REVIEW OF LITERATURE
Dopamine (DA) research has attracted increasing interest in the last two decades for several reasons. Endogenous dopamine (3,4-dihydroxyphenylethylamine) is the immediate metabolic precursor of noradrenaline and adrenaline. It is a pharmaco-logically active catecholamine with prominent effects on $\alpha$ and $\beta$-adrenergic receptors, although its potency is much less than that of epinephrine, norepinephrine, or isoproterenol (Goldberg et al., 1978). The presence of DA in the brain, first reported by Montagu (1957), was confirmed by Carlsson and coworkers, who also showed depletion of the putative neurotransmitter by reserpine and its replenishment by dopa (Carlsson et al., 1958). 80% of DA in the human brain is concentrated in the basal ganglia (Bertler and Rosengren, 1959; Carlsson 1959) as evidenced by marked deficiency of striatal DA in parkinsonian patients (Ehringer and Hornykiewicz, 1960).

DA, is a catecholamine, but differs structurally from other endogenous catecholamines in that it lacks one hydroxyl group (-OH) on the side chain (Fig.1). The extended conformation of dihydroxyphenylethylamine moiety with a trans isomeric form and the presence of two phenolic oxygens in the ring are essential for dopaminergic activity (Sharabi et al., 1976). The occurrence of DA is well documented...
STRUCTURE OF CATECHOLAMINES

No. 1
CATECHOLAMINE

CATECHOL ETHYLAMINE NUCLEUS SIDE CHAIN

No. 2
ADRENALINE

No. 3
NORADRENALINE

No. 4
DOPAMINE

No. 5
LEVODOPA

Fig. 1
in lower animals like shrimps, molluscs, insects and pigeons (Ostlund', 1954). It is interesting to know that DA is absent from the brains of birds and amphibians, species in which extrapyramidal control is poorly developed (Lewis, 1970). In mammalian brain, the caudate nucleus and putamen contain the highest concentration of DA (5-8 microgram/G), followed by the nucleus accumbens, substantia nigra, globus pallidus and the amygdaloid complex. DA is the main catecholamine in the spinal cord of rat, rabbit, ox, cat, hog and man (McGeer and McGeer, 1962). DA is also present in the retina, hypothalamus and the limbic system (Fig.2).

Dietary tyrosine serves as the natural precursor of DA (Fig.3). DA is the first catecholamine in the biosynthetic pathway for catecholamines. In the course of synthesis, the hydroxylation of tyrosine to dopa and the decarboxylation of dopa to DA take place in the intraneuronal cytoplasm. DA then enters the granules where it is converted to noradrenaline. Dopaminergic neurons lack the enzyme dopamine-β-hydroxylase (DBH) (Goldstein, Fuxe and Hokfelt, 1972), which converts DA to adrenaline in adrenergic neurons (Fig.4). DA is also synthesized in certain scattered chromaffin cells in the intestinal wall and other tissues. DA is released from the granules by the process of ecretidosis. The enzymes responsible for degradation of DA are monoamine oxidase (MAO) and catechol-
DOPAMINERGIC PATHWAYS IN THE RAT BRAIN.

Fig. 2
Figure 4: A schematic model of the central dopaminergic neurone.

Abbreviations: 
DOPAC = 3,4-Dihydroxyphenyl acetic acid
DA = Dopamine
MT = Methoxytyramine
HVA = Homovanillic acid
COMT = Catechol-o-methyl transferase
MAO = Monoamine oxidase

(Redrawn from Pharmacology eds. Rang and Date, Page No.458)
Fig. 4
O-methyltransferase (COMT). In the brain, DA is selectively metabolized by the enzyme MAO-B. The principal metabolites are homovanillic acid (3-methoxy-4-hydroxyphenylacetic acid) and DOPAC (3,4-dihydroxyphenylacetic acid) (Fig.5). DA neurons in the central nervous system possess highly specific uptake mechanism. DA has five times higher affinity than NA for the dopaminergic neurons of the striatum (Snyder and Coyle, 1969). Benztropine,amphetamine, chlorpromazine and compound GBR-13098 block the uptake of DA into the neurons (Bowman and Rand, 1983; Pileband and Engberg, 1986). Uptake of DA has been reported to be increased in Huntington's disease (Aminoff, Trenchard and Turner et al., 1974) and decreased in Parkinsonism (Barbeau and McDowell, 1970). The uptake characteristics for DA in platelets are different from those in the brain (Boullin and O'Brien, 1970).

Research on basic and clinical aspects of Parkinson's disease and the success of its treatment have advanced rapidly during the past few years. Parkinson's disease is a progressive neurological disorder, first described by James Parkinson in 1817. Its cardinal features are akinesia, tremor and rigidity, which occur as a result of imbalance between the concentration of two neurotransmitters acetylcholine (excitatory) and dopamine (inhibitory) in the basal ganglia. The understanding that Parkinsonism is a syndrome of DA deficiency caused by degeneration of dopaminergic
STEPS IN THE METABOLIC DISPOSITION OF DOPAMINE

H$_3$CO

HO-\(\text{CH}_2\text{COOH}\)  HOMOVANILLIC ACID

COMT

HO

HO-\(\text{CH}_2\text{COOH}\)  3,4-DIHYDROXY PHENYLACETIC ACID

MAO

HO

HO-\(\text{CH}_2\text{CH}_2\text{NH}_2\)  DOPAMINE

COMT

H$_3$CO

HO-\(\text{CH}_2\text{CH}_2\text{NH}_2\)  3-METHOXYTYRAMINE

MAO

H$_3$CO

HO-\(\text{CH}_2\text{COOH}\)  HOMOVANILLIC ACID

Fig. 5
nigrostriatal neurons, and that DA does not cross the blood brain barrier, resulted in the discovery of levodopa as an important drug for the treatment of this disease (Marks, 1974; Yahr, 1978; Calne, et al., 1979). The cause of death of pigmented DA-containing neurons in substantia nigra in Parkinson's disease is unknown. One suggestion is that there is increased basal lipid peroxidation in Parkinsonian nigra. Interest in this area has been recently stimulated by the finding that the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), via its active metabolite (MPP), may kill nigral DA-containing cells and cause Parkinsonian syndrome which responds to levodopa (Williams, 1984). MPTP has now achieved major status as a research tool in Parkinson's disease.

In Parkinson's disease, the essential dysfunction appears to be in the DA neuron and DA receptor. It has been suggested that this disease probably arises from dysfunction of D_2 receptors which are not linked to adenylate cyclase and exist in the terminals of nigrostriatal and corticostriatal neurons as well as in the corpus striatum. The role of bromocriptine, a direct DA receptor stimulant, in the current management of Parkinson's disease remains unclear although it is undoubtedly helpful in some patients. Recent interest in brain grafting has been prompted by the identification of discrete neuronal systems associated with specific functional effects. Neuronal transplantation studies demonstrate that these implants are able to
restore the functional CNS deficits. Also, grafts of foetal adrenal medulla from young rats have been shown to survive in the nigrostriatal pathway. Dopamine rich grafts might be a viable new surgical treatment for Parkinson's disease (Ajdorlund, Dunnett, Stenevi, Lewis and Iverson, 1980).

In recent years, emphasis has centered on biogenic amines in the CNS, their possible involvement in mental illness, and their probable mediation of many effects of psychotropic drugs. Introduction of relatively selective drug, chlorpromazine (in 1950), for the management of schizophrenic patient, encouraged formulation of biological concept of pathogenesis of this mental illness. In the early 1960s, it was suggested that interference with the transmitter function of DA in the mammalian forebrain might contribute to the neurological and the antipsychotic effects of neuroleptic drugs. This hypothesis arose largely from the observation that neuroleptic drugs consistently increased the concentrations of the metabolites of DA, but had variable effects on the metabolism of other neurotransmitters (Carlsson and Lindqvist, 1963). Later on, Matthysse and Sugarman (1978) furnished evidences to postulate that there is an overactivity of dopaminergic system in schizophrenia, particularly in DA neurons of the limbic system. A compelling body of data has now accumulated to support the theory that antagonism of DA-mediated synaptic neurotransmission is an important action of neuroleptic drugs (Carlsson, 1978;
Baldessarini and Larsy, 1979). Direct evidence of receptor blockade by neuroleptic drugs has been provided by their antagonism of a selective DA-sensitive adenylate cyclase system in homogenates of caudate or limbic tissue (Clement-Cormier et al., 1974; Greengard, 1978). The antipsychotic effects of neuroleptics are thought to occur via blockade of mesolimbic and/or mesocortical DA receptors, while their extrapyramidal adverse effects occur via blockade of nigrostriatal DA receptors (Meltzer and Stahl, 1976). Recently, cholecystokinin octapeptide (CCK-8) has been shown to occur as a co-transmitter along with DA in the mesolimbic dopaminergic pathway (Rehold, 1985). It is postulated that if the function of DA and neuroleptics could be altered via CCK, the activity of mesolimbic DA pathway (and, therefore, neuroleptic action) can be selectively augmented. Proglumide, a specific CCK-8 antagonist, has been reported to selectively enhance haloperidol's antipsychotic effect (Csernansky, Glick, and Mellentin, 1987), and hence, may be clinically useful as an adjunct to neuroleptic therapy.

Pharmacological research during the past two decades suggests the involvement of dopaminergic mechanisms in various CNS functions (Calcutt, Doggett, and Spencer, 1971; Puri, and Lal, 1973; Carlini and Lindsey, 1974; Gianutsos, Drawbaugh, Hynes and Lal, 1974; Cox and Lee, 1977). Brain DA has been implicated in analgesia, temperature regulation, locomotor
activity, aggressive behaviour, addiction, food and water intake, yawning response, reproduction; also, regulates release of various pituitary hormones such as prolactin, growth hormone, luteinizing hormone and melanocyte stimulating hormone.

