RELATION BETWEEN TREMORINE AND DOPAMINE AS A BRAIN TRANSMITTER

THESIS

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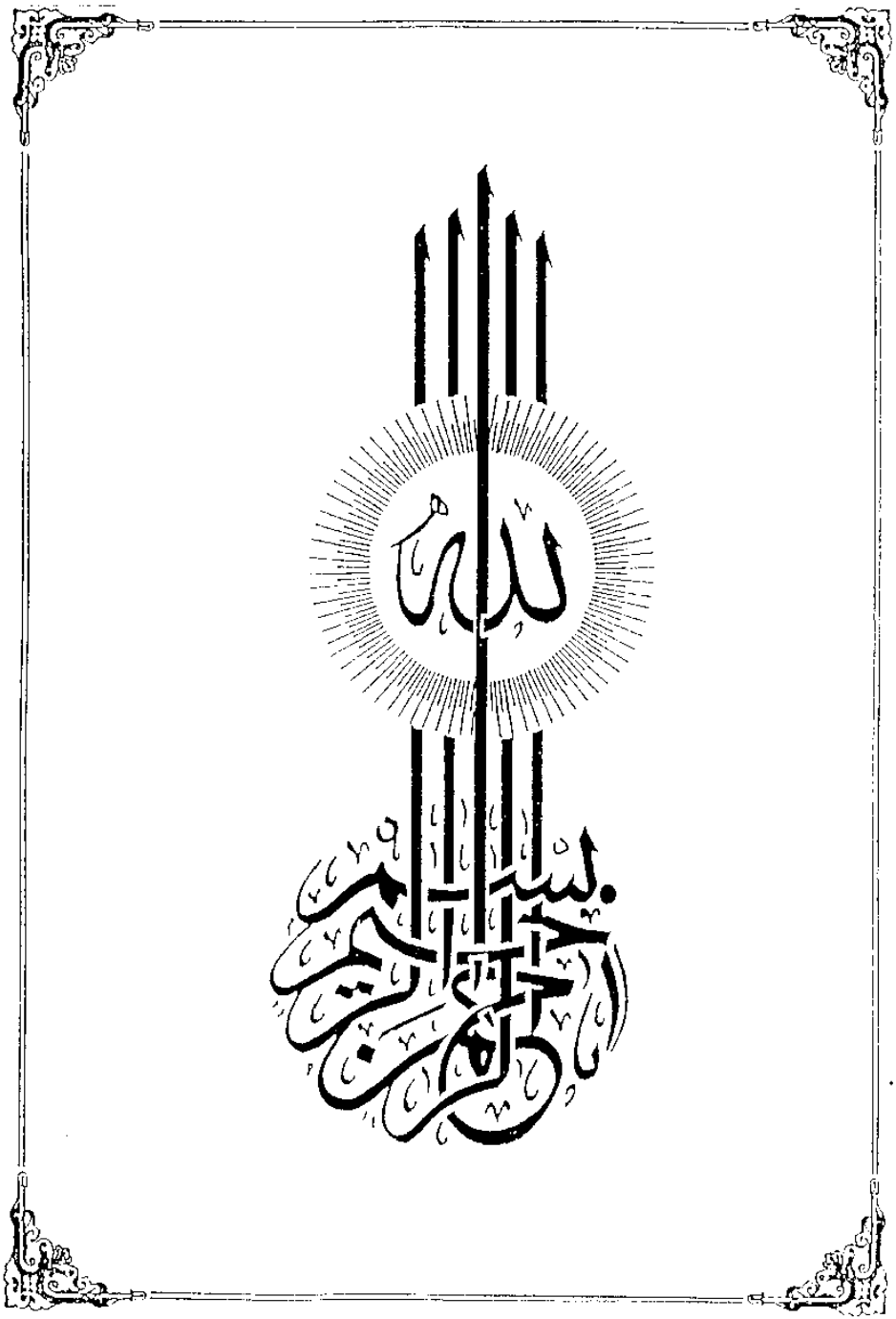

C O N T E N T S

INTRODUCTION

I N T R O D U C T I O N

Up to the sixties, the knowledge of neuronal interactions in the striatum was quite poor . However, it was known that dopamine neurons play a key-role in the regulation of muscle tone and extrapyramidal motility . Thus, in Parkinson's disease, hypokinesia , rigidity and tremors clearly appeared to be related to a primary degeneration of the nigrostriatal dopamine system (Hornykiewicz , 1966) .

