Introduction

Dopamine is a catecholamine neurotransmitter found in neurons of both the central and peripheral nervous systems. A total number of around 400,000 dopamine secreting neurons are found in the human brain. Their cell bodies are confined to a few small brain areas, but they send projections to many other brain areas and exert powerful effects on their targets. Dopamine plays an important role in extrapyrimidal motor regulation, behavior, cognition and drug induced reward, as well as inhibiting prolactin secretion and producing nausea and vomiting through stimulation of chemo receptor trigger zone.

Biosynthesis

Chemically, dopamine is a catecholamine. Dopamine synthesis mainly takes place in nerve cells and adrenal medullary cells. Although dopamine itself is found in many types of foods like bananas, it is not able to pass through blood brain barrier. It must therefore be synthesized inside the brain in order to perform its actions.
Biosynthesis includes the following steps

L-Phenylalanine $\rightarrow$ L-Tyrosine $\rightarrow$ L-DOPA $\rightarrow$ Dopamine

L-Phenylalanine is converted into L-Tyrosine by the enzyme PAH (Phenyl alanine hydroxylase)

Tyrosine hydroxylase enzyme converting L-Tyrosine into L-DOPA (Rate limiting step)

L-DOPA is converted into dopamine by DOPA decarboxylase

**Storage, Release, and Reuptake**

After synthesis, dopamine is transported by monoamine transporter protein (VMAT2) and stored in presynaptic vesicles. Dopamine is stored in and remains in these vesicles until depolarization occurs and causes the release of dopamine into the synapse. Once in the synapse, dopamine binds to and activates postsynaptic or presynaptic dopamine receptors. They are then absorbed back into the presynaptic axon by different reuptake mechanisms. Reuptake is mediated either by DAT or PMAT transport proteins. Once back in the cytosol, dopamine is subsequently repacked into vesicles by VMAT2, making it available for future release. Cocaine prevents dopamine reuptake by binding to dopamine transport proteins while amphetamine helps to release more dopamine, thereby increase dopamine concentration in the synapse. This causes prolonged feelings of pleasure and excitement leads to addiction.

**Degradation**

Dopamine is broken down into two inactive metabolites namely DOPAC (Dihydroxy phenyl acetic acid) and Homovanillic acid (HVA). Monoamine oxidase (MAO-A and MAO-B) and catechol-o-methyl transferase (COMT) enzymes are involved in the metabolism of dopamine. The metabolites produced are excreted in the urine and provides an index for the turnover of dopamine.

**Dopaminergic pathways**

1. **Nigro striatal pathway:** The brain has several distinct dopamine systems, the nigrostriatal pathway projecting from the substantia nigra to the striatum, the region involved in the control of extrapyrimidal motor function. 75 % of dopamine is present in this pathway. Degeneration of the dopaminergic neurons of the nigrostriatal pathway is associated with Parkinson's disease resulting in resting tremors and muscle rigidity often associated with dementia.
2. **The mesolimbic and mesocortical pathways:** Mesolimbic projections from the ventral tegmental area of mid brain to the limbic areas, associated with cognition, emotional behavior and drug induced reward system. Over activity of dopamine neurotransmission in the mesolimbic pathway is associated with positive symptoms of Schizophrenia, i.e. thought disorder, delusions and hallucinations. However, decreased activity in another dopaminergic pathway from mid brain to cortex i.e., mesocortical pathway may also be involved. The two pathways are thought to be responsible for different set of symptoms seen in schizophrenia.

Dopamine disorders in the frontal lobes can cause a decline in neurocognitive function, particularly those linked to the frontal lobes, such as memory, attention and problem solving. This function is particularly related to the mesocortical dopamine pathway.

3. **Tuberoinfundibular pathway:** Important projections from hypothalamic dopaminergic neurons go to anterior lobe of pituitary gland, where the secretion of prolactin hormone is decreased and growth hormone release is promoted.

4. **The posterior hypothalamus:** Dopaminergic cells project to the spinal cord are involved in Restless leg syndrome, a condition in which people have difficult sleeping due to an overwhelming compulsion to constantly move parts of the body, especially the legs.

5. **Retinal pathways:** An additional group of dopamine-secreting neurons are located in retina of the eye. These neurons have no axons. They release dopamine into the extracellular medium, and are specifically active during daylight hours, becoming silent at night. This retinal dopamine acts to enhance the activity of cone cells in the retina while suppressing rod cells.