Peripherally, DA produces effects mainly on the cardiovascular system. Curd (1937) demonstrated that DA increased the amplitude of contraction of isolated rabbit, cat and dog hearts. In man, DA produces dose-dependent cardiovascular effects. At low doses of 2-4 μg/kg/min., direct dopaminergic effects cause vasodilatation of renal and other vascular beds resulting in increased renal perfusion and a decrease in total peripheral resistance. Doses of 5-10 μg/kg/min., produce stimulation of β₁-adrenoceptors resulting in increased heart rate and cardiac contractility. At doses greater than 10 μg/kg/min., DA has an α₁-adrenoceptor effect resulting in vasoconstriction and a decrease in renal blood flow (Scheinburg and Scheinburg, 1985; Weiner, 1985). DA also controls the gastrointestinal motility and exocrine secretions by acting on DA receptors (Willems et al., 1985). DA alters transmission of impulses across the autonomic ganglia (Trendelenburg, 1967; Volle, 1980).

Thus, most of the actions of DA are mediated by DA receptors present either centrally or peripherally. With the advent
of intensified research pertaining to different categories of DA receptors, a number of therapeutically useful DA agonists and antagonists have been recently developed which are indicated for treatment of several clinical disorders.
NON-SELECTIVE DOPAMINE RECEPTOR AGONISTS

**APOMORPHINE**
(R)-5,6,6a,7-tetrahydro-6-methyl-4H-dibenzoquinoline-10,11-diol

**BROMOCRIPTINE**
2-bromo-12-hydroxy-2-(1-methyl-ethyl)-5-(2-methylpropyl)ergotamin-3',6',18-trione

**LERGOTIL**
2-chloro-6-methyl-ergoline-8β-acetonitrile

**LISURIDE**
3-(9,10-didehydro-6-methylergoline-3-yl)-1,1-diethylurea

**ME T ERGOLINE**
Benzyl N-(1,6-dimethyl-ergolin-B3-ylmethyl)carbamate

**PERGOLIDE**
8β-(methylthio-methyl)-6-propylergoline

**AMPHE TAMINE**
dl-alpha-methyl-phenyl alanine

**NOMIFENSINE**
8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydro-isoquinoline

**METHYL PHENIDATE**
-phenyl-2-piperidin2-acetic acid methyl ester

**AMINEPTINE**

![Chemical structures](image)

Fig. 6a
NON-SELECTIVE DOPAMINE RECEPTOR ANTAGONISTS

**FLUPHENTHIXOL**

\[ 4-[3-[(trifluoromethyl) -9H thioxanthen-9-ylidenepropyl] -piperazinethanol \]

**FLUPHENAZINE**

\[ 4-[3-[(2-(trifluoromethyl) -1 hydroxy-phenothiazine -10ylpropyl] -1-piperazine -thanol \]

**CHLORPROMAZINE**

\[ 2-chloro-10-(3-dimethyl-aminopropyl) phenothiazine \]

Fig. 6 b
**SELECTIVE DOPAMINE D<sub>3</sub> RECEPTOR AGONISTS**

**SKF 38393**

![Chemical Structure](image1)

2,3,4,5-tetrahydro-7,8-dihydroxy-1-N-n-propyl-3-benzazepine

**SKF 82526**

![Chemical Structure](image2)

6-chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-(4-hydroxyphenyl)-1H-3-benzazepine

**DIHYDROXYNOMIFENE**

![Chemical Structure](image3)

8-amino-1,2,3,4-tetrahydro-4-(3,4-dihydroxyphenyl)-2-methylisoquinoline

---

**SELECTIVE DOPAMINE D<sub>2</sub> RECEPTOR AGONISTS**

**N 0434**

![Chemical Structure](image4)

5-hydroxy-2N-n-propyl-N-2-phenylethyl-amino-tetraline

**RU 24926**

N-n-propyl di-beta-(3-hydroxyphenyl) ethylamine

**RU 24213**

N-n-propyl-N-phenylethyl-p-(3-hydroxyphenyl) ethylamine

**N 0437**

![Chemical Structure](image5)

5-hydroxy-2N-n-propyl-N-2-thienylethyl-amino-tetraline

**LY 141865**

![Chemical Structure](image6)

4,4a,5,6,7,8,8a,9-octahydro-5-n-propyl-2H-pyrazolo-3,4-8-quinoline

*Fig. 6c*
SELECTIVE DOPAMINE D₁ RECEPTOR ANTAGONISTS

SCH 23390

7-chloro 2,3,4,5-tetrahydro-3-methyl-5-phenyl-11H-3-benzazepine 7-ol
(very selective for dopamine D₁ receptor)

SELECTIVE DOPAMINE D₂ RECEPTOR ANTAGONISTS

YM 09151-2

N (benzyl-2-methyl pyrrolidin 3-yl)-5-chloro-2-methoxy-4-methyl amino-benzamide

PIMOZIDE

1-[4-4-Bis (4-Fluoro-phenyl) butyl]-4-piperidyl-1,3, dihydro-2H-benzimidazole.

HALOPERIDOL

4-[(4-p-chlorophenyl)-4-hydroxy piperidino]-4-fluorobutyrophophenone

METOCLOPRAMIDE

4-amino-5-chloro-N-[2-diethylaminol ethyl]-2-methoxy benzamide

SULPIRIDE

N-(1-ethyl-2-pyrrolidiny-methyl)-2-methoxy-5-sulphamoyl benzamide

Fig. 6d
Since the last twenty-five years, pharmacologists have been busy classifying and reclassifying DA receptors. It is well known that DA receptor agonists and antagonists are potentially effective therapeutic agents in a number of peripheral and central disorders (Woodruff, 1986).

History:

The first extensive review on peripheral DA receptors in mammals was written by Goldberg (1972). At that time, only a single postsynaptic DA receptor was known mediating renal and mesenteric vasodilatation. The first suggestion of two types of peripheral dopaminergic receptors was made by Willems et al. (1979), based on the parallelism between some effects of DA and \( \alpha \)-and \( \beta \)-effects of NA.

The process that led towards the concept of a central DA receptor began when the first neuroleptic drugs, chlorpromazine and haloperidol, were introduced for the treatment of schizophrenia. Neuroleptics were a guide leading to the DA receptor just like \( \alpha \)-bungarotoxin was for the nicotinic receptor (Laduron, P., 1980). In vivo and in vitro binding assays for the characterization of DA receptor, antagonists \([^3H]\) haloperidol and \([^3H]\) spiperone seemed to be the most appropriate ligands (Laduron, P., 1980). But like other receptor
systems, the DA receptor has not resisted the lure of the multiple site concept.

**Classification:**

Pharmacological evidence indicates the existence of several classes of DA receptors (Kebabian and Calne, 1979). It has been difficult to obtain a simple and acceptable classification for DA receptors. Previously DA receptors were designated as α-dopaminergic and β-dopaminergic, but these terms are now obsolete.

In 1979, Goldberg and Kohli confirmed the existence of two classes of peripheral DA receptors: DA₁ (i.e., vascular dopamine receptors) causing vascular smooth muscle relaxation in kidney or mesentery, and DA₂ (i.e., presynaptic dopamine receptors on sympathetic nerve terminals) causing inhibition of transmitter release. In 1982, Lokhandwala and Barrett introduced the terms "postsynaptic" DA receptors (Δ₁) for the vascular DA receptors and those in adrenal cortex, juxtaglomerular cells and renal tubules; and, "neurotropic" DA receptors (Δ₂) for the DA receptors located on sympathetic ganglia and sympathetic nerve terminals. First indication for existence of peripheral presynaptic DA receptor came from the experiments performed on nictitating membrane of cat (Langer, 1973). DA receptors in the sympathetic ganglia are involved in inhibiting ganglionic transmission in the dog and cat. The DA receptors in the gastrointestinal tract have not yet been classified.
Central DA receptors have been classified in different ways:

(I) The first classification proposed by Cools and Van Rossum (1980) differentiates between DA receptors mediating excitatory actions (DA$_E$) and those mediating inhibitory actions (DA$_I$). These two subtypes have different anatomical localization and show preference for different DA antagonists (Table 1).

(II) A second classification was summarized by Kebabian and Calne (1979) as follows: D-1 receptor is that which is linked to dopamine-sensitive adenylate cyclase, whereas D-2 receptor is not linked to adenylate cyclase. Apomorphine, butyrophenones and benzamides preferentially react with the D-2 receptor (Kebabian, 1984). D-1 receptor is found in the pars reticulata, the striatum and in melanotrophs of intermediate projection of melanocyte stimulating properties of these two types of DA.

