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

* Correspondence.

Table 2. *The effect of various doses of clonidine and cyproheptadine on shaking induced by nalorphine in morphine-dependent rats.* The drugs were given 1 h before nalorphine. $*P < 0.01$ (*t*-test). For other explanations see Table 1.

Treatment, dose (mg kg^{-1}, i.p.)	No. rats showing no shakes/Total no. of rats	No. shakes in 90 min (mean ±s.e.m.)
Saline	1/18	20·0 ± 2·7
Clonidine 0·1	0/7	13·9 ± 2·9
0·2	1/8	4·8 ± 1·3*
0·4	0/8	6·7 ± 1·8*
0·6	5/8	1·1 ± 0·5*
0·8	6/8	0·7 ± 0·5*
Cypro- 0·2	1/7	17·4 ± 5·3
heptadine 0·5	0/7	14·3 ± 2·0
1·0	0/7	20·7 ± 4·0
2·0	0/7	14·6 ± 4·5

Our results indicate that clonidine is able to counteract at least one behavioural syndrome appearing during precipitated withdrawal from opiates, and that the ability to inhibit "wet shakes" by clonidine is not shared by a presumptive 5-HT receptor blocking agent, cyproheptadine. However, it is not certain whether the action of clonidine is specifically related to opiate receptors, although it has been reported to produce some effects similar to that of morphine on noradrenaline neurons (see Gomes, Svensson & Trolin, 1976), and to induce analgesia (Paalzow, 1974).

Clonidine is a drug having a wide spectrum of action. The drug is regarded as an α-adrenoceptor agonist by Hoefke, Kobinger & Walland (1975) and by Kobinger & Pichler (1975), but its action on presynaptic receptors would inhibit noradrenaline release from adrenergic nerve endings, thus reducing transmission in the noradrenergic system (for review see Starke & Endo, 1976). The latter effect may possibly account for the depressing action of the drug on locomotor activity (Strömbom, 1976), but it is doubtful if this mechanism of action is involved in a variety of other behavioural effects of clonidine suggesting an antagonism toward the noradrenergic system (Laverty & Taylor, 1969; Maj, Sowińska & others, 1972; Vetulani, Leith & others, 1975; Bednarczyk & Vetulani, 1977). Although Andén, Grabowska & Strömbom (1976) suggest that some functional effects of clonidine are due to stimulation of the post-synaptic α-adrenoceptor, some post-synaptic α-adrenoceptors are inhibited by the drug: clonidine antagonizes the noradrenaline-stimulated increase in cyclic AMP accumulation in slices from various brain areas (Vetulani & others, 1975; Skolnick & Daly, 1975 a,b, 1976 a,b), and the locus of this action appears to be post-synaptic (Skolnick & Daly, 1975b, 1976a).

Clonidine was also found to affect (probably mostly indirectly, via noradrenaline neurons) the central serotoninergic system: it inhibits serotoninergic neurons (Svensson, Bunney & Aghajanian, 1975), inhibits 5-HT turnover in the whole brain and some of its regions (Andén, Corrodi & others, 1970; Scheel-Krüger & Hasselager, 1974; Rochette & Bralet, 1975), and abolishes apomorphine-induced elevation of brain concentration of 5-hydroxyindoleacetic acid (Maj, Baran & others, 1973). Our preliminary experiments have revealed that clonidine effectively inhibits a possible variation of shaking behaviour: "head twitches" precipitated in rats by serotoninergic agents, such as 5-hydroxytryptophan or 5-methoxytryptamine (Reichenberg, Wiszniowska & Marchaj, 1975; Przegaliński, Żebrowska-Łupina & others, 1977). In this respect the drug resembles cyproheptadine and other putative 5-HT receptor blocking agents, and thus a possible central antiserotoninergic action of clonidine cannot be excluded.

A protective action against body shakes is exerted also by haloperidol. Although the neuroleptic seems to be less effective than clonidine against "wet shakes" precipitated in rats by AG-3-5 (Wei, 1976), it efficiently blocks the shakes occurring during morphine abstinence (Lal & Numan, 1976). Haloperidol was also described to reduce the symptoms of heroin withdrawal and craving for the drug in addicts (Karkalas & Lal, 1973). It is tempting to speculate that body shakes during precipitated opiate abstinence syndrome may reflect a state of discomfort of the animal. As clonidine is a well-established therapeutic agent, of known toxicity and side-effects, it might be of help to addicts suffering withdrawal from opiates.

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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-

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