EXPERIMENTAL AND CLINICAL PHARMACOLOGY

Dopamine — mechanisms of action

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SYNOPSIS

Dopamine plays an important role both centrally and peripherally. The recent identification of 5 dopamine receptor subtypes provides a basis for understanding dopamine's central and peripheral actions. Changes in central dopamine neurotransmission are implicated in processes as diverse as muscle rigidity, hormonal regulation, thought disorder and cocaine addiction. Peripheral dopamine receptors mediate changes in blood flow, glomerular filtration rate, sodium excretion and catecholamine release. Increased knowledge of the roles of dopamine receptor subtypes raises hopes that more selective drugs, associated with fewer adverse effects, will be developed.

Index words: dopamine receptors, dopamine agonists, dopamine antagonists, localisation, function.

Introduction

Dopamine is a catecholamine neurotransmitter found in neurons of both the central and peripheral nervous systems. It is stored in vesicles in axon terminals and released when the neuron is depolarised. Dopamine interacts with specific membrane receptors to produce its effects. These effects are terminated by re-uptake into the presynaptic neuron by a dopamine transporter, or by metabolic inactivation by monoamine oxidase B (MAO-B) or catechol-O-methyltransferase (COMT) (Fig. 1).

Drugs affecting dopamine actions

The sites of action of drugs affecting dopamine transmission are shown in Fig. 1. Many drugs affect dopamine transmission directly by either blocking or stimulating its receptors. For example, antipsychotic drugs are dopamine antagonists, whereas bromocriptine, used to treat hyperprolactinaemia and Parkinson's disease, is a dopamine agonist.

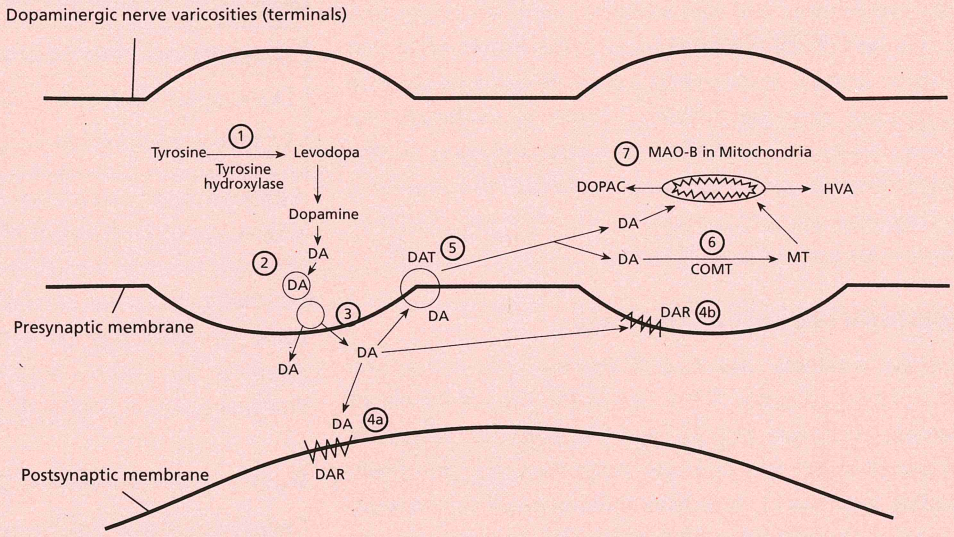
Several drugs of clinical importance act indirectly e.g. levodopa, which is converted to dopamine, or amphetamine, which releases dopamine from terminal stores. Other drugs increase the synaptic concentration of dopamine by blocking its uptake or metabolism. For example, cocaine is a potent inhibitor of the dopamine re-uptake transporter and this may be the basis of its addictive properties. On the other hand, selegiline, a MAO-B inhibitor, elevates dopamine concentrations by inhibiting its breakdown.

Regardless of the mechanism of action of these drugs, the

Fig. 1

The sites of action of drugs modulating changes in dopamine transmission.