In rodents , dopamine depletion induced by reserpine causes strong motor depression and tremor (Carlsson, 1959) which can be counteracted by the dopamine precursor, L-Dopa. When it was found that in humans, Parkinson's disease is a result of central dopamine deficiency , reserpinized rodents became accepted as an animal model of this disease, and dopaminergic agonists such as L-dopa and apomorphine were shown to be effective both as antagonists of reserpine-induced motor depression in rodents and in the treatment of Parkinson's disease (Carlsson , 1972) .

The extrapyramidal disorders seen in patients treated with neuroleptic drugs such as haloperidol which block dopaminergic transmission are relieved by anticholinergic drugs . On the other hand, centrally acting acetyl choline like compounds , such as oxotremorine , may induce catalepsy (Zettler, 1968 ; Costall and Olley, 1971) . Cholinergic and neuroleptic-induced catalepsy can be blocked by anti-cholinergic drugs (Costall and Olley, 1971 ; Corrodi et al., 1972) . The increase in central dopamine turnover induced by neuroleptics can be prevented by atropine-like agents (Anden, 1972 ; Corrodi et al., 1972) . Similarly, the activation of brain dopamine turnover by the acetyl-choline-like agents, oxotremorine may be blocked by atropine (Corrodi et al., 1967) .

Tremorine , the cholinomimetic drug was found to produce certain motor activities in experimental animals , such as tremors , rigidity and hypokinesia simulating those seen in Parkinson's disease in man , and these activities could be antagonized by the antiparkinsonian drugs . This pointed out to the importance of such a drug in the evaluation of newly-introduced antiparkinsonian drugs (Everett et al., 1956) .

In parkinsonian disease, striatal dopamine content is reduced resulting in predominance of cholinergic activity . Accordingly , parkinsonian disease is treated either by suppressing cholinergic hyperactivity or enhancing dopaminergic transmission (Hornykiewicz, 1966).

Oxotremorine and physostigmine produce transient tremors in rats by increasing cholinergic activity in the brain (Slater and Rogers , 1968 ; Sethy and Van Woert , 1973 a) .

In patients with Parkinson's disease, physostigmine aggravates tremors , rigidity and hypokinesia at a dose which has no neurological effects in normal subjects (Duvoisin , 1967 ; Weintraub and Van Woert , 1971) . This aggravation of the symptoms is decreased or blocked by pretreatment with L-dihydroxy phenyl alanine (L-Dopa) (Weintraub and Van Woert , 1971) . Moreover, in the spinal cord of rats, L-Dopa has been shown to antagonize the motor disturbances induced by physostigmine and oxotremorine (Jurna et al., 1969) .

Gothoni et al. (1983) found that amantadine which has been shown to enhance the synthesis and release of

dopamine in rat brain (Scatton et al., 1970 ; Farnebo and Hamberger,1971) could counteract the physostigmine or oxotremorine-induced cholinergic hyperactivity by activating the dopaminergic system . Bromocriptine , by activating the dopamine receptors in the basal ganglia (Fuxe et al., 1974 ; Ungerstedt , 1978), significantly antagonizes physostigmine and oxotremorine-induced tremors (Gothini et al., 1983) . On the other hand , it has been reported by Al-Shabibi and Dogget (1979) and Gothini et al. (1983) that pimozide which is a specific blocker of central dopamine receptors (Pinder et al., 1976) , significantly potentiated the tremor induced by oxotremorine .

