Pharmacology Biochemistry & Behavior, Vol 24, pp 925–930, 1986 © Ankho International Inc Printed in the U S A 0091-3057/86 $3 00 + 00

The Effect of Antihistaminic Drugs on Pentazocine Antinociception in the Rat[1]

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Received 16 August 1985

YEH, S Y *The effect of antihistaminic drugs on pentazocine antinociception in the rat* PHARMACOL BIOCHEM BEHAV 24(4) 925–930, 1986 —The antinociception produced by pentazocine, diphenhydramine, promethazine, chlorpheniramine, cyclizine and chlorcyclizine in the rat has been measured with a low-temperature (51.5°C) hot-plate from 15 to 75 min following drug administration The mean reaction times measured at 15 min and the area under the antinociception curves following administration of pentazocine (5 to 30 mg/kg) were linear Diphenhydramine, chlorpheniramine, promethazine, cyclizine, and chlorcyclizine showed mild antinociceptive potency The antinociception produced by SC pentazocine (5 and 10 mg/kg) was potentiated, rather than in a simple additive manner, by simultaneous IP administration of 20 mg/kg of diphenhydramine, promethazine, cyclizine, or chlorpheniramine, but not by chlorcyclizine After concurrent administration of pentazocine and diphenhydramine, diphenhydramine did not alter pentazocine concentrations in the brain and plasma 15 to 75 min following drug administration, nor did pentazocine change diphenhydramine concentrations Results of this study demonstrate that pentazocine antinociception can be potentiated by several antihistamines and that the potentiation was not due to a mutual effect on metabolism but rather through an as yet undefined mechanism

Antinociception Pentazocine Antihistamines Diphenhydramine Promethazine
Chlorpheniramine Cyclizine Chlorcyclizine Brain Plasma

THE abuse of pentazocine with tripelennamine by heroin addicts has prompted many studies to elucidate the mechanism of the interaction between these drugs [4, 5, 18, 19, 23, 24, 25] However, little information is available on the interaction between pentazocine and other antihistamines. Promethazine had an additive effect upon meperidine analgesia in man [10,13]. Methdilazine, promethazine, and diphenhydramine potentiated, while cinnarizine diminished, morphine analgesia; chlorpheniramine, pyrilamine and tripelennamine were ineffective in the rabbit tooth pulp test [11]. Diphenhydramine, cimetidine, chlorpheniramine and hydroxyzine potentiated the antinociception produced by morphine, fentanyl and nalbuphine, but not that induced by pentazocine in the mouse [3,22]. Pyrilamine (mepyramine) did not interfere with the development of morphine tolerance, but had a marked inhibitory effect on physical dependence [9].

The aims of this study were to investigate: (1) the effect of antihistamines other than tripelennamine on the antinociception produced by pentazocine; (2) the effect of antihistamines, using diphenhydramine as a representative, on pentazocine concentration in the brain and plasma; and (3) the effect of pentazocine on diphenhydramine concentration in the brain and plasma. Five representative antihistamines from the different classes (i.e., diphenhydramine, chlorpheniramine, cyclizine, chlorcyclizine and promethazine) were chosen for this study.

METHOD

Animals

Sprague-Dawley male rats, 125–150 g (Laboratory Supplies, Indianapolis, IN) were housed three per cage and were given unlimited access to Purina lab chow and water in an air-conditioned vivarium (22°C) with a 12/12 hr light/dark cycle. All animals were housed for one week after arrival before being used for an experiment.