1. Synthesis - e.g. alpha-methyl-para-tyrosine inhibits synthesis.
2. Storage - e.g. reserpine depletes storage granules.
3. Release - e.g. amphetamine increases release.
4a. Interactions with postsynaptic receptor subtypes - e.g. bromocriptine stimulates D_2; chlorpromazine blocks D_1 and D_2 subtypes.
4b. Interactions with presynaptic receptor subtypes - e.g. bromocriptine stimulates D_2 and so inhibits dopamine release; antagonists have reverse effect e.g. haloperidol.
5. Re-uptake - e.g. cocaine and imipramine inhibit dopamine transporter.
6. Metabolism - e.g. OR-462 inhibits COMT.
7. Metabolism - e.g. selegiline inhibits MAO-B.



Abbreviations:

COMT	catechol-O-methyltransferase	DOPAC	3,4-dihydroxyphenylacetic acid
DA	dopamine	HVA	homovanillic acid
DAR	dopamine receptor subtype	MAO-B	monoamine oxidase B
DAT	dopamine transporter	MT	3-methoxytyramine

Table 1
Effects mediated by dopamine receptor subfamilies which have therapeutic potential
(see text for more detail)

Receptor subfamily	*Location*	*Action*	*Therapeutic potential*
Central			
D_1 and D_2	substantia nigra and striatum	motor control	agonists – Parkinson's disease
D_1 and D_2	limbic cortex and associated structures	information processing	antagonists – schizophrenia
D_2	anterior pituitary	inhibits prolactin release	agonists – hyperprolactinaemia
Peripheral			
D_1	blood vessels	vasodilatation	agonists - congestive
D_1	proximal tubule cells	natriuresis	heart failure and
D_2	sympathetic nerve terminals	decreases release	hypertension

end effect is determined by the interaction of dopamine with its receptors, which in turn is dependent on the localisation and characteristics of the receptors involved (Table 1). Much research has focused on these two features to explain the many central and peripheral effects of dopamine.

Central dopaminergic pathways

Techniques to define dopaminergic neurons (which synthesise and release dopamine) and localise dopamine receptors have identified 8 distinct dopamine pathways in the brain (Fig. 2). Two of these pathways have attracted great interest because of their possible involvement in pathological processes:

- the nigrostriatal pathway projecting from the substantia nigra to the striatum (caudate and putamen), the region involved in the control of motor function. Degeneration of the dopaminergic neurons of the nigrostriatal pathway is associated with the motor symptoms of Parkinson's disease, i.e. bradykinesia, tremor and rigidity.
- the mesolimbic and mesocortical pathways projecting from the ventral tegmental area to the limbic areas and limbic cortex respectively, regions associated with cognition and emotionality. There is evidence that overactivity of dopamine neurotransmission in the mesolimbic pathway may underlie the positive symptoms of schizophrenia, i.e. thought disorder, delusions and hallucinations.

Dopamine receptor subtypes

Dopamine's effects cannot all be explained by interaction with a single receptor. This led to the classification of dopamine receptors into D_1 and D_2 subtypes, based on physiological or biochemical responses. D_1 receptors stimulate whereas D_2 receptors reduce, or do not change, adenylyl cyclase activity. (Adenylyl cyclase is the enzyme which converts adenosine triphosphate [ATP] to cyclic adenosine monophosphate [cAMP] which mediates the postsynaptic response to dopamine.) The development of agonists and antagonists selective for each subtype followed, enabling their localisation and function to be investigated. Although the D_1/D_2 classification initially appeared to account for most of dopamine's effects, further investigations raised questions about its adequacy.

