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Dopamine: Receptors, Functions, Synthesis, Pathways, Locations and Mental Disorders: Review of Literatures

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Abstract

Dopamine is monoamine neurotransmitter. Dopamine is produced in the dopaminergic neurons in the ventral tegmental area of the substantia nigra, midbrain and the arcuate nucleus of the hypothalamus. In the periphery, dopamine is found in the kidney where it functions to produce renal vasodilation, diuresis, and natriuresis. Dopamine neurons are more widely distributed than those of other monamines and it is found in hypothalamus, olfactory bulb, the midbrain substantia nigra and ventral tegmental area and in the periaqueductal gray and retina.

There are five subtypes of dopamine receptors, D1, D2, D3, D4, and D5, which are members of the large G-protein coupled receptor super family. The dopamine receptor subtypes are divided into two major subclasses: types 1 and 5 are similar in structure and drug sensitivity, and these two receptors are referred to as the "D1like" group or class of receptors. Dopamine receptor types 2, 3, and 4 are called the "D2like" group. Dopamine plays central role in pleasurable reward behavior, inhibition of prolactin production (involved in lactation), sleep, mood, attention, learning, behavior, control of nausea and vomiting and pain processing. In addition it also involved in controlling movement, emotion and cognition.

Due to extensive localization of dopamine receptor to brain areas and its role in wide range of functions, dopaminergic dysfunction has been implicated in the pathophysiology of schizophrenia, mood disorders, obsessive compulsive disorder (OCD), autism spectrum disorders, attention deficit–hyperactivity disorder (ADHD), tourette's syndrome, substance dependency, Parkinson's disease and other disorders.

Keywords: Dopamine; Receptors; Synthesis; Locations; Mental disorders

Dopamine Receptors

There are five subtypes of dopamine receptors, D_1, D_2, D_3, D_4, and D_5, which are members of the large G-protein coupled receptor super family [1]. The dopamine receptor subtypes are divided into two major subclasses: types 1 and 5 are similar in structure and drug sensitivity, and these two receptors are referred to as the "D1like" group or class of receptors. Dopamine receptor types 2, 3, and 4 are also similar in structure and are, therefore, grouped together as the "D2like" group [2]. Dopamine receptors are typically couple to G_s and G_i mediated transduction systems [3].

The ultimate effect of D1-like activation (D1 and D5) can be excitation (via opening of sodium channels) or inhibition (via opening of potassium channels); the ultimate effect of D2-like activation (D2, D3, and D4) is usually inhibition of the target neuron [2]. The effect of dopamine on a target neuron depends on which types of receptors are present on the membrane of that neuron and on the internal responses of that neuron to the second messenger cAMP [2]. D1 receptors are the most numerous dopamine receptors in the human nervous system and D2 receptors are the second most abundant receptors. D3, D4, and D5 receptors are present at significantly lower levels [2].

D1 and D5 receptors mostly involved in post synaptic inhibition. D2, D3, and D4 receptors are involved in both pre-and postsynaptic inhibition. D2 receptors regulates mood, emotional stability in the limbic system and movement control in the basal ganglia [3,4].

D_1 and D_2 receptors were distinguished on the basis of differential binding affinities of a series of agonists and antagonists, distinct effectors mechanisms, and distinct distribution patterns within the CNS. It was subsequently found that the therapeutic efficacy of antipsychotic drugs correlated strongly with their affinities for the D_2 receptor, implicating this subtype as an important site of antipsychotic drug action [3,4].

D_1 receptor has high affinity for the antagonist SCH 23390 and relatively low affinity for butyrophenones such as haloperidol. D_1 receptor activation stimulates cyclic adenosine monophosphate (cAMP) formation, D_2 receptor stimulation produces the opposite effect. In addition to the stimulation of adenylate cyclase, D_1 receptors may also stimulate phosphoinositide turnover and modulate intracellular calcium levels [1,3].