Drugs

dl-Pentazocine and N-butylnormetazocine (Sterling-Winthrop Research Institute, Rensselaer, NY), chlorpheniramine maleate (Schering Corp, Kenilworth, NJ), promethazine HCl (Wyeth Research Institute, Philadelphia, PA), cyclizine HCl and chlorcyclizine HCl (Burroughs Wellcome Company, Research Triangle Park, NC) were obtained as gifts Diphenhydramine HCl was purchased from Sigma Chemical Company (St. Louis, MO). dl-Pentazocine was dissolved in lactic acid (8 5%) and neutralized with 1 M sodium hydroxide solution. The ratio of lactic acid to sodium hydroxide solution was 3:2. Antihistamines were dissolved in sterilized 0 9% sodium chloride solution and cyclizine HCl in distilled water. The injection volume was 2 ml/kg. All doses were expressed as free base. Doses of pentazocine (5 and 10 mg/kg) and antihistamines (20 mg/kg) chosen for the

[1]Preliminary reports on these experiments appeared in *Fed Proc* 42: 4249, 1983, *Pharmacologist* 26: 162, 1984

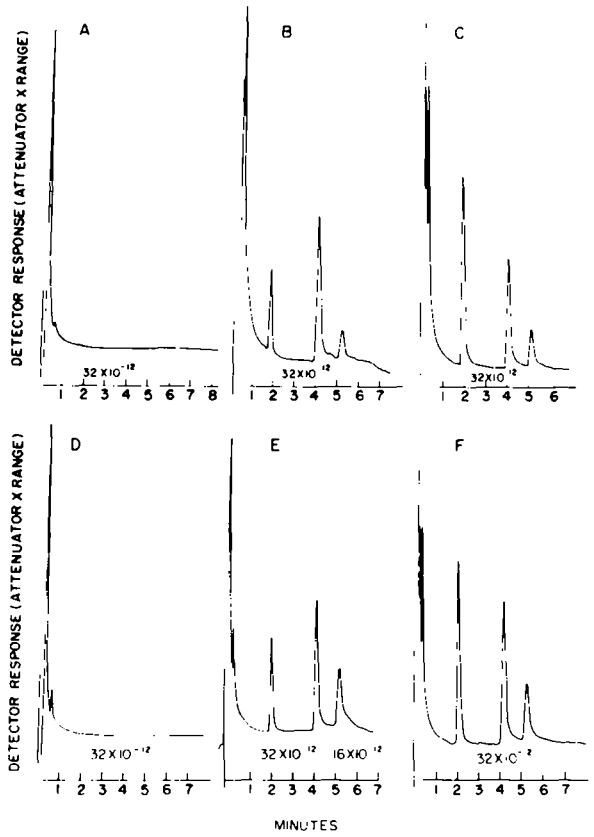

FIG 1 A and D are the chromatograms of the extract of the brain homogenate and plasma, respectively, of a control rat B and E are the chromatograms of the extract of the brain homogenate and plasma, respectively, of a control rat with added diphenhydramine (0 3 μg, peak 1, retention time=2 0 min), N-butylnormetazocine (0 5 μg, peak 2, retention time=4 2 min) and pentazocine (0 3 μg, peak 3, retention time=5 2 min) C and F are the chromatograms of the extract of the brain homogenate and plasma, respectively, of a rat killed 75 min following simultaneous administration of pentazocine, 10 mg/kg, SC and diphenhydramine, 20 mg/kg, IP

present study were based the results of the interaction study of pentazocine and tripelennamine [25]

Test of Antinociception

Antinociceptive activity of pentazocine and antihistamines in the rats was measured by the low temperature hot-plate (51.5°C) method of Eddy and Leimbach [6] as described previously [25].

Rats were divided into groups of 10 animals each (1) the pentazocine group, in which each animal received a single dose of pentazocine, 5 or 10 mg/kg, SC, (2) the antihistamine group, in which each animal received a single dose (20 mg/kg, IP) of one of the antihistamines, and (3) the pentazocine plus antihistamine group, in which each animal received a single dose of pentazocine, 5 or 10 mg/kg, SC, followed (within 10 sec) by a single dose of one of the antihistamines, 20 mg/kg, IP. In addition, a saline control group of 10 animals, in which each animal received 2 ml/kg of saline was studied

