Cardiovascular dopamine receptor stimulation antagonized by metoclopramide

Metoclopramide (*N*-(diethylaminoethyl)-2-methoxy-4-amino-5-chlorobenzamide) inhibits emesis in both laboratory animals (Justin-Besançon & Laville, 1964) and man (Handley, 1967). Radiological studies have shown that in man it is capable of stimulating gastric emptying and intestinal motility (James & Hume, 1968); recent evidence suggests a possible clinical effectiveness in the treatment of migraine (Matts, 1974).

Metoclopramide, like the anti-emetic butyrophenone derivative haloperidol, antagonizes apomorphine-induced stereotypy in animals (Hackman, Pentikainen & others, 1973) indicating possible involvement of central dopaminergic pathways in this response. In addition, haloperidol antagonizes the hypotensive action of dopamine in the anaesthetized dog (Sampson, Scroop & Louis, 1974) and it was therefore thought pertinent to study the effect of metoclopramide on the cardiovascular responses to dopamine.

14 Wistar rats of either sex, anaesthetized with sodium pentobarbitone (60 mg kg^{-1}, i.p.) were used. The average mean blood pressure was 105 mm Hg. Responses were measured as changes in mean blood pressure (mean blood pressure was calculated as diastolic pressure + 1/3 pulse pressure). In untreated animals doses of dopamine in the range 0·3 to 3 $\mu g\, kg^{-1}$ produced transient depressor responses whereas higher doses (3 to 100 $\mu g\, kg^{-1}$ produced dose-related increases in mean blood pressure. Blood pressure responses to noradrenaline and isoprenaline were abolished by pretreatment with a combination of phentolamine (3 mg kg^{-1}, i.v.) and propranolol (1 mg kg^{-1}, i.v.). In rats so treated the pressor responses to dopamine were converted to dose-related depressor responses. Intravenous metoclopramide (0·1–10 mg kg^{-1}) caused dose-related reductions in the depressor responses to dopamine (0·02–0·1 mg kg^{-1}, i.v.). After doses of 1 mg kg^{-1} or more of metoclopramide the response to dopamine were changed such that the depressor response was reduced and a pressor component appeared (Fig. 1). The depressor responses to dopamine (0·1 mg kg^{-1}) were progressively reduced by increasing doses of metoclopramide. After a total dose of 4·4 mg kg^{-1} of metoclopramide the depressor response to dopamine was abolished and was replaced by a small pressor response. Intravenous doses of metoclopramide (10 to 30 mg kg^{-1}) produced short-lived falls in mean blood pressure which were unaffected by haloperidol (10 mg kg^{-1}).

Further studies in 6 rats indicated that metoclopramide at doses below 10 mg kg^{-1} did not depress blood pressure responses to either noradrenaline or isoprenaline indicating a specific dopamine receptor antagonism.

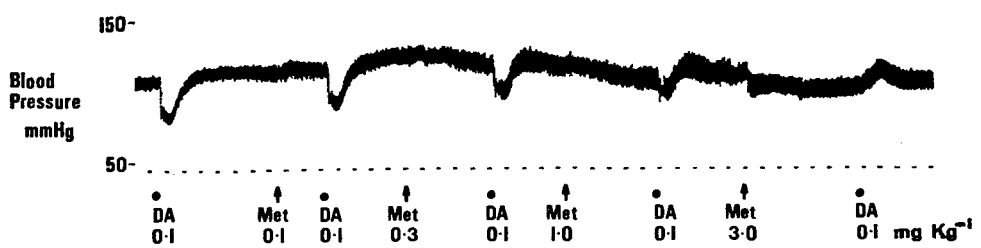

FIG. 1. Anaesthetized rat (350 g male) carotid blood pressure; responses to dopamine (0·1 mg kg^{-1}, i.v.) after α- and β-adrenoceptor blockade with phentolamine (3 mg kg^{-1} i.v.) and propranolol (1 mg kg^{-1} i.v.). Dopamine depressor responses were abolished and finally reversed by increasing doses of metoclopramide.

The hypotensive responses to dopamine are thought to be due primarily to vasodilatation in the coeliac, renal and mesenteric beds (Eble, 1964). In two cats anaesthetized with chloralose (85 mg kg^{-1}, i.v.) the effects of metoclopramide on dopamine responses on blood pressure and renal artery blood flow were measured. After intravenous administration of phentolamine (3 mg kg^{-1}) and propranolol (1 mg kg^{-1}) dopamine produced reproducible depressor responses and increases in renal artery blood flow. Both blood pressure and renal artery flow responses to dopamine were abolished by metoclopramide (10 mg kg^{-1}). In Fig. 2A are shown the responses to dopamine (0·1 mg kg^{-1}) and isoprenaline (1 μg kg^{-1}) after α-adrenoceptor blockade with phentolamine (3 mg kg^{-1}). Between 2A and 2B propranolol (1 mg kg^{-1}) was administered which abolished the isoprenaline response but did not greatly affect the response to dopamine. However, in 2B the dopamine responses were markedly reduced after metoclopramide (3 mg kg^{-1}). In both cats after doses of 10 mg kg^{-1} or more of metoclopramide the responses to dopamine were altered; a slight increase in blood pressure and decrease in renal artery blood flow appearing. In both cats and rats there was about 50% recovery in the dopamine responses 1 h after treatment with metoclopramide.

