DOPAMINE AND ITS EFFECTS IN A HUMAN BEING

2.1 Neurotransmitters

Neurotransmitters are the most common class of chemical messengers in the nervous system. Based on their chemical nature, neurotransmitters can be subdivided into two major groups (Fig: 2.1.1) - biogenic amines and small amino acids [72, 95].

A neuroactive substance has to fulfill certain criteria before it can be classified as a neurotransmitter.

- It must be of neuronal origin and accumulate in presynaptic terminals, from where it is released upon depolarization.
• The released neurotransmitter must induce postsynaptic effects upon its target cell, which are mediated by neurotransmitter-specific receptors.

• The substance must be metabolically inactivated or cleared from the synaptic cleft by re-uptake mechanisms.

• Experimental application of the substance to nervous tissue must produce effects comparable to those induced by the naturally occurring neurotransmitter.

A neuroactive substance has to meet all of the above criteria to justify its classification as a neurotransmitter.

2.2 Dopamine

Dopamine is a chemical naturally produced in the body. It is secreted from the chromaffin tissue that composes the adrenal gland's medulla. In the brain, dopamine functions as a neurotransmitter, activating dopamine receptors. Dopamine is also a neurohormone released by the hypothalamus. Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary. Dopamine has the chemical formula $C_6H_3(OH)2 - CH_2 - CH_2 - NH_2$. Its chemical name is 4 - (2 - amino ethyl) benzene - 1, 2 - diol and it is abbreviated as “DA”. The first successful synthesis of dopamine (3, 4 dihydroxy phenethylamine, or 3 hydroxytryptamine) was achieved in 1910, but in contrast to the other member of the catecholamine family (epinephrine, norepinephrine), little attention was paid to this monoamine.
It has been shown that dopamine is a prominent neurotransmitter in the brain with several potential functions and a distinct distribution. Dopamine has been found to be enriched, for example, in the substantia nigra and in the striatum, whereas norepinephrine is absent from these brain regions. The differential distribution of dopamine is suggestive of a specific function for this neurotransmitter in neuroregulative processes.

The essential biochemical difference between noradrenergic neurons and dopaminergic neurons is the presence of the enzyme dopamine - β-hydroxylase. This enzyme can be used as a marker for the differentiation of noradrenergic from dopaminergic neurons. Within dopaminergic neurons, the dopamine -β-hydroxylase catalyzes the formation of norepinephrine form dopamine. From a clinical point of view, dopamine attracted considerable interest since it became evident that this monoamine is involved in several major brain disorders, like Alzheimer’s, Parkinsonism and Schizophrenia.
2.3 Anatomy of Dopamine

Dopamine neurons are more widely distributed than those of other monoamines, residing in the midbrain substantia nigra and ventral tegmental area, and in the periaqueductal gray, hypothalamus, olfactory bulb, and retina. In the periphery, dopamine is found in the kidney, where it functions to produce renal vasodilatation, diuresis, and natriuresis [12]. Of particular relevance are three CNS dopamine containing system: (1) nigrostriatal, (2) mesocorticolimbic, and (3) tuberohypophyseal (Fig: 2.3.1). The nigrostriatal dopamine system has been the most extensively studied of the dopaminergic path ways. Dopamine cell bodies located in the pars compacta division of the substantia nigra send ascending projections to the dorsal striatum, particularly the caudate putamen. This projection modulates motor function, as highlighted by the motor disturbances of Parkinson's disease, a disorder characterized by degeneration of the nigrostriatal system. Prolonged use of dopaminergic agonist agents can result in abnormal movement or dyskinesia. Conversely, the extra pyramidal motor side effects of antipsychotic drugs are believed to result from the blockade of striatal dopamine receptors.

The midbrain ventral tegmental area lies medial to the substantia nigra and contains dopaminergic neurons that give rise to the mesocorticolimbic dopamine system. These neurons send ascending projections that innervate limbic structures, such as the nucleus accumbens and amygdale, as well as associated cortical structures, particularly the prefrontal cortex.
Fig: 2.3.1 Brain dopaminergic pathways. The three principal dopaminergic pathways: (1) nigrostriatal pathway, (2) mesocorticolimbic pathway, and (3) tuberohypophyseal pathway. AMG, amygdale; CTX, neocortex; HI, hippocampus; HY, hypothalamus; LC, locus ceruleus; NAc, nucleus accumbens; OB, olfactory bulb; PFC, prefrontal cortex; PI, pituitary; SNC, substantia nigra pars compacta; TE, tectum; TH, thalamus; VTA, ventral tegmental area.