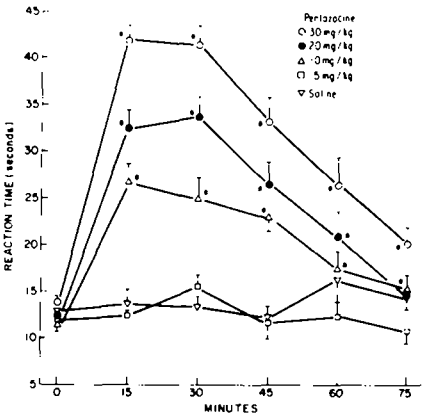

FIG 2 Antinociceptive activity of pentazocine in the rat measured with a low temperature (51 5°C) hot-plate procedure The asterisks indicate that the reaction time was significantly longer than the control reaction time at $p<0$ 05 level

The Effect of Diphenhydramine on Pentazocine Concentration, and Pentazocine on Diphenhydramine Concentration in the Brain and Plasma of Rats

Seventy-five rats were divided into three groups of 25 animals each One group received pentazocine, 10 mg/kg, SC The second group received pentazocine, 10 mg/kg, SC, followed (within a few seconds) by diphenhydramine, 20 mg/kg, IP The third group received diphenhydramine, 20 mg/kg, IP Each group was subdivided into five groups of five animals each and killed at 15, 30, 45, 60 and 75 min following drug administration At the time of sacrifice, each rat was lightly anesthetized with ether Blood (7 to 10 ml) was withdrawn from the abdominal aorta with heparin as anticoagulant Plasma was separated by centrifugation and frozen until drug analysis The plasma was thawed and centrifuged for 15 min at room temperature to remove any fibrous material

The brain was removed immediately following withdrawal of blood, rinsed with water, blotted dry, stored in a vial and frozen At the time of drug analysis the whole brain was weighed, thawed and homogenized with a teflon pestle tissue homogenizer in a sufficient quantity of 0 1 M hydrochloric acid to make a 10% (w/v) brain homogenate

Extraction of Pentazocine and Diphenhydramine From Brain Tissue and Plasma

Samples of the brain homogenate (2 0 ml) or plasma (2.0 ml), and N-butylnormetazocine (0 5 μg in 10 μl methanol, an internal standard (I S)), were placed in a 40 ml centrifuge tube The sample was alkalinized to pH 10 with 1 M sodium hydroxide solution, buffered with 1 ml of 1 M potassium phosphate buffer, pH 10, shaken with 5 ml of benzene-isopropanol (9 1) at 280 oscillations/min for 15 min, and centrifuged for 10 min The aqueous phase was aspirated without removal of a trace amount of the organic phase The organic phase was recentrifuged for 5 min to settle the emulsion on the glass wall to the bottom The organic phase was then transferred to another clean centrifuge tube, shaken with 2 ml of 1 M hydrochloric acid at 280 oscillations/min for 15 min, and centrifuged for 10 min

TABLE 1

ANTINOCICEPTIVE ACTIVITY OF PENTAZOCINE AND ANTIHISTAMINIC DRUGS IN THE RAT

Drugs	Antihistamine (20 mg/kg, IP)	Pentazocine (5 mg/kg, SC)	Pentazocine (5 mg/kg) + Antihistamine (20 mg/kg)	Pentazocine (10 mg/kg, SC)	Pentazocine (10 mg/kg) + Antihistamine (20 mg/kg)
	Area of Antinociception (minute-seconds), mean ± (S.E.)				
Diphenhydramine	301 ± 55	190 ± 80	1143 ± 113 $p<0.001$	725 ± 77	1853 ± 113 $p<0.001$
Chlorpheniramine	272 ± 79	190 ± 80	795 ± 134 $p<0.01$	725 ± 77	1084 ± 202 N.S.
Promethazine	340 ± 95			466 ± 74	1606 ± 134 $p<0.001$
Cyclizine	344 ± 84	175 ± 89	442 ± 113 N.S.	301 ± 82	932 ± 154 $p<0.01$
Chlorcyclizine	318 ± 90	176 ± 44	242 ± 97 N.S.	570 ± 166	749 ± 116 N.S.
Vehicle	67 ± 67				

