Potentiation of 2-Deoxy-D-Glucose Antinociception, but Not Hyperphagia by Zolantidine, a Histamine (H₂) Receptor Antagonist

JAMES E. KOCH,* LINDSAY B. HOUGH† AND RICHARD J. BODNAR‡[1]

*Department of Pharmacology, Mount Sinai School of Medicine, New York, NY 10029
†Department of Pharmacology, Albany Medical College, Albany, NY 12208
‡Department of Psychology and Neuropsychology Doctoral Sub-Program
Queens College, City University of New York, Flushing, NY 11367

KOCH, J. E., L. B. HOUGH AND R. J. BODNAR. *Potentiation of 2-deoxy-D-glucose antinociception, but not hyperphagia by zolantidine, a histamine (H₂) receptor antagonist.* PHARMACOL BIOCHEM BEHAV 41(2) 371-376, 1992.—Antagonism of the histamine (H₂) receptor reduces antinociception induced by naloxone-resistant foot-shock, naloxone-sensitive foot-shock, and morphine with a rank-order potency similar to their H₂ antagonism. The antimetabolic glucose analog 2-deoxy-D-glucose (2DG) produces antinociceptive and hyperphagic responses that dissociate from each other and are in part mediated by opioid systems. The present study determined the effects of the brain-penetrating H₂ receptor antagonist zolantidine (ZOL) on 2DG antinociception on the tail-flick and jump tests, as well as on 2DG hyperphagia, in rats. ZOL (0.01-1 mg/kg) potentiated the antinociceptive responses induced by a moderate (450 mg/kg) dose of 2DG, but had lesser effects upon antinociception induced by a lower (100 mg/kg) 2DG dose. ZOL itself slightly increased jump thresholds, but not tail-flick latencies. Combinations of ZOL and 2DG produced supraadditive antinociception, even though ZOL failed to significantly shift the 2DG dose-response curve to the left. In contrast, ZOL failed to alter basal intake or 2DG hyperphagia, supporting previous evidence implicating the H₁ but not the H₂ receptor in these effects. These results further dissociate the antinociceptive and hyperphagic effects of 2DG, and also support previous results indicating both pro- and antinociceptive roles for H₂ receptors.

Zolantidine   H₂ receptor   2-Deoxy-D-glucose   Histamine   Antinociception   Hyperphagia   Rats

THE CNS transmitter histamine (HA) and its receptors have been implicated in antinociceptive processes [see review: (17)]. HA microinjected into the dorsal raphe nucleus or adjacent periaqueductal gray induces antinociception characteristic of H₂ receptor mediation (12). Recent studies using selective H₂ antagonists confirm a mediating role for HA in both morphine (MOR)- and stress-induced antinociception. Systemic administration of the brain-penetrating H₂ blocker zolantidine [ZOL: (8)] inhibited MOR antinociception (15), naloxone-sensitive ("opiate") foot-shock-induced antinociception [FSIA (13,15)], and naloxone-resistant ("nonopiate") FSIA (13,14). Larger doses of ZOL were required to inhibit nonopiate FSIA relative to opiate FSIA or MOR. The inhibition of MOR antinociception by ZOL occurred in the absence of any affinity of ZOL for opiate and amine receptors, any changes in the

brain levels of MOR, any changes in basal nociceptive thresholds, and any alterations in MOR-induced hyperthermia, catalepsy, or lethality (15). Finally, the rank-order potency of inhibition of MOR antinociception by ZOL and other brain-penetrating H₂ antagonists (e.g., SK&F95456, SK&F95565, SK&F95495, SK&F94674, and SK&F95299) correlated highly with their H₂ receptor potency, strongly arguing for the proposition that blockade of brain H₂ receptors inhibits opiate antinociceptive responses (15). A similar array of H₂ antagonists failed to alter baseline nociceptive thresholds, but inhibited nonopiate FSIA with an order of potency commensurate with blockade of brain H₂ receptors (14).

