stimulation, determined from the same tissue samples, makes a mere coincidence most unlikely. Because the field-stimulated ACh output showed also a similar increase during that time period (Figure 1). In fact, the value of the field-stimulated ACh output that differed significantly ($p < 0.05$) from that of April 19 was found only in the week ending on June 7. Thus, an increase of the spontaneous ACh output in other words, an increase of ACh neuronal activity of the Auerbach's plexus during the week ending on June 7 in comparison with that of April 19 (Figure 1) is real. Because the week ending June 7 was 2 weeks prior to the beginning of summer 1974 and because the ACh output was not related to known geophysical effect, e.g., temperature (Figure 2),

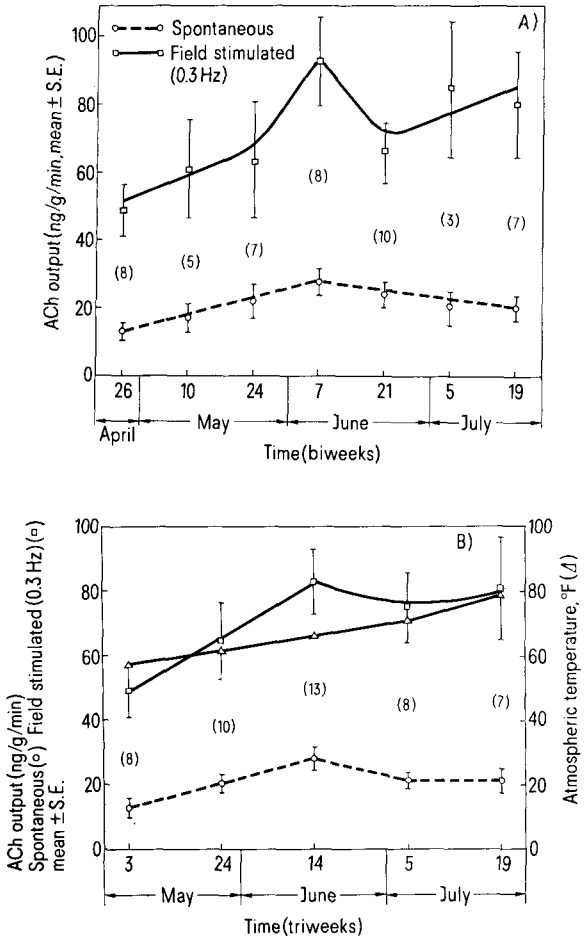

Fig. 3. Weekly data of Figure 1 and those that were excluded from Figure 1 composited and plotted on the basis of biweeks (A) and triweeks (B). Mean atmospheric temperature of each triweek period is also shown in (B). Number within parenthesis is number of animals.

it is likely that these neurons on one hand retained some common genetic component in spite of evolutionary changes, on the other respond to the approach of summer with a transient outburst of activity, although the guinea-pig is a non-hibernator[3].

This finding is unique; there is no published report on any neurotransmitter output change of this pattern either in a hibernator or a non-hibernator. There is, however, a published report on seasonal variation of the ACh output from brain during sleeping and waking in a non-hibernator. MONNIER and HERKERT[4] observed that the ACh output from the rabbit brain varied according to the season and that there was a good correlation between the ACh output and the external daily temperature, a parameter of seasonal condition used by these researchers. Because the over-all spontaneous ACh output from the Auerbach's plexus of guinea-pig ileum showed no relation to the external daily temperature (Figure 2), and because the spontaneous ACh output showed no change during the summer (Figures 1 and 2; summer began June 21 according to the United States Climatic Center), it is apparent that ACh neurons of the Auerbach's plexus from these guinea-pigs responded only to the seasonal transition from the spring to the summer. To demonstrate this transitional reaction, the weekly output data was composed and plotted in Figure 3 on a biweekly (3A) and a triweekly (3B) basis. As can be seen, there is a linear rise of the spontaneous ACh output up to 2 weeks (3A) or 1 week (3B) before the beginning of summer. Again, both points are significantly different ($p < 0.05$) from that of the corresponding initial point. Moreover, such a parallelism between the spontaneous and the field-stimulated curves of ACh output (3B) is difficult to reconcile as an epiphenomenon. Thus, data presented, suggest the existence of a seasonal transition effect on ACh output. Whether this seasonal transition response is common to all breeds of guinea-pigs and whether it varies from year to year are questions yet to be resolved.

