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 monoamines 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 superfamily. 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, D1, D2, D3, D4, and D5. These are members of the large G-protein coupled receptor superfamily [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 coupled to G, and Gi 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].

D1 and D2 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 D2 receptor, implicating this subtype as an important site of antipsychotic drug action [3,4].

D1 receptor has high affinity for the antagonist SCH 23390 and relatively low affinity for butyrophenones such as haloperidol. D1 receptor activation stimulates cyclic adenosine monophosphate (cAMP) formation, D1 receptor stimulation produces the opposite effect. In addition to the stimulation of adenylate cyclase, D1 receptors may also stimulate phosphoinositide turnover and modulate intracellular calcium levels [1,3].

D1 receptors are found in high concentration in the hippocampus, caudate, putamen, nucleus accumbens, hypothalamus, substantia nigra pars reticulata, olfactory tubercle and frontal and temporal cortex [3,5]. D1 receptors have been implicated in the cognitive functions of dopamine such as the control of working memory and attention. D1 receptors contribute significantly to the CNS effects of cocaine, suggesting the involvement of other receptors in addition to the D1 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 D2-like subtypes. D5 receptor has 50% homology with...
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].
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, reerpine 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 bufropin 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 hypoinactive 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].

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

<table>
<thead>
<tr>
<th>Receptors</th>
<th>Locations</th>
<th>Functions</th>
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</thead>
<tbody>
<tr>
<td>D1</td>
<td>Found in high concentration in mesolimbic, nigrostral and mesocortical areas, such as substantia nigra, olfactory bulb, nucleus accumbens, cuadate, putamen, striatum. Expressed in low level in cerebellum, hippocampus, thalamus, hypothalamus, kidney</td>
<td>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</td>
</tr>
<tr>
<td>D2</td>
<td>Expressed in high levels in as substantia nigra, olfactory bulb, cuadate, putamen, ventral tagemeral area (VTA), nucleus accumbens. Found in low level in hypothalups, septum, kidney, cortex, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia</td>
<td>Involved in working memory, reward-motivation functions regulate blood pressure, renal functions, gastrointestinal motility, vasodilatations, regulate locomotion-presynaptic receptors inhibit locomotion and post synaptic receptors activate locomotion</td>
</tr>
<tr>
<td>D3</td>
<td>Expressed only in CNS and it is not found outside the CNS. Found in olfactory bulb, nucleus accumbens</td>
<td>Involved in endocrine function cognitions, emotions, regulations of locomotor functions and modulates endocrine functions</td>
</tr>
<tr>
<td>D4</td>
<td>Substancia nigra, hippocampus, amygdala, thalamus, hypothalamus, kidney, frontal cortex, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia, globus pallidum, Lowest receptor found in CNS than all dopamine receptors</td>
<td>Regulations of renal functions, gastrointestinal motility, vasodilatations, blood pressure, modulations of cognitive functions</td>
</tr>
<tr>
<td>D5</td>
<td>Substancia nigra, hypothalamus, hippocampus, dental gyrus, kidney, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia</td>
<td>Involved in pain process, affective functions, endocrine functions of dopamine</td>
</tr>
</tbody>
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Table 2: Summary of dopamine pathways and major functions.

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Function</th>
</tr>
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<tbody>
<tr>
<td>Nigrostriatal</td>
<td>Movement and sensory stimuli</td>
</tr>
<tr>
<td>Mesolimbic</td>
<td>Pleasure and reward seeking behaviors, addiction, emotion, perception</td>
</tr>
<tr>
<td>Mesocortical</td>
<td>Cognition, memory, attention, emotional behavior, and learning</td>
</tr>
<tr>
<td>Tuberoinfundibular</td>
<td>Control of the hypothalamic pituitary endocrine system, inhibition of prolactin secretions</td>
</tr>
</tbody>
</table>

References


8. Nestler EJ (2014) Brain Reward Pathways. Icahn School of Medicine at Mount Sinai. Nestler Lab. The dorsal raphe is the primary site of serotonergic neurons in the brain, which, like noradrenergic neurons, pervasively modulate brain function to regulate the state of activation and mood of the organism.


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