Comparison was made between the antinociceptive area produced by pentazocine plus antihistamine and that of the sum of antinociceptive areas of pentazocine and antihistaminic drug alone

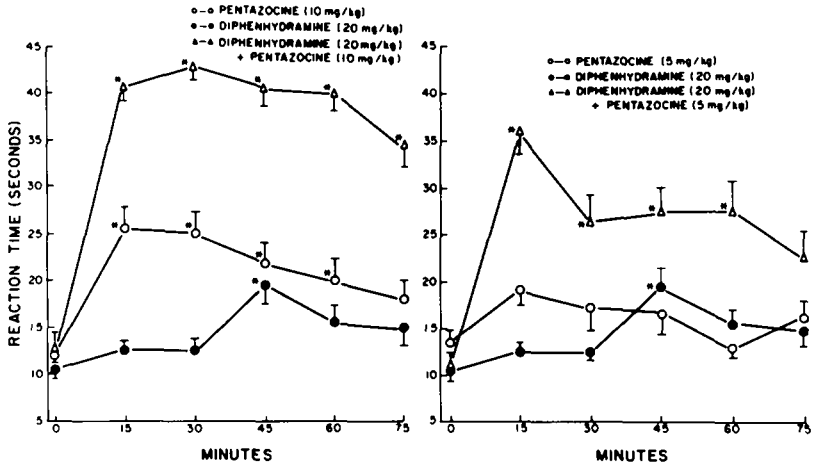

FIG 3 Potentiation of pentazocine antinociception by diphenhydramine in the rat. The asterisk indicates that the reaction time was significantly longer than that of the control at $p<0.05$ level

The organic phase was aspirated off. It should be pointed out that the organic phase and the hexane washing (below) were aspirated off completely, otherwise an extra peak having the same retention time of p-hydroxytripelennamine appeared in the chromatogram. The aqueous phase was washed with 5 ml of hexane by shaking for 15 min and centrifuged for 5 min. After aspiration of the hexane layer, the aqueous phase was adjusted to pH 10.0 (first with 2 ml of 10 M KOH, then titrated with 1.0 M of NaOH or HCl), buffered with 1 ml of 1 M potassium phosphate buffer, pH 10, and extracted with 5 ml of the organic solvent as mentioned above. After aspiration of the aqueous phase, all the organic phase, without any of the aqueous phase, was transferred to a 13 ml conical centrifuge tube. A few drops of 1 M hydrochloric acid in methanol was added to the extract, which was concentrated under a steam of nitrogen in a water bath at 50°C to about 0.1 to 0.2 ml. The tube was rinsed with 0.1 to 0.2 ml of methanol, and was vortexed. The methanol was evaporated under a steam of nitrogen in a water bath at 50°C just to dryness. The residue was dissolved in 50 μl of methanol, vortexed, and 1 μl of the solution was injected to a gas chromatograph.

A Varian aerograph (series 2700) equipped with a thermionic specific detector, and a 6 ft × 2 mm glass column packed with 3% OV-17 coated on 120/140 mesh Gas Chrom Q were used. The temperatures of the injector and detector were 220 and 275°C, respectively. The gas flow rate of nitrogen was 30 ml/min with hydrogen and air adjusted to optimum. The column temperature was programmed from 220 to 260°C at 10°C/min. Under these conditions, the retention times of diphenhydramine, N-butylnormetazocine and pentazocine were 2.0, 4.1 and 5.0 min, respectively. Concentrations of pentazocine and diphenhydramine as low as 50 to