(III) A third classification originally from studies using binding techniques and is mainly
### TABLE 1

<table>
<thead>
<tr>
<th>DA&lt;sub&gt;e&lt;/sub&gt;</th>
<th>DA&lt;sub&gt;i&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Excitation-mediating DA receptors</td>
<td>Inhibition-mediating DA receptors</td>
</tr>
<tr>
<td>2. Agonists α-rotamers</td>
<td>Agonists β-rotamers</td>
</tr>
<tr>
<td>3. Antagonists - Butyrophenones</td>
<td>Antagonists - Benzamides</td>
</tr>
<tr>
<td>4. Produces depolarization</td>
<td>Produces hyperpolarization</td>
</tr>
<tr>
<td>TYPES</td>
<td>D-1</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cyclase linkage</td>
<td>Yes</td>
</tr>
<tr>
<td>Location of prototype receptor</td>
<td>Bovine parathyroid</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Agonist (μ molar potency)</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Partial agonist or antagonist</td>
</tr>
<tr>
<td>Dopaminergic ergots</td>
<td>Potent antagonist (n molar potency)</td>
</tr>
<tr>
<td></td>
<td>weak agonist</td>
</tr>
<tr>
<td>Selective antagonist</td>
<td>None known as yet</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiolabelled ligand</td>
<td>cis-Flupenthixol</td>
</tr>
</tbody>
</table>
based on differences in absolute potency. According to Seeman (1980), there are four different DA receptor sites:

\[
D_1 = \text{Sensitive to agonists and antagonists in } \mu M \text{ concentration.}
\]

\[
D_2 = \text{Sensitive to agonists in } \mu M \text{ concentration and to antagonists in } nM \text{ concentration.}
\]

\[
D_3 = \text{Sensitive to agonists in } \mu M \text{ concentration and to antagonists in } nM \text{ concentration.}
\]

\[
D_4 = \text{Sensitive to agonists and antagonists in concentration.}
\]

From this classification, emerges the concept of two CNS dopamine receptors, D1 and D2 (Stoof and Kebabian, 1984). Only D2 site fulfills all the criteria for a receptor associated with dopaminergic behaviors and responses. Thus, the D2 receptor (Fig.7) is the DA receptor associated with stereotype, rotation, anti-parkinsonian locomotion, prolactin inhibition, emesis and antipsychotic action (Seeman, 1980).

There has been considerable progress in the isolation and purification of D2 receptors (Strange, 1986), but the knowledge regarding the role of D1 receptors in human brain remains elusive. It is just beginning to be understood that compounds like SCH 23390 (first selective D1 antagonist) might possess a novel antipsychotic action in man (Woodruff, 1986).
THE D₂ RECEPTOR

Fig. 7
Central Dopamine Receptors

A. Distribution:

By using the radio-ligand binding techniques, dopamine receptors have been identified in different areas of the brain, in different species.

<table>
<thead>
<tr>
<th>Dopamine Receptors present in</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>rat brain</td>
<td>Lauduron and Leysen, 1979</td>
</tr>
<tr>
<td>human putamen</td>
<td>Fields et al., 1977</td>
</tr>
<tr>
<td>human caudate</td>
<td>Creese et al., 1979</td>
</tr>
<tr>
<td>cerebral cortex of rat</td>
<td>Howlett and Nahorski, 1978</td>
</tr>
<tr>
<td>limbic cortex of rat</td>
<td>Howard et al., 1978</td>
</tr>
<tr>
<td>frontal cortex of rat</td>
<td>Pedigo et al., 1978</td>
</tr>
<tr>
<td>frontal cortex of calf</td>
<td>Seeman et al., 1980</td>
</tr>
<tr>
<td>frontal cortex of human</td>
<td>Field, 1977</td>
</tr>
<tr>
<td>occipital cortex of human</td>
<td>Field, 1977</td>
</tr>
<tr>
<td>occipital cortex of monkey</td>
<td>Thal, 1978</td>
</tr>
<tr>
<td>cerebellum of human</td>
<td>Fields, 1977</td>
</tr>
<tr>
<td>cerebellum of rat</td>
<td>Howlett and Nahorski, 1978</td>
</tr>
<tr>
<td>globus pallidus of human</td>
<td>Fields et al., 1977</td>
</tr>
<tr>
<td>hypothalamus of human</td>
<td>Fields et al., 1977</td>
</tr>
<tr>
<td>hippocampus of human</td>
<td>Fields et al., 1977</td>
</tr>
<tr>
<td>substantia nigra of human</td>
<td>Fields et al., 1977</td>
</tr>
<tr>
<td>substantia nigra of rat</td>
<td>Quik et al., 1979</td>
</tr>
<tr>
<td>Thalamus of human</td>
<td>Fields et al., 1977</td>
</tr>
</tbody>
</table>
B(i) Location of Dopamine D₁ Receptors:

Dopamine D₁ receptors are present in bovine parathyroid gland, retina and certain areas of mammalian CNS.

(a) Bovine parathyroid gland:

Dopamine elicits the biochemical signs characteristics of D₁ receptor activation, that is, enhanced adenylate cyclase activity and increased cyclic AMP production. This leads to an activation of cyclic AMP dependent protein kinase as well as physiological sign on receptor activation, i.e., an increase in rate of release of parathyroid hormone (Brown and Hughes, 1983; Blum et al., 1980). The receptor is stimulated by dopamine and SKF 38393 and conversely blocked by neuroleptics as well as by ergots lergotrile and lisuride (Brown et al., 1980).

(b) Retina:

Dopamine D₁ receptors occur in the retina of several mammalian species (Brown and Makman, 1972).

(c) Mammalian CNS:

Less is know about the dopamine D₁ receptor in the mammalian CNS. Although dopamine sensitive adenylate cyclase occurs in dopamine containing brain regions, the type of cell possessing this receptor was known only in one case. In the olfactory tubercle the enzyme occurs upon the pyramidal cells
Recently, a dopamine and adenosine 3',5'-monophosphate regulated phosphoprotein (DARPP-32) with molecular weight 32000 has been associated with the dopamine D_1 receptor by biochemical and anatomical criteria (Walaas and Greengard, 1984). DARPP is not the D_1 receptor; rather it is believed to be protein occurring in cells possessing a D_1 receptor. DARPP inhibits protein phosphate activity in vitro (Hemmings et al., 1984). Recently, Nestler and Greengard (1983) postulated that phosphorylation of DARPP-32 leads indirectly to a physiological by regulating the state of phosphorylation of other neuronal substrate protein. Localization of DARPP-32 in the CNS by immunohistochemistry confirmed the location of dopamine D_1 receptor upon the pyramidal cells of the olfactory tubercle and also suggested that the dopamine D_1 receptor has a discrete cellular location in other regions of the brain (Quimet et al., 1984).

Dopamine D_1 receptor stimulation in the rat brain may play a necessary 'enabling role' for dopamine D_2 mediated functional responses (White, 1987). Dopamine D_1 receptors in the zona incerta in rats are involved in the control of gonadotropin release and may have a physiological function in reproductive process (Margaret, 1987). The activation of postsynaptic dopamine D_1 receptor in rat striatum mediates the inhibitory effect of dopamine by reducing a voltage-dependent tetrodotoxin sensitive inward conductance (Calabresi...
et al., 1987). Sidhu et al., (1986) reported that the dopamine D₁ receptor contains N-ethyl maleimide sensitive SH groups either at or near the vicinity of the ligand binding sites which are critical both for receptor binding and function. Claus and Anderson (1987) reported that dopamine, D₁ receptor is a thiol protein and the thiol group is essential for ligand binding. The functional molecular mass for the agonist dopamine D₁ binding site was 132,800 daltons which is higher than the functional molecular of the antagonist dopamine D₁ binding site, approximately 80,000 daltons (Gredal and Nielsen, 1987).

(ii) **Location of Dopamine D₂ Receptors:**

(a) **Pituitary gland:**

This gland possess the prototype of dopamine D₂ receptor. This receptor occurs in both, mammotrophs (Onali et al., 1981; Euvrard et al., 1980) as well as in the melanotrophs (Cote, et al., 1982; Labrie et al., 1983). When tested upon mammotrophs, selective D₂ receptor agonists inhibit prolactin and cAMP production (Bach et al., 1980). D₂ receptor antagonists block the effect of dopaminergic agonists. The D₂ receptor is associated with the melanotrophs in the intermediate lobe and it also regulates cAMP formation and hormone release. Dopamine D₂ receptor agonists inhibit basal and stimulated cAMP formation (Grewe et al., 1982). Selective D₂ receptor antagonists can block the effect of agonists upon the interme-
The intermediate lobe dopamine $D_2$ receptor. The intermediate lobe of the pituitary gland is innervated by dopaminergic fibres which form synapse-like connections with the melanotrophs (Baumgarten et al., 1972). Dopamine $D_2$ receptor in the intermediate lobe provides an example of a postsynaptic dopamine $D_2$ receptor.

(b) **Striatum: Cholinergic Interneurons:**
Striatal acetylcholine levels are increased by dopamine $D_2$ receptor agonists and decreased by dopamine antagonists (Stoof and Kebabian, 1984). This data is consistent with the hypothesis that stimulation of a dopamine $D_2$ receptor upon the striatal cholinergic interneurons blocks the release of acetylcholine and thereby increases the content of acetylcholine. The selective dopamine $D_2$ receptor agonists, LY 141865 and RU 24926, inhibit the $K^+$ or electrically evoked release of $[^3H]$acetylcholine from striatal tissue. (-) Sulpiride reverses the inhibitory effect of either agonist. On the other hand, SKF 38393 does not inhibit the release of acetylcholine (Stoof and Kebabian, 1984).

(c) **Striatum dopaminergic neurons:**
Dopamine is the major neurotransmitter in the neostriatum. The release of dopamine from the terminals of the nigro-striatal dopaminergic neurons can be modulated by many substrates including dopamine and $D_2$ receptor agonists (Stoof et al., 1980).
Starke et al., 1978) YL 141865 inhibits K⁺ or electrically evoked release of dopamine; conversely, SKF 38393 is without effect. The inhibitory effect of LY 141865 can be antagonized by (-) sulpiride and other benzamides (Starke et al., 1983).