The mesoaccumbens projection is believed to regulate the rewarding properties of a wide variety of stimuli, including drugs of abuse. The mesolimbic projection is believed to be a major target for the antipsychotic properties of dopamine receptor antagonist drugs in their control of the positive symptoms of schizophrenia, such as hallucinations and delusions. Conversely, dopamine receptor antagonism in mesocortical circuits believed to be relatively under active in schizophrenia may, in fact, worsen the negative symptoms of this disorder. In this regard, the decreased predisposition of the atypical antipsychotic clozapine (Clozaril) to produce extra pyramidal motor side effects has been attributed to relatively selective actions on the mesocorticolimbic system versus the nigrostriatal system. The tuberohypophyseal system consists of dopaminergic neurons in the hypothalamic arcuate and periventricular nuclei and their projections to the pituitary gland. These projections provide inhibitory regulation of prolactin
release. The administration of dopamine receptor antagonist antipsychotic drugs may lead to a disinhibition of release, resulting in galactorrhea.

2.4 Dopamine pathway

Dopamine projections stem largely from two clusters of dopamine neurons located in portions of the ventral midbrain referred to as the substantia nigra and the ventral tegmental area [40] (Fig: 2.4.1). The nigral dopamine neurons project mainly to the striatum and have, therefore, been implicated in the well-known motor side effects of dopamine receptor blocked produced by antipsychotic drugs.

Fig: 2.4.1 Dopaminergic pathways. The nigrostriatal dopamine system originates in the substantia nigra and terminates in the main dorsal part of the striatum. The ventral tegmental areas rise to the mesolimbic dopamine system, the amygdaloid body, the frontal lobe, and some other basal forebrain areas. The tuberoinfundibular system innervates the median eminence and the posterior and intermediate lobes of the pituitary; dopamine neurons in the posterior hypothalamic project to the spinal cord.
Their axons extend in one of three specific but overlapping paths (via the medial forebrain bundle) to stimulate specific cortical and subcortical structures. In contrast, serotonin and norepinephrine patterns of distribution are far more diffuse.

The nigrostriatal pathway (in the subcortical areas of the brain) has a prominent role in motor planning and movement, plus cognition. The mesocortical pathway, which projects to the frontal and temporal cortices, is believed to be vital to concentration and executive functions such as working memory. The mesolimbic pathway, which projects into the limbic system, including the hippocampus and amygdale, "is particularly important for motivation, the experience of pleasure, and reward." The ventral tegmental area group project largely to the ventral or limbic striatum, including the nucleus accumbens, and to other limbic areas, such as the prefrontal cortex, though to be primary targets underlying the antipsychotic actions of dopamine.
receptor blockade. In addition, there is the tuberofundibular pathway. This pathway extends from one area of the hypothalamus to another, and regulates prolactin and growth hormone release in the pituitary system.

2.5 Dopamine Life Cycle

The dopaminergic axon terminal is the site of synthesis for dopamine. Dopamine is one of the three catecholamine neurotransmitters that are synthesized starting with the amino acid tyrosine [11]. The rate-limiting enzymatic step in the synthesis of any of the catecholamine is catalyzed by tyrosine hydroxylase. Therefore, dietary changes in tyrosine levels do not influence the synthesis of catecholamine. Tyrosine hydroxylase is a phosphoprotein that is subject to regulation by a range of protein kinesis and protein phosphates. Tyrosine hydroxylase transforms tyrosine into 3,4-dihydroxyphenylalanine (dopa). Because it is beyond the rate-limiting synthetic step, dopa may be administered orally to increase the rate of synthesis of its product, dopamine, and dopa is used for this purpose to treat Parkinson’s disease. Once dopamine is produced, it is taken into synaptic vesicles by specific transporters and then released into the synaptic cleft on depolarization of the axon terminal.