The D1 receptors are found in high concentration in the hypocampus, caudate, putamen, nucleus accumbens, hypothalamus, substantia nigra pars reticulata, olfactory tubercle and frontal and temporal cortex [3,5]. D_1 receptors have been implicated in the cognitive functions of dopamine such as the control of working memory and attention. D_1 receptors contribute significantly to the CNS effects of cocaine, suggesting the involvement of other receptors in addition to the D_2 receptor, in mediating rewarding effects of drugs of abuse [1,3,5].

D1 and D5 receptors have a higher degree of homology with each other than with the D_{2-4} subtypes. D5 receptor has 50% homology

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with D1. This structural similarity is reflected in the similar affinities of a wide variety of dopaminergic drugs for these two receptors. The main distinguishing feature of their binding profiles is that the binding affinity of dopamine is higher for the D_5 receptor than that for the D_1 receptor. D5 receptor is expression in nucleus of thalamus suggesting that role in pain stimuli [1,3,6].

D2 receptor is highly expressed in basal ganglia, septum, ventral tegmental area and nucleus accumbes. D3 receptors mediate positive regulatory influences of dopamine on production of neurotension. D4 receptors homology with D2 and D3 41% and 39% respectively and they are found in hippocampus and frontal cerebral cortex [6-8].

Although the D1like receptors are mentioned as a primary target for antipsychotic drugs, several findings indicate that they are not clinically relevant. Of the 3 D2 like receptors, only the D2 receptor itself is blocked by antipsychotic drugs in direct relation to their clinical antipsychotic potencies [3].

The D1 receptors are linked to adenylate cyclase which, when activated, produces cyclic AMP as a secondary messenger. The D2 receptors are not positively linked to adenylate cyclase and may owe their physiological effects to their ability to inhibit this enzyme. The D2 receptors are probably the most important postsynaptic receptors mediating behavioural and extrapyramidal activity. Most therapeutically effective neuroleptics block the D2receptors, while drugs like bromocriptine, which is a dopamine receptor agonist used in the treatment of parkinsonism, activate them. The correlation between the antagonist effect of a series of neuroleptics on brain [3,4].

Agonist stimulation of D1 receptors results in cyclic adenosinemonophosphate (cyclic AMP) synthesis followed by phosphorylation of intracellular proteins, including dopamine- and AMP-regulated phosphoprotein (DARPP-32). The receptor binding affinity of a dopamine agonist independent on the degree of association of the receptor and the guanine nucleotide binding regulatory protein, which is regulated by guanosinetriphosphate (GTP) and calcium or magnesium ions. Thus the D1 receptor may exist in a high or low agonist affinity state depending on the balance between GTP (which favors low affinity) and the divalent cations (which favor high affinity). The high affinity D1 receptor is classified as a D5 receptor [4,6].

The D3 and D4 receptors appear to be largely restricted to the limbic areas of the rat and human brain. These receptors are of particular interest as they have a high affinity for such atypical neuroleptics as clozapine. Such findings suggest that the D3 and D4 receptors in the human brain may mediate the antipsychotic actions of many typical and atypical neuroleptics. The restriction of these receptors to the limbic regions may lead to the development of neuroleptics which are specifically targeted to these areas [6,7] (Table 1).

Dopamine System and Functions

There are four major pathways for the dopaminergic system in the brain:

The Nigro-Stiatal Pathway, In which fibres originate from the substantia nigra (pars compacta) and project rostrally to become widely distributed in the basal ganglia (caudate nucleus and the putamen). In this pathway dopamine plays a significant role in movement (the control of motor function and in learning new motor skills). Degeneration of the nigrostriatal system causes Parkinson's disease [9-11]. Dopamine cell bodies in the pars compacts division of this region send ascending projections to the dorsal striatum (especially to the caudate and putamen) and thereby modulate motor control. The extrapyramidal effects of antipsychotic drugs are thought to result from the blockade of these striatal dopamine receptors [10,11].

