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Potentiation of Opioid and Nonopioid Forms of Swim Analgesia by Cimetidine

JUDITH A. ROBERTSON,* LINDSAY B. HOUGH† AND RICHARD J. BODNAR*[1]

**Department of Psychology and Neuropsychology Doctoral Sub-Program*
Queens College, CUNY, Flushing, NY 11367
and †Department of Pharmacology and Toxicology, Albany Medical College
Albany, NY 12208

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ROBERTSON, J. A., L. B. HOUGH AND R. J. BODNAR. *Potentiation of opioid and nonopioid forms of swim analgesia by cimetidine.* PHARMACOL BIOCHEM BEHAV 31(1) 107–112, 1988.—Antagonism of the H-2 receptor with cimetidine and other histaminergic receptor antagonists has been used to differentiate nonopioid and opioid forms of footshock analgesia which are mediated by neural mechanisms. Cimetidine reduces nonopioid footshock analgesia while potentiating an opioid form of this analgesia. The present study examined whether cimetidine altered the nonopioid, neurohormonal analgesia induced by either continuous cold-water swims (CCWS: 2°C for 3.5 min) or the opioid analgesia induced by intermittent cold-water swims (ICWS: 2°C, 18 10-sec swims, 18 10-sec recovery periods). Vehicle or cimetidine (10, 50, 100 mg/kg) injections were administered alone or paired with either CCWS or ICWS; tail-flick latencies, jump thresholds and core body temperatures were then measured. Cimetidine (100 mg/kg) significantly potentiated CCWS and ICWS analgesia and hypothermia, while having minimal effects upon basal thresholds. Lower cimetidine doses produced transitory effects on these measures. These data demonstrate dissociations between neural and neurohormonal forms of nonopioid analgesia following cimetidine treatment. The latter effect may be attributed to changes in stress responsiveness or thermoregulation rather than pain inhibition.

Cimetidine H-2 receptor Analgesia Stress Hypothermia Continuous cold-water swims Intermittent cold-water swims

NEUROPHARMACOLOGICAL analysis of the analgesic responses following environmental stressors has largely focused upon opioid and nonopioid characterizations [see reviews: (1, 6, 30, 31)]. However, histaminergic systems, among other neurotransmitters and neuropeptides, have received recent attention as possible mediators of nonopioid forms of environmental analgesia. Early studies demonstrated that a nonopioid form of footshock analgesia could be attenuated by pretreatment with either high doses of the H-1 receptor antagonist diphenhydramine (28) or the histidine decarboxylase inhibitor alpha-fluoromethylhistidine (29). The H-2 receptor has also been implicated in the mediation of nonopioid forms of footshock analgesia: cimetidine, ranitidine and oxmetidine each reduce footshock analgesia that is insensitive to high doses of naloxone, yet fail to affect a form of naloxone-sensitive footshock analgesia (20). Altering the intensity of footshock can produce analgesic responses that lie on a continuum of opioid to nonopioid sensitivity (30). In this paradigm, cimetidine reduced one form of naloxone-insensitive footshock analgesia (3.5 mA), but not another form (2.5 mA), and potentiated naloxone-sensitive footshock analgesia (2.0 mA) (19). The reduction by H-2 receptor antagonists of nonopioid footshock analgesia was confirmed using zolantidine, a brain-penetrating H-2 receptor antagonist (17). Experiments with chronic morphine and chronic footshock also confirmed the nonopioid nature of cimetidine-sensitive analgesia (32).

Varying the parameters of cold-water swims can activate opioid and nonopioid forms of analgesic responses [see review: (3)]. A continuous cold-water swim (CCWS) for 3.5 min at 2°C elicits an analgesic response which fails to develop cross-tolerance with morphine analgesia, is not significantly affected by naloxone, is potentiated by the irreversible opiate antagonist, naloxazone, and is reduced by putative anti-enkephalinase, D-phenylalanine (7–9, 23). An intermittent cold-water swim (ICWS) at 2°C in which the rat is exposed to eighteen pairs of 10-sec swims and 10-sec recovery periods over 6 min elicits analgesia which is both cross-tolerant with morphine analgesia and significantly reduced by naltrexone and naloxone in male rats (15, 16, 27). Neither the nonopioid, cimetidine-sensitive nor the nonopioid, cimetidine-insensitive forms of footshock analgesia are dependent upon hormonal influences (18). In contrast, CCWS analgesia is dependent upon the hypothalamo-hypophysial-

[1]Requests for reprints should be addressed to Richard J. Bodnar.