This situation has been partially resolved in the last two years by the application of molecular biology techniques resulting in the identification of 5 pharmacologically distinct dopamine receptor subtypes, D_1, D_2, D_3, D_4, D_5. These subtypes belong to a superfamily of receptors (which includes alpha and beta adrenoceptors and muscarinic receptors) characterised structurally by the presence of 7 membrane spanning regions (transmembrane domains) which form the dopamine binding site (Fig. 3). The D_1 and D_5 receptors are classified as members of the D_1 subfamily because they have 80% similarity (homology) of the amino acid sequences in the transmembrane domains. Similarly, because the D_2, D_3 and D_4 receptors also share substantial homology, they are classified as members of the D_2 subfamily. The two subfamilies differ in homology in the transmembrane domains and this provides a structural basis for their pharmacological selectivity.

Dopamine receptors

D_1 receptor subfamily – D_1 and D_5 receptor subtypes

D_2 receptor subfamily – D_2, D_3 and D_4 receptor subtypes

Although molecular biology has facilitated the identification and localisation of dopamine receptor subtypes, elucidation of their functions awaits the development of drugs which selectively activate or block particular subtypes. While some progress has been made in identifying selective drugs, it has mainly been confined to re-evaluating the pharmacological profile of existing drugs.

D_2 receptor subfamily

Localisation and functions

Postsynaptic D_2 receptors are present in dopaminergic projection areas such as the striatum, limbic areas (nucleus accumbens, olfactory tubercle), hypothalamus and pituitary. D_2 receptors are also located presynaptically in the substantia

nigra pars compacta, ventral tegmental area and striatum, where they function to inhibit the release of dopamine.

Activation of the striatal D_2 receptor subfamily in rats results in a behavioural syndrome known as stereotypy, made up of repetitive sniffing and gnawing, accompanied by an increase in the animals' activity. The repetitive behaviours observed in people following amphetamine ingestion may have a similar neurochemical basis. By contrast, blockade of the striatal D_2 receptor subfamily produces marked increases in muscle rigidity in rats and a Parkinson-like syndrome in humans. In both rats and humans, administration of a D_2 antagonist results in a rapid and large increase in prolactin release from the anterior pituitary, as dopamine's inhibition of prolactin release is blocked.

The D_3 and D_4 subtypes are much less abundant than the D_2 subtype and have a different distribution. D_3 receptors are located predominantly in limbic regions, with low concentrations in the striatum, whereas D_4 receptors are found in the frontal cortex, amygdala, mid-brain and medulla. The effects mediated by these receptors are not known, although an autoreceptor (presynaptic) role has been suggested.

Implications for therapy

The effects elicited by dopamine agonists and antagonists are dependent on their selectivity. Selective drugs affect one subtype predominantly and therefore would be expected to have fewer adverse effects than nonselective drugs which have a wider spectrum of activity. A consideration of the D_2 subfamily illustrates the potential therapeutic benefits of selective drug development.

The D_2 receptor subfamily has been implicated in the positive symptoms of schizophrenia, by the observation that the clinical potency of antipsychotic drugs is related to their affinity for the D_2, not D_1, receptor subfamily. However, because receptors of the D_2 subfamily are found in both limbic and striatal regions, their blockade results respectively in both the desired reduction in psychosis and the unwanted appearance of Parkinson-like adverse effects. Blockade of D_2 receptors which inhibit prolactin release results in increased plasma prolactin concentrations.

The recent cloning and identification of the D_3 receptor has attracted interest. Its localisation in the limbic areas suggests it may play a role in cognitive and emotional functions and so be an important target for antipsychotic drug therapy. This hypothesis is supported by findings that antipsychotic drugs previously thought to be selective for D_2 receptors (raclopride and pimozide), as well as nonselective antipsychotic drugs (flupenthixol and chlorpromazine) and the atypical drug, clozapine, all interact with D_3 receptors. If blockade of D_3 receptors is involved in antipsychotic effects, then selective D_3 antagonists may well provide antipsychotic drug therapy free from motor and hormonal adverse effects. Conversely, the use of dopamine agonists

Fig. 2

Sagittal section of human brain showing the dopaminergic pathways involved in the actions of antipsychotic drugs (see text for further information).