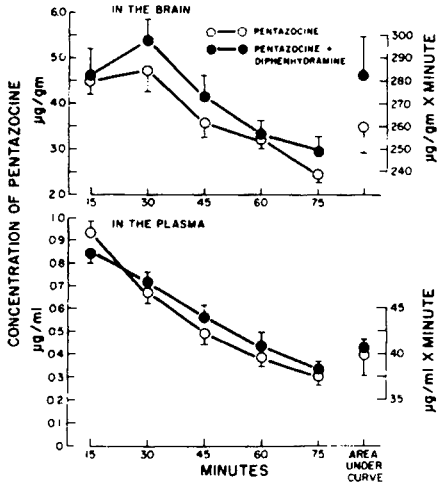

FIG 4 The effect of diphenhydramine on the concentration of pentazocine in the brain and plasma of rats

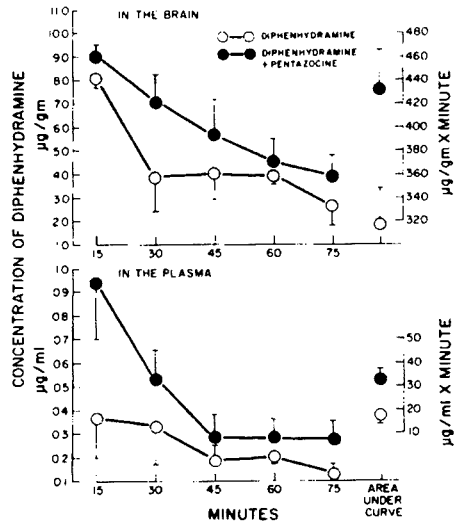

FIG 5 The effect of pentazocine on the concentration of diphenhydramine in the brain and plasma of rats

100 ng per ml of plasma or brain homogenate were detectable No interference was observed No metabolite of pentazocine and diphenhydramine was observed in the extract of the plasma and brain homogenate, although metabolites of these drugs could be extracted by the solvent (Fig 1) The drug concentrations in the samples were quantified by comparison of the peak height ratios of pentazocine or diphenhydramine to I S with those of a standard curve prepared with the brain homogenate or plasma of naive rat

Analysis of Data

Time-related antinociceptive responses and drug concentrations in the brain and plasma following single and combined drug or saline administration were evaluated by analysis of variance. In cases where F-value was significant, post-hoc analysis was performed using Dunnett's test The area under curve (AUC) of the antinociceptive responses and drug concentrations following single and combined drug or saline administration were evaluated by analysis of variance and comparison by Student-Newman-Keul's t-test $p<0$ 05 was used as the criterion for significance

RESULTS

Pentazocine antinociceptive activity was observed with the peak effect occurring between 15 and 30 min, and lasting to about 75 min (Fig 2) The mean analgesic potency increased at 15 min, and the antinociceptive AUC were increased proportionally to the administered doses (5 to 30 mg/kg) of pentazocine This confirmed the observation of O'Callaghan and Holtzman [11] The reaction time and the antinociceptive AUC after administration of 5 mg/kg of pentazocine were not significantly different from those of saline control.

The reaction time after diphenhydramine treatment showed a tendency towards an increase and was significantly longer at 45 min after diphenhydramine than the control reaction time. This suggested that diphenhydramine has a mild antinociceptive activity The antinociceptive AUC for the response to 20 mg/kg of diphenhydramine was smaller than that for 10 mg/kg of pentazocine and was not significantly different from that for 5 mg/kg of pentazocine or saline Antinociception produced by pentazocine (5 or 10 mg/kg, SC) was significantly potentiated by simultaneous administration of diphenhydramine, 20 mg/kg, IP (Fig 3) The antinociceptive AUC of pentazocine plus diphenhydramine was increased by 80 to 100% over the sum of the antinociceptive AUC for the individual drugs (Table 1)