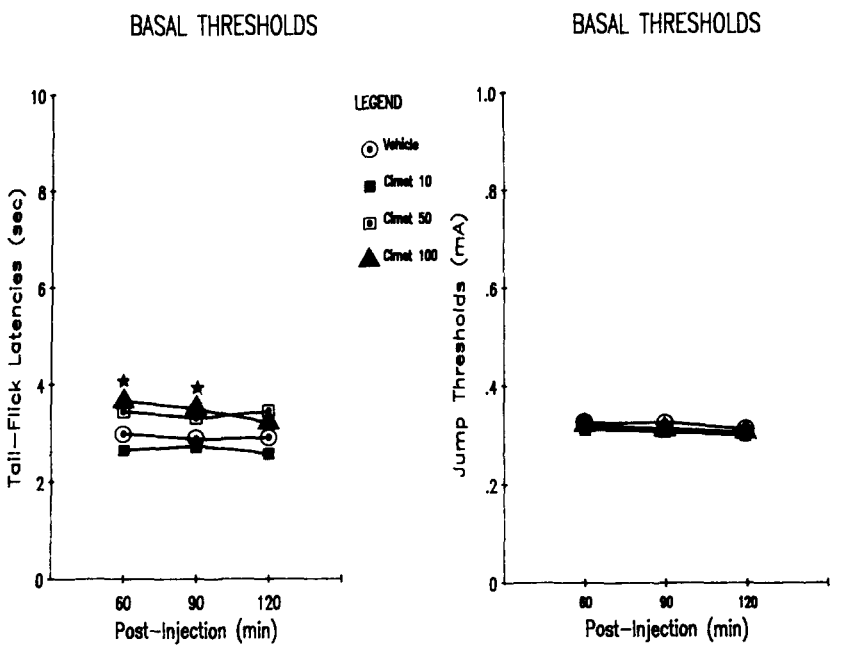

FIG. 1. Alterations in basal tail-flick latencies (left panel) and basal jump thresholds (right panel) following intraperitoneal injections of either vehicle or cimetidine (Cimet) doses of 10, 50 or 100 mg/kg. The stars denote significant differences (Dunnett comparisons, $p<0.05$) relative to corresponding vehicle treatment.

adrenal axis for its full expression (2, 4, 5, 10, 24–26). Pituitary-adrenal involvement in ICWS analgesia has not been ascertained, but given its opioid mediation, appears to serve as a logical counterpoint for CCWS analgesia. Therefore, to assess the generalizability of histaminergic involvement in nonopioid and opioid forms of analgesia, the present study evaluated whether the H-2 receptor antagonist, cimetidine dose-dependently altered CCWS and/or ICWS analgesia on the tail-flick (13) and jump (14) tests. To determine whether any effects were specific to analgesic systems, cimetidine effects upon CCWS and ICWS hypothermia were also evaluated.

METHOD

Twenty-three male albino Sprague-Dawley rats (350–700 g) were housed individually in wire mesh cages with Purina rat chow and water available ad lib in the Queens College Vivarium facility. All animals were maintained on a 12 hr light:12 hr dark cycle at ambient temperatures between 21 and 25°C.

Baseline tail-flick latencies and jump thresholds were determined for each rat over four days. The stimulus source (IITC Company, Woodland Hills, CA) for the tail-flick test was mounted 8 cm above the dorsum and 3–9 cm proximal to the tip of the tail of a lightly-restrained animal. The intensity of the thermal stimulus was set so as to produce stable baseline tail-flick latencies between 2.5 and 4 sec. Each tail-flick test session consisted of three latency determinations separated by 10-sec intertrial intervals. In order to avoid tissue damage, a trial was automatically terminated if a response did not occur within 10 sec. Immediately following tail-flick determinations, electric shock was delivered through 16 grids of a 30 cm by 24 cm chamber to each rat by a shock generator (BRS/LVE) through a shock scrambler (Campden Instruments). Using an ascending method of limits procedure, the jump threshold was defined in mA as the lowest of two consecutive intensities in which the animal sumultaneously removed both hindpaws from the grids. Each trial began with the animal receiving a 300-msec footshock at a current intensity of 0.10 mA. Subsequent shocks were increased in 0.05 mA increments at 10 sec intervals until the jump threshold was determined. After each trial, the current intensity was reset to 0.10 mA and the procedure repeated until six trials were completed. The order of tail-flick and jump determinations was employed because it yields minimal carry-over effects in baseline testing (22).

