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Influence of Naloxone on H_2-Receptor Blocker Drugs Effects in the "Behavioral Despair" Test

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SUNAL, R. *Influence of naloxone on H_2-receptor blocker drugs effects in the "behavioral despair" test.* PHARMACOL BIOCHEM BEHAV **25**(3) 511–513, 1986.—The influence of H_2-receptor blockers (ranitidine and cimetidine) in a "behavioral despair" test in mice was studied. Both ranitidine and cimetidine shortened the immobility time at 20 mg·kg^{-1} and 30 mg·kg^{-1}. Naloxone at 2 mg·kg^{-1} antagonized this reduction in immobility time.

"Behavioral despair" test H_2-receptor blockers Naloxone Mice

RECENT reports indicate that endogenous opioid peptides have anti-depressant activity and beta endorphine has been proposed as an anti-depressant [6]. Naloxone, which is reported to have antimanic activity [5], reversed the shortened immobility time caused by anti-depressant drugs (clomipramine, desipramine, clorgyline and endogenous enkephalins) in the "behavioral despair" test. These results suggest an action at opiate receptor sites [3,8].

In a recent study, we have shown that H_2-receptor blockers enhance conditioned avoidance responses and antagonize reserpine-induced ptosis and akinesia suggesting that H_2-receptor blockers have anti-depressant activity [11].

In this work, we investigated (1) the effect of H_2-receptor blockers in the "behavioral despair" test, and (2) naloxone as an antagonist of H_2-receptor blockers in the "behavioral despair" test.

METHOD

Animals

Male albino mice bred locally and weighing 25–30 g were used. They were housed in a well-ventilated room. The room temperature was maintained at about 22°C. Food was freely available. Experiments were conducted between 9:00 a.m. and 2:00 p.m.

"Behavioral Despair" Test

The procedure described by Porsolt *et al.* [9] was employed. Naive mice were placed in a vertical Plexiglas cylinder (25 cm high, 10 cm diameter) containing 6 cm water 21–23°C, and were forced to swim. After initial struggling, the animals could stay immobile and float. The duration of this immobility during the following 4 min period was measured.

Drugs and Solutions

The drugs used were cimetidine (Tagamet, SKF), ranitidine (Zantac, Glaxo), and naloxone (Narcan, Endo Pharmaceuticals).

Drugs were diluted in 0.9% NaCl and were administered 30 min prior to testing by IP injection, except for naloxone which was injected 10 min prior to testing. All mice, including controls, were administered injections 30 and 10 min before testing. Treatment protocol is given in Table 1.

Statistical Analysis

The results were analyzed by means of a single factor analysis of variance and Student's *t*-test.

RESULTS

The effect of cimetidine (15 mg·kg^{-1}) on the duration of immobility was not significant. But, as the dose increased, (20 mg·kg^{-1}, 30 mg·kg^{-1}), the immobility time was significantly reduced (Fig. 1).

Ranitidine showed no statistically significant effect at 15 and 20 mg·kg^{-1} doses although it had a significant effect at 30 mg·kg^{-1} (Fig. 1).

Naloxone alone did not change the duration of immobility (Fig. 1). The effect of cimetidine (20 mg·kg^{-1} and 30 mg·kg^{-1}) and rantitidine (30 mg·kg^{-1}) was reversed by naloxone (Fig. 2).

DISCUSSION

Results obtained in this study confirm our previous work on H_2-receptors and anti-depressant activity. We also show that naloxone reserves the action of H_2-receptor blockers to shorten immobility time.

Research performed with endogenous opiates and forced

TABLE 1
TREATMENT PROTOCOL

IP injector 30 min prior to testing	IP injection 10 min prior to testing	
	0.9 % NaCl (20 mg·kg^{-1})	Naloxone (1 mg·kg^{-1})
Control (0.9 % NaCl,20 mg·kg^{-1}	n = 15	n = 15
Cimetidine (15 mg·kg^{-1})	n = 14	n = 15
Cimetidine (20 mg·kg^{-1})	n = 15	n = 15
Cimetidine (30 mg·kg^{-1})	n = 13	n = 15
Ranitidine (15 mg·kg^{-1})	n = 14	n = 13
Ranitidine (20 mg·kg^{-1})	n = 15	n = 15
Ranitidine (30 mg·kg^{-1})	n = 13	n = 14

