5 receptors could represent targets to develop new pharmacological approaches to prevent synapse failure in Alzheimer's disease [82].

Different toxicological observations could lead to possible therapeutic applications. Dopaminergic deficit leads to multiple drug-seeking behavior [5, 83] and also the fact that, in alcohol preferring rodents, gene therapy has shown that DNA-directed compensatory over-expression of the DRD2 receptors can release the alcohol craving behavior [84] and in high alcohol preferring rats, D2 receptor agonists have the ability to reduce alcohol intake [85, 86]. These facts may open new therapeutic possibilities. Furthermore, several publications made a strong link between the dopaminergic system and some drugs. Previously, reward circuit has been proposed to involve dopaminergic imbalances [84] and studies carried out with *Drosophila* showed a role of dopaminergic systems in the cocaine's effects [87-89]. Heightened dopamine overflow in striatal regions was associated with amphetamine repeated administration [90, 91] and, in animals, dopaminergic system role was confirmed in the methamphetamine -or cocaine- induced sensitization [10]. Importantly, morphine, METH, nicotine and other abused drugs increase the dopamine release in the NAc [9] and hyperactivity of the dopaminergic system has been involved in addiction to both alcohol [92] and cocaine [93], and in the development of tardive dyskinesia [64]. Papers have, in addition, suggested that a dysfunction in the brain reward circuitry, especially in the dopaminergic system, causes a hypodopaminergic trait [94] and individuals with lack of D2 receptors show an important risk for multiple addictive, severe alcoholism, cocaine, heroin, marijuana and nicotine use [50-57, 59-62, 95].

These toxicological observations need to be completed by further studies that would map the related implicated mechanisms which could eventually allow the development of a new generation of drugs that would be useful in drugs withdraw and to treat drugs abuse-related symptoms.

4. PERSPECTIVES AND CHALLENGES

We expect more advances in the therapeutics of the dopaminergic system especially with the development of new study methods. For instance, *Drosophila* that has the major neurotransmitters and pathway mechanisms that exist in mammals' neural function [96, 97], represents a model to study the divers aspects of the dopaminergic system. The "knockout" is also a laboratory approach that allows a better understanding of the dopaminergic functions. It is possible to destroy dopaminergic neurons with 6-hydroxydopamine (6-OHDA) [9] or use genetically-derived animals lacking receptors genes [1]. For example, we mention the use of "Bio-neuter" chemicals to modify the receptors expression which will create a new condition for a better study of the receptors pharmacological properties [98]. Since DRs represent GPCRs, taking into consideration the new factors that can influence GPCRs' system functions [99] could be helpful in both the study of the dopaminergic system and the development of the related drugs. Importantly, the establishment of assays for high throughput drug screening allows the identification of a higher number of active compounds [100, 101].

However, The lack of agents for the several DR subtypes remains an obstacle for the research [4]. However, some agonist and antagonists exist in the literature. For example, the dopamine D1 receptor (D1R) agonist SKF38393, the D2 receptor agonist quinpirole [67], dopamine D1R antagonist SCH23390 and D2 receptor (D2R) antagonist raclopride [102] have been reported. On the other hand, in disorders linked to dopaminergic hyperactivity can be therapeutically reversed using oligodeoxynucleotides [4] which illustrates possible therapeutic and laboratory usages for such kind of compounds. Importantly, pharmacognosy has introduced DRs agonists [71] which will enrich the compounds libraries the literature already has.

In pharmacovigilance, the interactions dopaminergic system may have with both drugs and neurotransmitters is a main element that should be taken into consideration especially if we consider the neurotransmitters as a part of a neural network within which many elements are in continuous interactions [103]. The dopaminergic system may interfere with some drugs for example individuals with low D2 receptors liked the effects of psychostimulants [104] which may link the dopaminergic expression with the drugs' effects. It has also been suggested that serotonergic and dopaminergic agonists could attenuate drug seeking behavior [44]. In addition, in some medium spiny projection neurons D1 and D2 receptors are co-localized [105] in both human and rat neurons [106] supposing an inert-influence between the two receptors subtypes. Furthermore, while, D1 receptor stimulation can increase NMDA and GABA transmission, D2-receptor activation produces the opposite effect [2, 68, 107] and dopamine release is facilitated via P2 receptor activation in the mesolimbic system [108-110]. The concept of increased DA release following GABA inactivation has also been reported [44]. Dopamine D5 receptors have also been reported in the somata, dendrites, and axons of cholinergic cells [111]. In addition, dopaminergic system plays important

roles within the neuro-tumoral interactions and has effects on both cancer growth and anticancer drugs[112]. These examples illustrate the interaction that the dopaminergic system has with the other neuronal networks. In addition to the possible interactions and inter-influences the dopaminergic system may have on therapeutics, these data point the importance of rigorous studies of the related pharmacovigilance.

However, pharmacological possibilities of the dopaminergic system, which belong to the big family of the GPCRs systems, remain important and need further investigations that could be supported-due to the similarities and common properties of the GPCRs- by novel advances about other GPCRs systems and related pathways. This might lead to find out both new pharmacotherapies and novel descriptions for various pathogenic phenomena[113]. Importantly, studies of the physiological basis and biological mechanisms constitute basic points to start form the pharmacological properties and reach therapeutical implications.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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