The first two groups (n=9 each) of rats received the following five conditions in counterbalanced order at 3–6 hr into the light cycle: vehicle/no swim, and swims paired with intraperitoneal injections of either vehicle or cimetidine doses of 10, 50 and 100 mg/kg. Rats received CCWS (Group 1, 2°C for 3.5 min) or ICWS (Group 2, 2°C, 18 pairs of 10-sec swims and 10-sec recovery periods). Each of the conditions were separated by a one-week interval to prevent adaptation effects (5,11). Cimetidine was diluted with saline from the injectable formulation (Tagament; Smith, Kline and French Inc.). Since this formulation contained phenol (5 mg/ml), vehicle solutions were saline containing equivalent concentrations of phenol. All injections occurred 30 min prior to preswim core body temperature determinations and swim conditions. Tail-flick latencies, jump thresholds and core body temperatures were measured at 30 min intervals following the swim (i.e., 60 min after cimetidine) for up to 90 min in the first group, and for up to 120 min in the second group. Core body temperature was assessed by inserting the rectal

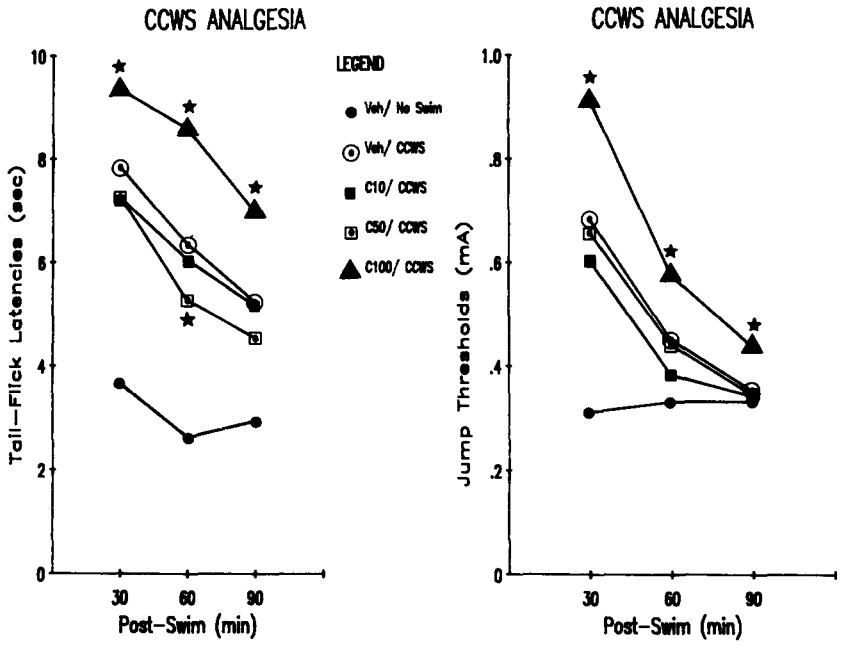

FIG. 2. Alterations in tail-flick latencies (left panel) and basal jump thresholds (right panel) following a continuous cold-water swim (CCWS; 2°C for 3.5 min) paired with either vehicle or cimetidine doses of 10, 50 or 100 mg/kg relative to a control vehicle/no swim condition. All swim conditions displayed analgesia relative to vehicle/no swim values (Dunnett comparisons, $p<0.05$). The stars denote significant differences (Dunn comparisons, $p<0.05$) induced by cimetidine relative to corresponding vehicle/CCWS values.

probe of a digital thermometer until stable readings were determined. To determine whether any changes in CCWS or ICWS analgesia by cimetidine were due to corresponding shifts in basal thresholds, a third group (n=5) of rats received either vehicle or cimetidine doses of 10, 50 and 100 mg/kg at weekly intervals. Determinations of postinjection tail-flick latencies and jump thresholds, and pre- and postinjection core body temperatures were adjusted to correspond with the postswim conditions.

Analyses of variance were performed to discern significant main and interaction effects. The Dunnett test ($p<0.05$) was performed to assess significant drug and/or swim-induced changes relative to vehicle or vehicle/no swim values. The Dunn test ($p<0.05$) was performed to assess significant cimetidine-induced changes in CCWS or ICWS measures relative to corresponding vehicle/swim values.