The actions of dopamine are terminated by two general routes. First, dopamine can be taken back up into the presynaptic neuron and recycled as a neurotransmitter; this pathway is generally referred to as the reuptake
mechanism. Reuptake occurs by the passage of the dopamine molecule from the synaptic space, through the presynaptic dopamine transporter, into the intracellular space, where it is packaged into vesicles. Second, dopamine can be metabolized. The two major enzymes involved in the metabolism of dopamine are MAO and, less importantly, Catechol-O-Methyltransferase (COMT) [125]. MAO is localized on the outer mitochondrial membrane, principally in the presynaptic terminal, where it acts on dopamine that has been taken up into the presynaptic terminal but not yet repackaged into vesicles. COMT is a soluble enzyme localized in the cytoplasm of the postsynaptic cell and of glial cells and, possibly also, extracellularly. When dopamine is metabolized extraneuronally by COMT, the resulting metabolites are then taken back into the neuron and further metabolized by MAO.

As discussed above there are two types of MAOs; MAO\textsubscript{B} selectively metabolizes dopamine. The primary metabolite of dopamine is homovanillic acid (HVA), and many research studies of cerebrospinal fluid, urine, and serum attempt to assess dopamine activity in the CNS by measuring concentration of HVA

2.6 Dopamine Receptors

There are five subtypes of dopamine receptors, as shown in Table: 2.6.1. The dopamine receptors are divided into two families. The “D\textsubscript{1} family” consists of the D\textsubscript{1} and D\textsubscript{5} receptors [52, 121]. Both of these receptors are linked to
G-proteins that stimulate adenylyl cyclase. In contrast, the D2, D3, and D4 receptors are linked to G proteins that inhibit adenylyl cyclase and that are referred to as the “D2 family.” The dopamine receptors have very different distributions in the brain. D1 and D2 are found almost predominantly in the neostriatum, whereas D3 receptors are found in the nucleus accumbens, where they may play a significant role in the pleasure circuit. D3 receptors are the most sensitive, requiring less dopamine to trigger them than the others. The D1 and D4 receptors are found in the cortex; and D3 in the hypothalamus and the hippocampus.

<table>
<thead>
<tr>
<th>Second Messenger System</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>D4</th>
<th>D5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location in brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neo- and ventral striatum</td>
<td>Activate Adenylyl Cyclase</td>
<td>Inhibit adenylyl cyclase</td>
<td>Activate Adenylyl Cyclase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neo- and ventral striatum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventral striatum, hypothalamus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal cortex, medulla, midbrain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocampus, hypothalamus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-/Postsynaptic</td>
<td>Postsynaptic</td>
<td>Both pre- and postsynaptic</td>
<td>Postsynaptic</td>
<td>Postsynaptic</td>
<td>Postsynaptic</td>
</tr>
<tr>
<td>Human chromosome</td>
<td>5</td>
<td>11</td>
<td>3</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Affinity for dopamine</td>
<td>2,000</td>
<td>2,000</td>
<td>30</td>
<td>450</td>
<td>250</td>
</tr>
</tbody>
</table>

Table: 2.6.1. Dopamine Receptors

2.7 Dopamine synthesis, Storage, release and degradation

Dopamine is synthesized from the amino acid L-tyrosine by the following steps: L-tyrosine is hydroxylated to L-dopa (by tyrosine hydroxylase) and then decarboxylated (by aromatic -L-amino-acid
decarboxylase) to form dopamine. Oral administration of L-dopa increases dopamine synthesis. In Parkinson's disease, dopaminergic neurons are damaged and have a much reduced capacity to synthesis dopamine. Adjacent glial cells retain dopamine synthetic capacity and, during L-dopa therapy, dopamine may leak out from these glial cells to stimulate surviving supersensitive dopamine receptors.

Dopamine is stored in presynaptic complexes of dopamine, ATP, magnesium, calcium, copper and chromogranins [28]. Drugs that disrupt the storage of noradrenaline, like Rauwolfia alkaloids and tetrabenazine, also disrupt dopamine storage complexes, and many of the behavioral sequences of their administration may be related to the action of dopamine storage rather than on noradrenaline.