Several observations suggest that brain HA may also mediate hyperalgesic responses. For example, although HA produced antinociception when administered into the dorsal

[1] Requests for reprints should be addressed to Dr. R. J. Bodnar, Department of Psychology, Queens College, CUNY, 65-30 Kissena Boulevard, Flushing, NY 11367.

raphe nucleus, hyperalgesic effects were observed following HA administration into the nucleus raphe medianus (12). Supportive evidence for HA-mediated hyperalgesia was also derived from the above H_2 antagonist studies such that higher doses of H_2 antagonists reversed the inhibitory effects induced by the lower H_2 antagonist doses upon MOR antinociception, as well as opiate and nonopiate FSIA, thereby yielding U-shaped dose-response curves (13-15). Although the mechanism(s) accounting for such U-shaped dose-response functions remains to be established unequivocally [see discussion in (15)], a parsimonious explanation is that H_2 receptor antagonism may be able to modify antinociceptive responses in both directions. Clearly, one approach to understanding these dual actions of ZOL is the exploration of its effects in a wider array of antinociceptive test systems.

The antimetabolic glucose analogue 2-deoxy-D-glucose (2DG) activates such physiological responses as glucoprivation, peripheral sympatho-medullary discharge, and hyperglycemia (7,16,30). 2DG elicits antinociceptive (3) and hyperphagic (26) responses that dissociate from each other [see discussion in (5)]. Indeed, the opioid mediation of 2DG antinociception and 2DG hyperphagia dissociate as well. 2DG antinociception, but not 2DG hyperphagia, displays tolerance and cross-tolerance with MOR antinociception (1,5,28). In contrast, 2DG hyperphagia, but not 2DG antinociception, is reduced following administration of the opiate receptor antagonist naloxone (4,19).

In an attempt to characterize further the pharmacology of H_2 receptor antagonists in the mediation of antinociceptive systems, the present study initially examined whether the brain-penetrating H_2 receptor antagonist ZOL would alter 2DG antinociception on the tail-flick (10) and jump (11) tests. Since the effectiveness of ZOL in inhibiting MOR antinociception as well as opiate and nonopiate FSIA were dependent upon pretreatment interval and dose (14,15), different doses of ZOL were administered either 30 min prior to or simultaneously with different doses of 2DG. The present study subsequently examined the effects of ZOL upon 2DG hyperphagia since: 1) 2DG antinociception and hyperphagia dissociate [see (5)] and 2) HA mediation of food intake appears to be mediated through the H_1 and not the H_2 receptor subtype (22, 23,25).

METHOD

Male, albino Sprague-Dawley rats (300-550 g) were housed individually on a 12L:12D cycle with ad lib access to rat chow and water.

Nociceptive Tests

Tail-flick latencies were ascertained with a radiant heat source (IITC Analgesia Meter) in which heat was applied to the dorsum of the rat's tail 3-8 cm proximal to the tip. Each session consisted of three latency determinations made at 10-s intertrial intervals. To avoid tissue damage, the determination was terminated if no response occurred after 10 s. Immediately thereafter, jump thresholds were ascertained in a chamber (30 × 24 × 26.5 cm) with 14 grid bars spaced 1.9 cm apart. Electric shocks (0.3 s) were delivered through the grids by a shock generator (BRS/LVE) and shock scrambler (Campden Instruments). An ascending method of limits procedure was employed for each of six trials with shock initially delivered at 0.1 mA and increased in 0.05-mA increments at 5-s intervals. The jump threshold was defined as the lowest of

two consecutive intensities at which the rat simultaneously removed both rear paws from the grids or if a cutoff of 1.0 mA was reached.

ZOL and 2DG Antinociception

Following 4 days of baseline latency and threshold determinations to ensure stability, rats received the following subsets of conditions. First, the effects of 2DG (Sigma Chemical Co.) at doses of 100 ($n = 6$), 450 ($n = 10$), and 700 ($n = 10$) mg/kg were compared with a vehicle control ($n = 20$). Second, the effects of ZOL (1 mg/kg Smith, Klein, Beecham Research, ($n = 6$) relative to a vehicle control were assessed. Third, the ability of ZOL at doses of 0.01 ($n = 6$), 0.1 ($n = 6$), and 1 ($n = 10$) mg/kg to alter 2DG (450 mg/kg) antinociception were assessed under two conditions: 1) simultaneous treatment and 2) ZOL pretreatment 0.5 h prior to 2DG. Fourth, to assess ZOL effects across the 2DG dose-response function further subsets of rats ($n = 6$/group) received ZOL (1 mg/kg) either 30 min prior to or simultaneously with 2DG at doses of 100 and 700 mg/kg. Whereas ZOL was administered subcutaneously in a disodium maleate (1 mg/ml/kg) vehicle, 2DG was administered intraperitoneally in a distilled water vehicle. Tail-flick latencies and jump thresholds were assessed 30, 60, 90, and 120 min following the last injection in each condition. The subsets of rats tested in experimental conditions were matched for similar vehicle latencies and thresholds, as well as for similar magnitudes of 2DG antinociception. All injections were administered between 2 and 6 h into the light cycle, and 1 week elapsed between the different treatment conditions.

