INTRODUCTION
It is more than thirty years since dopamine (DA) was shown to be a neurotransmitter in the central nervous system (CNS). In the early 1970s, many studies showed the effects of DA to be inconsistent with the concept that a single receptor mediates all the physiological functions of this catecholamine. Thus at that time it was suggested that the existence of two DA receptor populations or subtypes, termed D₁ and D₂, could account for most, if not all, of the findings in the literature. Although others have been proposed, the D₁/D₂ receptor classification is still the most widely recognized (Creese et al., 1983; Stoof and Kebabian, 1984; Clark and White, 1987). The two receptor subtypes differentially influence adenylate cyclase activity. D₁ DA receptors act via stimulation of adenylate cyclase whereas D₂ receptors are either inhibitory (Weiss et al., 1985; Kelly et al., 1987) or not coupled to this enzyme (Creese et al., 1983; Stoof and Kebabian, 1984). The possibility of a functional interaction between these two receptor subtypes has arisen from the use of highly selective D₁ and D₂ DA agonists in biochemical, physiological and behavioural studies.

In the CNS, disturbances in DA (Fig.1) neurotransmission and DA receptors have been implied in several neuropsychiatric disorders (Murphy et al., 1971; Carlsson, 1988) such as schizophrenia and Parkinson's disease. It is generally conceded that the therapeutic
efficacy of antipsychotics derives from the high affinity binding to D2 receptors; there being excellent correlations between the affinities of such drugs for D2 receptors and the average daily dose used to treat schizophrenia (Seeman et al., 1976). Although some authors repeatedly suggested that antipsychotic agents interact to a variable extent with more than a single DA receptor subtype (Schwartz et al., 1984), this remained controversial, in spite of the substantial clinical relevance. Currently, it is believed that blockade of D2 DA receptors in limbic and cortical areas is responsible for the antipsychotic effect of drugs. Many antipsychotic agents are also associated with adverse reactions, especially with extrapyramidal (Parkinsonian) motor side effects that are thought to result from the blockade of D2 receptors in the striatum (a typical motor

\[ \text{OH} \]
\[ \text{HO} \]
\[ \text{CH}_2 - \text{CH}_2 - \text{NH}_2 \]

Fig.1. Structure of dopamine
region of basal ganglia). Some antipsychotic drugs - the so-called atypical antipsychotics such as clozapine, sulpiride and thioridazine—are less likely to induce extrapyramidal side effects, whereas typical antipsychotics such as haloperidol and spiperone are more often associated with such complications. This difference has been explained in several ways: the atypical drugs may preferentially block limbic/cortical D_2 receptors (Strange, 1990), they may penetrate more effectively into limbic/cortical regions or they may have a stronger blocking action on muscarinic acetylcholine receptors (Miller and Hiley, 1974), thereby suppressing the side effect. None of these explanations is entirely satisfactory. The discovery of a third DA receptor, by means of gene cloning techniques (Sokoloff et al., 1990; Giros et al., 1990), has provided new insights into the typical/atypical dichotomy and also into the mechanism of the antipsychotic effect.

In the past few years gene cloning techniques have considerably advanced the study of neurotransmitter receptors. Isolation of genes encoding several receptors has shown that pharmacological studies have underestimated receptor diversity (Lefkowitz et al., 1989). Availability of cloned gene sequences for receptors has also opened the way for localization of these receptor subclass to be achieved by in-situ hybridization. By expressing a unique receptor gene in a clonal animal cell line, highly specific screening systems for new drugs are available.
The advent of molecular biology methods have confirmed the existence of additional DA receptors; their existence throwing a new light onto the modes of action and side effects of many drugs used in neurology and psychiatry. The first cloning of a DA receptor gene, that of the D$_2$ receptor (Bunzow et al., 1988), paved the way for the cloning of a series of DA receptor genes, based upon the significant sequence homology these receptors display. Quite expectedly, the D$_1$ receptor, which is nearly as abundant as the D$_2$ receptor in brain, was the first to follow (Dearry et al., 1990; Monsma et al., 1990; Sunahara et al., 1990; Zhou et al., 1990). Then came the genes of a series of less abundant and less expected receptors which markedly expand the DA receptor family: the D$_3$ (Sokoloff et al., 1990), D$_4$ (Van Tol et al., 1991) and D$_5$ (Sunahara et al., 1991) receptors. These receptors belong to a larger superfamily, that of receptors with seven transmembrane domains and are coupled to their intracellular transduction systems by a guanine nucleotide (G)-protein. The various genes for the DA receptor family can be classified into two groups according to their organisation: (1) intronless genes i.e. those of the D$_1$ and D$_5$ receptors, in which the coding nucleotide sequence is continuous; and (2) genes whose coding sequence is contained in discontinuous deoxyribonucleic acid (DNA) segments (exons
interspersed among sequences (introns) that do not form a part of the mature messenger ribonucleic acid (mRNA). The last organization, found in rhodopsin gene or in the D2, D3 and D4 receptor genes, may potentially lead to the biosynthesis of several distinct proteins encoded by a unique gene via a mechanism of alternative splicing. Thus, molecular cloning has shown that D1 subclass (termed "D1-like") consists of several distinct molecular forms including D1A (Deary et al., 1990; Monsma et al., 1990; Sunahara et al., 1990; Zhou et al., 1990; Gingrich et al., 1991), D1B (Tiberi et al., 1991) and D5 (Sunahara et al., 1991), although this area is still controversial. The D2 subclass (termed "D2-like") consists of at least four forms. D2long and D2short (Bunzow et al., 1988; Eidne et al., 1989; Giros et al., 1989; Monsma et al., 1990); D3 (Sokoloff et al., 1990) and D4 (Van Tol et al., 1991) receptors. In general, D1-like receptors are often linked functionally to stimulation of cAMP synthesis and preferentially recognize 1-phenyl-tetrahydrobenzazepines (e.g. SCH 23390) over benzamides (e.g. sulpiride). There may be other members of the D1-like class with similar pharmacology that are not coupled to adenylate cyclase (Mailman et al., 1986). The D2-like receptors often are linked to inhibition of cAMP synthesis, and have the opposite pharmacological specificity (i.e. preferring sulpiride over SCH 23390). Within each major group, however, there are important differences in
drug recognition (e.g. higher affinity of clozapine for the $D_4$, $V$, or $D_3$ receptors). Although these molecular studies have provided important information about DA receptor subtypes, their functional role in the nervous system is still not well understood, in part due to the lack of subtype-selective ligands. For example, the functional importance of $D_1$-like receptors in CNS was largely misunderstood until the selective $D_1$ antagonist SCH 23390 (Iorio et al., 1983) became available. It rapidly became clear that $D_1$ receptor antagonists could affect $D_2$-mediated behaviours (Mailman et al., 1986; Christensen et al., 1984), leading to focus on $D_1/D_2$ receptor interactions (Clark and White, 1987).

