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Modulation of footshock aggression in rats by clonidine: involvement of both α_1- and α_2-adrenoceptors

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The involvement of brain monoamines in aggressive behaviour has been well documented (Daruna 1978). Clonidine, a potent antihypertensive agent, is thought to stimulate central α-adrenoceptors and decrease neuronal release of noradrenaline (Stark & Altman 1973). This imidazoline derivative is also known to act on the c.n.s. and modulate various behavioural patterns (Laverty & Taylor 1969). Clonidine has also been reported to induce aggression in mice (Morpurgo 1968). Besides stimulating central α-adrenoceptors, clonidine also stimulates H_2-receptors in the brain (Schwartz 1977; Finch et al 1978). We have shown (Ray et al 1981) that central H_2-receptors are involved in the modulation of footshock aggression in rats and we now have evaluated the effect of clonidine on footshock aggression in rats and the possible mechanisms involved therein.

Materials and methods

Male albino rats (150–180 g) of Wistar strain were screened for aggressive behaviour by exposing them to footshock in an aggressometer (Techno Electronics). The stimulation parameters were: 150 V, 0·5 mA, 5 shocks s^{-1}, and pulse duration 5 ms. On footshock, the rats adopted an upright posture on their hindlimbs and struck at, wrestled with or bit at each other (with or without bleeding). One strike with forepaws was scored as 1, one wrestling bout as 2, one bite without bleeding as 3 and one bite with bleeding as 4. Rats which showed more than one such fighting score in 1 min exposure to footshock were labelled as aggressive and selected for the study. A pair of rats were footshocked at a time before and after drug administration for 3 min and the total score during this period was counted with the help of a digital counter.

The drugs used were: clonidine hydrochloride (Unichem), piperoxan hydrochloride (Rhone Poulenc), phenoxybenzamine hydrochloride and cimetidine (Smith, Kline & French). Drugs were dissolved in 0·9% NaCl (saline) except cimetidine, which was dissolved in minimal quantity of 0·5 M HCl and neutralized with 0·5 M NaOH to attain a pH of 6·0 and then diluted to an appropriate volume with saline. The drugs were administered intraperitoneally (i.p.) in a volume of 5 ml kg^{-1} except cimetidine, which was given intracerebroventricularly (i.c.v.) in a volume of 20 μl over 10 s. A group of rats were implanted with polyethylene (PE-10) cannulae into the lateral cerebral ventricle (Noble et al 1967) under pentobarbitone (40 mg kg^{-1} i.p.) for i.c.v. drug administration and used 72 h after cannulation. Both rats in a pair received the same drug treatment.

The nociceptive response was seen by the procedure of tail flick to heated resistance wire (0·5 ohm cm^{-1}, at 6·5 A) by an analgesiometer.

The results were analysed statistically by Student's *t*-test.

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Results

Clonidine (25 μg kg^{-1}) potentiated shock-induced aggressive behaviour (P <0·001) (Table 1). However, a higher dose of clonidine (250 μg kg^{-1}) inhibited significantly (P <0·001) footshock fighting score. Both these effects were evident 30 min after drug administration.

Table 1. Effect of clonidine on footshock aggression in rats.

Drugs (dose kg^{-1} i.p.)	Fighting score (mean ± s.e.m.)* Before drug	After drug
Saline (5 ml)	108·0 ± 6·25	114·5 ± 5·82
Clonidine (25 μg)	115·8 ± 5·38	171·0 ± 6·99[a]
Clonidine (250 μg)	111·0 ± 6·97	60·4 ± 4·65[a]
Piperoxan (1 mg)	123·8 ± 6·05	116·2 ± 5·25
Piperoxan + clonidine (25 μg)	100·2 ± 8·95	109·6 ± 6·22
Piperoxan + clonidine (250 μg)	99·8 ± 6·44	36·6 ± 5·06[ab]
Phenoxybenzamine (10 mg)	104·8 ± 5·64	94·8 ± 9·38
Phenoxybenzamine + clonidine (25 μg)	95·6 ± 5·0	140·0 ± 7·22[a]
Phenoxybenzamine + clonidine (250 μg)	120·2 ± 6·69	112·4 ± 5·78
Cimetidine (40 μg)**	107·2 ± 8·08	98·0 ± 6·09
Cimetidine + clonidine (25 μg)	96·0 ± 4·44	159·0 ± 6·76

* Five pairs of rats were used for each set of experiments.
** I.C.V. per rat.