ZOL and 2DG Hyperphagia

Twelve naive rats received the following injection pairs according to an incompletely counterbalanced design: 1) vehicle/vehicle ($n = 11$); 2) vehicle/2DG (700 mg/kg; $n = 9$); 3) ZOL (1 mg/kg)/vehicle ($n = 9$); and ZOL/2DG (700 mg/kg) at ZOL doses of 4) 0.01 ($n = 9$), 5) 0.1 ($n = 11$), and 6) 1 ($n = 11$) mg/kg. Food intake was assessed 2, 4, and 6 h after the last injection by weighing food pellets prior to and after each time point in each condition. All intakes were adjusted for spillage, which was collected by paper under the wire mesh cage. All conditions began 2 h into the light cycle with ZOL injections occurring 30 min prior to 2DG injections. A 1-week interval elapsed between injection conditions.

Statistical Analyses

Split-plot analyses of variance (ANOVA's) assessed differences among vehicle, each of the 2DG doses, ZOL and ZOL paired with 2DG across the time-course in the antinociception protocol, and for each intake point in the hyperphagia protocol. Significant 2DG effects relative to vehicle and significant ZOL effects relative to 2DG were assessed with Dunnett and Dunn comparisons, respectively. To determine alterations in 2DG dose-response functions under vehicle and ZOL pretreatment, linear regression analyses evaluated peak (60 min) and total antinociceptive effects relative to the logarithmic transformation of 2DG doses to determine differences between slopes and intercepts. Calculation of the total antinociceptive effect for each condition relative to vehicle was accomplished by summing the differences between each experimental and vehicle score across the time-course.

RESULTS

ZOL and 2DG Antinociception

In assessing 2DG antinociception at a 450-mg/kg dose, significant differences were observed among conditions (tail-

flick: $F(8,67) = 6.90$, $p < 0.0001$; jump: $F = 68.72$, $p < 0.0001$), across the time course (tail-flick: $F(3,201) = 13.09$, $p < 0.0001$; jump: $F = 77.93$, $p < 0.0001$), and for the interaction between condition and time (tail-flick: $F(24,201) = 1.92$, $p < 0.009$; jump: $F = 5.72$, $p < 0.0001$). 2DG at a dose of 450 mg/kg significantly increased tail-flick latencies (Fig. 1) and jump thresholds (Fig. 1b) across the time course. ZOL (1 mg/kg) significantly potentiated the magnitude of 2DG (450 mg/kg) antinociception on the tail-flick test for up to 60 min following both simultaneous treatment (158–168% increases) and pretreatment (131–141% increases) (Fig. 1a). ZOL (1 mg/kg) significantly potentiated the magnitude of 2DG (450 mg/kg) antinociception on the jump test across the 2-h time course following both simultaneous treatment (88–116% increases) and pretreatment (29–62% increases) (Fig. 1b). Whereas ZOL itself failed to alter tail-flick latencies (Fig. 1a), it significantly increased jump thresholds by 19–23% across the time course. The total antinociceptive effects on the tail-flick test induced by either simultaneous (9.20 s) or

pretreatment (7.97 s) ZOL and 2DG conditions were, respectively, 54 and 33% higher than the sum (5.98 s) of antinociceptive effects induced by ZOL alone (1.61 s) and 2DG alone (4.37 s). The total antinociceptive effects on the jump test induced by either simultaneous (1.689 mA) or pretreatment (1.226 mA) ZOL and 2DG conditions were, respectively, 44 and 5% higher than the sum (1.171 mA) of antinociceptive effects induced by ZOL alone (0.337 mA) and 2DG alone (0.834 mA). Thus, it appears that the interactions between 2DG and ZOL produce effects greater than the additive effects of ZOL and 2DG themselves under both simultaneous and pretreatment conditions on the tail-flick test and under the simultaneous condition on the jump test.