Dopamine is released from central dopaminergic terminals by two discrete mechanisms that differ in their sensitivity to dopamine uptake inhibitors (Table: 2.7.1). An energy-dependent transport mechanism for dopamine uptake is inhibited by nomifensine, benzotropine and cocaine. A second carrier-independent mechanism for dopamine release is dependent upon extra cellular Ca$^{2+}$ concentrations and involves fusion of dopamine-containing vesicles with the presynaptic membrane upon the Ca$^{2+}$ influx which follows action potentials. This type of release is facilitated by amphetamine at concentrations much lower than those required for amphetamine to stimulate
postsynaptic catecholaminergic receptors. Amphetamines stimulate rapid release of dopamine, inhibit its uptake from the synaptic cleft and also inhibit its degradative enzyme monoamine oxidase.

<table>
<thead>
<tr>
<th>Presynaptic Site of action</th>
<th>Effect</th>
<th>Drug</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis</td>
<td>Inhibits</td>
<td>α-Methyl tyrosine</td>
<td>Occasionally in phaeochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Increases</td>
<td>L-Dopa</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Storage</td>
<td>Inhibits</td>
<td>Tetrabenazine α-Methyl tyrosine Reserphine</td>
<td>Chorea As above Occasionally in treatment of refractory psychoses</td>
</tr>
<tr>
<td>Release</td>
<td>Increases</td>
<td>Amphetamine γ-Hydroxybutyrate</td>
<td>Experimental</td>
</tr>
<tr>
<td></td>
<td>Inhibits</td>
<td>Amphetamine γ-Hydroxybutyrate</td>
<td>Experimental</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postsynaptic Receptor</th>
<th>Tissue</th>
<th>Agonist</th>
<th>Antagonist</th>
<th>Molecular mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>Cell bodies and presynaptic terminals of intrinsic striatal neurons</td>
<td>Pergolide SKF 38393</td>
<td>Lisuride SCH 23390</td>
<td>↑ Adenylate cyclase</td>
</tr>
<tr>
<td>D2</td>
<td>Neuronal cell bodies of striatum and presynaptic terminals of dopaminergic striatal neurons</td>
<td>Bromocriptine Pergolide Lisuride Apomorphine</td>
<td>Butyrophenones Sulpiride</td>
<td>↓ Adenylate cyclase or no effect</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Degradation Site of action</th>
<th>Effect</th>
<th>Drug</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uptake</td>
<td>Inhibits</td>
<td>Benztropine Nomifensine Cocaine Amitriptyline</td>
<td>Parkinson’s disease Experimental Experimental Antidepressant</td>
</tr>
</tbody>
</table>

Table: 2.7.1 Dopaminergic pharmacology
Monoamine oxidase inhibitors like tranylcypromine reduce the degradation of dopamine by monoamine oxidase. Tranylcypromine also reduce uptake of dopamine, but this is probably not relevant to its antidepressant action because drugs such as bentropine (a potent dopamine uptake inhibitor) are not effective antidepressants. In contrast the actions of the monoamine oxidase B inhibitor deprenyl seems to be less on the metabolism of amines and more on the reduction of oxidative stress and its concomitant neurotoxicity. A recent multicentre trial suggests strongly that pretreatment with deprenyl slows the progression of symptoms of Parkinson's disease.

2.8 Function of Dopamine

Dopamine stimulates the heart, increases the blood flow to the liver, spleen, kidneys, and other visceral organs, and controls muscle movements and motor coordination through an inhibitory action over stimuli response. In the frontal lobes, dopamine controls the flow of information from other areas of the brain and it is the primary neuroendocrine regulator of the secretion of prolactin from the anterior pituitary gland. Dopamine is commonly associated with the pleasure system of the brain, providing feelings of enjoyment and reinforcement to motivate us to do certain activities.