Summary. Acetylcholine release from Auerbach's plexus of guinea-pig ileum, in vitro, both spontaneous and evoked by field-stimulation, responds to the seasonal transition from the spring to close to the beginning of summer. It did not change during the summer, however, tended to be higher than during the initial period (3 weeks after the beginning of spring).

J. HAZRA[5]

863 Squire Court,
Cary (North Carolina 27511, USA), 10 July 1975.

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An Evaluation of Apomorphine Action on Dopaminergic Receptors

A large number of behavioural, biochemical and electrophysiological studies provide considerable evidence to prove that apomorphine has a direct action on central dopaminergic receptors. Thus, apomorphine induced decreased dopamine turnover in corpus striatum[1], modified stereotype behaviour in 6-OHDA-treated rats[2], pecking response in pigeons[3] and gnawing behavior in rats[4] are reported to be a direct effect of the drug on the dopaminergic neurones of CNS.

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However, in more recent years this assumption has been questioned, on the grounds that if apomorphine-induced pecking is dopaminergic in nature, at least dopamine, L-dopa and amantadine should also produce this response, which they do not[5]. Similarly apomorphine, in contrast to dopamine, produces the fighting and biting response[6]; blocks dopamine synthesis[7]; inhibits DA uptake in rats, striatal synaptosomes[8] and fails to produce a complex stereotypy in open field situation[9] (a dopamine mediated response) suggesting that it has a different central site of action than dopamine. In Parkinsonian patients also, apomorphine, unlike L-dopa, corrects tremors first, rather than akynesia and akethesia[10], and no cross tolerance is known to exist between the two[11]. Furthermore, the side effects of both these drugs are not additive but antagonistic, e.g. the awakening effects, involuntary movements and nausea induced by L-dopa are antagonized by apomorphine, while apomorphine induced sedation is counteracted by L-dopa[12].

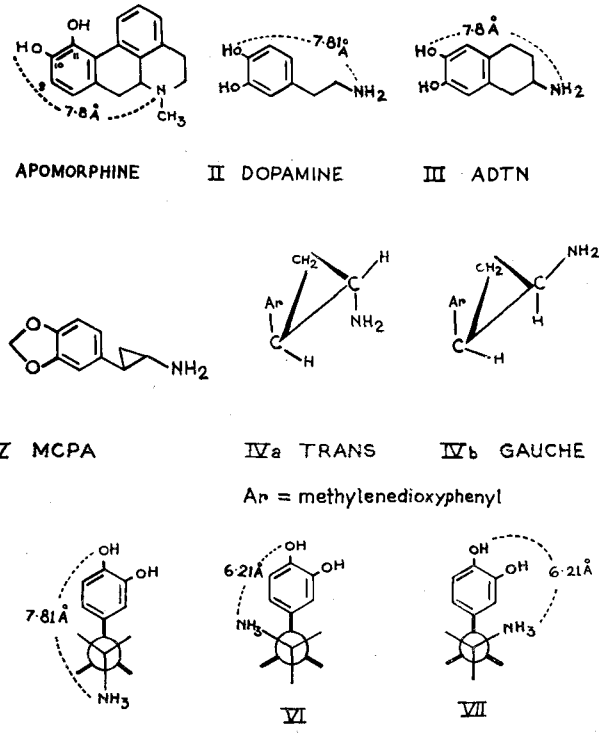
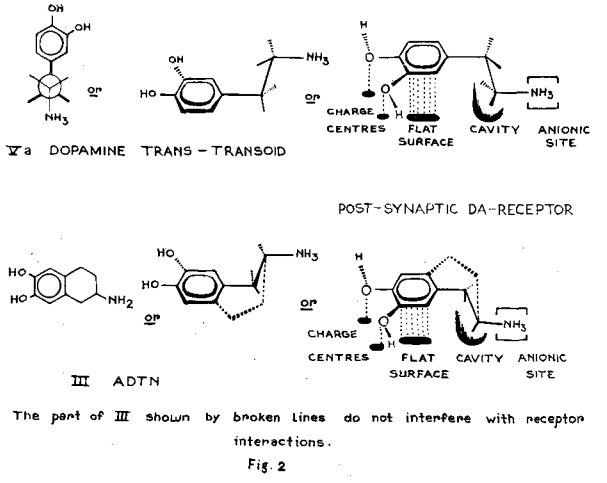
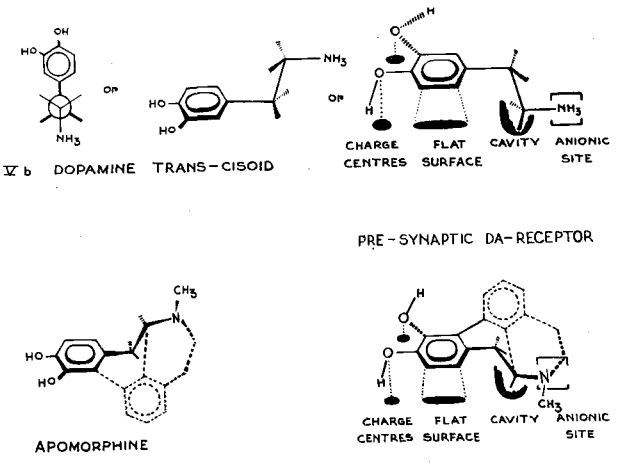


