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Effect of quipazine and fluoxetine on analgesic-induced catalepsy and antinociception in the rat

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Recent evidence indicates that brain 5-hydroxytryptamine (5-HT) may be implicated in morphine activity in the rat. For example, depletion of 5-HT with *p*-chlorophenylalanine (Goerlitz & Frey 1972; Tenen 1968), or 5,6-dihydroxytryptamine (Genovese et al 1973; Vogt 1974) reduces morphine analgesia. Destruction of either the midbrain ascending 5-HT system (Samanin et al 1970) or the descending medullary 5-HT system (Proudfit & Anderson 1975; Chance et al 1978) also blocks the analgesic effect of systemically administered morphine. Increasing 5-HT concentrations by injection of 5-hydroxytryptophan (Tulunay et al 1976) potentiates morphine-induced antinociception.

Recently, Sugrue & McIndewar (1976) reported that fluoxetine a potent inhibitor of rat brain 5-HT re-uptake (Fuller et al 1975), potentiated the antinociceptive effect of morphine but not that of methadone and pethidine.

Quipazine, a new type of antidepressant (Rodriguez & Pardo 1971) can increase central 5-HT-ergic activity by a direct action on central 5-HT receptors (Rodriguez et al 1973).

We describe the influence of quipazine and fluoxetine on two of the most characteristic effects of morphine in rats: analgesia and catalepsy. We have also used the analgesics codeine, fentanyl and pentazocine which is devoid of cataleptogenic activity (Malec et al 1977).

Male albino Wistar rats, 160–220 g, were used. Catalepsy was measured in six tests according to Simon et al (1969) these were: 3 cm block, 9 cm block, parallel bars, four corks, Buddha test, limb crossing. In the first four tests the catalepsy was considered as present if the rat remained immobile for at least 10 s. In the other tests the time was at least 2 s. The number of positive responses was counted in all tests for each animal at 15, 30, 45, 60, 90 and 120 min after i.p. injecton of analgesics.

The antinociceptive effect of analgesics was tested by the hot plate method (56 °C) using as reaction time the time between the rat being placed on the hot plate and it licking its paws or jumping off. Animals failing to reach the end point after 30 s, were removed and scored 30. Each rat was exposed to the hot plate once before treatment and again at 30 min after injection of morphine, codeine, pentazocine, and 15 min after fentanyl. The time between exposures was 60 min. Fluoxetine (10 mg kg^{-1}) and quipazine (10 and 15 mg kg^{-1}) were injected i.p. 30 min before morphine, codeine, pentazocine and 45 min before fentanyl (the action of fentanyl is short lasting). In other experiments, quipazine (15 mg kg^{-1}) was injected 10 min after morphine, codeine, pentazocine, and simultaneously with fentanyl. All doses refer to the salts.

Fluoxetine (10 mg kg^{-1}) significantly increased and prolonged catalepsy induced by morphine, codeine and fentanyl, although after 15 min of observation a reduction in morphine catalepsy was observed (Table 1). Similarly, quipazine (10 mg kg^{-1}), when injected before an analgesic, increased catalepsy (Table 1). This dose of quipazine did not alter the rat behavioural activity (Green et al 1976), but after a higher dose of quipazine alone (15 mg kg^{-1}), we observed, 5–60 min after injection, an increase in locomotor activity, stereotyped sniffing and the other effects, which suggest (Grabowska et al 1974a; Green et al 1976) the involvement of brain dopamine, as well as 5-HT. Grabowska et al (1974b) reported that quipazine (2·5, 10 mg kg^{-1}) reduced turn-

* Correspondence.

Table 1. Effect of quipazine and fluoxetine on morphine-, codeine-, and fentanyl-induced catalepsy (doses mg kg^{-1}). Maximally % of catalepsy was 100. Each value represents mean ± s.e. % of catalepsy in the group (5–6 rats). Quipazine and fluoxetine were administered 30 min before morphine and codeine, and 45 min before fentanyl injection. Statistical significances were calculated (Student's *t*-test) on absolute values.