Abnormal low levels of dopamine are associated with tremors, muscular rigidity, low blood pressure, and low cardiac input. Therefore, dopamine and dopaminergic agonist drugs are administered to treat shock and
congestive heart failure and to improve motor functions in patients with Parkinson's disease and other movement disorders. The balance between two neurotransmitter levels, acetylcholine and dopamine, is essential for motor and fine movement coordination. The balance is frequently found altered in movement disorders, due to a dopamine deficiency that results in excessive stimulation of skeletal muscles. In Parkinson's disease, either dopamine levels or the number of dopamine receptors are progressively decreased, resulting in tremors, slowness of movements, muscle rigidity, and poor posture and gait (manner of walking).

Dopamine can be supplied as a medication that acts on the sympathetic nervous system, producing effects such as increased heart rate and blood pressure. However, since dopamine cannot cross the blood – brain barrier, dopamine given as a drug does not directly affect the central nervous system (CNS). To increase the amount of dopamine in the brains of patients with diseases such as Parkinson's disease and Dopa-Responsive Dystonia, a synthetic precursor to dopamine such as L-Dopa can be given, since this will cross the blood – brain barrier.

2.9 Dopamine and Drugs

In the past, the potency of antipsychotic compounds has been correlated with their affinity for the D2 receptor. Since blockade of dopamine receptors, particularly the D2 receptor has been associated with the efficacy of
antipsychotic drugs, long term administration of dopamine receptor antagonists results in an up regulation in the number of dopamine receptors present. This up regulation may be involved in the development of tardive dyskinesia. The development of a new class of highly effective antipsychotic agents, called the serotonin-dopamine antagonists because they block predominantly the serotonin type 5-HT2 and, to a lesser extent, the D2 receptors, has led to a reassessment of the D2 receptor affinity hypothesis of antipsychotic potency. Serotonin-dopamine antagonists are associated with a greatly reduced risk of development of Parkinsonian side effects and tardive dyskinesia, and not only do they treat the positive symptoms of schizophrenia, effectively treated by pure D2 receptor antagonists (psychosis, hallucinations, agitation), they also improve the negative symptoms of schizophrenia (blunted affect, ambivalence, catatonia).

Other substances that affect the dopamine system are amphetamines and cocaine. Amphetamines cause the release of dopamine, and cocaine block the uptake of dopamine. Thus, the substances increase the amount of dopamine present in the synapse. Cocaine and methamphetamine (Desoxyn) are among the most addicting substances. Their use may permanently deplete the brain’s stores of dopamine. The dopaminergic systems may be particularly involved in the brain’s so-called reward or pleasure seeking system, and this involvement may explain the high addiction potential of cocaine. Mutant “knockout mice”, in which the dopamine transporter gene has been experimentally deleted, do
not respond biochemically or behaviorally to cocaine. This suggests that the dopamine transporter is necessary for the pharmacological effects of cocaine. Studies in rats showed that D2 receptors agonists increased cocaine self-administration, while D1 receptor agonists lowered the desire for cocaine. Nicotine, the most psychoactive ingredient in cigarette smoke, stimulates the release of dopamine and glutamate. Epidemiological studies have found that smokers have a reduced risk of developing Parkinson’s disease, Alzheimer’s disease, and ulcerative colitis. A nicotine analogue that stimulates dopamine release is under study for treatment of Parkinson’s disease, and the nicotine transdermal patch is being studied to counteract the cognitive impairment caused by treatment with haloperidol (Haldol). The nicotine stained fingers of many schizophrenia patients may be a sign that they are medicating themselves unknowingly with their powerful neurotransmitter.

The dopamine transporter may be blocked by benztropine (Cogentin) and bupropion (Wellbutrin), though it is unlikely that sufficient CNS concentrations of these drugs are routinely obtained to have an appreciable effect on dopamine transport. The transporter is the portal of entry of the neurotoxin methylphenyltetrahydropyridine (MPTP), which may cause Parkinsonism by killing the nigral dopaminergic neurons. Dopamine-containing storage vesicles are depleted irreversibly by reserpine (Serpasil) and reversibly by tetrabenazine.
2.10 Methodological considerations: Effects of Long-term ALCAR administration increased Dopamine Output in Mesocorticolimbic Areas

Acetyl-L-Carnitine (ALCAR) is the acetyl ester of Carnitine that has been reported to be beneficial in depressive disorders and Alzheimer's disease. A 7-day administration of ALCAR in rats increased dopamine and serotonin output in the nucleus accumbens shell and it prevented the development of escape deficit produced by acute exposure to unavoidable stress.

