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Dopamine: The Amazing Molecule

Mehveş Ece Genç and Emine Nur Özdamar

Abstract

Dopamine (DA) is a neurotransmitter in the central nervous system (CNS) and has been implicated in the pathogenesis of various diseases of motor functions and psychiatric conditions. Dopamine is also the key modulator for motivational behavior and brain reward system and regulates food intake as well. It has some neuroendocrine function too. It is noteworthy that dopamine has so many diverse roles in the CNS. DA has various pathways such as the Nigrostriatal pathway, Mesolimbic pathway, Mesocortical pathway and Tuberohypophyseal pathway. It has D1, D2, D3, D4 and D5 metabotropic receptors and interacts with cholinergic, GABAergic, opioidergic and glutamatergic systems. DA also activates diverse second messengers and pathways. These complicated interactions partly explain its diverse actions. The aim of the present chapter is to summarize data on the contribution of DA in the pathogenesis of many conditions such as Parkinson's disease, Schizophrenia, Attention Deficit Hyperactivity Disorder and addiction.

Keywords: dopamine, Parkinson's disease, Attention deficit hyperactivity disorder, valproic acid

1. Introduction

Dopamine is a neurotransmitter both in the periphery and in the central nervous system. It is synthesized from the amino acid tyrosine. Tyrosine is first hydroxylated by the rate limiting enzyme tyrosine hydroxylase to Levodopa (L-DOPA) and L-DOPA is further converted to Dopamine with the action of L-Amino acid decarboxylase.

2. Dopamine and Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive loss of dopamine (DA) neurons in substantia nigra pars compacta. According to the epidemiological studies cigarette smoking, coffee, anti-inflammatory agents and high serum uric acid are protective against PD. Teaching staff, medical personnel, people who work in farms, people who are exposed to lead or manganese and people who are deficient of vitamin D have increased risk of getting the disease [1].

There is a prodromal phase in PD before the disease fully develops. Hyposmia and constipation appear first, then depression follows, and finally the motor symptoms become evident such as bradykinesia (slowness of movement), tremor (involuntary shaking, most commonly of the hands) and rigidity (stiff or inflexible muscles), [2]. The cardinal features of PD are summarized in **Figure 1**.

Figure 1.
Cardinal features of Parkinson's disease.

3. Incidence and prevalence of Parkinson's disease

The prevalence and incidence of PD may differ depending on various determinants such as age and gender [3]. A higher incidence of PD were reported in males than females with a ratio ranging between 1.37 to 3.7 [4]. Several studies reported that the prevalence and incidence of PD rises with age [5], with a prevalence rate of 108–257 per 100.000 persons and incidence rate of 11–19 per 100.000 persons [6].

4. Features of Parkinson's disease

Hyposmia is an important feature of Parkinson's disease and might be a significant and valuable sign to take some precautions. As well known olfactory function declines as people age and might have detrimental effects in those people [7].

Dopamine is part of the neuronal system in olfactory system. Gamma Aminobutyric Acid (GABA), Acetylcholine and norepinephrine have been the other transmitters [7].

More recently α -synuclein (α -syn) overexpression in olfactory bulb has been observed and it was related to symptoms and pathology of Parkinson's disease [8]. Scientists developed methods to detect protein aggregation by nasal brushing as a guidance to early diagnosis [9]. Nasal brushing is a non-invasive technique to pick up olfactory epithelium from the olfactory mucosa which is thereafter analyzed by real-time quaking-induced conversion (RT-QuIC) assay. This method has a high sensitivity (97%) and specificity (100%) for Creutzfeldt–Jakob disease (a neurodegenerative disease) diagnosis [10].

In addition to Parkinson's disease, other neurodegenerative disorders such as Alzheimer's disease and Amyotrophic Lateral Sclerosis are characterized by accumulation of particular proteins in cellular aggregates.

α -Syn is an important molecule of the synapse, under physiologic conditions it regulates synaptic function in its soluble form. In PD patient brains monomers form amyloid- β sheet fibrils that aggregate into Lewy bodies [11]. These presynaptic alterations mediated by accumulation of α -Syn change the size of vesicle pools and function of vesicles, impair neurotransmitter exocytosis, vesicle recycling and neural communication [2].

5. Neuroinflammation and Parkinson’s disease

Injury, environmental toxins, endogenous proteins, infection or age cause microglia to become activated and release of inflammatory cytokines such as IL1- β , TNF- α , nitric oxide (NO) and reactive oxygen species (ROS) that cause dopaminergic neuronal deterioration. Damaged neurons further stimulate microglia by α -Syn, ATP and ROS [12]. The events related with neuroinflammation are summarized in **Figure 2**.

Neuroinflammation has been implicated in DA cell loss during Parkinson’s disease [13]. In experiments conducted on rats and mice Kurkowska and colleagues have shown that dexamethasone treatment prevented striatal DA depletion and protected DA neurons in substantia nigra (SN) [14].

Aspirin given orally increases the expression of tyrosine hydroxylase in the nigra and upregulates DA in the striatum in both normal and α -syn transgenic mice, indometacin on the other hand, protects neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD and diminishes microglial activation in the effected area [15, 16].