Neuroleptic drugs, apart from their therapeutic antipsychotic action, commonly produce, among their unwanted side effects, drug-induced parkinsonian symptoms (Klawans , 1973) . Both the antipsychotic action and the extrapyramidal parkinsonian side effects of these drugs generally correlate well with their potency in blocking dopamine receptors as revealed by Horn et al. (1974), in vitro, and by Anden et al. (1970), in vivo . However, it has been reported that some neuroleptics, notably thioridazine and clozapine

produce only minimal parkinsonian syndrome (Costall and Naylor, 1975) , although they are potent blockers of dopamine effects in vitro (Miller et al., 1974) . Since drug-induced extrapyramidal effects can be alleviated by antimuscarinic drugs (Shintami and Yamamura, 1973), it is possible that the recently demonstrated anti-muscarinic action of clozapine and thioridazine (Miller and Hiley, 1974 ; Snyder et al., 1974) might account for their minimal parkinsonian side effects . Alleviation of parkinsonian symptoms , by antimuscarinic agents, is the observed antagonistic effects of muscarinic agents and drugs acting on dopamine receptors in the striatum (Costall et al., 1972) .

Kelley and Miller (1975) had demonstrated that central cholinergic stimulation produced by oxotremorine can block methamphetamine-induced turning, and conversely, the antimuscarinic agent scopolamine produced turning in the same direction as methamphetamine . The neuroanatomical basis of these cholinergic-dopaminergic interactions could involve both the substantia nigra and the striatum . Local application of cholinomimetic agents to the substantia nigra .

decreased the turnover of dopamine in the nigrostriatal dopaminergic neurons, while antimuscarinic drugs had the opposite effect, suggesting that cholinergic synapses are involved in an inhibitory effect in nigrostriatal neurons (Javoy et al., 1974) .

A further sight of cholinergic-dopaminergic interaction was investigated by Kelley and Miller (1975) who observed that turning produced by the dopamine agonist , apomorphine, was inhibited by the cholinomimetic agent , oxotremorine . Since apomorphine-induced turning is thought to result from direct stimulation of the supersensitive denervated striatal dopamine receptors (Ungerstedt, 1971), the effect of oxotremorine on apomorphine-induced turning might be due to increased striatal cholinergic activity which antagonizes the dopaminergic activity .

The atypical neuroleptic drug, sulpiride, does not produce catalepsy or major extrapyramidal defects except in toxic doses (Costall and Naylor, 1975) . Several studies indicated that sulpiride is devoid of anticholinergic properties in laboratory animals as it does not antagonize tremors and salivation induced by the cholinomimetic drug , oxotremorine , (Stille and Hippius,1971).

This lack of extrapyramidal lesion with sulpiride, could not be explained by anticholinergic activity as in case of clozapine . This difference between sulpiride and the classical neuroleptics might be due to lack of interaction of sulpiride with receptors responsible for production of catalepsy .

On account of the atypical behaviour and biochemical antidopaminergic profile of the neuroleptic, sulpiride , the possibility of the presence of more than one type of dopamine receptors was considered and that sulpiride might preferentially interact with one of these receptors (Spano et al., 1979) .

Dopamine receptors in the body were categorized by Kebabian and Calne (1979) , on the basis of biochemical or pharmacological criteria, into two distinct forms , D_1 and D_2 , as represented in the table thereafter :

Name	D_1	D_2
- Cyclase linked	Yes	No
- Location of prototype receptor	Bovine parathyroid	Mammotroph of anterior pituitary
- Dopamine	Agonist (U molar potency)	Agonist (n molar potency)
- Apomorphine	Partial agonist or antagonist .	Agonist (n molar potency) .
- Dopaminergic ergots	Potent antagonist (n molar potency). Weak agonist (U molar potency)	Agonist (n molar potency)
- Selective antagonist	None known as yet.	Metoclopramide , Sulpiride .
- Radiolabelled ligand	Cis-flupenthixol	Dihydroergocriptine

Table(1): Quoted from(Kebabian J. and Calne D., 1979 ; Multiple receptors for dopamine, Nature, Volume 277 , P. 93 - 96) .