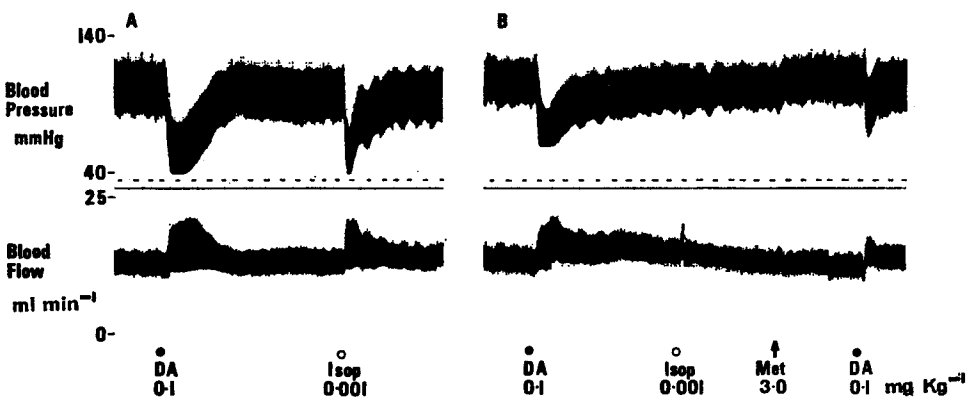

FIG. 2. Chloralose-cat (1·02 kg female) blood pressure and renal artery blood flow records (with electromagnetic flow meter). Responses in A were measured after α-adrenoceptor blockade with phentolamine (3 mg kg^{-1}, i.v.). Between A and B propranolol (1 mg kg^{-1}, i.v.) was administered which abolished isoprenaline responses but did not greatly affect the dopamine responses. In B the dopamine responses were markedly reduced after metoclopramide (3 mg kg^{-1}, i.v.).

Our results suggest that metoclopramide is capable of antagonizing some effects of dopamine. However, it may do so in a manner different from other dopamine antagonists such as haloperidol and bulbocapnine (Tseng & Walaszek, 1970; Sampson & others, 1974); metoclopramide reversed the effects of dopamine, an action which has been reported for morphine on dopamine responses in the anaesthetized cat (Dhasmana, Dixit & others, 1969).

The effect of metoclopramide in antagonizing dopamine may be of importance in elucidating the mechanisms whereby it produces its clinically useful effects in man.

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Some further observations of the effect of β-phenethylamine on locomotor activity in mice

β-Phenethylamine (PE), identified as a naturally occurring amine in man and other animals (Nakajima, Kakimoto & Sano, 1964; Oates, Nirenberg & others, 1963; Jackson & Temple, 1970), on injection into mice and rats produces increased locomotion, particularly after monoamine-oxidase inhibition (MAOI) (Mantegazza & Riva, 1963; Fischer, Ludmer & Sabelli, 1967; Fuxe, Grobecker & Jonsson, 1967; Jackson, 1972). Without MAOI, higher doses must be given to produce an effect and in these circumstances a biphasic stimulation has been reported to occur in mice (Jackson, 1972, 1975).

A first phase occurred almost immediately and appeared to be produced by release of newly synthesized endogeneous catecholamines, and a temporally later phase was postulated to be due to direct dopamine receptor stimulation by a PE metabolite (Jackson, 1972), which metabolite, however, did not appear to be β-hydroxy-β-phenethylamine (Jackson, 1975). Recently, Jackson, Andén & Dahlström (1975) applied PE bilaterally to the nucleus accumbens of rat brain and produced a marked rise in coordinated locomotor activity in MAOI pretreated rats. This activity was markedly reduced by prior reserpine pretreatment, and completely blocked by the tyrosine hydroxylase inhibitor, α-methyltyrosine (α-MT). No direct receptor stimulation was seen in this model.

Because of the suggestion by some authors (Saavedra & Fischer, 1970; Sabelli & Mosnaim, 1974) that PE may be a "modulator" in the central nervous system, and because of the reported direct receptor stimulant action in non-MAOI mice (Jackson, 1972) in contrast to the purely indirect actions reported after direct application to the nucleus accumbens (Jackson & others, 1975), I decided to reinvestigate the mode of action of systemically administered PE in producing locomotor stimulation. Mice were pretreated with nialamide, a MAOI, to prevent the production of potentially active deaminated metabolites.

Female N.M.R.I. mice (Anticimex, Stockholm) 20–24 g, kept at 25 ± 1° for at least 2 days before use, under normal lighting conditions, were pretreated with various