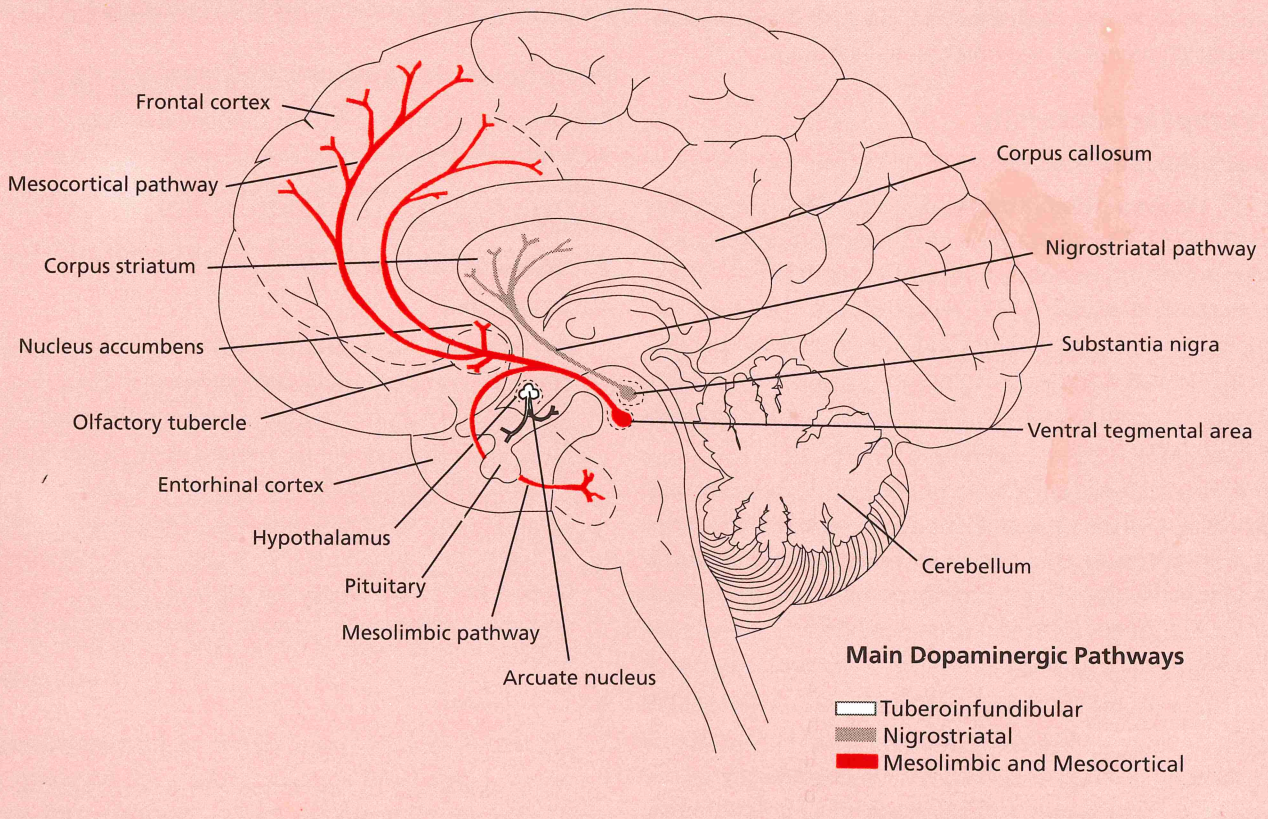
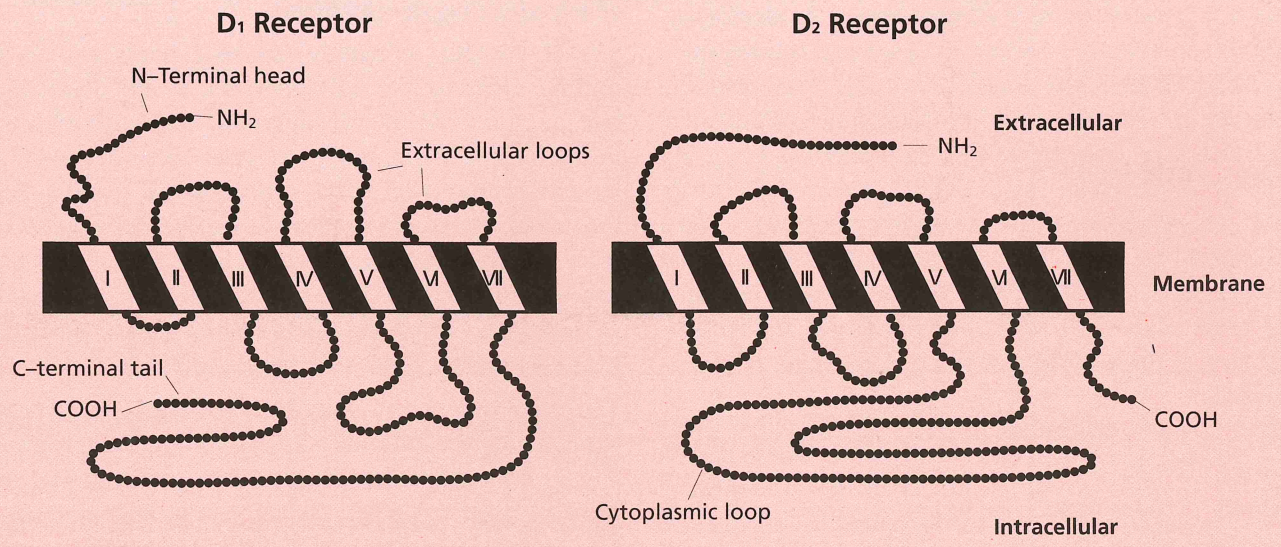