(d) Dopaminergic Regulation of brain peptide release:

Dopamine inhibits the release of beta-endorphin by stimulating a dopamine D₂ receptor. In the neostriatum dopamine and D₂ receptor agonists (RU-24926 and LY 141865) potentiate enhanced release of cholecystokinin-like immunoreactivity (Mayer and Krauss, 1983). This effect of dopamine D₂ receptor agonists was blocked by (-) sulpiride and dopamine. Striatum, in addition to dopamine D₂ receptors, also possesses dopamine D₁ receptors.

The dopamine D₂ receptors mediate the yawning response. These receptors are connected with dopamine D₁ receptor in such a way that the blockade of the D₁ receptors results in the functional inactivation of the former (Seera et al., 1987). The D₂ receptors also regulate the release of dopamine from dopaminergic neurons originating in the ventral tegmenta are as well as in the substantia nigra of rat (Plantje et al., 1987).

Dopamine D₂ receptors are also involved in the mediation of ocular hypotensive effect of a variety of dopamine agonists...
in rabbits and monkeys. It may also involve presynaptic dopamine D_2 receptor stimulation of noradrenergic nerve endings in the ciliary body (Turner and Mekki, 1985). D_2 receptors are involved in the antidipsogenic effect of neuroleptics in rats (Gilbert and Copper, 1987). Dopamine D_2 receptor generally are linked to adenylate cyclase in a positive way. Some dopamine D_2 receptors, coupled to cAMP generating system in an inhibitory way, are present in the adrenal glomerulosa and are functionally involved in the regulation of aldosterone production (Liberini et al., 1985). The dopamine D_2 receptor may be coupled to a guanine nucleotide regulatory protein (David and Beart, 1986). The functional molecular mass of D_2 agonist 81000 daltons was smaller than the molecular mass of D_2 antagonist (37,000 daltons) (Gredal and Nielser, 1987).

(iii) **Cellular Locations of D_1 and D_2:**

D_1 sites are not found in dopamine containing neurons but are located on neurons postsynaptic to dopamine cells. Moreover, several lesion studies have shown differences in the location of D_1 and D_2 receptors.

(a) About 50% to 60% of the [^3H] neuroleptic-binding sites (mostly D_2) in the striatum are situated on cell bodies residing in the striatum; these sites are eliminated by intrastriatal kainic acid. (Schwarcz et al., 1978).
(b) About 20% to 30% of $[^{3}\text{H}]$-neuroleptic binding sites (mostly $D_2$) in the striatum are situated on nerve terminals coming from the cerebral cortex; these sites are eliminated by decortication (Garau et al., 1970).

(c) All the $D_4$ sites in the striatum are situated on cell bodies within the striatum; these sites, therefore, are completely eliminated in the first few weeks after kainic acid lesion (Garau et al., 1978; Schwancz et al., 1978).

(d) About 50% of the $[^{3}\text{H}]$ Spiperone-binding sites ($D_2$) in the nigra are on cell bodies residing in the nigra; these sites, are eliminated by lesions that destroy the nigral dopamine-containing cells (Quik et al., 1979).

(e) All the $D_4$ sites in the nigra are situated on terminals from cells arising from the striatum or elsewhere; these are 75% reduced by lesions of striatal neurons (Quik et al., 1979; Spano et al., 1977).
C. Comparison of D₁ and D₂ receptors:

(a) **Biochemical manifestation:**

<table>
<thead>
<tr>
<th>D₁</th>
<th>D₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in cAMP formation linked to adenylate cyclase</td>
<td>No change or decrease in cAMP formation not linked or negatively linked to adenylate cyclase</td>
</tr>
</tbody>
</table>

(b) **Physiological manifestation:**

<table>
<thead>
<tr>
<th>Receptor site induces bovine parathyroid hormone release</th>
<th>Inhibition of prolactin and alpha melanocyte stimulating hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetitive firing of growth hormone producing cells in CNS of Lymnaeo stagnalis</td>
<td>Inhibition of acetylcholine and dopamine release (rat neostriatum)</td>
</tr>
<tr>
<td>Inhibition of beta-endorphin release</td>
<td>Inhibition of firing rate of dopaminergic neurons</td>
</tr>
<tr>
<td>Inhibition of chemosensory discharge in rabbit carotid body; hyperpolarization of growth hormone producing cells in CNS of Lymnaeo stagnalis</td>
<td></td>
</tr>
</tbody>
</table>

(c) **Pharmacology:**

<table>
<thead>
<tr>
<th>Selective Agonist</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>SKF 38393</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>SKF 82526</td>
<td>RU 24926</td>
</tr>
<tr>
<td>Dihydroxy nomifensine</td>
<td>RU 24213</td>
</tr>
<tr>
<td></td>
<td>N 0434</td>
</tr>
<tr>
<td></td>
<td>N 0437</td>
</tr>
<tr>
<td></td>
<td>LY 147865</td>
</tr>
</tbody>
</table>
D. Role of DA in CNS:

Dopamine plays an important role in the regulation of various functions of the brain. There are three major classes of dopaminergic neurons in the brain (Moore and Bloom, 1978). They are:

1. Ultrashort neurons within the amacrine cells of the retina and periglomerular cell of the olfactory bulb.

2. Intermediate length neurons within tuberobasal ventral hypothalamus that innervate median eminence and intermediate lobe of pituitary, incertohypothalamic neurons that connect the dorsal and posterior hypothalamus with the lateral septal nuclei, and small series of neurons within the perimeter of the dorsal motor nucleus of the vagus, the nucleus of the solitary tract, and the periaqueductal grey matter.

3. Long projections between the major dopamine containing nuclei in the substantia nigra and ventral tegmentum and their targets in the striatum, in the limbic zones of the cerebral cortex and in other major regions of the limbic system, except the hippocampus.

The neurophysiological activity of dopaminergic neurons are generally inhibitory; however, in some sites, it may be
excitatory (Hornykiewicz, 1966). Dopaminergic neurotransmission plays an important role in the maintenance of normal locomotor activity and behaviour. Administration of dopa (3,4-dihydroxyphenylalanine) produces marked stimulation of locomotor activity accompanied by behavioral changes in the treated animals (Hornykiewicz, 1966). It induces autonomic signs like piloerection, salivation, hyperpnea, pupillary dilatation, blanching of ears, urination, defection and ejaculation. Straub's tail raising phenomenon is very common; 'catatonic' postures and fear reactions have also been described (Vadervende and Spoerlein, 1962). These actions of dopa are due to dopamine as dopa is converted to dopamine in the brain (Carlsson et al., 1958). In addition administration of dopa to rabbits, cats and monkey causes an 'arousal reaction' in the electroencephalogram (Kiruchi, 1962).

The involvement of dopaminergic system in Parkinson's Disease was demonstrated mainly from the studies done with reserpine. Reserpine depletes the brain of its dopamine content (Carlsson et al., 1958), causing a deficiency of the amine in the striatum and other dopamine containing regions (substantia nigra, pallidum). Based on these data, it was suggested that the extrapyramidal symptomatology induced by reserpine both in animals and in man is the consequence of dopamine deficiency in the extrapyramidal centres (Bertler...
Parkinsonism is a clinical syndrome characterized by muscular rigidity, akinesia and tremors; DA deficiency has been demonstrated in the brain of patients who suffered from this disease (Ehringer and Hornykiewicz, 1966). Thus dopamine plays an important role in the regulation of extrapyramidal functions of the brain.

The involvement of dopaminergic system of the brain in the behaviour was demonstrated based on the actions of phenothiazines. Most phenothiazines produce a parkinsonian-like syndrome in man, resembling very closely the extrapyramidal effects of reserpine (Hornykiewicz, 1966). In view of the close similarity between the extrapyramidal symptoms caused by reserpine and phenothiazines, it may be speculated that both drugs might have essentially the same mechanism of action. Phenothiazine derivatives are known to block the actions of catecholamines in the periphery (Courvoisier et al., 1951) and the same has been suggested for the brain (Carlsson et al., 1962). It was hypothesized that the dopamine blocking action of phenothiazines is responsible for its extrapyramidal actions (Hornykiewicz, 1966). Mattysse and Sugarman (1978) furnished evidence to postulate that there is an overactivity of dopaminergic system in schizophrenia, particularly in the dopaminergic neurons of the limbic system. The antipsychotic effect of
phenothiazines is by virtue of its antidopaminergic activity in the limbic system (Baldessarini, 1985). These evidences indicate that dopamine plays a major role in the normal behaviour of man. Mood or affective state is the result of a balance between the activities of the various amine-containing neurons such as dopaminergic neurons and cholinergic neurons in the brain (Bowman and Rand, 1983). The affective disorders, depression and mania, are probably a direct consequence of imbalance between these neuronal systems (Bowman and Rand, 1983). There is considerable evidence for the hypothesis that an increase in monoamine level in the brain is associated with elevation of mood, since monoamine oxidase inhibitors produce these effects, and that a decrease in monoamine levels is associated with depression, since reserpine produces these effects (Bowman and Rand, 1983). In patients with chorea, it was reported that there is an increase in dopamine levels in the putamen (Bowman and Rand, 1983).

Dopaminergic systems of the brain also play an important role in the control of regulation of various pituitary hormones. Central dopaminergic stimulation is responsible for the beneficial effects of bromocriptine in hyperprolactinaemic states. The tuberoinfundibular dopamine neurons play an important role in the feedback loop of prolactin secretion.
A high prolactin level activates the tuberoinfundibular dopamine neuron to synthesize dopamine which acts on dopaminergic receptors on pituitary mammotrophs and inhibit adenylate cyclase system which normally activates the cell to secrete prolactin (Tuomisto and Mannisto, 1985). Activation of central DA receptors stimulates growth hormone secretion (Lai, et al., 1977), but strongly inhibits the secretion of thyroid stimulating hormone.