Fig: 2.10.1 Dopamine and serotonin basal levels (A and B) and accumulation (C and D) in the NACs after a 7-day ALCAR treatment. Rats received saline (Control) or ALCAR for seven days, they underwent surgery on day 8, and then micro dialysis experiments were performed 48 h after the last treatment. (Control, n = 10; ALCAR, n = 10).
A process of neuronal plasticity dependent on NMDA receptor activity, as subcutaneous dizocilpine infusion during ALCAR treatment prevented the development of the protective effect on stress. Chronic stress exposure maintains an escape deficit condition that is reverted by a long-term treatment with antidepressants, but the same condition was not modified by long-term ALCAR administration.

Comparisons were made by t-test when two experimental groups were compared. Otherwise, comparisons were made by 1-way analysis of variance (ANOVA), followed by post-hoc Bonferroni's or Dunnett's test, when applicable \((p < .05)\). When the criteria for parametric statistics were not met by the data, non-parametric analysis of variance was used; when differences between groups were significant \((p < .05)\), the data were subjected to post-hoc analysis using Dunnett's test, a variation of Bonferroni's test for non-parametric ANOVA.

In the mPFC, no significant differences were observed between groups in the basal values and in the accumulation after uptake inhibition of DA and 5-HT. Repeated ALCAR administration consistently produced an increase in DA and 5-HT output in the NACs associated with a protective effect on acute stress exposure, on the basis of the present results, ALCAR does not seem to conform to the criteria that we use to define a compound as an antidepressant.
2.11 Dopamine and Psychopathology

The dopamine hypothesis of schizophrenia grew from the observation that drugs that block dopamine receptors (e.g., haloperidol) have antipsychotic activity and drugs that stimulate dopamine activity (e.g., amphetamine) can induce psychotic symptoms in non schizophrenic persons when given in high enough doses. The dopamine hypothesis remains the leading neurochemical hypothesis for schizophrenia, but room is being made for a role for serotonin, based on the therapeutic success of the serotonin-dopamine antagonists.

A recent series of studies showed that plasma concentrations of HVA are in fact, reduced in many schizophrenic patients who respond to antipsychotic drugs. A major problem with the hypothesis is that blockade of dopamine receptors reduces psychotic symptoms in virtually any disorder, such as psychosis associated with a brain tumor and psychosis associated with mania. Thus, some as yet unrecognized neurochemical abnormality in schizophrenia may be unique to the condition.

Dopamine may also be involved in the pathophysiology of mood disorders. Dopamine activity may be low in depression and high in mania. Amphetamines, which potentiate dopamine activity, are highly effective antidepressants. The observation that levodopa (Larodopa) can cause mania and psychosis in some Parkinsonian patients also supports the hypothesis.
Some studies have found low levels of dopamine metabolites in depressed patients.

### 2.12 The dopamine hypothesis of schizophrenia

The ‘dopamine hypothesis of schizophrenia’, simply stated postulates that certain dopaminergic pathways are overactive in schizophrenia and so cause the symptoms of an acute schizophrenic episode. Clinical studies indicate that drugs like L-dopa or amphetamine which potentiate dopaminergic activity may induce or exacerbate schizophrenic symptoms [71].

Carlsson and Lindqvist [20] first suggested that dopamine receptor blockade was the basis of neuroleptic effects. The low activity of butyrophenone antipsychotic at dopamine receptor sites linked to adenylate cyclase stimulation was seen as evidence against this idea. It was supported, however, by the recognition of two types of dopamine receptor. One (called D₁) was linked to adenylate cyclase stimulation and another, higher affinity one (called D₂) sometimes associated with adenylate cyclase inhibition and for which there was preferential binding of butyrophenones.

Some of the newer ‘atypical’ antipsychotic agents are weak dopamine receptor antagonists, all effective antipsychotic are believed to share the ability to impair dopaminergic neurotransmission. Postmortem studies of schizophrenic brains have demonstrated increased dopamine receptor (D₂)
densities, but these densities are probably considerably influenced by antemortem drug treatments. Positron emission tomography studies on D$_2$ receptor binding in neuroleptic-naïve schizophrenic patients have provided conflicting results.

