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Modification of the amphetamine-induced stereotypy in rats following inhibition of the noradrenaline release by FLA 136

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Although the stereotyped behaviour induced by amphetamine is very much dependent on dopamine release in the basal ganglia of the mammalian brain (Randrup & Munkvad, 1974) it may also be influenced by central noradrenaline transmission as suggested recently by Mogilnicka & Braestrup (1976). Generally, impairment of transmission in noradrenaline synapses potentiated the amphetamine-induced stereotypy in rats.

FLA 136 alone and in combination with yohimbine was used to test the above hypothesis. FLA 136 resembles clonidine both in structure and in blood pressure lowering effect (Eriksson & Florvall, 1976). The drug also shares with clonidine the ability to decelerate noradrenaline synthesis and utilization (Andén & Grabowska, 1977). These effects result from stimulation of α-adrenoceptors which might occur on the noradrenaline neurons (Andén, Grabowska & Strömbom, 1976). FLA 136 differs from clonidine, however, since it does not stimulate peripheral or central postsynaptic α-adrenoceptors. In the present work, FLA 136 was given at a dose of 15 mg kg^{-1}, i.p., since higher doses can block α-adrenoceptors (Andén & Grabowska, 1977).

The results presented in Table 1 show that under the influence of FLA 136 at a dose of 15 mg kg^{-1}, i.p., the amphetamine-induced stereotypy in rats was significantly potentiated. All items of stereotypy were changed similarly, so that the rats with, for example, score 3 following amphetamine alone were indistinguishable from those with the same score following FLA 136 and amphetamine.

Yohimbine, an α-adrenoceptor blocking agent, shows much greater affinity for the receptors involved in noradrenaline synthesis and utilization than for those mediating functional effects such as stimulation of motor activity and flexor reflex activity (Andén & others, 1976). Under the influence of yohimbine both the synthesis and the utilization of noradrenaline in the rat central nervous system are greatly enhanced. In the experiments presented, the amphetamine-induced stereotypy in rats was inhibited by yohimbine almost in a dose-dependent manner (Table 1). At the same time yohimbine (3·0 mg kg^{-1}, i.p.) abolished the potentiation of the amphetamine-induced stereotypy caused by FLA 136 (Table 1). A similar antagonism between yohimbine and FLA 136 has been found in biochemical experiments where the deceleration of noradrenaline utilization produced by FLA 136 was almost completely inhibited by yohimbine (Andén & Grabowska, 1977).

Table 1. *Influence of FLA 136 (15 mg kg^{-1}, i.p.) and yohimbine on the amphetamine-induced stereotypy in rats.*

Treatment (mg kg^{-1}, i.p.)	Stereotypy score	*P*
Amphetamine (5·0)	28·0 (12)	—
FLA 136 + amphetamine (5·0)	53·5 (12)	<0·001
Yohimbine (3·0) + amphetamine (5·0)	10·0 (6)	<0·001
FLA 136 + yohimbine (3·0) + amphetamine (5·0)	28·0 (6)	n.s.
Amphetamine (10·0)	57·0 (5)	—
Yohimbine (1·0) + amphetamine (10·0)	48·0 (6)	<0·05
Yohimbine (3·0) + amphetamine (10·0)	43·0 (5)	<0·025
Yohimbine (10·0) + amphetamine (10·0)	23·0 (6)	<0·01

FLA 136 and yohimbine were injected 120 and 30 min before the amphetamine injection, respectively. The intensity of stereotypy was evaluated according to the method of Costall, Naylor & Olley (1972) at 10 min intervals up to 3 h following the amphetamine injection. The values given are medians of the sums of the scores during 3 h with the number of animals in parenthesis. The *P* values refer to differences from the stereotypy following amphetamine alone (Mann-Whitney U-test).

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The experiments presented confirm the hypothesis of Mogilnicka & Braestrup (1976) about the modulatory influence of noradrenaline on the amphetamine-induced stereotypy.

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Depression by clonidine of shaking behaviour elicited by nalorphine in morphine-dependent rats

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Clonidine is reported to inhibit the "wet dog shakes" produced in rats by the drug AG-3-5 [1-(2-hydroxyphenyl)-4-(3-nitrophenyl)-1,2,3,6-tetrahydropyrimidine-2-one] (Wei, 1976) or by immersion in ice-cold water (Wei, 1975). We have tested it in morphine-dependent rats in which the shakes were elicited by nalorphine. As 5-hydroxytryptamine (5-HT) is implicated in the action of morphine (see review by Way & Shen, 1971), we also tested if a presumptive 5-HT receptor blocking agent, cyproheptadine, affected the shakes.

Male Wistar rats (170–200 g) were made tolerant to morphine by increasing daily intraperitoneal doses of morphine HCl (Polfa) according to the schedule of Buckett (1964). On day 1 the rats received two doses of 20 mg kg^{-1} at 9 a.m. and 4 p.m., and on each subsequent day they were injected, at the same times, with a dose of 40 mg kg^{-1} over that of the previous day. On day 8 the rats received two injections of 300 mg kg^{-1}, and on day 9 they were challenged with 10 mg kg^{-1} of nalorphine hydrochloride (Chinoin) at 12 noon. Some of the rats displayed infrequent shakes on the morning of day 9. After nalorphine injection the "wet dog shakes" (rapid, oscillatory movements of the head and upper trunk or of the whole body along the longitudinal axis; Winkler, Green & others, 1960) appeared: they were most frequent during the first 30 min after the injection, but occasionally they appeared later. The shakes were observed in 24 out of 25 rats tested, and were recorded for 90 min.

To establish the time course of clonidine action, the drug (clonidine hydrochloride, courtesy of Boehringer Sohn) was given at a dose of 0·8 mg kg^{-1} simultaneously with, or at various intervals before nalorphine. Clonidine effectively reduced the number of shakes or completely prevented the shaking behaviour, its action lasting for over 2 h. The best protection was offered if clonidine was given 1 h before nalorphine challenge (Table 1).

Given at various doses, 1 h before nalorphine, clonidine inhibited the shakes in a dose-dependent manner (Table 2). The ID50 of clonidine (the dose offering full protection in 50% of rats) was calculated according to Litchfield & Wilcoxon (1949), and found to be 0·54 mg kg^{-1} (0·36 — 0·76 mg kg^{-1}; 95% confidence limits. Slope value S = 1·81 (1·15 — 2·86)). Cyproheptadine hydrochloride (Merck, Sharp & Dohme), given 1 h before nalorphine, at doses up to 2 mg kg^{-1} did not protect the rats in full, and only insignificantly reduced the frequency of shakes.

Table 1. *Time course of the inhibitory action of clonidine on shaking induced by nalorphine in morphine-dependent rats.* Morphine-dependent rats received nalorphine (10 mg kg kg^{-1}, i.p.) 20 h after the last dose of morphine (300 mg kg^{-1}, i.p.). They were injected with clonidine (0·8 mg kg^{-1}, i.p.) at various intervals before being challenged by nalorphine. Body shakes were recorded for 90 min following nalorphine injection. n = 7 for each group, $*P < 0.02$ (*t*-test).

Treatment	Time before nalorphine (h)	No. of rats displaying no shakes	No. shakes in 90 min (mean ±s.e.m.)
Saline	1	0	14·3 ± 4·2
Clonidine	0	3	1·0 ± 0·4*
	0·5	3	2·3 ± 0·3*
	1	7	0
	2	3	1·9 ± 0·1*
	4	0	6·3 ± 2·0

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