There exists a dose relationship between DA and luteinizing hormone releasing factor (Hokfelt, and Fuxe, 1971). Tuberoinfundibular dopamine system is an inhibitory regulator in the luteinizing hormone secretion (Tuomisto and Mannisto, 1985) and in the castrated rats the inhibitory effect occurs at a suprapituitary site (Rose and Richards, 1986). In Cushing's syndrome, dopamine seems to be important in inhibiting adrenocorticotrophic hormone release (Tuomisto and Mannisto, 1985). Dopamine, given intracerebroventricularly (i.c.v.), has a stimulating effect on the vasopressin release from the neurohypophyseal system (Ivangi et al., 1986). Dopaminergic pathway is important in the in vivo regulation of pituitary intermediate lobe activity of dogs (Kemppainen and Sartin, 1986). Dopamine induces inhibition of melanocyte stimulating hormone release.
Dopamine may have a physiological function in reproductive process (Margaret et al., 1987) and may be involved in the ejaculatory behaviour in copula of rats (Clark and Smith, 1987).

DA plays an important role in the maintenance of normal feeding behaviour (Zigmond and Striker, 1972) as well as in water consumption (Gilbert, 1987) and is involved in the rewarding effects of food and water (Nakajuna, 1986). D₂ receptors are involved in the antidipsogenic effect of neuroleptics in rats (Gilbert and Cooper, 1987). The yawning response is behavioral correlate of increased. DA transmission mediated by postsynaptic DA receptors of D₂ type; these receptors are connected with D₁ receptors in such a way that the blockade of latter results in functional inactivation of the former (Serra et al., 1987). The ocular hypertensive effect of a variety of DA agonists has been demonstrated in rabbits.
Peripheral Dopamine Receptors

A. Peripheral postsynaptic DA receptors:

Historically, postsynaptic dopamine receptors were the first to be pharmacologically characterized (Goldberg et al., 1978). It has been demonstrated that the renal vascular bed of canine and other species is rich in postjunctional dopamine DA₁ receptors. Stimulation of these receptors lead to a reduction in renal vascular resistance (Goldberg et al., 1978). Dopamine release from renal dopaminergic neurons in the renal cortex may play a role in the physiological control of renal blood flow (Bell et al., 1978; Dinerstein et al., 1975). It has been speculated that a rise in arterial pressure due to an increase in sympathetic tone, may trigger the release of dopamine from renal dopaminergic neurons; this would cause renal vasodilation, natriuresis, and thus, a diuretic effect (Cavero et al., 1982). Dopamine can reduce blood pressure in dogs pretreated with alpha and beta-adrenoceptor blocking agents by stimulating dopamine DA₁ receptor located postjunctionally in some parts of the arterial tree (Cavero et al., 1982).

Dopamine has been reported to produce natriuresis which is associated with an increased diuresis in humans, dogs, cats, and rats. This effect was shown to be independent of changes
in renal blood flow, glomerular filtration rate or renal sympathetic activity. Thus a tubular site of action, rather than a modification in renal resistance, might be responsible for the dopamine induced natriuresis (Wassermann et al., 1980).

The involvement of postsynaptic dopamine receptor in this action has been suggested (Goldberg and Weber, 1983). Typical dopamine DA1 receptors are located postsynaptically in the mesenteric arterial beds. The stimulation of these receptors leads to vascular smooth muscle relaxation.

The dopamine receptors involved with natriuresis, regulation of renin release, response of carotid body to CO2, electrical coupling between cells in retina, and the secretion of various hormones have not been characterized clearly. Dopamine receptors are involved in renin release (Goldberg and Weber, 1980). Several reports indicate that infusions of dopamine increases plasma renin activity in experimental animals and that this effect is specifically blocked by haloperidol (Cavero et al., 1982). Aldosterone secretion in rats is modulated by a mechanism involving DA2 receptors (Barett et al., 1987).
B. Peripheral presynaptic DA receptors:

In the past decade, it has become apparent that endogenous and exogenous substances can modify the release of transmitter from postganglionic sympathetic nerve endings through an effect on receptors located on these nerve endings, the so-called presynaptic receptors. As pointed out by Haeusler (1976), the term 'prejunctional' would be more appropriate, as the junctions between the sympathetic nerve endings and smooth muscle cells are morphologically different from a synapse. However, the term presynaptic is generally accepted.

As far as adrenergic substances are concerned, inhibitory alpha adrenoceptors and facilitatory beta-adrenoceptors have been described on sympathetic nerve endings in several organs, and the presynaptic regulation of noradrenaline release has been extensively reviewed (Langer, 1979, 1981; Patel et al., 1981; Starke et al., 1977 and Westfall, 1977). Some sympathetic nerve endings are also endowed with an inhibitory receptor selective for dopamine. The distribution of the presynaptic dopamine receptor is limited with regard to different organs as well as different species (Maixner et al., 1983). Presynaptic dopamine receptors have been identified in:

(a) Nictitating membrane:

The first indication for the existence of a peripheral presynaptic dopamine receptor came from the experiments of Langer et al., (1973 and 1975) in the in vitro nictitating membrane preparation of the cat. In presence of cocaine,
dopamine was equipotent with noradrenaline in inhibiting the nerve stimulation evoked release of $[^3H] \text{noradrenaline}$, since dopamine is 40 times less potent than noradrenaline at postsynaptic alpha-adrenoceptors. Langer (1973) first suggested that both noradrenaline and dopamine interacted with a presynaptic alpha-adrenoceptor which was different from the postsynaptic alpha-adrenoceptor. However, apomorphine mimicked the effect of dopamine, and the effect of dopamine and apomorphine was antagonized by chlorpromazine and pimozide at concentrations that did not affect the inhibitory effect of noradrenaline. Phenolamine, on the other hand, blocked the effect of noradrenaline, but much lesser than that of dopamine. Phenoxycarbamine antagonized the effects of noradrenaline, dopamine and apomorphine (Enero and Langer, 1975; Langer, 1973). On the basis of these findings, it was concluded that dopamine inhibits the release of noradrenaline via dopamine receptors.

Observations in the cat confirmed that known dopaminergic agents also interfered in vivo with nerve stimulation induced contractions of the nictitating membrane via a dopamine receptor. Dopamine in the presence of cocaine (Gyorgy et al., 1977), apomorphine (Gyorgy et al., 1977 and 1983) bromocriptine and piribedil (Gyorgy et al., 1983) inhibited these contractions. The effect of dopamine was antagonized by haloperidol (Gyorgy et al., 1977), the effect of piribedil by sulpiride (Gyorgy et al., 1983), the effect of apomorphine by haloperidol.
and sulpiride but not by phentolamine (Gyorgy et al., 1977).
The experimental observations whereby DA and DA receptor agonists produced a presynaptic inhibitory effect in the nictitating membrane are listed (Table No. 3).

(b) **The heart:**

*In vivo* experiments in the cat show that dopamine (after cocaine administration) and apomorphine inhibit the increase in heart rate evoked by cardioaccelerator nerve stimulation, and that this effect was not marked at lower stimulation frequencies (Long et al., 1975). Haloperidol antagonized the effects of dopamine, but, high doses of phentolamine were needed to block dopamine effects (Ilhan and Long, 1975; Ilhan et al., 1974). The experimental observations whereby DA and DA receptor agonists produced a presynaptic inhibitory effect in the heart are listed (Table No. 3).

(c) **The vascular system:**

**Rabbit ear artery**

Dopamine is equipotent with noradrenaline in inhibiting noradrenaline release from sympathetic nerve endings in the isolated rabbit ear artery (McCulloch et al., 1973). In the same preparation, DA also inhibits the vasoconstrictor responses induced by low frequency field stimulation without affecting vasoconstrictor responses produced by exogenous noradrenaline
<table>
<thead>
<tr>
<th>Agonist</th>
<th>Species</th>
<th>Dose(nM)</th>
<th>Antagonized by</th>
<th>Not antagonized by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Cat</td>
<td>105/kg iv</td>
<td>Haloperidol</td>
<td>Pimozide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bulbocapnine</td>
<td>Phentolamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>Dog</td>
<td>26-52/kg/min.</td>
<td>Haloperidol</td>
<td>Pimozide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pimozide</td>
<td></td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Cat</td>
<td>19-103/kg/iv</td>
<td>Haloperidol</td>
<td>Phentolamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bulbocapnine</td>
<td>Pimozide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pimozide</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Cat</td>
<td>22/kg iv</td>
<td>Haloperidol</td>
<td>Pimozide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chlorpromazine</td>
<td>Pizotifen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sulpiride</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pimozide</td>
<td></td>
</tr>
</tbody>
</table>

Inhibition of the chronotropic response to field stimulation in vitro.

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Species</th>
<th>Dose(nM)</th>
<th>Antagonized by</th>
<th>Not antagonized by</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Rabbit</td>
<td>30 x 10^3</td>
<td>cis-fluphen-9thiokol</td>
<td>Phentolamine</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Cat</td>
<td>8,43,580 (IC_50)</td>
<td>Haloperidol</td>
<td>Pimozide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pimozide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>10,000</td>
<td>cis-fluphen-thiokol</td>
<td></td>
</tr>
</tbody>
</table>
(Rand et al., 1975; McCulloch et al., 1973). Above observations led to the suggestion that these dopamine effects were mediated via presynaptic dopamine receptors. The hypothesis that a presynaptic dopamine receptor was involved in this inhibitory effect on sympathetic nerve evoked responses was further tested with selective antagonists and some known dopamine receptor agonists. Measuring field stimulation induced release of noradrenaline, it was found that the inhibitory effect of dopamine was blocked by metoclopramide and pimozide in concentrations which did not antagonize the presynaptic effect of noradrenaline. The dopamine induced inhibition of the vasoconstrictor responses in the rabbit ear artery is markedly reduced by haloperidol but not by phentolamine (Bell et al., 1977).