Fig. 1



The part of III shown by broken lines do not interfere with receptor interactions.

Fig. 2



The part of APO shown by broken lines keep away from receptor sites.

Fig. 3

More recently LANGER[13] has proposed the presence of pre- and postsynaptic DA receptors, which are not identical in nature. Similarly COSTALL et al.[14] believe that apomorphine-induced stereotypy is not mediated by a direct action on central dopaminergic receptors, rather presynaptic events are more important in the manifestation of this response[15].

All these reports raise the questions whether apomorphine and dopamine share a common receptor, and if apomorphine acts preferentialy on presynaptic dopamine receptor, what may be the topographic difference between pre and post-synaptic dopamine receptors? We, therefore, feel that the critical examination of the chemical configuration of simpler models like apomorphine (I), dopamine (II) and the tetraline derivative, 2-amino-6,7-dihydroxy (1,2,3,4)-tetrahydronaphthalene, ADTN (III) (Figure 1), in relation to their pharmacological activity, may provide vital clues and new insight into solving this complex problem.

The flexible nature of the ethylamine side chain of dopamine allows the existence of 1 *trans*-(V) and 2 *gauche*-(VI and VII) conformers with a slight preference of the former[16] (Figure 1); and it is now clear that the dopamine-like activity resides in the *trans*-conformer[17].

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Thus the *trans*-isomer of 2-(3,4-methylenedioxyphenyl) cyclopropylamine (MPCA) (IVa), but not the *gauche* (IVb) is active in inducing dopamine-like effects in the striatum[17]. Similarly a rigid molecule like ADTN (III), which is conformation-wise almost identical to *trans*-dopamine, has been reported to be a dopamine receptor agonist[18]. Recently HORN[19] has also provided evidence that, besides being a dopamine receptor agonist, ADTN is a potent inhibitor of dopamine uptake and thus the preferred conformation for dopamine at the uptake site should be akin to that of ADTN i.e. *trans* (O-N bond distance of 7.8Å is identical both in V and III).

But we have to keep in mind that dopamine has 2 conformational centres. One centre results in structure (V–VII) as depicted by RAKKER et al.[20] and COSTALL et al.[17] (Figure 1) while the other conformational variable depends on the rotation of the catechol ring. Thus, more precisely, the dopamine structure embedded in the ADTN molecule is certainly *trans*, but with the catechol ring *transoid* to α- and β carbons of dopamine (Va) (Figure 2). Thus, post-synaptically the preferred conformation of dopamine could be *trans-transoid* (Va). Figure 2 also depicts a topographical sketch of the complimentary post-synaptic dopamine receptor and explains how the *trans-transoid* dopamine and ADTN fit into the proposed receptor sites.