COX-2 inhibitor celecoxib has also been found to be effective in rats injected with 6-hydroxydopamine (6-OHDA) in the striata, a method that caused retrograde neuronal damage, by reducing DA cell degeneration [17].

Figure 2.
Stressed DA neurons and release of irritating mediators and producing a vicious cycle [8].

In addition to these drugs, the antiinflammatory cytokine IL-10 and peroxisome proliferator-activated receptor gamma (PPAR- γ) ligand rosiglitazone have been found effective in 6-OHDA rat and MPTP mouse models of PD [18, 19].

However, unlike animal studies there are conflicting results in human reports. While several epidemiologic studies reported that the use of non-steroidal anti-inflammatory drugs (NSAIDs) decrease the risk of PD [20], recent metaanalyses found no association between NSAIDs and the risk of Parkinson's disease [21, 22].

6. Parkinson's disease and valproic acid

Valproic acid (VPA) is an inhibitor of histone deacetylases (HDACs), and has been used in the treatment of epilepsy, migraine, schizophrenia and bipolar

Figure 3. Photomicrographs demonstrate TUNEL positive neurons and graph comparing TUNEL positive neurons in right substantia nigra pars compacta. Sham operated (S), sham operated and VPA treated (SV), sham operated and L-DOPA treated (SL), Nigrally 6-OHDA injected (PD), Nigrally 6-OHDA injected and VPA treated (PV), Nigrally 6-OHDA injected and L-DOPA treated (PL), Nigrally 6-OHDA injected and VPA and L-DOPA treated (PVL) groups. Apoptotic neuron (TUNEL positive neuron) is demonstrated with arrow. The magnification is x20. Scale bar represents 100 μ m. Nigrally 6-OHDA injected and VPA and L-DOPA treated (PVL) groups. Data are presented as percentage of apoptotic neurons in right substantia nigra pars compacta compared to total neurons in right substantia nigra pars compacta. Data are expressed as mean $\pm$ SEM. *** $p < 0.001$ vs. S, SV, SL; ### $p < 0.001$ vs. PD; $\Theta\Theta\Theta p < 0.001$ v PL.

disorders [23]. It increases GABA activity, blocks Ca^{++} and Na^{+} channels and decreases N-methyl-D-aspartate (NMDA) mediated excitation [24, 25].

In a study conducted in our laboratory, VPA was found to be effective in a PD model induced by 6-OHDA injected into the SN of rats. Sham operated animals demonstrated trace amounts of apoptotic neurons, 6-OHDA caused significantly increased amounts of TUNEL positive neurons in substantia nigra pars compacta as compared with sham operated groups. Valproic acid treatment significantly diminished the apoptotic neurons in substantia nigra pars compacta as compared with 6-OHDA lesioned and saline treated animals. Valproic acid treatment also significantly diminished the apoptotic neurons as compared with 6-OHDA lesioned and levodopa treated animals [26]. The results of the experiment have been illustrated in **Figure 3**.

The neuroprotective effects of VPA could be associated with the glycogen synthase kinase-3 (GSK3) α and β , Akt, ERK and phosphoinositol pathways, tricarboxylic acid cycle, GABA and oxidative phosphorylation (OXPHOS) system [27].

7. Parkinson's disease and therapeutic aids

Parkinson patients are being treated with DA precursor L-DOPA that increases the synthesis of dopamine in the substantia nigra; Catechol-O-methyltransferase (COMT) inhibitors that increase the central uptake of levodopa (entacapone, talcapone), Monoamine oxidase B inhibitors (MAO-B inhibitors) that decrease the metabolism of dopamine (selegiline, rasagiline) and finally D1 and D2 receptor agonists pramipexole and ropinirole.

However, chronic use of dopaminergic medications in the treatment of Parkinson's disease (PD) might cause some motor and non-motor behavioral side effects such as dyskinesias, impulse control disorders (ICDs), (uncontrollable gambling, shopping, binge eating, hypersexuality), punding (aimless, stereotypical repetitive behaviors) and compulsive medication use [28]. The prevalence of ICDs in PD patients using dopamine agonists was reported to range from 2.6% to 34.8% [29]. This brings us to another significant function of dopamine which is IMPULSIVITY.

8. Dopamine and impulsivity

Impulsivity implicates a variety of behaviors that are unsuitable or overly risky, immature, poorly planned, and often results with undesired consequences. Impulsivity is the main symptom of a wide range of psychiatric disorders such as ICDs and drug addiction. Moreover, attention deficit hyperactivity disorder (ADHD) and mania, also contribute to the expression of impulsivity [30]. It is thought that dopamine has an important role in impulsive behavior, based on the therapeutic effects of psychostimulant drugs such as amphetamine and methylphenidate that increase dopaminergic transmission in attention deficit hyperactivity disorder. Namely, there is a paradox regarding why dopamine releasing psychostimulant drugs ameliorate ADHD symptoms, while the drugs that enhance dopamine transmission increase impulsivity, as in the case of medication induced adverse reactions in PD. This discrepancy means that other neurotransmitters also influence impulsivity [31].