Lower doses of ZOL also potentiated antinociception induced by a 450-mg/kg dose of 2DG. ZOL at doses of 0.1 and 0.01 mg/kg significantly potentiated the magnitude of 2DG antinociception on the tail-flick test following both simultaneous treatment (30 min: 34–70% increases) and pretreatment (30–60 min: 119–238% increases) (data not shown). ZOL at
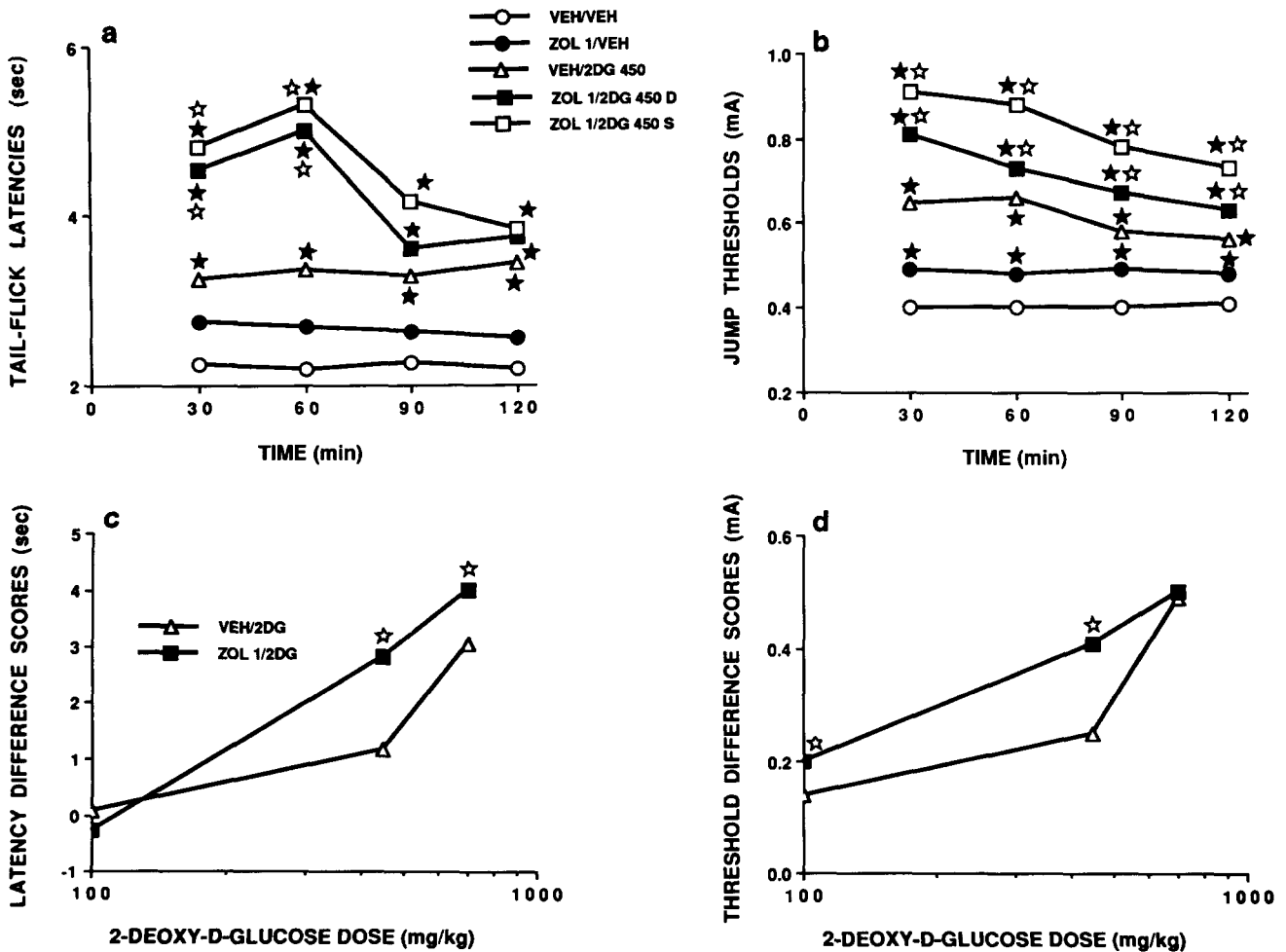

