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Dopaminergic stimulation enhances the utilization of noradrenaline in the central nervous system

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Persson & Waldeck (1970) have reported that apomorphine accelerates the disappearance of noradrenaline in the mouse brain induced by the tyrosine hydroxylase inhibitor, α-methyltyrosine methylester, or by the dopamine-β-hydroxylase inhibitor, FLA-63 (bis-(4-methyl-1-homopiperazinyl-thio carbonyl disulphide). Recently, Maj, Kapturkiewicz & Michaluk (1976) found that apomorphine and memantine (1,3-dimethyl-5-aminoadamantane) could accelerate the disappearance of noradrenaline in the rat brain induced by another dopamine-β-hydroxylase inhibitor, sodium diethyldithiocarbamate. It is well known that apomorphine does not act directly or indirectly on the noradrenaline receptors e.g. it does not influence the hind limb flexor reflex in spinal rats (Andén, Rubenson & others, 1967; Ernst, 1967), thus it might be expected that the apomorphine-induced changes in the concentration of noradrenaline, mentioned above, are secondary and are due to the primary dopaminergic stimulation. A similar supposition concerning the dopamine-noradrenaline interaction has been drawn from our earlier experiments in which locomotor activity was measured after combined treatment with dopaminergic drugs and agents affecting the noradrenaline neurons (Maj, Grabowska & Gajda, 1972).

We have now made further attempts to elucidate the hypothesis of an indirect (via dopamine receptor activation) stimulation of noradrenaline neurons. Besides apomorphine we used memantine which stimulates dopamine receptors without exerting a direct (postsynaptic) or indirect (presynaptic) action on noradrenaline neurons and without influence on the flexor reflex in spinal rats (Svensson, 1973; Maj, Sowińska & others, 1974).

Male Wistar rats, 200–250 g, were used. The utilization of noradrenaline in the brain regions was investigated by measuring its disappearance for 2 h after treatment with FLA-63 which is a good model for studies on noradrenaline turnover alone (Andén, Corrodi & Fuxe, 1972). Rats were killed by thoracotomy and exsanguination under light chloroform anaesthesia. The limbic system, neocortex and thalamus + hypo-

* Correspondence.

Table 1. *The effects of apomorphine (5 mg kg^{-1}) and memantine (40 mg kg^{-1}) on the FLA-63 (30 mg kg^{-1}) induced disappearance of noradrenaline in the brain regions of normal and spiperone (1 mg kg^{-1}) pretreated rats.*

Treatment†	Noradrenaline concn (%) means ± s.e.m. (*P*)		
	Limbic system	Neocortex	Thalamus + hypothalamus
I FLA-63††	100 ± 7·5	100 ± 4·5	100 ± 7·5
II Apomorphine + FLA-63	63 ± 6·3 (II *vs* I < 0·01)	67 ± 4·9 (II *vs* I < 0·001)	42 ± 2·9 (II *vs* I < 0·001)
III Spiperone + FLA-63	111 ± 6·8 (III *vs* I N.S.)	98 ± 12·4 (III *vs* I N.S.)	57 ± 4·7 (III *vs* I < 0·001)
IV Spiperone + apomorphine + FLA-63	105 ± 2·4 (IV *vs* III N.S. IV *vs* II < 0·001)	99 ± 3·6 (IV *vs* III N.S. IV *vs* < 0·001)	76 ± 1·5 (IV *vs* III < 0·01 IV *vs* II < 0·001)
I FLA-63††	100 ± 5·5	100 ± 8·9	100 ± 5·0
II Memantine + FLA-63	72 ± 5·4 (II *vs* I < 0·001)	31 ± 5·0 (II *vs* I < 0·001)	73 ± 8·4 (II *vs* I < 0·02)
III Spiperone + FLA-63	96 ± 8·4 (III *vs* I N.S.)	108 ± 9·4 (III *vs* I N.S.)	71 ± 6·6 (III *vs* I < 0·01)
IV Spiperone + memantine + FLA-63	89 ± 6·3 (IV *vs* III N.S. IV *vs* II N.S.)	61 ± 6·8 (IV *vs* III < 0·01 IV *vs* II < 0·01)	76 ± 5·4 (IV *vs* III N.S. IV *vs* II N.S.)

The statistical significance of the differences was calculated by Student's *t*-test. Each group consisted of 5 rats.
† Spiperone (i.p.) was injected 1 h 15 min, apomorphine (s.c.) and memantine (s.c.) were given 15 min before FLA-63 (i.p.) injection. The animals were killed 2 h after FLA-63.
†† FLA-63 reduced the noradrenaline concentrations by about 50% compared to vehicle group.

thalamus were taken for analyses. Noradrenaline was determined spectrofluorimetrically according to Karasawa, Furukawa & others (1975).

Apomorphine (5 mg kg^{-1}) and memantine (40 mg kg^{-1}) markedly accelerated the disappearance of noradrenaline after synthesis inhibition by FLA-63 in the brain regions (Table 1). Spiperone (1 mg kg^{-1}), a dopamine receptor blocker, given alone, was ineffective in the FLA-63-induced disappearance in the limbic system and neocortex but accelerated it in the thalamus + hypothalamus. Spiperone counteracted the effect of apomorphine in all the brain regions. The antagonistic effect of spiperone to memantine is not so clear. It has a strong effect in the neocortex but no significant effect in the limbic system and in the thalamus + hypothalamus. It may be the reason, as shown in behavioural experiments, that memantine relatively easily reverses the spiperone action, whereas apomorphine has not this ability.

The results obtained indicate that dopaminergic stimulation, as induced in rats by apomorphine and memantine, activates noradrenaline neurons in the brain what might support the hypothesis above. Histochemical data indicating such an interaction has been already reported in our Institute (Śmialowska, 1975; 1976).

We are grateful to Janssen Pharmaceutica for a generous supply of spiperone and to Merz & Co for memantine.

March 25, 1977

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