**Hindleg vasculature:**

The first indication that inhibition of transmitter release from sympathetic nerve ending via a presynaptic dopamine receptor might have a significant effect on vascular resistance came from experiments in the canine hindleg vasculature. Apomorphine, injected in the femoral artery, produced a marked but transient vasodilation (Laubie et al., 1977; Buylaert et al., 1977), not antagonized by beta-adrenoceptor blocking agents, atropine or by a combination of mepyramine and metiamide (Buylaert et al., 1978), in doses sufficient...
to block the vasodilatory effects of the respective agonists. The femoral vasodilation produced by apomorphine was antagonized by haloperidol in doses that did not influence the responses to isoprenaline, acetylcholine, histamine and nitroglycerine (Buylaert et al., 1978). The vasodilator effect of apomorphine was restored when vascular tone was raised by electrical stimulation of the sympathetic innervation, but not when tone was increased by noradrenaline infusion. These observations suggested the presence of a presynaptic dopamine receptor, although dopamine did not produce a similar effect, presumably because of its alpha-adrenoceptor mediated vasoconstrictor properties.

Renal and mesenteric vasculature:

As far as other blood vessels are concerned, special attention has been paid to the renal and mesenteric vasculature, since postsynaptic dopamine receptors have first been described in these blood vessels in the dog (Goldberg et al., 1972). It was therefore, of interest to know whether a presynaptic mechanism also pays a role in the dopamine induced vasodilation in these vessels when sympathetic tone is present. In the dog renal vasculature, a presynaptic inhibitory effect has been described for dopamine, which was antagonized by pimozide (Lokhandwala and Barrett, 1982).
Dopamine reduces the noradrenaline outflow induced by field stimulation from isolated bovine renal artery and this effect is antagonized by metoclopramide and pimozide. As far as the mesenteric vasculature is concerned, DA has been shown to inhibit the nerve stimulation induced mesenteric vasoconstriction in different animal species: the dog, (Roby et al., 1979), the cat (Sanders et al., 1975), the rat (Anwar et al., 1981 and 1979), the rabbit (Anwar et al., 1981) and the mouse (Anwar et al., 1981). In cat, rat, and rabbit, this occurs without influencing the vasoconstrictor response of noradrenaline; in the rat and rabbit, the effect was mimicked by apomorphine and antagonized by haloperidol, but not by yohimbine. In the dog, the effect was mimicked by piribedil, and this inhibition was antagonized by pimozide (Laubie et al., 1978). This suggests the presence of presynaptic dopamine receptors in the mesenteric vasculature of rat, rabbit, and dog.

Other blood vessels:

Other blood vessels in which inhibitory presynaptic dopamine receptors have been suggested are the rat portal vein (Enero, 1979) and the human omental vein (Skjarne and Brundin, 1975). A presynaptic inhibitory effect of dopamine
has been described in the dog saphaneous vein, where it is mimicked by apomorphine (Buylaert and Willems, 1976).

(d) Other organs:

The presence in mammalian organs of selective dopamine receptors, mediating presynaptic inhibitory effects has been further postulated at several sites other than the nictitating membrane and the cardiovascular system.

Spleen:

Some evidence for the presence of presynaptic dopamine receptors has been found in the spleen of cat and dog. Dopamine and apomorphine inhibit the rise in perfusion pressure of the spleen induced by nerve stimulation (Hope et al., 1978) and reduce the stimulation-induced outflow of noradrenaline (Hope et al., 1978; Langer, 1973), dopamine being equi-potent with noradrenaline (Langer, 1973). The effects of dopamine and apomorphine were selectively blocked by s-sulpiride (Hope et al., 1978) in a concentration that has no effect on presynaptic alpha2 adrenoceptors, whereas they were not antagonized by phentolamine in a concentration sufficient to block alpha2 adrenoceptors.

Vas deferens:

In the isolated vas deferens of the rat, dopamine inhibits the contractions induced by hypogastric nerve
stimulation (Tayo, 1977) or field stimulation (Gyorgy et al., 1981; Tayo, 1979 and 1981) without influencing the contractions evoked by exogenous noradrenaline (Gyorgy et al., 1981). Dopamine was more potent than noradrenaline at this presynaptic site and its effect was mimicked by apomorphine and bromocriptine. Pimozide antagonized dopamine and apomorphine in concentrations that did not antagonize noradrenaline (Tayo, 1979; Tayo, 1981). Haloperidol antagonized dopamine and apomorphine and also noradrenaline (Tayo, 1977); it did not antagonize bromocriptine (Gyorgy et al., 1981).

It was suggested that in the rat vas deferens, the presynaptic effect of dopamine is mediated via α₂ adrenoceptors. The same applies to the vas deferens of the mouse (Gibson et al., 1979; Hurst et al., 1979) and the guinea pig (Bell, 1980). The presynaptic effect of dopamine on nerve stimulation evoked twitch contractions are blocked by yohimbine and phentolamine but not by cis-flupenthixol, pimozide or haloperidol).

Others:

A presynaptic effect of bromocriptine has been described in the anococcygeus muscle of the rat, but no antagonists were studied (Gibson et al., 1977). In the human bladder, dopamine does not produce a specific effect (Heffron et al., 1980), and metoclopramide does not modify bladder function (Vaidyanathan et al., 1980).
Characteristic of the presynaptic dopamine receptor:

Presynaptic dopamine receptor versus presynaptic alpha$_2$ adrenoceptor:

It appears from previous sections that the presence of a presynaptic dopamine receptor on sympathetic nerve endings in different organs has been accepted because the presynaptic effects of dopamine agonists and antagonists cannot be explained by an interaction with alpha-adrenoceptor. In most cases, it was possible to block selectively the presynaptic effects of noradrenaline with doses of phenolamine or other alpha-adrenoceptor antagonists that did not interfere with the presynaptic effects of dopamine or dopamine receptor agonists. Conversely, it was possible to block the presynaptic effect of dopamine with dopamine receptor antagonists without antagonizing the alpha adrenoceptor mediated presynaptic inhibition. Furthermore, substances such as dopamine, aminotetrinaline, apomorphine, ergot alkaloids and their derivatives, which are agonists for the presynaptic dopamine receptor, behave quite differently on the alpha-adrenoceptor, either as agonists, partial agonists or antagonists.

C. Physiological and Pharmacological significance of presynaptic dopamine receptors:

Physiological role:

Dopamine and presynaptic DA$_2$ receptors participate in the negative feedback of noradrenaline release in situations of
prolonged nerve activity. It was proposed that, under these conditions, dopamine is released from noradrenergic nerves and acts on presynaptic DA$_2$ receptors to decrease the noradrenaline release in order to save transmitter (Head and Berkowtiz, 1979; Hope et al., 1979). The presynaptic DA$_2$ receptors are located on noradrenergic nerve terminals. It has been suggested that dopaminergic nerves exist in the periphery, liberating dopamine as their neurotransmitter; they have been described mainly in the kidney in several species and in the canine hindpaw (Bell, 1982; Bell et al., 1978). Whether these presynaptic DA$_2$ receptors are present on these dopaminergic nerve terminals and mediate a negative feedback on dopamine release is not clear. Their role seems to be to regulate local blood flow and natriuresis via postsynaptic DA$_1$ receptors (Bell, 1984; Lokhandwala and Barrett, 1982).

**Pharmacological role:**

Although it is not clear whether presynaptic DA$_2$ receptors play a physiological role in the regulation of sympathetic nerve transmitter release, they are of interest from pharmacological point of view. Presynaptic inhibition of sympathetic tone, with reduction of peripheral vascular resistance and heart rate, might be useful in the treatment of hypertension, while the after load reduction might be useful in heart failure and shock. It has been suggested that an alteration
of the negative feedback control mechanism of noradrenaline release plays a role in the increased peripheral resistance observed in hypertension (Lokhandwala and Eikenburg, 1983).

D. Peripheral actions of DA:

(i) Cardiovascular System:

DA exerts a positive inotropic effect on the myocardium, acting as an agonist at β₁ receptors. In addition, it has the capacity to release NA from nerve terminals, and this also contributes to its effects on the heart (Weiner, 1985). DA appears to increase systolic and pulse pressure and has either no effect or slightly increases the diastolic blood pressure. The effect of DA on renal vasculature appears to be mediated by a specific DA receptor. Low doses of DA infusion cause an increase in the glomerular filtration rate, renal blood flow and sodium excretion. Hence, DA is useful in the management of some types of shock. High doses of DA infusion tend to elevate the blood pressure as a consequence of renal vasoconstriction. DA may also be of value in the treatment of chronic refractory congestive cardiac failure (Goldberg, 1974). DA increases plasma renin activity (Cavero et al., 1982). It inhibits aldosterone secretion in rats through dopaminergic nerves supplying the adrenal medulla (Jungmann et al., 1986). DA also increases the metabolic clearance of angiotensin II, possibly by altering blood flow through renal vascular beds, which degrade the peptide (Connell et al., 1987).
(ii) **Autonomic Ganglia:**

Neurotransmission in autonomic ganglia is described as a complex process. Morphological studies indicate that catecholamine-containing cells are present in the ganglia. DA and NA cause hyperpolarization of ganglia. Many evidences point towards the involvement of one or several catecholamines in the generation of IPSP (inhibitory postsynaptic potential). The evidences in favour of DA's inhibitory action on ganglionic transmission is that this catecholamine reduces vascular resistance in the hindleg of dog when injected into the blood supply of paravertebral lumbar ganglia (Bogaert and Deschaepdryver, 1967). Also, when injected close to the superior cervical ganglion, DA inhibits contraction of the nictitating membrane elicited by preganglionic stimulation (Trendelenburg, 1967). Two mechanisms have been suggested: one via the postsynaptic ganglionic neuron; the other via the presynaptic preganglionic nerve ending. The postsynaptic inhibition involves postsynaptic hyperpolarization mediated by cAMP, via stimulation of membrane-bound DA sensitive adenylate cyclase (Greengard and Kebabian, 1974). The presynaptic mechanism involves the release of acetylcholine (ACh) from preganglionic nerve endings. DA also induces ganglionic facilitation presumably via a postsynaptic mechanism (Volle, 1980). The DA receptor subtype involved has not yet been identified.
(iii) **Carotid Body:**

The carotid body contains DA and ACh. ACh granules are present in the afferent nerve endings whereas DA-containing granules are present in glomus cells. Hypoxia reduces the release of DA from the glomus cells, possibly by inhibiting its synthesis. This activates the carotid body to discharge action potentials. Thus, DA plays a major role in the functioning of carotid body (Bowman and Rand, 1983).