Dopamine receptors are present in the basal ganglia, the mesolimbic system, the tuberoinfundibular region and, to a much lesser extent, in the cerebral cortex. Studies on the effects of dopaminergic transmission of psychotomimetic agents such as amphetamine, PCP and benzomorphan point to a possible common mechanism of psychotic action.

2.13 Dopamine in the Brain

Dopamine has a wide variety of applications in the brain. Dopamine controls the flow of information to the frontal lobe from other parts of the brain. Disorders in dopamine levels cause declines in neurocognitive functions like memory, attention, and problem-solving. Dopamine's role in pleasure and motivation is critical. It is heavily associated with the pleasure system in the brain, and its continued release provides feelings of enjoyment and reinforces the activities that provide those feelings. Food, sex, and other naturally-rewarding experiences release dopamine; in addition, neutral stimuli associated with pleasure (for instance, sexual fetishes) and certain drugs also release dopamine. Cocaine and amphetamines in particular seem directly
related to dopamine release, and in theories of addiction have been given the reputation of pathologically altering dopamine pathways in addicted people.

Dopamine is released when negative stimuli are encountered, leading one to wonder just how close pleasure and pain truly are. It also works in previously-unpredicted ways toward pleasure; for instance, when a reward is greater than anticipated, the dopaminergic neurons associated fire more often, with a commensurately lower than anticipated reward, they fire less.

Drugs like antipsychotics that inhibit dopamine activity reduce people's desire for pleasure. When a dopamine path has been damaged by addiction, it would make this decision-making dysfunctional by overemphasizing the priority of the drug in relation to other variables. Blocking dopamine receptors chemically increases, instead of decreases, drug-taking behavior.

2.14 Biological Effects of Dopamine

The differential distribution of the diverse dopaminergic systems indicates that dopamine influences a variety of brain functions. For instance, dopamine is involved in the modulation of arterial blood-flow, higher brain functions like cognition and learning and in anxiety-related behavior. Therefore it is not surprising that the dopaminergic systems serve as a target for antipsychotic drugs, i.e. in schizophrenia treatment. Many chronic diseases result from the overproduction or underproduction of dopamine. Shortage of dopamine, particularly the death of dopamine neurons in the nigrostriatal
pathway, causes Parkinson's disease, in which a person loses the ability to execute smooth, controlled movements. If the flow of dopamine throughout the nervous system is not allowed to circulate as usual, then schizophrenia follows.

The nigro-striatal system is concerned with the initiation and maintenance of motor behavior. The mesolimbic and mesocortical systems appear to be involved in goal-directed and reward-mediated behavior and in motivation-dependent behavior. A dysfunction in these systems alters normal associative processes.

An enhancement of dopaminergic transmission in the mesolimbic system is linked with reinforcing effects of psycho stimulant drugs. The hypothalamic-hypophyseal axis in the form of the tuberoinfundibular system plays a major role in the regulation of pituitary and hypothalamic peptides, for instance in the release of prolactin. An increase in dopamine activity in this system results in an inhibition of prolactin release. Thus, dopamine constitutes the prolactin-inhibiting factor. Dopamine produced by neurons in the arcuate nucleus of the hypothalamus is secreted into the hypothalamo-hypophysial blood vessels of the median eminence, which supply the pituitary gland. The lactotrope cells that produce prolactin, in the absence of dopamine, secrete prolactin continuously; dopamine inhibits this secretion. Feeding, as well as drinking activities initiated by the ventromedial and lateral hypothalamic nuclei including the zona incerta, are also modulated by dopamine.
Dopamine disorders in this region of the brain can cause a decline in neurocognitive functions, especially memory, attention and problem-solving. Reduced dopamine concentrations in the prefrontal cortex are thought to contribute to attention deficit disorder and negative schizophrenia.

Dopamine is released (particularly in areas such as the nucleus accumbens and striatum) by naturally-rewarding experiences such as food, sex, use of certain drugs and neutral stimuli that become associated with them. Dopamine can also be used with shock to increase cardiac output and blood pressure in patients who are in distress.