	Catalepsy (%)				
15 min	30 min	45 min	60 min	90 min	120 min
Saline + morphine 20					
78 ± 6	68 ± 10	52 ± 10	35 ± 10	15 ± 7	4 ± 2
Quipazine 10 + morphine 20					
93 ± 4	93 ± 4*	80 ± 3**	76 ± 7**	23 ± 16	7 ± 4
Fluoxetine 10 + morphine 20					
30 ± 16*	63 ± 13	83 ± 8*	93 ± 5***	63 ± 8 ***	30 ± 6*
Saline + codeine 40					
75 ± 13	67 ± 13	38 ± 13	25 ± 10	15 ± 9	5 ± 3
Quipazine 10 + codeine 40					
90 ± 9	90 ± 9	87 ± 6**	83 ± 8**	67 ± 11**	27 ± 8*
Fluoxetine 10 + codeine 40					
37 ± 51	70 ± 12	83 ± 3**	70 ± 11**	47 ± 12*	20 ± 10
Saline + fentanyl 0·25					
80 ± 8	38 ± 10	19 ± 8	10 ± 4	7 ± 4	2 ± 2
Quipazine 10 + fentanyl 0·25					
71 ± 9	71 ± 12*	67 ± 12**	37 ± 10*	13 ± 12	4 ± 4
Fluoxetine 10 + fentanyl 0·25					
80 ± 3	83 ± 0***	73 ± 10***	47 ± 13*	37 ± 16	17 ± 9

* $P < 0.05$, ** $P < 0.02$, *** $P < 0.005$. Times (min) are from injection of analgesics.

over rate of brain 5-HT 60–180 min after injection. This result may indicate that 5-HT-ergic stimulation is maintained at that time. Therefore, we performed our tests with quipazine at times of continuing stimulation of the 5-HT receptors, while the effects that probably originate from mixed dopamine-5-HT stimulation are coming to the end. The increase and prolongation of analgesic catalepsy by quipazine was statistically significant (Table 1).

We also performed an additional test in which quipazine (15 mg kg^{-1}) was injected 10 min after morphine (15 mg kg^{-1}), codeine (40 mg kg^{-1}) and simultaneously with fentanyl (0·2 mg kg^{-1}). Table 2 shows that morphine catalepsy was increased and prolonged, that of fentanyl was less prolonged and codeine catalepsy was not significantly enhanced.

Analgesic-induced catalepsy in rats, like neuroleptic catalepsy (Stille & Lauener 1971), is associated with striatal dopamine metabolism (Kuschinsky & Hornykiewicz 1972; Ahtee & Käärinäinen 1974) and is antagonized by dopaminergic stimulants (Kuschinsky & Hornykiewicz 1972; Lal et al 1975; Malec et al 1977). 5-HT manipulation is known to modify dopamine-dependent behaviour, for example, reduction of central 5-HT mechanisms has been reported to decrease neuroleptic-induced catalepsy in rats (Kostowski et al 1972; Maj et al 1975). Recently Carter & Pycock (1977) reported that quipazine (5–40 mg kg^{-1}) potentiated the cataleptic response of the neuroleptic haloperidol, although Grabowska et al (1974a) observed a reduction of neuroleptic catalepsy by quipazine and this anti-cataleptic effect was well correlated in time with the locomotor stimulation, sniffing and gnawing. Some authors also reported that 5-HT-ergic agents influence morphine catalepsy in rats: Groppe & Kuschinsky (1975) reported that *p*-chloro-*N*-methylamphetamine, an inhibitor of 5-HT synthesis, inhibited, while 5-hydroxytryptophan enhanced, morphine catalepsy. Similarly, the 5-HT antagonist metergoline antagonized this effect of morphine (Scheel-Krüger et al 1977). However, lesions placed in the dorsal/median raphe, in the ventral raphe or in the reticular formation had no significant effect on the catalepsy produced by morphine in rats (Yaksh et al 1977). Our results indicate that stimulation of the brain 5-HT system by quipazine and fluoxetine potentiates cataleptogenic activity of morphine, codeine and fentanyl, and quipazine's effect is better observed when the first phase of dopaminergic stimulation it produces has disappeared (i.e. 45 min after injection of quipazine).