For some time it has been apparent that when animal behaviour is studied $D_1$ and $D_2$ agonists are observed to interact in either an additive or synergistic manner (Clark and White, 1987). Behavioural as well as electrophysiological studies have indicated a close interaction of $D_1$ and $D_2$ receptors (Braun and Chase, 1986; Robertson and Robertson, 1986; Arnt and Perregaard, 1987; Arnt et al., 1987). In contrast, when biochemical parameters (i.e. adenylate cyclase activity) are studied $D_1$ and $D_2$ agonists often have opposing actions (Clark and White, 1987). Faced with this paradox, it was proposed that a part of the explanation for $D_1/D_2$ interplay might be that...
the D\textsubscript{1} and D\textsubscript{2} DA receptors concerned have separate locations (Robertson and Robertson, 1987). Activation of D\textsubscript{1} receptors in the substantia nigra may, in part, explain some of the synergistic effects of D\textsubscript{1} and D\textsubscript{2} agonists in animal models of Parkinson’s disease. It has been further suggested that DA, acting on D\textsubscript{1} and D\textsubscript{2} receptors, activates distinct efferent pathways from the striatum. Using oligonucleotide cDNA probes for D\textsubscript{1} and D\textsubscript{2} receptor mRNA combined with fluorogold track-tracing techniques, it has now been shown that D\textsubscript{1} receptors are for the most part located on striatonigral -projecting neurons while D\textsubscript{2} DA receptors are located on striatopallidal neurons. (Gerfen et al., 1990). Only a few interneurons appear to express the cDNA for both the receptors. This interaction between D\textsubscript{2} agonists acting in substantia nigra and D\textsubscript{2} agonists acting in the striatum can provide plausible explanation for DA receptor interactions. Clinical studies suggest that these findings may have important implications for the treatment of Parkinson’s disease. The cloning of D\textsubscript{5} receptor, which has pharmacological characteristics similar but not identical to D\textsubscript{1} receptor, will provide a new tool to examine the regulation of DA receptors and the functional interaction between D\textsubscript{1}/D\textsubscript{5} and D\textsubscript{2}/D\textsubscript{3}/D\textsubscript{4} receptors.

Recently, considerable attention has been focussed on investigating the modulatory role of DAergic transmission on other neurotransmitter systems in the basal ganglia.
Among the various neurotransmitters which participate in the functions of basal ganglia DA and excitatory amino acids especially glutamate play a major role. The growing evidence for a disturbed glutamate function in schizophrenia and interaction between DA and glutamate systems has led to an improved understanding of the mechanisms involved in the pathophysiology of psychic disorders. Pharmacological interference with glutamatergic transmission at the level of N-methyl-D-aspartate (NMDA) receptor complex - one subtype of receptor activated by glutamate (Anis et al., 1983) - can precipitate psychosis similar to schizophrenic disorder (Javitt, 1987). The ability of drugs whose primary pharmacological action is non-competitive allosteric antagonism of NMDA-stimulated cationic conductance to precipitate a schizophreniform psychosis has stimulated interest in a "glutamatergic hypothesis" of schizophrenia. The existence of a glutamatergic deficiency in the pathophysiology of schizophrenia would support intervention strategies designed to facilitate glutamatergic transmission. In addition, it is suggested that glutamatergic antagonists may be valuable supplements in the treatment of Parkinson's disease. These drugs may act in a additive or synergistic manner with a conventional antipsychotic or antiparkinsonian drug and help reduce the dose of the latter, thereby reducing the risks associated
with the acute and delayed side effects of the conventional therapy.

In the background of these developments, the present study was undertaken to further explore the role of D₁/D₂ DA receptor subtypes and their interplay in terms of physiological functions and drug actions. Detailed investigations, using behavioural, electrophysiological and biochemical approaches, have been done to study the role and the involvement of D₁/D₂ DA receptor subtypes in the regulation of certain physiological functions such as body temperature, memory processes and behavioural patterns. The modulatory influence of D₁/D₂ stimulation on other neurotransmitter systems has also been explored. The findings have been discussed in terms of their relevance in DA-mediated neuropsychiatric disorders and drug abuse.