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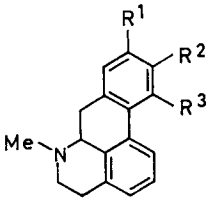
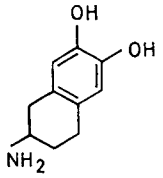
LETTERS TO THE EDITOR

On apomorphine and dopamine receptors

Apomorphine (I) produces stereotyped gnawing in rats as a result of stimulation of inhibitory dopaminergic neurons in the corpus striatum by a mechanism involving interaction with dopamine receptors (Ernst, 1967; Ungerstedt, Butcher & others, 1969; Menge & Brand, 1971). We recently showed (Pinder, Buxton & Green, 1971) that this dopamine-like action of apomorphine is dependent upon the dihydroxytetrahydroamino-naphthalene moiety and not as Kier & Truitt (1970) suggested upon the tetrahydroisoquinoline part of the molecule. Our work has been supported by new molecular orbital calculations and nmr spectroscopy of dopamine which demonstrate the errors in Kier & Truitt's analysis (Bustard & Egan, 1971), and by observations that the N-OH distances in apomorphine correspond almost exactly to those in the *trans-* and possibly in the *gauche-* conformers of dopamine (Rekker, Engel & Nys, 1972). It is possible that 9,10-dihydroxyaporphine (II, isoapomorphine) might have dopamine-like activity, and one of us (Woodruff, 1971) has proposed that the dopamine receptor may be such as to accommodate a fragment of this molecule in 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (III).



(I), $R^1 = H$; $R^2 = R^3 = OH$
(II), $R^1 = R^2 = OH$; $R^3 = H$
(IV), $R^1 = R^2 = R^3 = H$



III

Gnawing was measured in male Porton rats (200–250 g) in metal cages with wire grid bottoms (Ernst, 1967). Isoapomorphine (Cannon & Aleem, 1971) and 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene (Thrift, 1967) were administered (i.p.) as their hydrobromides. In contrast to apomorphine hydrochloride (5 mg/kg, i.p.), which consistently produced a syndrome of stereotyped licking accompanied by periods of gnawing in both normal and iproniazid-pretreated rats, these compounds produced no gnawing or licking movements at doses up to 50 mg/kg. The dimethyl ethers of II and III were similarly ineffective in accordance with the reported inactivity of both monomethyl ethers, and the dimethyl ether, of apomorphine (Cannon, Smith & others, 1972).

The effect of the compounds was also investigated on the activity of specific dopamine-sensitive neurons in the central nervous system of the snail *Helix aspersa* (Woodruff & Walker, 1969), a preparation in which apomorphine has no dopamine-like activity. Compound III was consistently effective (5 preparations) in producing hyperpolarization and inhibition in *Helix* neurons, its mean equipotent molar ratio to dopamine being 45 (Range, 10–80). These dopamine-like effects were confirmed by the lack of action on cells unaffected by dopamine and by the blocking action of ergometrine (Walker, Woodruff & others, 1968). Isoapomorphine, the dimethyl ethers of II and III, and the parent alkaloid aporphine (IV) had no dopamine-like action in the *Helix* neurons.

The results in *Helix aspersa* confirm the postulate (Woodruff, 1971) about the topology of the dopamine receptor in this species, since Dreiding models suggest that isoapomorphine would fit as poorly as apomorphine, which is itself without effect, while the tetralin derivative (III), which fits well, has dopamine-like activity. They also demonstrate a further discrepancy between the ability of compounds to stimulate the *Helix* dopamine receptor and their ability to induce stereotype behaviour in the rat. Thus, apomorphine is a potent dopamine-like agent in the mammalian brain but has no such actions in *Helix* whereas 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene is effective in *Helix* but does not affect rat behaviour. The possibility that the latter compound, and isoapomorphine, fail to reach the brain after systemic administration is unlikely in view of their close structural similarity to apomorphine, and it seems possible that dopamine receptors in *Helix aspersa* and the rat have slight but significant differences in topology. Such results put in doubt the possible use of *Helix* neurons as a simple test organ for dopamine-like and dopamine blocking drugs (Woodruff & Walker, 1969), provided that the central actions of apomorphine in the rat are due solely to activation of dopamine receptors. With regard to the dopamine-like action of apomorphine in the rat, the necessity of both hydroxyl groups in the correct spatial relationship to the nitrogen atom is emphasized by the inactivity of isoapomorphine and its molecular fragment (III), and is supported by the weak (Granchelli, Neumeyer & others, 1971) and lack of (Cannon, & others, 1972) effects of 10-hydroxy-, 10-hydroxy-11-methoxy-, and 11-hydroxy-10-methoxy-aporphines.

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