Pharmacology of β-(3,4-dimethoxyphenyl)ethyl amine: lack of peripheral and central antidopaminergic properties

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The diversity of molecular structures capable of antagonizing the central and peripheral actions of dopamine (Goldberg, 1975 a,b; Iversen, 1975) has prompted consideration of the minimum structure to display blockade. Whether structurally simple compounds with selective central or peripheral activity could be developed on the concept of a minimum blocking structure and thus become the basis for probing dopamine receptor chemical topography remains an open question. Successful receptor differentiation using complicated molecules is portended by work suggestive of central dopamine inhibitory and excitatory receptors (Cools, Struyker Boudier & van Rossum, 1976). It is also apparent in the pimozide differentiation of peripheral dopamine receptors from apomorphine sensitive central dopamine receptors (Setler, Pendleton & Finlay, 1975).

In contrast to the complicated molecular structures presented by most antidopaminergic compounds, dopamine dimethyl ether (DMPEA) has been reported to have been both central (Ernst, 1969) and peripheral (Elie, Barbeau & others, 1969) dopamine blocking activity. It has been implicated in schizophrenia (Friedhoff & Van Winkle, 1962 a,b), reported to induce catalepsy in various species as a high dose effect (DeJong, 1945; Brown, Lang & Gershon, 1965) and to elicit various autonomic responses including a pressor action, a depressor action and β-adrenergic blockade (Epstein, Gunn & Virden, 1932; Brown & others 1965). The effects of DMPEA on L-3,4-dihydroxyphenylalanine (L-dopa) or apomorphine-induced gnawing in the rat have been assessed to determine its ability to block central dopamine receptor systems. It was reported to antagonize stereotypy as measured by a shortened recovery from drug-induced gnawing (Ernst, 1965) and decreased gnawing intensity (Ernst, 1969). Contrary to the reports of dopamine-blocking action, our investigation of DMPEA pharmacology shows the compound to have no antidopaminergic properties. In non-toxic doses the peripheral action of DMPEA is that of an α-adrenergic agonist; centrally, DMPEA potentiates apomorphine-induced climbing behaviour as indicated by haloperidol blockable (Protais, Costentin & Schwartz, 1976) climbing in mice.

Male Swiss Webster mice (25–30 g), housed in a light controlled environment with free access to food were administered apomorphine hydrochloride (s.c.) or DMPEA (i.p.), dissolved in 0·9% saline (0·2 ml). Apomorphine-induced climbing was used since it has been shown to be a convenient and reliable method of assessing mouse striatal dopaminergic stimulation (Protais & others, 1976). 30 min after dosing with saline control or DMPEA the mice were dosed with apomorphine hydrochloride (1 mg kg^{-1}) and placed in cylindrical wire mesh cages. The climbing behaviour was scored at 10 and 20 min post apomorphine dosing as follows: all paws on floor (0), forefeet holding wall (1), four paws holding wall (2). The scores for each animal were averaged. Ten mice were studied using the saline control and at each of four DMPEA doses.

Cardiovascular experiments were conducted on mongrel dogs of either sex (7–13 kg) under pentobarbitone anaesthesia (20 mg kg^{-1}, i.v.), using morphine sulphate premedication (5 mg kg^{-1}). After endotracheal intubation the right femoral artery and vein were cannulated. All drugs were given in solution as above. Injections were made via a venous catheter and followed with 2 ml of heparinized saline flush. Blood pressure and heart rate recordings were made via an arterial catheter using a Model 4 Physiograph equipped with a P-1000 AM transducer. The animals were atropinized (1 mg kg^{-1}) to eliminate vagal reflex bradycardia, and tested for catecholamine sensitivity with noradrenaline (0·2 μg kg^{-1}), isoprenaline (0·2 μg kg^{-1}) and dopamine (2, 3 and 5 μg kg^{-1}). Phenoxybenzamine, (5 mg kg^{-1}), was given in most cases to eliminate any pressor component from dopamine responses. In those cases where the cardiovascular action of DMPEA was studied no phenoxybenzamine was used. All doses of DMPEA were followed by dopamine challenge immediately on resumption of control cardiovascular conditions, i.e. within 30 s at DMPEA doses having no pressor effect but with a delay of up to 5 min at a dose of 1·5 mg kg^{-1}.

The apomorphine-induced climbing behaviour was not attenuated by DMPEA (Table 1). On the contrary, the compound potentiated this effect, the trend reaching statistical significance at 50 mg kg^{-1}; this dose is well below that eliciting behavioural or toxic signs (Epstein & others, 1932). At 200 mg kg^{-1} there is evidence of inhibition of climbing behaviour by DMPEA. This is not evidence of dopaminergic blockade but rather of typical DMPEA toxicity that is duplicated in animals dosed only with that compound. At this high dose 60% of the animals either convulsed or showed bizarre motor activity during the test. The mechanism of DMPEA potentiation of apomorphine-induced climbing behaviour is unclear.

The cardiovascular response to dopamine in atropinized, phenoxybenzamine-treated dogs is depressor only.

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Table 1. *Effect of DMPEA on apomorphine-induced mouse climbing.* Each experimental group comprised 10 animals. All subjects received apomorphine hydrochloride (1 mg kg^{-1}, s.c.) 30 min after either DMPEA or saline.

Dose (DMPEA, mg kg^{-1})	Average climbing score ± s.e.
Saline	1·30 ± 0·20
25	1·40 ± 0·22
50	1·85 ± 0·10†
100	1·75 ± 0·14
200	0·80 ± 0·22

† Significantly greater than saline + apomorphine ($P < 0{\cdot}025$) by a 2-tail Student's *t* test.

This test system was used because even at 3 μg kg^{-1} the dopamine response is biphasic, with a preliminary fugitive pressor action appearing before the typical low dose dopamine lowering of both systolic and diastolic pressures. DMPEA was deployed against a standard 3 μg kg^{-1} dose of dopamine in phenoxybenzamine-treated and untreated dogs. The DMPEA dosing sequence ranged from 1 μg kg^{-1} to 1·5 mg kg^{-1} and began by increases from 1 μg kg^{-1} in 10 μg increments to 100 μg kg^{-1}, subsequent doses were 0·5, 0·7, 1·0 and 1·5 mg kg^{-1}. In the absence of α-blockade DMPEA begins to show pressor effects but no tachycardia at 100 μg kg^{-1} and at 1·5 mg kg^{-1} this action is prolonged, the average diastolic pressure rising from a control of 60 to a peak of 84 mm Hg and systolic pressure rising from 120 to 150 mm Hg. The pressor action of DMPEA was only partially antagonized by doses of phenoxybenzamine completely blocking the pressor phase of dopamine action. When any dose of DMPEA was challenged by dopamine there was no attenuation of dopamine specific depressor action (Goldberg, 1975).

In view of these results, it is not possible to hold the view that DMPEA is a pharmacological antagonist at receptor sites selective for dopamine or dopaminergic agonists. This view is supported by a similar lack of DMPEA blocking action in the cockroach salivary gland cell preparation (Ginsborg, Turnbull & House, 1976).

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