(iv) **Gastrointestinal Tract:**

DA has inhibitory effects on the smooth muscle activity and exocrine gland secretion of the GIT. The inhibitory effect of DA on motility in some experimental preparations has been explained by an interaction with a specific DA receptor. Significant amounts of DA have been found in the gastrointestinal wall of several mammalian species (Holzbauer and Sharman, 1972) and in human gastric juice (Haggendal, 1967). DA inhibits pentagastrin-stimulated acid secretion in dog (Valenzuela and Grossman, 1976) and man (Valenzuela et al., 1979).

DA agonists exert a strong protective effect against gastric lesions induced by stress (Hernández, Adcock and Orlando et al., 1984) and administration of aspirin reserpine, phenylbutazone (Parmar, et al., 1984) as well as antagonists (Sikiric et al., 1986).
Involvement of central DA receptor in the regulation of gastrin release has been suggested (Mascu, et al., 1984). DA stimulates the exocrine secretion of dog and rat pancreas, but not of human pancreas. DA also has a stimulatory effect on salivary secretion, and this effect is due to activation of \( \alpha \) - and \( \beta \)-adrenoceptors as well as DA receptors (Abe and Dawes, 1982).

Bromocriptine, a specific DA receptor agonist, has been shown to have a beneficial effect in hepatic coma.
Dopamine Autoreceptors

The regulation of nigrostriatal and mesolimbic dopamine neurons in brain is assumed to be partly exerted by so-called autoreceptors, i.e., receptors located on the neurons, activated by the neuron's own transmitter and exerting an inhibitory feedback influence on nerve activity (Carlsson, 1975; Roth, 1979). These autoreceptors can be detected by a decrease in dopamine cell firing rate, dopamine turnover and motor activity. On the other hand, activation of post-synaptic dopamine receptors causes contralateral turning after unilateral nigrostriatal denervation, stereotyped behaviour and an increase in motor activity. Dopamine agonists such as apomorphine, bromocriptine and dopamine itself activate both autoreceptor and postsynaptic receptor. The autoreceptors seem more sensitive than the postsynaptic receptor. The autoreceptors seem more sensitive than the postsynaptic receptors since low doses of most dopamine agonists activate preferentially autoreceptors (Strombom, 1976; Skirboll et al., 1979). Administration of low doses of dopamine agonists decrease the plasma prolactin levels indicating that pituitary lactotroph dopamine receptors, in common with autoreceptors, are more sensitive than the postsynaptic dopamine receptors in the striatum and the limbic system (Annuziato, 1979). The autoreceptors may be present in the nerve terminal, or cell body, or dendrites. The properties of dopamine autoreceptors are given below (Bannon and Roth, 1983).
(i) Nerve terminal autoreceptors modulate the impulse induced synthesis and release of DA.

(ii) Cell body/dendritic autoreceptors regulate the physiological activity (firing) of the dopamine cell.

(iii) In any particular DA system, autoreceptors are either present on or absent from both the nerve endings and cell bodies/dendrites.

(iv) Within any given DA system, nerve terminal and cell body/dendritic autoreceptors appear to have similar or identical pharmacological properties.

(v) Nerve terminal autoreceptors on the mesolimbic DA neurons appear to be more sensitive to DA agonists than autoreceptors on nigrostriatal nerve endings.

(vi) Autoreceptors differ from postsynaptic DA receptors in their pharmacological responsiveness (e.g., the enhanced sensitivity of autoreceptors to DA agonists).

(vii) The responsiveness of autoreceptors is altered following chronic exposure to various pharmacological agents.
Dopamine autoreceptors are located predominantly in the nigrostriatal, mesolimbic and mesopiriform dopaminergic pathways. However, they are absent in dopaminergic neurons of mesocortical, mesoprefrontal and mesocingulate pathway. Dopaminergic neurons which lack the autoreceptors have different characteristics when compared with those possessing these autoreceptors. Bannon and Roth (1983) have described the unique characteristics of mesocortical dopamine neurons as compared to those possessing autoreceptors:

1. A higher dopamine turnover rate.
2. A higher rate of physiological activity (firing) and different pattern of activity (more bursting).
3. Greatly diminished responsiveness to dopamine agonists and antagonists.
4. Lack of development of tolerance following chronic antipsychotic drug administration.
5. Resistance of development of depolarization-induced inactivation following chronic antipsychotic drug administration.
The drug B-HT 920, (2-amino-6-allyl-5,6,7,8-tetrahydro-4-hydrothiazol(4,5-d)azepine) is an azepine derivative reported to be an agonist of central and peripheral alpha₂-adrenoceptors (Kobinger and Pichler, 1980). Like all other alpha₂ adrenoceptor agonists, it causes hypotension and bradycardia and also decreases motor activity of mice. This decrease in motor activity is readily reversed by administration of postsynaptically active doses of dopamine agonist apomorphine (Evivksson et al., 1985). Furthermore, B-HT 920 decelerated both, the disappearance of dopamine after tyrosine hydroxylase inhibition and accumulation of DOPA in dopamine-rich brain structures after decarboxylase inhibition in animals administered either gamma-butyrolactone or reserpine (Ericksson, 1985). These events which were antagonized by the dopamine antagonist haloperidol, indicate reduced dopamine synthesis and turnover seen after dopamine receptor activation. In contrast, B-HT 920 showed no signs of postsynaptic dopamine receptor activation such as stereotype behaviour or increased locomotion, in normal or reserpinized rats. It has been proposed that B-HT 920 also has dopamine agonist activity with selectivity for autoreceptors (Anden et al., 1982 and 1983).

Recently, a number of dopamine agonists have been reported exhibiting either selectivity for autoreceptors, or apparently opposite action at dopamine autoreceptors and...
dopamine postsynaptic receptors. Thus, 4-(2-di-n-propylaminoethyl indole (DPAI) appears to be devoid of affinity at postsynaptic dopamine receptor while it effectively activates dopamine autoreceptors (Clemens et al., 1984). 

(-)-3-(3-hydroxyphenyl) N-n-propylpiperidine((-)-3-PPP) (Hjorth et al., 1983; Clark et al., 1984) and transdihydro-lisuride (IDHL) (Wachtol and Dorow, 1983) both appear as agonists or partial agonists with high intrinsic activity at dopamine autoreceptors, while they behave as antagonists at postsynaptic dopamine receptor. Interestingly, DPAI, IDHL and (-)-3-PPP also cause a decrease in plasma prolactin at doses similar to those causing autoreceptor activation. Moreover, the effect of (-)-3-PPP on prolactin is effectively antagonized by dopamine antagonists such as metoclopramide and sulpiride which have putative selectivity for autoreceptors, while preferentially postsynaptic antagonists such as pimozide and clozapine appear less active (Eriksson et al., 1983). These findings suggest that the dopamine receptors at the lactotrophs are pharmacologically more similar to dopamine autoreceptors than to postsynaptic dopamine receptors in the brain (Eriksson et al., 1983). This hypothesis is reinforced by the fact that B-HT 920 decreases plasma levels of prolactin in a dose-dependent manner in reserpinized rats (Eriksson, et al., 1985).
Both dopamine autoreceptors and dopamine receptors at the lactotrophs are designated as D₂ since they do not stimulate adenylate cyclase activity (Kebabian and Caine, 1979). Both the receptors are 'nonsynaptic' being located at a certain distance away from the release of dopamine and thus exposed to lower concentrations of dopamine than are the 'postsynaptic' D₂ receptors in the striatum and limbic system (Carlsson, 1983; Eriksson et al., 1985). Selective agonist at 'nonsynaptic' DA receptor, such as B-HT 920, can be used as an antipsychotic agent as well as a specific tool for hyperprolactinemia (Eriksson et al., 1985).

Dopamine Receptor Alterations In Various Conditions

(1) Parkinson's Disease:

In Parkinson's disease, there is development of denervation supersensitivity in the striatum (Birkmayer et al., 1975). The number of dopamine D₂ (postsynaptic) receptors was elevated by 50% to 100% in the postmortem brain striata of patients with Parkinson's disease (Lee et al., 1978). As for D₁ sites in the striatum of patients with Parkinson's disease, Shibuya (1979) indicates no differences from normal.
(2) Schizophrenia:

Dopamine D₂ receptor density in schizophrenics significantly rises (Owen et al., 1978; Mackay et al., 1978). However, there is no significant alteration in the D₁ sites in schizophrenia as measured by the binding of [³H]cis-flupenthixol (Cross et al., 1980).