The dopamine system and D2 receptors seem to be closely related to impulsive choice. The activation of D2 receptors in the nucleus accumbens region causes an increase in motor impulsivity. There are many studies highlighting the relationship

between serotonin, norepinephrine and dopamine dysregulation and impulse control disorders. Particularly, studies with human and animal subjects demonstrated the role of serotonin and dopamine in impulsivity. The importance of serotonin and dopamine interaction in the nucleus accumbens is underlined for impulse control disorders [32, 33].

9. Dopamine and attention deficit hyperactivity disorder

ADHD is one of the most common psychiatric disorders of childhood which is characterized by problems in attention, concentration, mobility and impulse control. Dopamine and noradrenaline levels are low and dysregulated in ADHD and it is thought that symptoms of inattention may indicate dopamine and/or noradrenaline dysfunction in important regions of the cerebral cortex that control cognitive functions [34]. Neuroanatomical regions (cortical-striatal-thalamic-cortical network) that are thought to be important in ADHD are regions known to be the area of dopamine concentration.

Dopamine and norepinephrine are the most well studied neurotransmitters in understanding the etiology of ADHD. These neurotransmitters and their degradation products are found at a lower rate in the cerebrospinal fluid (CSF), blood and urine of children with ADHD. Molecular genetics and neuroimaging studies, as well as therapies with stimulant drugs, have also supported the hypothesis of dopamine dysfunction in ADHD etiology. The fact that methylphenidate, which acts by preventing dopamine reuptake in ADHD pharmacotherapy, has brought the dopaminergic system to the fore in candidate gene studies. Molecular genetic studies have indicated some candidate genes related to the dopamine system, such as D1, D2, D3, D4 and D5 receptors and dopamine transporters (DAT). Among these, the genes that are most emphasized and with positive findings are DRD4 (D4) and DAT1 genes (Table 1).

Since stimulant drugs provide increase in extracellular DA by blocking DAT, molecular neuroimaging studies have mostly focused on the DAT [34]. In the meta-analysis of positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies, higher striatal DAT density was reported in patients with ADHD [35].

Receptor	Enzyme-Transporter
Dopamin D1 receptor gene (DRD1)	Tyrosine hydroxylase gene (TH)
Dopamin D2 receptor gene (DRD2)	Catechol-O-methyl- transferase gene (COMT)
Dopamin D3 receptor gene (DRD3)	Monoaminoxidase A gene (MAO-A)
Dopamin D4 receptor gene (DRD4)	Dopamine transporter gene (DAT1/SLC6A3)
Dopamin D5 receptor gene (DRD5)	

Table 1.
Candidate genes studied in the dopaminergic pathway.

10. Dopamine and addiction

Addiction is defined as seeking and using substances and chemicals such as alcohol, cannabis, morphine, metamphetamine, nicotine despite their physical and psychological negative effects on individuals. The negative effects are characterized

by having trouble in stopping the intake after starting to use and by causing negative emotional states such as dysphoria, anxiety and irritability in case of discontinuation. In addition to addiction, these substances cause changes in the reward system, decision-making, memory and brain structures related to memory.

The mesocorticolimbic system, which is formed by the integration of mesolimbic and mesocortical pathways, is an important part of the reward system and dopamine (DA) is the main neurotransmitter in this system. The addictive substances essentially activate the mesolimbic dopamine pathway. Apart from the mesocorticolimbic system, another dopaminergic pathway, the nigrostriatal pathway also plays a role in addiction development.

There is good evidence that synaptic changes in mesolimbic pathways are involved in food and drug addiction. Namely, drug addiction and obesity are related to decreased striatal dopamine D2 receptor levels [36, 37]. Decreased D2 receptor levels in the striatum was also reported in patients with alcohol dependence [38]. In addition, lower striatal dopamine D2/D3 receptor levels were reported in cocaine and metamphetamine addicted subjects [39].

Even though the drugs that enhance DA activity could be effective for alcohol and/or substance use disorders, contradictory results have been reported by several studies. Hence, there is not enough evidence regarding the use of DA agonists for addiction [40].

11. Dopamine and schizophrenia

The neurotransmitter systems that have been investigated in schizophrenia are dopamine, noradrenaline, serotonin, glutamate and GABA. The most well-studied neurotransmitter in schizophrenia is dopamine. The fact that psychostimulant agents that increase dopamine activity such as amphetamine and cocaine cause schizophrenia-like symptoms in normal individuals and that neuroleptics that block postsynaptic dopamine D2 receptors regress the symptoms of schizophrenia supports the dopamine hypothesis. Overactivation of the dopaminergic neurons in the mesolimbic pathway is thought to play a role in the emergence of delusions and hallucinations, which are positive symptoms of psychosis. Neuroreceptor imaging studies indicated the higher levels of dopamine D2 receptor availability in individuals with schizophrenia [36]. The main mechanism of action of the current antipsychotic drugs is the antagonism of mainly dopaminergic D2 receptors [41].

12. Conclusion

As can be observed easily dopamine is involved in the pathogenesis of many conditions such as Parkinson's disease, Schizophrenia and Attention Deficit Hyperactivity Disorder. It is the key substance for impulsivity and addiction as well.

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