RESULTS

Basal Thresholds

Significant differences in basal tail-flick latencies were observed only among conditions, $F(3,12)=34.39$, $p<0.0001$. The 50 and 100 mg/kg doses of cimetidine significantly increased latencies over vehicle values for 90 and 60 min following injection respectively (Fig. 1, left panel). However, the magnitude of these increases never exceeded 0.7 sec (22% increase over baseline). Basal jump thresholds failed to differ among conditions across the time course or for the interaction between conditions and times (Fig. 1, right panel). Significant differences in core body temperatures were observed only among conditions, $F(3,12)=6.75$, $p<0.006$. The 50 and 100 mg/kg doses of cimetidine produced significant hypothermia relative to corresponding vehicle values with the largest effect (2°C) occurring 30 min following the highest cimetidine dose (data not shown).

CCWS Analgesia

CCWS significantly increased tail-flick latencies and jump thresholds over no swim values in all injection conditions. Significant differences in postswim tail-flick latencies were observed among conditions, $F(3,24)=26.88$, $p<0.0001$, and across the time course, $F(2,16)=57.37$, $p<0.0001$. The 50 mg/kg dose of cimetidine transiently, but significantly lowered CCWS analgesia 60 min following the swim. However, the 100 mg/kg dose of cimetidine significantly potentiated CCWS analgesia across the entire time course on the tail-flick test with the magnitude of analgesia increasing between 30% (30 min) and 78% (90 min) relative to vehicle/CCWS values (Fig. 2, left panel). Significant differences in postswim jump thresholds were observed among conditions, $F(3,24)=8.03$, $p<0.0007$, across the time course, $F(2,16)=28.70$, $p<0.0008$, and for the interaction between conditions and times, $F(6,48)=2.67$, $p<0.026$. The 100 mg/kg dose of cimetidine significantly potentiated CCWS analgesia across the entire time course on the jump test with the magnitude of analgesia increasing between 62% (30 min) and 118% (60 min) relative to vehicle/CCWS values (Fig. 2, right panel). This dose of cimetidine prolonged CCWS analgesia on the jump test to 90 min after the swim.

ICWS Analgesia

ICWS significantly increased tail-flick latencies and jump thresholds over no swim values in all injection conditions.

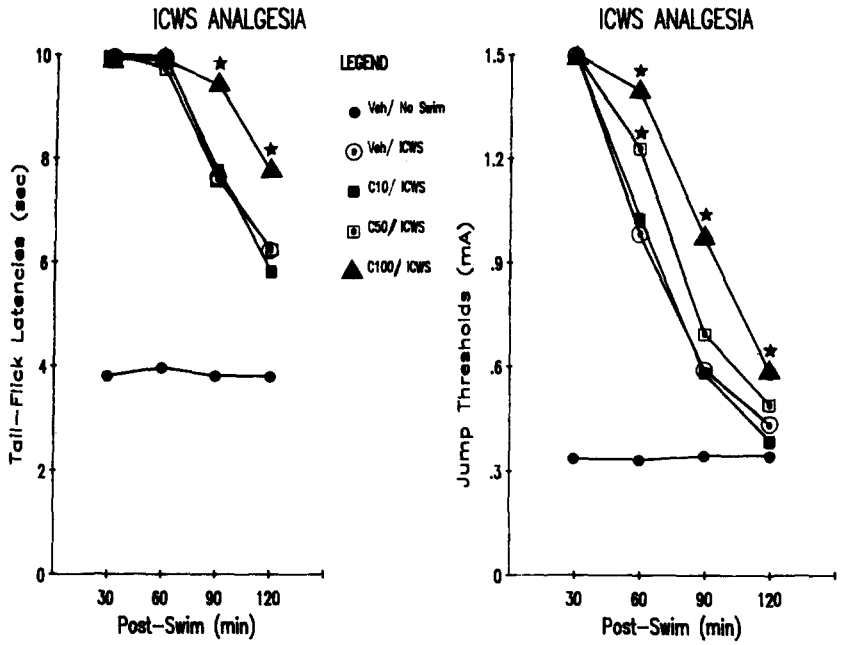

FIG. 3. Alterations in tail-flick latencies (left panel) and basal jump thresholds (right panel) following an intermittent cold-water swim (ICWS; 2°C, 18 10-sec swims and 18 10-sec recovery periods) paired with either vehicle or cimetidine doses of 10, 50 or 100 mg/kg relative to a control vehicle/no swim condition. All swim conditions displayed analgesia relative to vehicle/no swim values (Dunnett comparisons, $p<0.05$). The stars denote significant differences (Dunn comparisons, $p<0.05$) induced by cimetidine relative to corresponding vehicle/ICWS values.