FIG. 1. (a) and (b). Alterations in (a) tail-flick latencies and (b) jump thresholds by 2DG and ZOL. The effects of 2DG (450 mg/kg) are evaluated relative to vehicle (VEH) in rats receiving either pretreatment (D, delay) or simultaneous (S, simultaneous) treatment with ZOL (1 mg/ kg). Solid stars denote significant differences relative to VEH/VEH (Dunnett comparisons, $p < 0.05$). Open stars denote significant differences relative to VEH/2DG (Dunn comparisons, $p < 0.05$). (c) and (d). Alterations in the magnitude of peak (60 min) antinociceptive responses across the 2DG dose-response curve following delayed pretreatment with either VEH or ZOL. Open stars denote significant differences relative to VEH/2DG (Dunn comparisons, $p < 0.05$).

doses of 0.1 and 0.01 mg/kg significantly potentiated the magnitude of 2DG antinociception on the jump test across the time course following both simultaneous treatment (54-118% increases) and pretreatment (94-187% increases) (data not shown).

Evaluations of interactions between ZOL (1 mg/kg) and a lower (100 mg/kg) 2DG dose revealed significant differences among conditions (tail-flick: $F(4,39) = 5.09$, $p < 0.002$; jump: $F = 43.54$, $p < 0.0001$) and across the time-course (jump: $F(3,117) = 2.90$, $p < 0.037$). ZOL significantly increased the magnitude of 2DG antinociception on the jump test across the time course following simultaneous treatment (37-108%) and pretreatment (45-98%) (data not shown). However, total antinociceptive effects on the jump test following either simultaneous or pretreatment pairing of ZOL and 2DG failed to differ from the additive effects of ZOL alone and 2DG alone. Indeed, both simultaneous and pretreatment pairing of ZOL and 2DG (100 mg/kg) actually eliminated the latter's small antinociceptive effect on the tail-flick test.

Evaluations of interactions between ZOL (1 mg/kg) and a higher (700 mg/kg) 2DG dose revealed significant differences among conditions (tail-flick: $F(3,38) = 20.35$, $p < 0.0001$; jump: $F = 151.53$, $p < 0.0001$), across the time course (tail-flick: $F(3,114) = 8.16$, $p < 0.0001$; jump: $F = 49.32$, $p < 0.0001$), and for the interaction between condition and time (tail-flick: $F(9,114) = 6.12$, $p < 0.0001$; jump: $F = 22.34$, $p < 0.0001$). 2DG antinociception on the tail-flick test was significantly reduced by ZOL pretreatment after 30 min (51% reduction) and then significantly potentiated at 60 and 90 min (31-49% increases) (data not shown). Antinociception induced by the pairing of ZOL and 2DG was similar to the additive antinociceptive effects of ZOL alone and 2DG alone. ZOL failed to alter 2DG (700 mg/kg) antinociception on the jump test. It should be noted that 2DG antinociception at this dose in the presence and absence of ZOL approached cutoff values.

Figure 1 (c and d) displays the changes in peak 2DG antinociception on the tail-flick and jump tests following vehicle and ZOL pretreatment. Regression analyses revealed that 2DG dose-response curves following vehicle or ZOL (1 mg/kg) pretreatment failed to differ from each other for peak, $F(2,44) = 1.90$, and total, $F = 1.28$, antinociception on the tail-flick test and for peak, $F = 2.95$, and total, $F = 3.16$, antinociception on the jump test.

ZOL and 2DG Hyperphagia

Significant differences in food intake among vehicle, 2DG, and ZOL conditions were observed after 2 ($F(5,55) = 4.36$, $p < 0.002$), 4 ($F = 12.65$, $p < 0.001$), and 6 h ($F = 10.85$, $p < 0.001$). Figure 2 illustrates the ability of 2DG to increase intake across the time course regardless of whether rats were pretreated with either vehicle or the different ZOL (0.01-1 mg/kg) doses. ZOL itself failed to alter intake across the time-course relative to vehicle treatment.