The Mesolimbic Pathway, where the dopaminergic projections originate in the ventral tegmental area, and then spread to the amygdala, pyriform cortex, lateral septal nuclei and the nucleus accumbens. In this pathway dopamine functions in emotion and reward systems. Mesolimbic dopamine mediates pleasure in the brain. It is released during pleasurable situations and stimulates one to seek out the pleasurable activity or occupation. This means food, sex, and several drugs of abuse are also stimulants of dopamine release in the brain, particularly in areas such as the nucleus accumbens and prefrontal cortex. In addition dopamine plays major role in addictions in this pathway. All known drugs of abuse activate the mesolimbic pathway, and plastic changes in this pathway are thought to underlie drug addiction. Antipsychotic drugs that decrease positive symptoms of schizophrenia by blocking dopamine receptors in the mesolimbic pathway [10,12,13].

The Mesocortical Pathway, In which the dopaminergic fibers also arise from the A10 region (the ventral tegmental area) and project to the frontal cortex and septohippocampal regions. Mesocortical dopmine mediates cognitive and emotional behaviour. Levels of dopamine in the brain, especially the prefrontal cortex, help in improved working memory and attentions. However, this is a delicate balance and as levels increase or decrease to abnormal levels, memory suffers. Antipsychotic drugs worsen negative symptoms of schizophrenia by blocking dopamine receptors in the mesocortical pathway [10,12,13].

The Tuberoinfundibular Pathway which originates in the arcuate nucleus ofthe hypothalamus (arcuate and paraventricular nuclei) and projects to pituitary gland (the median eminence). Dopamine in this pathway inhibit prolactin release. Antipsychotic drugs that block dopamine receptors in the pituitary may thus disinhibit prolactin release and cause galactorrhea. Dopamine is the main neuroendocrine inhibitor of the secretion of prolactin from the anterior pituitary gland. Dopamine produced by neurons in the arcuate nucleus of the hypothalamus is released in the hypothalamo-hypophysial blood vessels of the median eminence, which supply the pituitary gland. This acts on the lactotrope cells that produce prolactin. These cells can produce prolactin in absence of dopamine. Dopamine is occasionally called prolactin-inhibiting factor (PIF), prolactin-inhibiting hormone (PIH), or prolactostatin [14] (Table 2).

Dopamine Synthesis

Dopamine is synthesized from the amino acid tyrosine, which is taken up into the brain via an active transport mechanism. Tyrosine is produced in the liver from phenylalanine through the action of phenylalanine hydroxylase. Tyrosine is then transported to dopamine containing neurons where a series of reactions convert it to dopamine [15,16]. Within catecholaminergic neurons, tyrosine hydroxylase catalyzes the addition of a hydroxyl group to the meta position of tyrosine, yielding L-dopa. This rate-limiting step in catecholamine synthesis is subject to inhibition by high levels of catecholamines (end-product inhibition). Because tyrosine hydroxylase is normally saturated with substrate, manipulation of tyrosine levels does not readily impact the rate of catecholamine synthesis. Once formed, L-dopa is rapidly converted to dopamine by dopa decarboxylase, which is located in the cytoplasm. It is now recognized that this enzyme acts not only on L-dopa but also on all naturally occurring aromatic L-amino acids, including tryptophan, and thus it is more properly termed aromatic amino acid decarboxylase [15,16].

Receptors	Locations	Functions
D1	Found in high concentration in mesolimbic, nigrostratal and mesocortical areas , such as substancia nigra, olfactory bulb, nucleus accumbens, cuadate, putamen, striatum, Expressed in low level in cerebellum, hippocampus, thalamus, hypothalamus, kidney	Voluntary movements, regulate growth and development, regulations of feeding, affect, attentions, reward, sleep, impulse control, reproductive behaviors, working memory, learning, control of rennin in kidney
D2	Expressed in high levels in as substancia nigra, olfactory bulb, cuadate, putamen, ventral tagemental area(VTA), nucleus accumbens Found in low level in hypothalamus, septum, kidney, cortex, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia	Involved in working memory, reward-motivation functions regulate blood pressure, renal functions, gastrointestinal motility, vasodilatations, regulate locomotion-presynatic receptors inhibit locomotion and post synaptic receptors activate locomotion
D3	Expressed only in CNS and it is not found outside the CNS. Found in olfactory bulb, nucleus accumbens	Involved in endocrine function cognitions, emotions, regulations of locomotor functions and modulates endocrine functions
D4	Substancia nigra, hippocampus, amygdala, thalamus, hypothalamus, kidney, frontal cortex, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia, globus palidum, Lowest receptor found in CNS than all dopamine receptors	Regulations of renal functions, gastrointestinal motility, vasodilatations, blood pressure, modulations of cognitive functions
D5	Substancia nigra, hypothalamus, hippocampus, dental gyrus, kidney, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia	Involved in pain process, affective functions, endocrine functions of dopamine

Table 1: Summary of dopamine receptors, locations and functions.

