Studies on the centrally mediated cardiovascular effects of apomorphine in the anaesthetized rat

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Apomorphine is a potent dopamine receptor agonist (Anden Rubenson, Fuxe & Hokfelt, 1967; Struyker Boudier, 1975), which on intravenous injection in both cats and rats produces a short lasting fall in blood pressure associated with an intense bradycardia (Barnet & Fiore, 1971; Finch & Haeusler, 1973). These effects are centrally mediated, since a pressor response is obtained in spinalized preparations. More recently Dutta, Guha & Pradhan (1975) found that intraventricular (i.c.v.) apomorphine produced depressor responses in anaesthetized cats, an effect which was not dose related.

In this study we have examined the effect of i.c.v. injections of apomorphine on the resting blood pressure and heart rate in anaesthetized renal hypertensive rats.

Apomorphine (1-100 μg i.c.v.) caused a short lasting dose related fall in blood pressure and heart rate in the urethane-anaesthetized rat preparation. Pretreatment with fluphenazine (0.5 mg/kg i.p.), haloperidol (0.5 mg/kg i.p.) or metoclopramide (10 mg/kg i.p.) abolished the depressor response to apomorphine (10 μg i.c.v.), but pretreatment with piperoxan (200 μg i.c.v. or 10 mg/kg i.p.) did not affect the depressor response to apomorphine (10 μg i.c.v.). Furthermore atropine (1 mg/kg i.p.) pretreatment abolished the cardiovascular effects of apomorphine (10 μg i.c.v.).

Pretreatment 3 days earlier with *p*-chlorophenylalanine (400 mg/kg i.p.), which causes depletion of brain 5-hydroxytryptamine levels (Miller, Cox, Snodgrass & Maickel, 1970), did not affect the depressor response to apomorphine (10 μg i.c.v.).

In renal hypertensive rats, intravenous injections of apomorphine (0.01-1.0 mg/kg i.v.) produced short lasting falls in blood pressure associated with an intense bradycardia. Low doses of apomorphine (0.01-0.1 mg/kg i.v.) could be antagonized by pretreatment with haloperidol (0.5 mg/kg i.v.) or metoclopramide (10 mg/kg i.v.). The highest dose was reduced but not abolished.

These results suggest that central dopamine receptors rather than adrenoceptors or serotonin receptors are involved in the mediation of the central hypotensive action of apomorphine in the anaesthetized rat.

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The interpretation of responses of motoneurone field potentials to 5-hydroxytryptamine

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A previous communication to the society (Barasi & Roberts, 1974a) reported that 5-hydroxytryptamine (5-HT) applied by microiontophoresis in the ventral horn of the rat spinal cord, increased the amplitude of antidromically evoked field potential responses of motoneurones. This response to 5-HT closely resembled the effect on motoneurones of stimulating the raphe nuclei. Comparison of these actions of 5-HT with the effect of intravenously administered L-tryptophan on the dorsal root evoked monosynaptic reflex, suggested that 5-HT may, by an unknown

mechanism, be increasing the excitability of spinal motoneurones (Barasi & Roberts, 1974b). Several publications, however, have indicated an opposite action of 5-HT (Clineschmidt & Anderson, 1970; Engberg, Flatman & Kadzielawa, 1974) although other reports seem to indicate an increased excitability of motoneurones following administration of monoamines and other drugs (Banna & Anderson, 1968; Marley & Vane, 1967; Sinclair & Sastry, 1974).

In recent studies with the halothane anaesthetized rat conditioning stimulation of nucleus raphes medianus increased lumbar flexor motoneurone field potentials on 22 occasions and had no effect on 10. The extensor field potentials were increased on 16 occasions and unaffected on 4. Iontophoretically applied 5-HT increased flexor potentials on 38 occasions and had no effect on 13. Similarly extensor fields were increased on 32 occasions and unaffected on 8.

To assist with the interpretation of changes in the field potential amplitude, glycine, glutamate and potassium were applied by iontophoresis into the ventral horn. Glycine reduced the amplitude of the field potential on 12 occasions, having no effect on 3. Glutamate increased the potential amplitude on 10 occasions, had no effect on 12 occasions but also reduced the field potential on 8 occasions. Potassium increased the field on 10 occasions in 24 studies but never reduced the amplitude. These observations are compatible with the suggestion that an increased field potential amplitude may be an index of increased motoneurone excitability.

A further test of this postulate involved stimulating the ventral root or muscle nerve (with lumbar dorsal roots sectioned) with 3 to 6 stimuli at 80-200 Hz. The field potential progressively declines in amplitude during the train, presumably due to the failure of propagation of the antidromic spike from axon to soma in a progressively larger proportion of the population of activated motoneurones (Eccles, 1950). 5-HT, glutamate and potassium all tended to prevent this progressive decrease in amplitude. This provides further support for the postulate that motoneurone excitability is increased by these drugs.

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The selective inhibition of 5-hydroxytryptamine re-uptake by Org 6582

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Re-uptake by the membrane pump is considered to be the major means by which monoamines are inactivated at the neural synapse. Numerous studies have shown that tertiary tricyclics, such as chlorimipramine, preferentially inhibit the membrane amine pump of central 5-hydroxytryptaminergic (5-HT) neurones whereas secondary tricyclics, such as desipramine, preferentially block the membrane amine pump of central noradrenergic (NA) neurones (Bopp & Biel, 1974). Several recent reports have emphasized the desirability of compounds exerting a specificity of effect on monoamine re-uptake (Iversen, 1974; van Praag, 1974). The studies to be reported reveal Org 6582 (*dl*-8-chloro-11-anti-amino-benzo-(b)-bicyclo [3.3.1] nona-3,6a (10a) diene hydrochloride) to be a selective inhibitor of 5-HT re-uptake.

In vivo blockade of 5-HT re-uptake was studied