The reaction time showed a trend toward an increase following administration of chlorpheniramine and was significantly longer at 75 min after chlorpheniramine than the control reaction time The antinociceptive AUC for the response to 20 mg/kg of chlorpheniramine was smaller than that for 10 mg/kg pentazocine, and was not significantly different from that for either 5 mg/kg of pentazocine or saline The antinociceptive AUC for the response to 5 mg/kg of pentazocine plus chlorpheniramine, but not 10 mg/kg of pentazocine, was significantly larger than that for pentenzocine alone (Table 1)

The reaction time showed a trend toward an increase following administration of promethazine and was significantly longer at 30 min after promethazine than the control reaction time The antinociceptive AUC for response to 20 mg/kg of promethazine was not significantly different from that for 10 mg/kg of pentazocine Pentazozine antinociception was potentiated by promethazine After simultaneous administration of pentazocine (10 mg/kg, SC) and promethazine the antinociceptive AUC increased by 100% over the sum of the antinociceptive AUC for individual drugs (Table 1)

After administration of cyclizine, the reaction times measured at 15 and 30 min were significantly increased as compared with the control reaction time The antinociceptive AUC for the response to cyclizine was not significantly different from those for 5 or 10 mg/kg of pentazocine The antinociceptive AUC for the response to cyclizine plus 10 mg/kg, but not 5 mg/kg, of pentazocine was significantly larger than that for pentazocine alone (Table 1)

The reaction time showed a trend toward an increase following the administration of chlorcyclizine and was significantly longer at 45 min after chlorcyclizine as compared with the control reaction time The antinociceptive AUC for the response to 20 mg/kg of chlorcyclizine was not significantly

different from those for 5 or 10 mg/kg of pentazocine or saline. Potentiation of pentazocine antinociception by chlorcyclizine was not observed (Table 1).

After SC administration of 10 mg/kg pentazocine the mean brain concentrations of pentazocine were 4 55, 4.71, 3.55, 3 26 and 2.38 μg/g tissue at 15, 30, 45, 60 and 75 min, respectively. The plasma concentrations at the respective time intervals were 0.93, 0.67, 0.49, 0.38 and 0.31 μg/ml. These results agree with those obtained previously [25]. The brain to plasma ratios of pentazocine are comparable to those of 5.59, 6.11 and 7.33 observed at 15, 30 and 60 min in the rat administered 15 to 20 mg/kg of the drug SC [2,7]

After IP administration of 20 mg/kg diphenhydramine, the mean brain concentrations of diphenhydramine were 8.1, 3 9, 4.1, 3 9 and 2 6 μg/g tissue at 15, 30, 45, 60 and 75 min, respectively. The plasma concentrations at the respective intervals were 0.37, 0.33, 0 19, 0.21 and 0.13 μg/ml. The brain to plasma ratio of diphenhydramine at 30 min was comparable to that (brain, 2.0 μg/g, plasma, 0.1 μg/ml after IP administration of 5 mg/kg) of diphenhydramine in the rat observed by Glazko and Dill [8].

After concurrent administration of pentazocine and diphenhydramine, concentrations of pentazocine and diphenhydramine in the brain and plasma at all time intervals as well as the area under concentration-time curves were not statistically different from those obtained after administration of pentazocine or diphenhydramine alone (Figs 4 and 5)

DISCUSSION

The results of the present study, based on the reaction time, but not the antinociceptive AUC, demonstrated that at the one time tested all tested representative antihistamines have mild antinociceptive activity. Tripelennamine, chlorpheniramine, pyrilamine and diphenhydramine have shown antinociceptive activity in the earlier studies [1, 23, 24] Local anesthetic properties of antihistamines also have been observed. Diphenhydramine and tripelennamine were the most effective and least toxic among eight antihistamines (tripelennamine, diphenhydramine, antazoline, promethazine, dimenhydrinate, methapyrilene, chlorpheniramine and pyrilamine) evaluated [12,17]. Antinociceptive effects of antihistaminics have been recently reviewed [15] and have been shown to be dose dependent [25].