Fig. 3

Structural features of the human D_1 and D_2 receptor subfamilies.



free of D_3 activity in Parkinson's disease would be predicted to reduce the incidence of psychosis-like adverse effects.

The most recently discovered member of the D_2 subfamily, the D_4 receptor, is also attracting interest for similar reasons. Of particular note are findings from a postmortem study which showed a 6-fold increase in D_4 receptor binding in the brains of people diagnosed with schizophrenia compared with controls. Clozapine has a 10-fold greater affinity for the D_4 than the D_2 receptor and this may be the basis of its antipsychotic action. Clozapine's lack of extrapyramidal adverse effects may be related to the fact that only low levels of D_4 receptors are found in the striatum.

D_1 receptor subfamily

Localisation and functions

The D_1 receptor differs structurally from the D_2 in several ways (Fig. 3). The distribution of D_1 receptors corresponds to the projection regions of dopaminergic neurons. Thus, the highest amounts of D_1 receptors are found in the striatum, nucleus accumbens and olfactory tubercle. The effects mediated by D_1 receptors in humans are unclear, although D_1 agonists produce intense grooming and vacuous chewing behaviours in experimental animals.

Similarly, the function of the recently cloned D_5 receptor is unknown. It is less abundant than the D_1 receptor and has a different distribution in the brain, being found in highest amounts in the hippocampus and hypothalamus, with lower amounts in the striatum and frontal cortex.

Interestingly, in experimental studies, the effects mediated by receptors of the D_2 receptor subfamily are dependent on concurrent stimulation of the D_1 receptor subfamily and so an 'enabling' function has been ascribed to the D_1 receptor subfamily. The neurochemical basis of this 'enabling' effect of the D_1 receptor on D_2 mediated actions is unclear, but does not relate to changes in adenylyl cyclase activity. A consequence of this complex interaction is that since extrapyramidal adverse effects can be produced by both D_1 and D_2 antagonists, efforts to reduce their incidence by using antagonists with more D_1 activity have been unsuccessful. Conversely, the involvement of D_1 receptors in motor control may explain why the D_2 agonist, bromocriptine, is more effective when administered with levodopa (since dopamine has D_1 and D_2 activity) in the management of the motor symptoms of Parkinson's disease.