DISCUSSION

The present study found that 2DG antinociception on the tail-flick test was significantly potentiated by the brain-penetrating H_2 receptor antagonist ZOL. On the jump test, ZOL had slight antinociceptive effects alone that were synergistic with 2DG. Similar ZOL/2DG interactions occurred on both tests following either ZOL pretreatment or simultaneous coadminstration with 2DG. ZOL/2DG interactions were most pronounced at that 2DG dose (450 mg/kg) that produced a
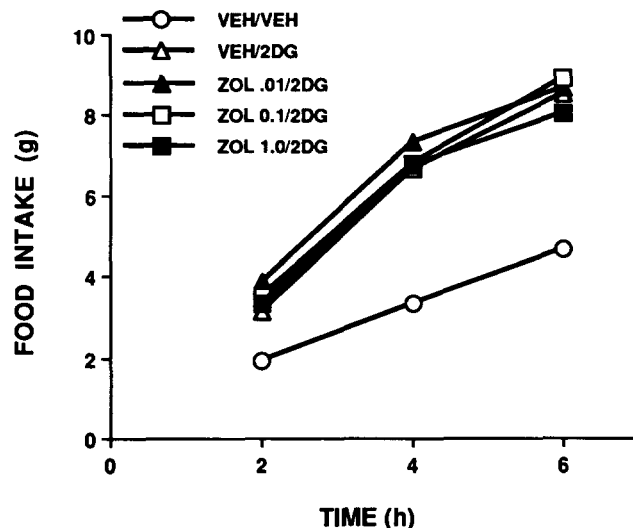

FIG. 2. Alterations in food intake (g) by 2DG (700 mg/kg) in rats pretreated with either VEH or ZOL (0.1-1 mg/kg).

moderate degree of antinociception. Increasing the 2DG dose to 700 mg/kg reduced the magnitude of ZOL's potentiation of 2DG antinociception on the tail-flick test (Fig. 1c) and mitigated the ZOL/2DG synergism on the jump test (Fig. 1d). The use of cutoff latencies and thresholds may explain the relative failure of ZOL to increase antinociception at this higher 2DG dose. More intriguing was the ability of ZOL to inhibit the slight, but significant, antinociception induced by the lower (100 mg/kg) 2DG dose. In contrast to these effects on 2DG antinociception, ZOL (0.01-1 mg/kg) failed to alter 2DG hyperphagia. These findings are evaluated in terms of: 1) histaminergic mechanisms influencing antinociception and 2) the dissociation of the antinociceptive and hyperphagic actions of 2DG.

Histaminergic mechanisms of antinociception. As discussed in the Introduction, previous pharmacological studies suggest that activation of brain H_2 receptors is important for the expression of several types of antinociceptive responses (12-15). In addition, microinjection studies with H_2 agonists (17) and antagonists (Hough et al., submitted), together with more recent neuroanatomical (21) and microdialysis (K. Barke and L. B. Hough, submitted) studies, support the hypothesis that systemically administered μ-opiates relieve tonic pain in part by the release of HA in the mesencephalic periaqueductal gray. These studies utilized thermal nociceptive tests (e.g., hot-plate and tail-flick), and ZOL failed to alter baseline responses over a wide dose range (13,15). This contrasts with the present results with the jump test in which ZOL (1 mg/kg) possessed mild antinociceptive activity (Fig. 1b).

Given the link between MOR and 2DG antinociception in cross-tolerance (28) and synergy (4) studies, it has been suggested that 2DG antinociception is mediated in part by endogenous opioids. If activation of H_2 receptors contributed to the mechanism suggested for MOR antinociception and opiate-sensitive FSIA, one would have predicted inhibition, not the observed potentiation, of 2DG antinociception by ZOL. At face value, the present results suggest that, after 2DG, brain H_2 receptors contribute to hyperalgesic, and not analgesic, responses. This is supported by the observation that central HA microinjections produced antinociception in the dorsal

raphe nucleus and hyperalgesia in the nucleus raphe medianus (12). Further, ZOL-induced inhibition of MOR antinociception and opioid FSIA followed a U-shaped curve with inhibition noted at moderate doses, but not at low or high doses (13-15). Although U-shaped curves were not observed in the present study for ZOL, its inhibition of antinociception on the tail-flick test induced by low (100 mg/kg) 2DG doses suggests modulation of antinociception in both directions. Finally, the direct antinociceptive effects of ZOL on the jump test are consistent with a hyperalgesic H_2 receptor role.