With respect to future research in this area of dopamine receptors in schizophrenia, it is important to note that [³H]-spiperone binds to serotonin S₂ sites in addition to dopamine D₂ receptors (Seeman, 1980). It will be necessary to measure these serotonin S₂ sites separately in diseased tissues, since there may be abnormalities in the serotonin system in schizophrenia (Bennett et al., 1979). Patients with Huntington's disease and Tourette's disease exhibit an elevated density of D₂ receptors in the striatum (Reisine et al., 1977; Feinberg and Carroll, 1979). Since clonidine can control Tourette's disease, it is important to measure alpha₂ adrenoceptors in this syndrome (Cohen et al., 1979). It would be important to investigate the state of various opiate receptors in schizophrenic brain. Opiates can indirectly control the release of dopamine (Sampath et al., 1976).
(3) **Dopaminergic supersensitivity after administration of Neuroleptics:**

(i) **Tardive dyskinesia:**
Long-term receptor blockade with neuroleptics elicits dopaminergic supersensitivity in animals in association with an elevated dopamine D$_2$ receptors (Seeman, 1980) and tardive dyskinesia is a slowly developing syndrome of involuntary motor movements appearing as a late effect of neuroleptic therapy (Larsy and Baldessarini, 1976).

(ii) **Early supersensitivity after a single dose of neuroleptic:**
A single dose of neuroleptic can leave a residual block of autoreceptors and enhance the release of dopamine (Schwartz et al., 1978).

(iii) **Behavioral Dopaminergic supersensitivity after long-term neuroleptics:**
Long-term administration (weeks or months) of all neuroleptic results in behavioral supersensitivity to dopamine-mimetic drugs (Seeman, 1980).

(iv) **DA receptors and neuroleptic-induced DAergic supersensitivity:**
The changes in D$_1$ following long term neuroleptics are small (Muller and Seeman, 1978). However, the D$_2$ receptors
invariably increase in density in the striatum after long-term administration of various neuroleptics (Muller and Seeman, 1977). The long-term neuroleptic therapy may also induce changes in GABAergic synapses (Lloyd and Hornykiewicz, 1977), as well as those for acetylcholine (Gianutsos and Lal, 1976), serotonin (Muller and Seeman, 1977), noradrenaline (Muller and Seeman, 1977), Substance P (Hong, et al., 1978), and endogenous opiates (Hong, et al., 1978a).

(4) DAergic supersensitivity after denervation of dopamine neurons:

Denervation of dopamine-containing nigral neurons results in dopaminergic supersensitivity in the postsynaptic neurons of the striatum (Fibiger and Grewal, 1974; Iversen and Creese, 1975)

(5) DAergic supersensitivity and Oestrogen:

Oestrogens have strong antidopaminergic action. For example, estrogens inhibit the prolactin-lowering action of dopamine (Rick et al., 1979), inhibit apomorphine-induced rotation and neuroleptic induced parkinsonism (Bedard et al., 1978), alleviate dopaminergic dyskinesia (Betard et al., 1978) and inhibit dopamine sensitive adenylate cyclase (Lang and Colzias, 1977). The neuroleptic like quality of estrogens
results Da,... supersensitivity (Gordon et al., 1979) and an increase in the number of $D_2$ receptors (Dipaola et al., 1979), after long-term estrogen administration. The molecular mechanism may be that estrogen may directly compete with dopamine at the $D_2$ receptor (Schatter and Hsueh, 1979) or that the estrogen may release the electrical inhibition of the membrane potentials by DA (Dufy et al., 1979). In addition to the direct action of estrogen on the brain, there is also an indirect action of estrogen in its elevation of prolactin, which in turn separately elevates $D_2$ receptors (Wuttke and Beck, 1977).

Dopaminergic Linkage With Cholinergic And Opiate Systems:

(i) DA link with Cholinergic System:

In the striatum, $D_2$ receptor agonists increase the acetylcholine level and $D_2$ receptor antagonists decrease it (Stoof and Kebabian, 1984). The selective $D_2$ receptor agonists LY 141865 and RU 24926 inhibit the $K^+$ or electrically-evoked release of ($^3$H) acetylcholine from striatal tissue, whereas SKF 38393 does not. The DA autoreceptor stimulation in the nigrostriatal dopaminergic neurons may alter the release of acetylcholine in the striatum of rat (Schmidt et al., 1986). The mesencephal dopaminergic system plays an important role in modulating the activity of the
septo-hippocampal cholinergic system under stress (Gilad et al., 1986). D₂ receptor is also reported to mediate inhibition of intracellular calcium mobilization and release of acetylcholine from guine pig neostriatal slices (Fajwara et al., 1987).

(ii) **Dopaminergic system linked to opiate system:**

Dopamine has been attributed to play a significant role in the production of morphine dependence and withdrawal (Wood and Richard, 1982, Genget et al., 1983). Fetrail and Baggic (1982) have shown that lisuride, a dopamine agonist, can increase naloxone-induced escape attempts in morphine-dependent rats by stimulation of dopamine receptors. Wood and Richard (1982) have suggested that in rats, morphine appears to act exclusively at the presynaptic opiate receptors of dopaminergic and nerve endings in the striatum and activation of these receptors results in enhancement of dopamine synthesis.
THERAPEUTIC USES OF VARIOUS DA AGONISTS AND ANTAGONISTS

Dopamine is implicated in a range of apparently unrelated disorders, and therefore, DA agonists and antagonists have great therapeutic potentials.

(1) Dopamine:

DA, due to its hemodynamic and renal effects, is now being increasingly used for the treatment of same types of shock (cardiogenic, bacteremic, traumatic or hypovolemic), as well as for profound hypotension following removal of phaeochromocytoma. DA appears to be particularly appropriate for this purpose, because of its ability to produce vasoconstriction while maintaining flow through the renal and mesenteric vascular beds. Dopamine hydrochloride is administered as intravenous infusion which has to be carefully monitored. DA may also be of value in treatment of refractory congestive cardiac failure (Goldberg, 1974).

(2) Levodopa (L-DOPA):

The use of L-DOPA for treatment of Parkinson's disease has been the subject of several symposia and extensive reviews (Marks, 1974; Yahr, 1975; Calne et al., 1979). Concurrent administration of L-DOPA with a peripheral dopa decarboxylase inhibition (Carbidopa or benserazide) may be advocated when the symptoms became serious. The efficacy of L-DOPA in
Parkinsonism has prompted clinical trials of the drug for a number of other neurological conditions such as torsion dystonia, cerebral palsy and progressive supranuclear palsy. L-DOPA has been found to improve cognitive performance in humans in Alzheimer's disease.

Oral L-DOPA has been tried for long-term treatment of heart failure as it produces hemodynamic improvement. Administration of levodopa may provoke "awakening" of patients in hepatic coma (Morgan et al., 1977).

(3) Apomorphine:

It is a mixed D_1-D_2 agonist, and was the first dopaminergic agonist reported to have beneficial effects in Parkinsonism. It is commonly used as an emetic agent in the treatment of oral drug poisoning.

(4) Ergolines:

The dopaminergic ergots are potent DA receptor agonists. Bromocriptine, a D_2 receptor agonist, has wide therapeutic applications. It is being used for treatment of Parkinson's disease, suppression of lactation (physiological and pathological), galactorrhea-amenorrhea syndrome and acromegaly.
(5) **N-0437** :

It is a 2-aminotetralin derivative, and is a potent $D_2$ agonist (Horn, 1987). Centrally acting $D_2$ agonists are clinically effective antiparkinson agents.

(6) **SKF 38393 and Fenoldopam** :

SKF 38393 is a specific $DA_1$ agonist which produces selective renal vasodilatation. At present, it has only experimental use, but may prove to be clinically useful in disease states in which renal ischemia is a prominent component (Pendleton et al., 1978).

Fenoldopam is a structural analog of SKF 38393 and is a novel selective $DA_1$ agonist with antihypertensive activity. It has been reported to increase intraocular pressure in man (Karnezis et al., 1988).

(7) **Neuroleptics** :

Classical neuroleptics are either $D_1/D_2$ unselective or selective $D_2$ blockers. Neuroleptic agents-phenothiazines, butyrophenones and diphenylbutyl piperidines seem to be especially effective in acute idiopathic psychoses and acute exacerbations of schizophrenia. Recently, it has been reported that selective DA autoreceptor agonists (3-PPP, transdihydrolisuride, R-III 920) might prove to be beneficial in treatment.
of schizophrenia (Wikstran, 1987). Treatment with haloperidol in autistic patients produces significant decrease in behavioral symptoms and acceleration in learning capability (Anderson et al., 1984).

SCH 23390 is a benzamine derivative which has selective D₂ antagonistic property (Hytter, 1983). It is a unique neuroleptic, widely used as a research tool.

8) Metoclopramide and Domperidone:

Metoclopramide is a selective D₂ antagonist with powerful central-cum-peripheral anti-emetic property. It is a valuable agent for treatment of nausea and vomiting resulting from various causes, peptic ulcer, reflux oesophagitis, hiccups and chronic gastric stasis.

Domperidone, a peripherally acting D₂ antagonist, has been recently introduced into clinical practice. Its distinct advantages over metoclopramide are:

(i) dosage flexibility and good absorption by different routes.
(ii) suitable for geriatric patients.
(iii) does not cross the blood brain barrier, even at high doses, and hence does not produce extrapyramidal dystonias as sedation.
(9) *L*-Sulpiride, Clebopride, Molindone:

They are D₂ receptor antagonists having anti-emetic and antipsychotic uses.