In the present studies, all four analgesics produced statistically significant antinociceptive action in the hot plate test (Table 3). Fluoxetine, 10 mg kg^{-1}, given alone, had no apparent effect on reaction time. Samanin et al (1976) found doses of 10 and 20 mg kg^{-1} of quipazine had an analgesic effect in the hot plate test. In our experiments, however, doses of 10 and 15 mg kg^{-1} had no significant influence on the hot plate reaction time, only 20 and 30 mg kg^{-1} inducing significant prolongation. Quipazine, 10 mg kg^{-1}, did not affect the antinociceptive action of the drugs, but at 15 mg kg^{-1}, it enhanced the effect of morphine (8 mg kg^{-1}) when injected 10 min after the morphine (reaction time: 21·1 ± 3·2 $P < 0.02$) and also when given 30 min before the morphine (Table 3). The effect of fentanyl was not influenced by quipazine. Fluoxetine significantly potentiated the action of morphine and fentanyl. The antinociceptive effect of codeine was not changed by

Table 2. The effect of quipazine (15 mg kg^{-1}) injected 10 min after morphine and codeine, and simultaneously with fentanyl (doses mg kg^{-1}) on analgesic catalepsy. Maximum possible % of catalepsy was 100. Each value represents mean ± s.e. percent of catalepsy in the group (6 rats). Quipazine was administered 10 min after morphine and codeine, and simultaneously with fentanyl. Other details as Table 1.

	Catalepsy (%)				
15 min	30 min	45 min	60 min	90 min	120 min
Morphine 15 + saline					
11 ± 8	39 ± 20	47 ± 21	19 ± 10	6 ± 6	3 ± 3
Morphine 15 + quipazine 15					
58 ± 16*	92 ± 5*	81 ± 7	53 ± 11*	17 ± 4	8 ± 3
Codeine 40 + saline					
86 ± 10	55 ± 18	53 ± 16	28 ± 17	30 ± 16	0
Codeine 40 + quipazine 15					
92 ± 3	83 ± 10	78 ± 5	44 ± 13	42 ± 11	11 ± 5
Fentanyl 0·2 + saline					
66 ± 21	58 ± 20	45 ± 19	25 ± 9	3 ± 3	3 ± 3
Fentanyl 0·2 + quipazine 15					
59 ± 17	64 ± 19	67 ± 16	59 ± 11*	39 ± 14*	27 ± 7**

* $P < 0.05$, ** $P < 0.01$.

Table 3. Effect of quipazine and fluoxetine on the antinociceptive activity of morphine, codeine, fentanyl and pentazocine (doses mg kg^{-1}). 6–7 rats were used in the group. Morphine, codeine and pentazocine were injected 30 min, and fentanyl 15 min before the test. Quipazine (10 and 15 mg kg^{-1}) and fluoxetine (10 mg kg^{-1}) were administered 45 min before fentanyl and 30 min before the other analgesics.

Before treatment	Reaction times (s) Saline-treated	Quipazine-treated 10	Quipazine-treated 15	Fluoxetine-treated 10
Saline 3·6 ± 0·3	3·7 ± 0·7	4·1 ± 0·6	5·0 ± 0·8	3·9 ± 0·6
Morphine 8 3·5 ± 0·3	7·9 ± 1·6**	9·2 ± 1·8	15·6 ± 2·9*	18·0 ± 3·9*
Codeine 20 4·3 ± 0·4	11·7 ± 2·6**	15·1 ± 2·0	14·4 ± 2·9	13·0 ± 3·4
Fentanyl 0·06 3·6 ± 0·3	8·6 ± 1·2**	8·1 ± 1·6	5·4 ± 0·6*	23·3 ± 3·2‡
Pentazocine 30 3·8 ± 0·3	7·4 ± 1·2**	8·4 ± 1·7	9·8 ± 2·6	10·3 ± 2·1

** $P < 0.02$, compared with reaction time before treatment: * $P < 0.05$, ‡ $P < 0.005$, compared with saline + analgesic-treated group.

either 5-HT stimulant. The antinociceptive effect of pentazocine was unchanged by fluoxetine and quipazine (Table 3). We also observed a toxic interaction when quipazine 15 mg kg^{-1} was injected 10 min after pentazocine (about 30% of rats died).

From these results is evident that the antinociceptive effect of morphine is influenced by both of the 5-HT stimulants, but this is not so for codeine or pentazocine. The situation is complicated with fentanyl, because quipazine attenuates and fluoxetine enhances its antinociceptive activity.

In conclusion, our results support the concept that 5-HT is involved in the cataleptogenic effects of analgesics and in the antinociceptive activity of morphine. In this respect, the mechanism of codeine, fentanyl and pentazocine antinociception seems to be different from that of morphine.

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