Interestingly, while ADTN elicits characteristic dopamine-like activity on specific dopaminergic neurons of the snail *Helix aspersa*, apomorphine does not[21]. This dramatic selectivity of ADTN by snail dopaminergic receptors may account for the fact that the snail receptors may resemble mammalian post-synaptic dopamine receptors and that apomorphine may not act post-synaptically, a suggestion in accordance with recent reports[8]. Structure activity studies on apomorphine analogues have made it abundantly clear that the presence of 11-OH group in correct spatial relationship to nitrogen is essential for dopamine-like activity[22]. Therefore, it seems probable that this structural requirement for apomorphine is specific and complimentary to a distinctly different pre-synaptic dopamine receptor. More precisely the dopamine conformation embedded in the apomorphine molecule is also *trans*-like (V) but with catechol ring *cisoid* to α- and β-carbons of dopamine side chain (Vb) (Figure 3). Thus, pre-synaptically the preferred dopamine conformation appears to be *trans-cisoid* (Vb). A topographical sketch of the proposed pre-synaptic dopamine receptor, on which apomorphine may interact, is also shown in Figure 3. After careful evaluation of the arguments for and against the direct action of apomorphine and ADTN on the dopamine receptors, we propose that the post-synaptic and pre-synaptic receptor of dopamine differ in the conformational restrictions they impose on agonist molecules. Rigid molecules like ADTN hold *trans-transoid*, while apomorphine incorporates *trans-cisoid* conformation of dopamine and may interact with post-synaptic and pre-synaptic receptors respectively; while dopamine by virtue of its molecular flexibility can fit in both. The approach may appear to be an over-simplification; nevertheless, the proposed hypothesis should provide a useful framework for designing new agents for further investigations.

Summary. The controversial literature reports leave open a question whether apomorphine (APO) and dopamine (DA) share a common receptor? After careful evaluation of the arguments, both for and against, about direct action of APO on DA receptor we propose that rigid molecules like APO hold *trans-cisoid* conformation and preferably interact with the pre-synaptic DA receptors while ADTN (2-amino-6,7-dihydroxy, 1,2,3,4-tetrahydronaphthalene) incorporates *trans-transoid* conformation and primarily acts on post-synaptic DA receptors. Dopamine, by virtue of its molecular flexibility, can act on both the receptors.

P. C. DANDIYA, H. L. SHARMA, S. K. PATNI and R. S. GAMBHIR

Department of Pharmacology, S.M.S. Medical College, Jaipur (India 302004), 24 January 1975.

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The Uptake of ^{35}S by Hypothalamic and Neurohypophysial Proteins Following Intraventricular Injection of L-Cysteine-^{35}S-Hydrochloride in Rats Dehydrated and Reserpinized

There is some evidence showing that the neural input to the supraoptic and paraventricular neurones is noradrenergic as well as cholinergic, the former being inhibitory and the latter stimulatory[1]. In the hydrated rats, however, both adrenergic and cholinergic mechanisms were recently observed to provoke the release of vasopressin[2]. The data concerning changes of vasopressin liberation as influenced by reserpine-induced inhibition of monoaminergic transmission are so far not consistent: an augmentation[3,4], a decrease[5,6] and only negligible effect[7] have been reported. Reserpine has been found to inhibit the vasopressin response to hyperosmotic stimulation[8] and to diminish the block of the milk ejection reflex induced by stress[9].

The present work deals with the incorporation of ^{35}S into TCA-precipitable proteins of the hypothalamo-neurohypophysial system in white rats dehydrated and reserpinized.

Material and methods. Male rats of F_1 generation, weighing 275–350 g, bred of August males and Wistar females were used. The animals were maintained in a 14-h light,

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