	Treatment	t-value	Degree of freedom	P
a.	Clonidine (CLO) (25 μg)	13·6	4	<0·001 (n = 5)
	CLO (250 μg)	13·8	4	<0·001
	Piperoxan + CLO (250 μg)	21·8	4	<0·001
	Phenoxybenzamine + CLO (25 μg)	11·6	4	<0·001
b.	Piperoxan + CLO vs CLO (250 μg)	2·73	8	<0·05 ($n_1 - n_2 = 10$)

When rats were pretreated with piperoxan (1 mg kg^{-1}) 30 min before clonidine, the potentiation of footshock aggression by clonidine was blocked but there was no antagonism of the clonidine-induced fall in the fighting score; rather the fall was significantly more ($P < 0.05$) when compared to the effect of the higher dose of clonidine (250 μg kg^{-1}) alone. Phenoxybenzamine (10 mg kg^{-1}), when administered 90 min before clonidine, failed to modify significantly the facilitation of footshock fighting score by the low dose of clonidine (25 μg kg^{-1}); but on the other hand, it antagonized the clonidine (250 μg kg^{-1})-induced inhibition of footshock fighting. Cimetidine (40 μg i.c.v.) pretreatment 15 min before clonidine (25 μg kg^{-1}) also failed to modify significantly ($P > 0.05$) the facilitation in the footshock fighting score by clonidine. Piperoxan, phenoxybenzamine and cimetidine alone had no significant effect on the shock-induced aggression.

Furthermore, at the doses used, clonidine had no significant effect on the latency of the tail-flick response, when compared with saline controls ($P > 0.05$).

Discussion

The results indicate that the effect of clonidine on footshock aggression is dose-related. Whereas the low dose facilitates footshock fighting, the higher dose is inhibitory. Since the potentiation of shock-induced aggression is blocked by piperoxan, a specific α_2-adrenoceptor antagonist, clonidine (25 μg kg^{-1}) appears to act through a pre-synaptic (α_2) adrenoceptor by inhibiting noradrenaline release (Stark & Altman 1973). Noradrenaline has been shown to have an inhibitory modulation on footshock aggression (Daruna 1978). Similarly, since the inhibition of footshock aggression by clonidine (250 μg kg^{-1}) is antagonized by phenoxybenzamine, predominantly an α_1-adrenoceptor blocker, the higher dose appears to act through a post-synaptic (α_1) adrenoceptor. The observation, that in the presence of piperoxan, clonidine (250 μg kg^{-1}) inhibits the footshock aggression more ($P < 0.05$) than its effect alone, points to the involvement of both α_1- and α_2-adrenoceptors in this response, blockade of α_2-receptors tilting the balance favourably towards the α_1-receptor response. It could be that α_1-adrenoceptors play a dominant role at this dose. However, the fact that phenoxybenzamine pretreatment failed to influence significantly the clonidine (25 μg kg^{-1})-induced rise in the footshock fighting score suggests that at the low dose only the pre-synaptic (α_2-) receptors are involved. Earlier studies (Ray et al 1981) have shown that activation of H_2-receptors in the brain facilitates footshock aggression in rats and that clonidine also acts as an H_2-agonist in the brain (Schwartz 1977). We found that clonidine-induced facilitation of footshock fighting was not antagonized by cimetidine, a H_2-receptor blocker, thereby ruling out any involvement of H_2-histaminergic mechanisms in the facilitatory effect of clonidine on this behaviour. There are reports that clonidine induces analgesia (Paalzow 1978). The observation that clonidine in the doses used did not show any significant analgesia when compared with saline controls ($P > 0.05$) rules out any interference by pain sensitivity in this effect of clonidine.

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