One of the striking examples of multiple variants of dopamine receptors within the same tissues in the body is the corpus striatum (brain dopamine receptor) which was shown to possess five identifiable binding sites as schematically represented thereafter :

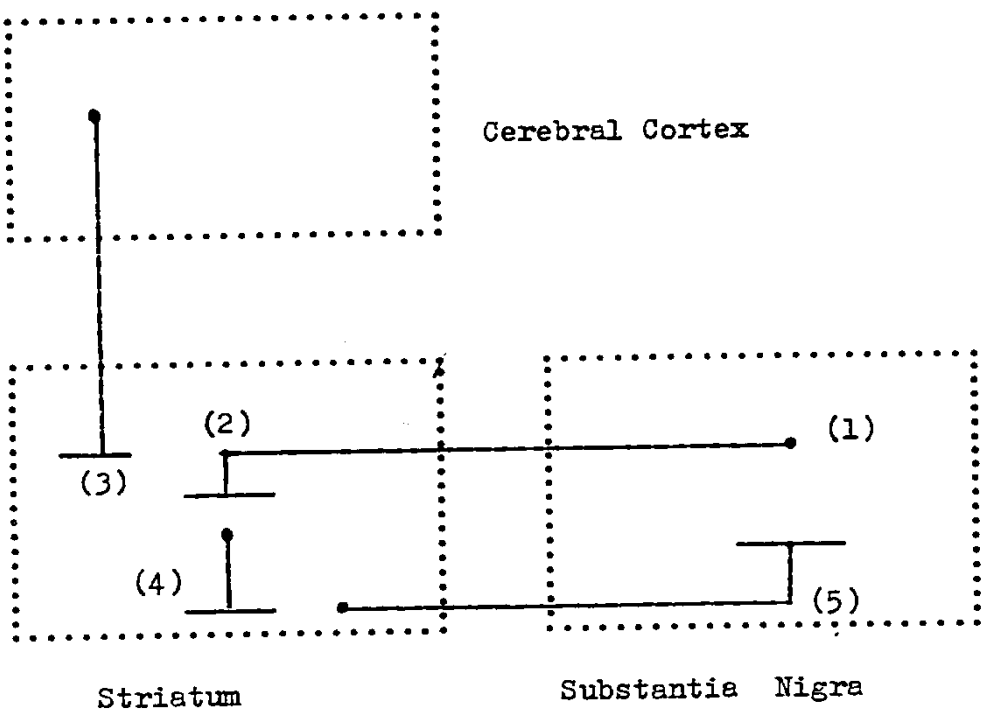

Fig. (1): A schematic representation of neurons in the nigrostriatal axis (Kebabian J. and Calne D., 1979 ; Multiple receptors for dopamine, Nature, Volume 277 , P. 93 - 96) .

These dopaminergic neurons contain autoreceptors which regulate either electrical firing of site (1) cells in the substantia nigra or tyrosine hydroxylase activity at site (2) on the terminals . In addition, there are cortical neurons which project to the striatum at site (3) and intrinsic caudate neurons at site (4) . Finally, terminals of striatal neurons project to substantia nigra at site (5) . 1 - 3 dopaminergic sites of D_2 type are not associated with enhanced adenyl cyclase activity, the functional role of 4 and 5 binding sites of D_1 type are linked with the modulation of adenyl cyclase enzyme activity.

Spano et al. (1979) had found that the classical neuroleptic , haloperidol, prevented both the sedative and hypnotic effect caused by the stimulant effect of apomorphine on the inhibitory D_2 dopamine autoreceptors as well as the improvement of parkinsonian symptoms produced through stimulation of apomorphine to the postsynaptic excitatory D_1 receptors . On the contrary , the atypical neuroleptic , sulpiride, can only antagonize the sedative and hypnotic effect of apomorphine without affecting the apomorphine-induced improvement in parkinsonian syndrome. This suggested that while sulpiride is a sole specific D_2 antagonist, the classical neuroleptics are both D_1 and D_2 antagonists .