Dissociation of 2DG antinociception and 2DG hyperphagia. As indicated previously, whereas 2DG antinociception displays tolerance and cross-tolerance with morphine, 2DG hyperphagia is unaffected by either manipulation (1,5,28). Further, the hyperphagic, but not the antinociceptive response, to 2DG is reduced by naloxone pretreatment (4,19). The potentiation of 2DG antinociception by ZOL is similar to effects upon 2DG antinociception exerted by the muscarinic receptor antagonist scopolamine and the dopamine receptor antagonist chlorpromazine (6,27), and contrasts with the reduction of 2DG antinociception by the dopamine receptor agonist apomorphine (2). In contrast, 2DG hyperphagia was reduced by blockade of dopamine and muscarinic receptors (27,29). The present data indicate that the brain-penetrating H_2 receptor antagonist ZOL potentiated 2DG antinociception, but failed to affect 2DG hyperphagia. HA typically acts to reduce food intake (9,18). In contrast, blockade of H_1, but not H_2, receptors stimulates feeding (20,22,23,25), as does

α-fluoromethylhistadine, a histamine synthesis inhibitor (24). The present observation that ZOL failed to alter basal intake or 2DG hyperphagia extends these observations.

In conclusion, 2DG antinociception, but not 2DG hyperphagia, was enhanced by either simultaneous or prior treatment with the brain-penetrating H_2 receptor antagonist ZOL. These results support previous studies (15) showing that H_2 receptors can contribute to both pro- and antinociceptive mechanisms. If both mechanisms are operative after treatment with MOR, as suggested by previous studies (15), then the ZOL-induced potentiations of 2DG antinociception may be a useful tool for understanding the mechanism(s) of the biphasic actions of ZOL on μ-opiate antinociception.

NOTE ADDED IN PROOF

Large zolantidine doses (20–40 mg/kg) potentiate opioid-mediated swim antinociception (Oluyami, A. O.; Hart, S. L. Involvement of histamine in nalaxone-resistant and nalaxone-sensitive models of swim stress–induced antinociception in the mouse).

REFERENCES

1. Bodnar, R. J.; Kelly, D. D.; Brutus, M.; Glusman, M. Chronic 2-deoxy-D-glucose treatment: Adaptation of its analgesic, but not hyperphagic, properties. Pharmacol. Biochem. Behav. 9:763–768; 1978.
2. Bodnar, R. J.; Kelly, D. D.; Brutus, M.; Greenman, C. B.; Glusman, M. Reversal of stress-induced analgesia by apomorphine, but not amphetamine. Pharmacol. Biochem. Behav. 13:171–175; 1980.
3. Bodnar, R. J.; Kelly, D. D.; Brutus, M.; Mansour, A.; Glusman, M. 2-Deoxy-D-glucose-induced decrements in operant and reflex pain thresholds. Pharmacol. Biochem. Behav. 9:543–549; 1978.
4. Bodnar, R. J.; Kelly, D. D.; Glusman, M. 2-Deoxy-D-glucose analgesia: Influences of opiate and non-opiate factors. Pharmacol. Biochem. Behav. 11:297–301; 1979.
5. Bodnar, R. J.; Kramer, E.; Simone, D. A.; Kirchgessner, A. L.; Scalisi, J. Dissociation of analgesic and hyperphagic responses following 2-deoxy-D-glucose. Int. J. Neurosci. 24:225–236; 1983.
6. Bodnar, R. J.; Nicotera, N. Neuroleptic and analgesic interactions upon pain activity measures. Pharmacol. Biochem. Behav. 16:411–416; 1982.
7. Brown, J. Effects of 2-deoxy-D-glucose on carbohydrate metabolism: A review of the literature and studies in the rat. Metabolism 11:1098–1112; 1962.
8. Calcutt, C. R.; Ganellin, C. R.; Griffiths, R.; Leigh, B. K.; Maguire, J. P.; Mitchell, R. C.; Mylek, M. E.; Parsons, M. E.; Smith, I. R.; Young, R. C. Zolantidine (SKF95282) is a potent, selective, brain penetrating histamine H_2-receptor antagonist. Br. J. Pharmacol. 93:69–78; 1988.
9. Clineschmidt, B. V.; Lotti, V. J. Histamine: Intraventricular injection suppresses ingestive behavior in the cat. Arch. Int. Pharmacodyn. 206:288–298; 1973.
10. D'Amour, F. E.; Smith, D. L. A method for determining loss of pain sensation. J. Pharmacol. Exp. Ther. 72:74–79; 1941.
11. Evans, W. O. A new technique for the investigation of some analgesic drugs on a reflexive behavior in the rat. Psychopharmacology (Berl.) 2:318–325; 1961.