Significant differences in postswim tail-flick latencies were observed among conditions, $F(3,24)=18.43$, $p<0.0001$, across the time course, $F(3,24)=80.16$, $p<0.0001$, and for the interaction between conditions and times, $F(9,72)=11.67$, $p<0.0001$. The 100 mg/kg dose of cimetidine significantly potentiated ICWS analgesia on the tail-flick test at 90 and 120 min after the swim with the magnitude of analgesia increasing between 47% (90 min) and 63% (120 min) relative to vehicle/ICWS values (Fig. 3, left panel). Significant differences in postswim jump thresholds were observed among conditions, $F(3,24)=15.89$, $p<0.0001$, across the time course, $F(3,24)=186.56$, $p<0.0001$, and for the interaction between conditions and times, $F(9,72)=4.95$, $p<0.0001$. The 50 mg/kg dose of cimetidine transiently, but significantly potentiated ICWS analgesia on the jump test at 60 min after the swim. The 100 mg/kg dose of cimetidine significantly potentiated CCWS analgesia on the jump test from 60–120 min after the swim with the magnitude of analgesia increasing between 63% (60 min) and 163% (90 min) relative to vehicle/ICWS values (Fig. 3, right panel). This dose of cimetidine prolonged CCWS analgesia on the jump test to 120 min after the swim.

CCWS and ICWS Hypothermia

Both swim parameters produced significant hypothermia in all injection conditions. Significant differences in CCWS hypothermia were observed among conditions, $F(3,24)=16.43$, $p<0.0001$, across the time course, $F(2,16)=251.03$, $p<0.0001$, and for the interaction between conditions and times, $F(6,48)=3.13$, $p<0.012$. The 100 mg/kg dose of cimetidine significantly potentiated CCWS hypothermia over the time course with the magnitude of effect ranging between 2.6° C (30 min) and 4.8°C (90 min) (Fig. 4, left panel). Significant differences in ICWS hypothermia were observed among conditions, $F(3,24)=11.72$, $p<0.0001$, across the time course, $F(3,24)=345.82$, $p<0.0001$, and for the interaction between conditions and times, $F(9,72)=2.41$, $p<0.019$. ICWS hypothermia was both inhibited (10 mg/kg, 60 min) and potentiated (50 mg/kg, 90 min) by cimetidine. In contrast, the 100 mg/kg dose of cimetidine significantly potentiated ICWS hypothermia over the time course with the magnitude of effect ranging between 1.3°C (30 min) and 3.1°C (90 min) (Fig. 4, right panel).

DISCUSSION

Antagonism of the H-2 receptor with cimetidine significantly potentiated both CCWS analgesia, which is a nonopioid, neurohormonally-mediated response (2, 4, 5, 7–10, 24–26), and ICWS analgesia, which is an opioid-mediated response (15, 16, 27). Cimetidine potentiated swim analgesia on both the tail-flick test which measures reactivity to heat, and the jump test which measures reactivity to shock. The most consistent and pronounced effects upon analgesia occurred following the highest cimetidine dose, and appeared not to be the result of additive interactions between cimetidine and each of the swim effects. The small, but significant increases in basal tail-flick latencies could not account for the potentiations of both CCWS and ICWS analgesia. Since cimetidine failed to affect basal jump thresholds, this certainly did not account for the potentiations in CCWS and ICWS analgesia on this measure.