Pathway	Function
Nigrostriatal	Movement and sensory stimuli
Mesolimbic	Pleasure and reward seeking behaviors, addiction, emotion, perception
Mesocortical	Cognition, memory, attention, emotional behavior, and learning
Tuberoinfundibular	Control of the hypothalamic pituitary endocrine system, inhibition of prolactin secretions

Table 2: Summary of dopamine pathways and major functions.

Dopamine and Mental Disorders

Due to extensive localization of dopamine receptor to brain areas and its role in wide range of functions, dopaminergic dysfunction has been implicated in the pathophysiology of schizophrenia, mood disorders, obsessive compulsive disorder (OCD), autism spectrum disorder, attention deficit–hyperactivity disorder (ADHD), tourette's syndrome, substance dependency, Parkinson's disease and other disorders.

The role of dopamine in schizophrenia

Dopamine is among the common neurotransmitters involved in pathogenesis of schizophrenia, largely based on patients' responses to psychoactive agents [17-20]. The role of dopamine in schizophrenia is based on the dopamine Hypothesis which evolved from two observations. First, drug group which blocks dopamine function, known as the phenothiazines, could reduce psychotic symptoms. Second, amphetamines, which increase dopamine release, can induce a paranoid psychosis and exacerbate schizophrenia and that disulfiram inhibits dopamine hydroxylase and exacerbates schizophrenia [17-19].

The role of dopamine in mood disorders

The findings on dopamine in mood disorders suggest that decreased dopamine activity is involved in depression, while increased dopamine function contributes to mania [21]. The role of dopamine in mood disorders is based on evidence that drugs that reduce dopamine concentrations for example, reserpine and diseases that reduce dopamine concentrations (e.g., Parkinson's disease) are associated with depressive symptoms. In contrast, drugs that increase dopamine concentrations, such as tyrosine, amphetamine, and bupropion reduce the symptoms of depression. Recent theories about dopamine and depression are that the mesolimbic dopamine pathway may be dysfunctional in depression and that the dopamine D_1 receptor may be hypoactive in depression [21-25].

The role of dopamine in addictions

Most addictive drugs share the common property of increasing dopamine release in the striatum. The dopamine input to the striatum is provided by a very dense network of axon terminals arising from cell bodies in the midbrain–substantia nigra pars compacta and ventral tegmental area. The increased locomotor activity and stereotypy caused by psychostimulants seem especially to involve dopamine release in ventral and dorsal parts of striatum, respectively. The ventral striatum includes the "core" and "shell" of the nucleus accumbens, blockade of dopamine neurotransmission in this region attenuates most rewarding effects of addictive drugs, such as conditioned place preference The dopaminergic projection to ventral striatum has therefore been intensely investigated for its potential involvement in addictions[26-28].

The role of dopamine in attention-deficit hyperactivity disorder (ADHD)

Dopamine is among the common neurotransmitters involved in pathogenesis of Attention-Deficit Hyperactivity Disorder (ADHD). Defects in dopamine metabolism have long been implicated in the etiology of ADHD. The impulse and behavior problems found in Attention-Deficit Hyperactivity Disorder (ADHD) appear related to low levels of Dopamine in the brain. Stimulants increase catecholamine concentrations by promoting their release and blocking their uptake. Stimulants has been helpful in treating hyperactivity. Other drugs that have reduced hyperactivity include tricyclic drugs and monoamine oxidase inhibitors (MAOIs), which indicate role of dopamine in Attention-Deficit Hyperactivity Disorder (ADHD) [29,30].

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