**Dopamine receptors**

Five subtypes of dopamine receptors have been identified, D₁ to D₅. All of them are metabotrophic GPCRs, D₁ receptors are abundant in the central nervous system, D₂ receptors are next, D₃, D₄, and D₅ receptors are less. The D₁ and D₅ receptors belong to D₁ family, whereas the D₂, D₃ and D₄ receptors belong to D₂ family. Pharmacological agents targeting dopaminergic neurotransmission have been clinically used in the management of several neurological and psychiatric disorders, including Parkinson's disease, Schizophrenia, Bipolar disorder, Huntington's disease and Attention deficit hyperactivity disorder (ADHD).
Enhanced sensitivity of postsynaptic D_2 dopamine receptors is observed in Schizophrenia. Significantly decreased striatal D_1 and D_2 dopamine receptor densities and a selective reduction in D_2 dopamine receptor binding were reported in patients suffering from Parkinson's disease. D_4 and D_5 have been linked to ADHD and the D_2 receptor has been associated with substance abuse, prolactin-secreting pituitary adenomas and several other conditions. D_2 receptor stimulatory action on CTZ produce nausea and vomiting. Presynaptic D_3 autoreceptors act to inhibit dopamine synthesis and release from presynaptic axonal membrane by negative feedback mechanism.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Type of GPCR</th>
<th>Location</th>
<th>Function</th>
<th>Agonists</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>D₁</td>
<td>Gₛ</td>
<td>Cortex</td>
<td>Arousal, Mood, Emotions</td>
<td>Non selective</td>
<td>And less potent</td>
</tr>
<tr>
<td>Family</td>
<td></td>
<td>Limbic system</td>
<td>Emotions</td>
<td></td>
<td></td>
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<tr>
<td>(D₁, D₅)</td>
<td></td>
<td>Basal ganglia</td>
<td>Motor control</td>
<td></td>
<td>Dopamine</td>
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<td></td>
<td></td>
<td>Hypothalamus</td>
<td>Endocrine and autonomic control</td>
<td>Apomorphine</td>
<td>Bromocriptine</td>
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<tr>
<td>D₂</td>
<td>Gᵢ</td>
<td>Cortex</td>
<td>Arousal, Mood, Emotions</td>
<td>Non selective</td>
<td>And more potent</td>
</tr>
<tr>
<td>Family</td>
<td></td>
<td>Limbic system</td>
<td>Motor control</td>
<td>Chlorpromazine(D₂, D₃)</td>
<td></td>
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<tr>
<td>(D₂, D₃, D₄)</td>
<td></td>
<td>Basal ganglia</td>
<td>Inhibits Prolactin secretion</td>
<td>Haloperidol (D₂, D₃, D₄)</td>
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<td></td>
<td></td>
<td>Pituitary gland</td>
<td></td>
<td>Spiperone (D₂, D₃, D₄)</td>
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<td></td>
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<td>Sulpiride (D₂)</td>
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<td></td>
<td></td>
<td></td>
<td>Clozapine (D₄)</td>
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Drugs acting on dopamine receptors

Dopamine agonists: Therapeutic uses

1. L-DOPA, is used in the treatment of Parkinson's disease. It can cross blood brain barrier and up on entering into CNS, it is converted into dopamine and acting on dopamine receptors.
2. Dopamine receptor agonists like Bromocriptine, Pergolide, Lisuride are used in the treatment of Parkinson's disease alone or along with L-DOPA.
3. Dopamine receptor agonists like Ropinirole and Pramipexole are FDA-approved drugs for the treatment of Rest Leg Syndrome.
4. Dopamine receptor agonists like Bromocriptine and Cabergoline can treat Prolactin-secreting pituitary tumors by decreasing prolactin secretion and often reducing the size of the tumor.
5. Apomorphine is an injectable, rapid-acting dopamine agonist and used during occasional episodes of immobility when muscles become "stuck" or "frozen".
6. Dopamine-activating stimulants such as cocaine and amphetamine are addictive in high doses, but are used at lower doses to treat ADHD.
7. Bupropion can increase dopamine neurotransmission in the frontal cortex of the brain by inhibiting dopamine reuptake and used to treat depression and ADHD.
8. Low dose dopamine is used to treat cardiogenic shock. Dopamine increase renal perfusion through renal vasodilatation and maintains glomerular filtration.

Dopamine antagonists: Therapeutic uses

1. Typical anti psychotic drugs like Chlorpromazine, Haloperidol, Thioridazine are antagonists at D2 dopamine receptors and used to treat Schizophrenia. Atypical anti psychotic drug, Clozapine is a weak antagonist at D4 receptors and also acts on 5HT receptors and is preferred to treat Schizophrenia.
2. D2 receptor antagonists Triethylperazine and Metaclopramide are used as antiemetic drugs to treat emesis associated with uremia, radiation and cancer chemotherapy.
3. D2 receptor antagonists Domperidone and Metaclopramide are used as prokinetic agents through their peripheral actions on GIT. They are increasing gut motility and gastric emptying and useful in the treatment of GERD (Gastro Esophageal Reflux Disease).
4. Anti psychotic drugs like Chlorpromazine, Haloperidol and Clozapine are sometimes used to reduce the symptoms of Huntington's disease.
5. D₂ receptor antagonist, Domperidone is the safest option to stimulate or increase breast milk production.

6. Haloperidol can be used as an antidote for Cocaine, Amphetamine or dopamine agonist’s poisoning.

**Peripheral Actions:**

Outside the nervous system, dopamine mediates several peripheral actions through D₁ receptors:

- In the blood vessels it inhibits norepinephrine release and acts as a vasodilator
- In the heart it increases cardiac contractility
- In the kidneys it increases sodium excretion and urine output
- In the pancreas it reduces insulin production
- In the digestive system it reduces gastrointestinal motility and protects intestinal mucosa
- In the immune system it reduces the activity of lymphocytes.
- With the exception of the blood vessels, dopamine in each of these peripheral systems synthesized locally and exerts its effects on cells that are located near the cells that release it.

**References**

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