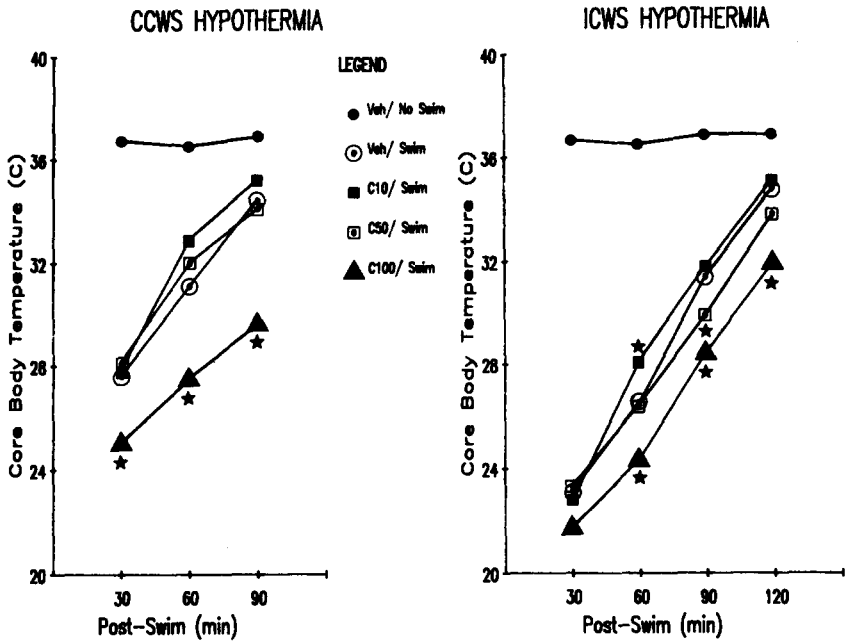

FIG. 4. Alterations in core body temperatures following CCWS (left panel) or ICWS (right panel) paired with either vehicle or cimetidine doses of 10, 50 or 100 mg/kg relative to a control vehicle/no swim condition. All swim conditions displayed hypothermia relative to vehicle/no swim values (Dunnett comparisons, $p<0.05$). The stars denote significant differences (Dunn comparisons, $p<0.05$) induced cimetidine relative to corresponding vehicle/swim values.

The potentiation of nonopioid-mediated CCWS analgesia by cimetidine stands in contrast to previous findings (19,20) showing cimetidine-induced reductions in nonopioid footshock analgesia. Clearly, one interpretation of our present results is that H-2 receptors do not mediate the analgesia elicited by CCWS. This differential effect of cimetidine on these two nonopioid analgesic systems adds to other known differences. For example, hypophysectomy reduces CCWS analgesia (5), but has no effect on nonopioid, cimetidine-sensitive footshock analgesia (18). These observations add to the evidence for the existence of multiple endogenous nonopioid pain-inhibitory systems.

The potentiation of nonopioid CCWS analgesia by cimetidine could possibly be due to an action on H-2 receptors related to analgesia, but is more likely to be related to actions on body temperature. The highest dose of cimetidine produced a small, but significant hypothermia, consistent with earlier studies (12), and also significantly potentiated CCWS and ICWS hypothermia across their respective time courses. Indeed, the alterations in CCWS and ICWS analgesia and hypothermia following cimetidine were strikingly similar, suggesting that a common mechanism of action might modulate both response systems. Such parallel effects question an implicit assumption of environmental analgesia studies, namely that changes in response output by a given manipulation is necessarily the exclusive result of that manipulation's effects upon the output (i.e., pain-inhibitory) system. Typically, footshock analgesia paradigms employ a physiological or pharmacological manipulation paired with the footshock, and examine effects upon a single response measure (typically, tail-flick latencies). Any latency changes by the footshock-manipulation pairing are typically described as intrinsic to pain inhibition. However, the manipulation could conceivably alter coping or response strategies to the footshock, which may in turn account for subsequent changes in latencies. The latter scenario attributes changes to stress responsiveness, and not analgesic output systems. The swim paradigms employed here allow the analysis of multiple analgesic endpoints (tail-flick and jump tests) as well as a different physiological endpoint (hypothermia). The parallel changes in analgesia and hypothermia argue strongly against an exclusive role for the H-2 receptor antagonist in analgesic processes. Rather it suggests that either cimetidine may be working directly upon hypothermia which in turn affects analgesic responsivity, or cimetidine may be working on a stress input system which in turn affects hypothermia and analgesia independently. However, the ability of cimetidine (50 mg/kg) to significantly, but transiently reduce CCWS analgesia (Fig. 2) while potentiating hypothermia (Fig. 4) suggests that a role for H-2 receptors in CCWS analgesia cannot be completely dismissed.

Our laboratory has previously found many instances in which changes in CCWS analgesia and CCWS hypothermia can be dissociated [see review: (3)]. CCWS analgesia, but not CCWS hypothermia is reduced following hypophysectomy, repeated preexposure to CCWS and D-phenylalanine. Aging, muscarinic receptor antagonism and gender/gonadectomy manipulations reduce CCWS analgesia and potentiate CCWS hypothermia. Desipramine and yohimbine each potentiate CCWS analgesia, but not CCWS hypothermia. However, associations between CCWS analgesia and CCWS hypothermia have been observed with corresponding

increases following clonidine pretreatment and reductions following neonatal monosodium glutamate pretreatment. Cimetidine effects in the present study upon CCWS and ICWS appear largely similar to this latter category, and raise the possibility that the H-2 receptor is just as involved in the processing of stressful stimuli and/or body temperature changes, as it might be in the modulation of endogenous pain-inhibitory systems.

ACKNOWLEDGEMENTS

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