12. Glick, S. D.; Crane, L. A. Opiate-like and abstinence-like effects of intracerebral histamine administration in rats. Nature 273:547–549; 1978.
13. Gogas, K. R.; Hough, L. B. Effects of zolantidine, a brain-penetrating H_2-receptor antagonist, on naloxone-sensitive and naloxone-insensitive forms of footshock-induced analgesia. Neuropharmacology 27:357–362; 1988.
14. Gogas, K. R.; Hough, L. B.; Inhibition of naloxone-resistant antinociception by centrally administered H_2-antagonists. J. Pharmacol. Exp. Ther. 248:262–267; 1989.
15. Gogas, K. R.; Hough, L. B.; Eberle, N. B.; Lyon, R. A.; Glick, S. D.; Ward, S. J.; Young, R. C.; Parsons, M. E. A role for histamine and H_2 receptors in opioid antinociception. J. Pharmacol. Exp. Ther. 250:476–484; 1989.
16. Himsworth, R. L. Hypothalamic control of adrenaline secretion in response to insufficient glucose. J. Physiol. 198:451–465; 1970.
17. Hough, L. B. Cellular localization and possible functions for brain histamine: Recent progress. Prog. Neurobiol. 30:469–505; 1988.
18. Itowi, N.; Nagai, K.; Nakagawa, H.; Watanabe, T.; Wada, H. Changes in the feeding behavior of rats elicited by histamine infusion. Physiol. Behav. 44:221–226; 1988.
19. Lowy, M. T.; Maickel, R. P.; Yim, G. K. W. Naloxone reduction of stress-related feeding. Life Sci. 26:2113–2118; 1980.
20. Ookuma, K.; Yoshimatsu, H.; Sakata, T.; Fujimoto, K.; Fukagawa, K. Hypothalamic sites of neuronal histamine action on food intake by rats. Brain Res. 490:268–275; 1989.
21. Panula, P.; Pirvola, U.; Auvinen, S.; Airaksinen, M. S. Histamine-immunoreactive nerve fibers in the rat brain. Neuroscience 28:585–610; 1989.
22. Sakata, T.; Fukagawa, K.; Fujimoto, K.; Yoshimatsu, H.; Wada, H. Feeding induced by blockade of histamine₁-receptor in rat brain. Experentia 44:216–218; 1988.
23. Sakata, T.; Fukagawa, K.; Ookuma, K.; Fujimoto, K.; Yoshimatsu, H.; Yamatodani, A.; Wada, H. Modulation of neuronal histamine in control of food intake. Physiol. Behav. 44:539–543; 1988.

24. Sakata, T.; Fukagawa, K.; Ookuma, K.; Fujimoto, K.; Yoshimatsu, H.; Yamatodani, A.; Wada, H. Hypothalamic neuronal histamine modulates ad libitum feeding by rats. Brain Res. 537: 303–306; 1990.
25. Sakata, T.; Ookuma, K.; Fukagawa, K.; Fujimoto, K.; Yoshimatsu, H.; Shiraishi, T.; Wada, H. Blockade of the histamine$_1$-receptor in the rat ventromedial hypothalamus and feeding elicitation. Brain Res. 441:403–407; 1988.
26. Smith, G. P.; Epstein, A. N. Increased feeding response to decreased glucose utilization in the rat and monkey. Am. J. Physiol. 217:1083–1087; 1969.
27. Sperber, E. S.; Kramer, E.; Bodnar, R. J. Effects of muscarinic receptor antagonism upon two forms of stress-induced analgesia. Pharmacol. Biochem. Behav. 25:171–179; 1986.
28. Spiaggia, A.; Bodnar, R. J.; Kelly, D. D.; Glusman, M. Opiate and non-opiate mechanisms of stress-induced analgesia: Cross-tolerance between stressors. Pharmacol. Biochem. Behav. 10: 761–765; 1979.
29. Stricker, E. M.; Zigmond, M. J. Effects on homeostasis of intraventricular injection of 6-hydroxydopamine in rats. J. Comp. Physiol. Psychol. 86:973–994; 1974.
30. Wick, A. N.; Drury, D. R.; Nakada, H. I.; Wolfe, J. B. Localization of the primary metabolic block produced by 2-deoxy-D-glucose. J. Biol. Chem. 224:963–979; 1957.