2.15 Neurological Disorders and Neurodegenerative Diseases

Dopamine is an essential neurotransmitter in manifold cerebral functions. Consequently, dysfunction in the dopaminergic transmission influences a variety of neurological and psychiatric disorders. Some dysfunctions may result in hyperactivity of the dopaminergic system. Such hyperactivity leads to an accumulation of the neurotransmitter in the synaptic cleft and/or hypersensitivity of dopaminergic receptors. Dopaminergic hyperactivities have been found to be linked to some psychotic disorders, including hallucinations and manic states.

Hypoactivity of the system seems to be primarily involved with motor dysfunction, deficits in motivation-dependent behavior and imbalance of
emotional perception. Thus one has to expect a combination of different clinical symptoms if the balance of the dopaminergic system is affected. The basal ganglia, including the striatum, play a crucial role in the control of movement. The importance of dopamine in the striatum becomes evident in patients with Parkinson’s disease (PD).

Normal motor function depends on the highly regulated synthesis and release of dopamine, by neurons projecting from the substantia nigra to the striatum. Degeneration of the dopaminergic neurons located in the substantia nigra pars compacta (SNpc) and a subsequent loss of dopaminergic nerve terminals in the striatum are responsible for most of the movement disorders. There is a gradual decline in dopaminergic neurons of the SNpc during aging, which is accompanied by a reduction of the striatal DA content.

2.16 Stress and Dopamine Neuron Activity

Stress appears to affect many monoamine systems. Stress plays a role both in acute behavioral responses and adaptations to chronic stressful conditions. Although the non-adrenergic system has played a major role in these processes, recent evidence supports a role for the DA systems as well. Studies have shown that, on presentation of stress, there are differential increases in DA dynamics depending on the brain regions involved. Thus, stressful stimuli tend to cause the largest increase in DA levels in the PFC region, with markedly smaller changes in the limbic and dorsal striatal regions;
however, this relationship is altered by lesions of different nuclei. Thus, stress cause release of DA in the amygdale, and lesions of the amygdale tend to block stress-induced increases in PFC DA levels. Lesions of the PFC also affect this response. Studies in which the PFC DA innervations is lesioned show that subsequent stressors cause a much larger increase in DA levels within the nucleus accumbens, particularly with respect to the duration of the response. This suggests that PFC DA released in response to stress actually blunts the responsiveness of the sub cortical limbic DA system. In contrast, 6-OHDA lesions of PFC DA levels were found to decrease the basal electrophysiological activity of VTA DA neurons. Given that basal DA levels in the accumbens are accumbens are normal, one interpretation is that the DA release system has adapted to the diminished DA neuron drive, allowing normal levels of DA transmission to occur. However, if a stimulus then causes an increase in DA neuron firing, the compensated release mechanism would produce an augmented response. Thus, the magnitude of increase in action potential-dependent DA release into the accumbens that occurs in response to a challenge may be augmented when the PFC DA response is attenuated.

Repeated stress also has important clinical implications with regard to the DA system and exacerbation of schizophrenia. A recent study examined how chronic stress in the form of cold exposure affects the discharge of VTA DA neurons. Thus, after exposing rats to cold, there was a 64% decrease in the number of spontaneously active DA neurons, with no significant alteration in
their average firing rate. Nonetheless, there was a subpopulation of neurons that exhibited excessive burst activity in the exposed rats. Therefore, unlike acute exposure to stressful or noxious stimuli, chronic stress actually attenuates DA neuron baseline activity. Such a decrease in baseline activity could enable the system to show a magnified response to activating stimuli, thereby producing a sensitized DA response.

The functions of dopamine are numerous, but in general it inhibits transmission of nerve impulses. This transmitter is found throughout the body, though mainly housed in the brain’s interior basil ganglia, in the frontal lobe of the information-processing center of the brain, or in the limbic system. Dopamine levels are sometimes induced by stress factors. Certain dopamine levels will facilitate certain corresponding behavior. The inability of dopamine to circulate throughout the nervous system causes schizophrenia and Parkinson disease. It is obvious that dopamine levels normally should be balanced, adjusting according to the presence of stress factors to help an individual cope with life experiences.