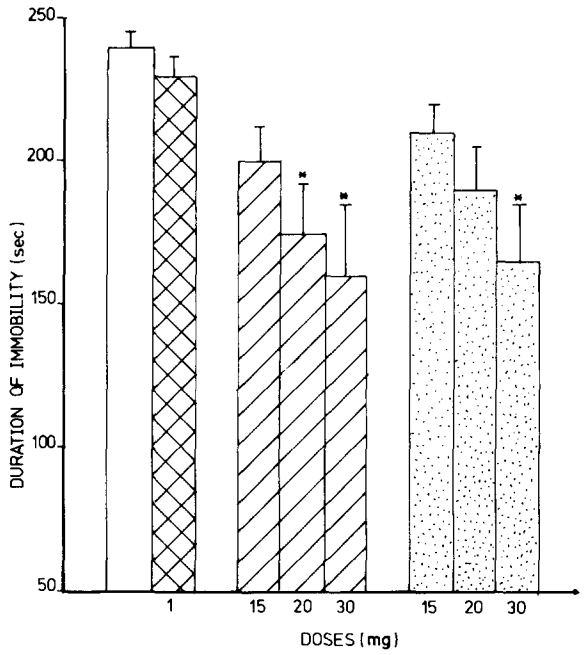

FIG. 1. Effects of H_2-receptor blockers—hatched bars: cimetidine, stippled bars: ranitidine and cross-hatched bars: naloxone, on immobility time in "behavioral despair" test. Protocol of drug administration and (n) is given in Table 1. The bars represent SEM. *$p<0.05$ versus control values.

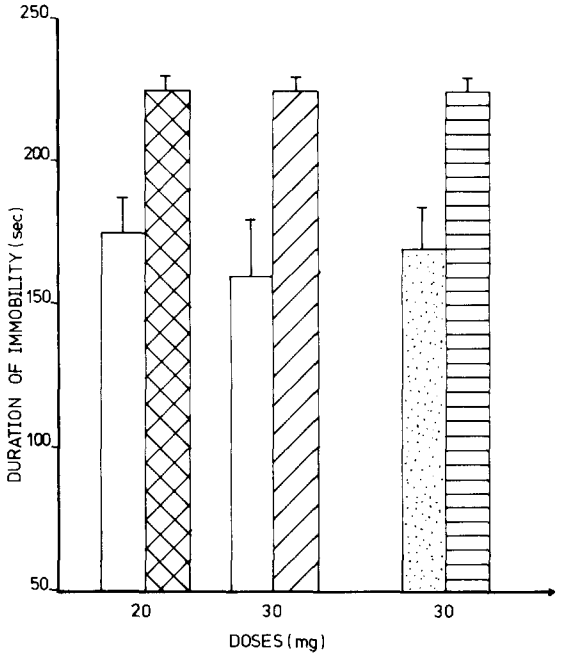

FIG. 2. Naloxone effects on (open bars) cimetidine induced shortening of immobility duration (cross-hatched bars: cimetidine 20 mg·kg^{-1} + naloxone; hatched bars: cimetidine 30 mg·kg^{-1} + naloxone); stippled bars: ranitidine induced shortening of immobility duration (horizontal bars: ranitidine 30 mg·kg^{-1} + naloxone).

swimming suggests that the possible action of antidepressants is at opiate receptors. Of the tricyclic antidepressants, the activities of clomipramine [2] and desipramine were antagonized by naloxone, but the inhibition of MAOI was not significant [3].

The antinociceptive action of morphine was potentiated by tricyclic anti-depressants [7] and tricyclic antidepressants were reported to have analgesic properties that could be reduced by naloxone (G. G. Plaza *et al.*, 1983).

Although enhanced cholinergic activity is known to increase endogenous opiate peptide secretion [10], naloxone did not antagonize atropine in a forced swimming test [3]. Therefore, cholinergic mechanisms cannot be implicated in a naloxone-anti-depressant interaction.

Serotoninergic drugs were ineffective in a forced swimming test [1]; therefore serotonin involvement in the mechanism is minimal.

Noradrenergic drugs are effective in behavioral despair tests. Desipramine is reversed by naloxone but the activity of mianserin at doses blocking alpha$_2$-receptors was not inhibited by naloxone. Research on an opiate-noradrenergic mechanism reveals an inhibitory role of endogenous opiate peptides on noradrenaline secretion [4].

The investigations carried out thus far suggest an interaction of opioid receptor sites and anti-depressants. Our results in this study show an involvement of endogenous opiate peptides in the anti-depressant action of H_2-receptor blockers. Further work is needed to clarify the role of histamine H_2-receptors and endogenous opiates in anti-depressant action.

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