The anticociceptive potency, expressed as antinociceptive AUC, of pentazocine plus antihistamine increased from equal to the sum of and to about 80 to 100% over the sum of the antinociceptive AUC of the individual drugs, indicating that the mechanism on the potentiation of pentazocine antinociception by an antihistamine appeared to be additive or synergetic effect, depending on the drugs used and the dosages (Table 1).

After concurrent administration of pentazocine and diphenhydramine, diphenhydramine did not alter pentazocine concentrations nor did pentazocine change diphenhydramine concentrations in the brain and plasma. These findings suggest that diphenhydramine did not alter pentazocine metabolism and pentazocine did not change diphenhydramine metabolism Similar results were obtained in a study of the effect of tripelennamine on pentazocine concentration and pentazocine on tripelennamine concentration in the brain and plasma of rats [25] Also, a similar result was observed related to the effect of tripelennamine on the concentration of total radioactivity of [^{3}H]morphine in mice [4], although conflicting results were reported in the rat [24].

Our previous studies [25] have shown that potentiation of pentazocine antinociception by another antihistamine, tripelennamine, was not observed when tripelennamine was administered 2 hr prior to pentazocine administration and chronic tripelennamine treatment for 14 days did not affect pentazocine antinociception [25]. These data suggest that tripelennamine administered acutely or chronically did not affect pentazocine metabolism.

The potentiation of opioid antinociception by antihistamines has been hypothesized that antihistamines may (1) facilitate the binding of opioids to the opioid receptors and or (2) replace opioids bound to nonspecific receptors The role of opiate receptor binding in the potentiation of pentazocine antinociception by antihistamines is not clear. Combinations of tripelennamine with pentazocine resulted in an enhanced displacement of [^{3}H]dihydromorphine, which may be due to an enhanced affinity of pentazocine for the *mu* receptor [19]. However, in another assay for opioid *mu* receptor binding, tripelennamine had no significant effect on the inhibition of [^{3}H]naloxone binding by pentazocine, and tripelennamine alone did not affect [^{3}H]naloxone binding [18]. The latter observation coincides with the results that tripelennamine antinociception in the rat was not antagonized by naloxone, further suggesting that tripelennamine may not act at *mu* opioid receptor site [25]. Tripelennamine displaced [^{3}H]SKF-10,047 in the *sigma* opioid receptor binding assays, suggesting that tripelennamine probably was interacting at the *sigma* opioid receptor site [18,20]. Tripelennamine and diphenhydramine have been shown to be relatively inactive (IC_{50}=10,000 nM) in inhibiting [^{3}H]ethylketocyclazocine (*kappa* opioid) binding [21]

The possible mechanism for potentiation of pentazocine antinociception by antihistamines could be due to a possible antiserotoninergic effect exerted by antihistamines and a consequent release of β-endorphine. For example, fluoxetine, a serotonin uptake blocker has been shown to increase circulating β-endorphine levels in the rat [16]. Whether antihistamine could stimulate release of pituitary β-endorphine has yet to be determined The mechanisms of antinociceptive effects of antihistamines have recently been reviewed [15]. Rumore and Schlichting [15] stated that there is considerable evidence to support the hypothesis that: (1) a direct serotonergic pathway exists to modulate noxious input; (2) several antihistamines (brompheniramine, chlorpheniramine, diphenhydramine, phenindamine, pyrilamine and tripelennamine) have been shown to block norepinephrine, dopamine, and serotonin uptake in synaptosomes; and (3) the increased availability of the amines causes a reduction in central pain response by some as yet undetermined mechanism.

Based on the results obtained in the present study, it is concluded that enhancement of pentazocine antinociception by antihistamines appears to be either potentiative or additive effect, depending on the antihistamines and doses employed. The potentiation may result from antihistamines being able to exert either additive or synergetic effect on the pain pathway responsible for pentazocine in the central nervous system.

ACKNOWLEDGEMENT

The author thanks Ms Pat Ilhoff for aid in the preparation of this manuscript

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