Peripheral dopamine receptors

Peripheral dopamine receptors mediate a variety of effects including changes in blood flow, glomerular filtration rate, sodium excretion, catecholamine release and inotropic effects on the heart.

Localisation and functions

i. *D_1 subfamily*

D_1 receptors have been localised on vessels in the cerebral, coronary, renal and mesenteric beds and the splenic artery. Activation results in vasodilatation. They have also been shown at various sites in the kidney, including the inner and outer medulla, the glomeruli and the proximal convoluted tubules, where their activation increases sodium and water excretion. Recent cloning studies have confirmed that both D_1 and D_5 receptor subtypes expressed in the brain are also expressed in the kidney.

ii. *D_2 subfamily*

D_2 receptors have been found in heart, mesenteric artery, kidney and adrenal medulla. D_2 receptors are located on sympathetic nerve terminals and cause

vasodilatation by inhibiting noradrenaline release. Two populations of D_2 receptors have been identified, one of which is thought to be the same as the central D_2 receptor. Messenger RNA for the D_3 receptor has been found in kidney, but confirmation of the similarities between central and peripheral D_2 subfamilies awaits the results of further cloning studies.

Therapeutic implications

Dopamine has important roles in cardiovascular regulation through its effects on blood vessels and its renal actions, although its central role in blood pressure control remains unresolved. Evidence that dopamine acts as an intrarenal natriuretic hormone and that intrarenal dopamine formation is defective in essential hypertension is of particular interest. This has led to the search for drugs which selectively stimulate peripheral D_1 receptors to treat hypertension and congestive cardiac failure. Although this goal is yet to be realised, the use of D_1 agonists like fenoldopam has provided further insights into dopamine's role in the periphery and has paved the way for future drug development.

Conclusion

The past decade has brought a wealth of new information about dopamine's actions in the brain and the periphery, and has established its role in pathologies as varied as schizophrenia, Parkinson's disease and essential hypertension. More recently, the application of molecular biology techniques has revealed the existence of at least 5 dopamine receptor subtypes which facilitate an understanding of the diversity of dopamine's actions. The scene is now set for the development of drugs selective for particular receptor subtypes which can be used to elucidate receptor subtype function and treat disorders of dopamine function.

FURTHER READING

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Self-test questions

The following statements are either true or false (answers on page 23)

7. Blockade of D_2 receptors by antipsychotic drugs inhibits the release of prolactin.
8. Degeneration of dopaminergic neurons in the nigrostriatal pathway is associated with Parkinson's disease.

EXPERIMENTAL AND CLINICAL PHARMACOLOGY

Dopamine — clinical applications i. neurology

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SYNOPSIS

The current treatments of Parkinson's disease aim to improve central dopaminergic neurotransmission. This may be achieved by using a prodrug (levodopa), directly-acting agonists or inhibitors of dopamine metabolism. Successful management of Parkinson's disease generally requires the staged introduction of drugs from each of these groups.

Index words: Parkinson's disease, levodopa, dyskinesias.

Introduction

The greatest concentration of dopamine in the brain is found within the basal ganglia. Clinical interest in dopamine began with the observation that brain dopamine is profoundly depleted in Parkinson's disease. We now know that the loss of dopamine is not simply the result of a metabolic defect, but is due to loss of the terminals of dopaminergic nerves from the mid-brain, principally the nigrostriatal tract. The basis of this degeneration remains unknown, but is not simply due to ageing. Surviving nigral neurons show changes of increased oxidative activity. Within the basal ganglia, the principle target for dopaminergic innervation is the neostriatum (caudate and putamen) and here the principle receptors are the D_1 and D_2 subtypes.

Excess dopaminergic stimulation leads to involuntary movements (principally choreiform). Conversely, blocking dopaminergic transmission reduces movement and, even in