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Naltrexone, Serotonin Receptor Subtype Antagonists, and Glucoprivic Intake: 1. 2-Deoxy-D-Glucose

IWONA W. BECZKOWSKA,* JAMES E. KOCH† AND RICHARD J. BODNAR*†[1]

*Department of Psychology and Neuropsychology Doctoral Subprogram
Queens College, City University of New York, Flushing, NY 11367
†Department of Pharmacology, Mount Sinai School of Medicine, New York, NY 10029

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BECZKOWSKA, I. W., J. E. KOCH AND R. J. BODNAR. *Naltrexone, serotonin receptor subtype antagonists, and glucoprivic intake: 1. 2-Deoxy-D-glucose.* PHARMACOL BIOCHEM BEHAV 42(4) 661-670, 1992.—Inhibition of deprivation-induced intake by naloxone was significantly enhanced by the 5-hydroxytryptamine$_3$ (5-HT$_3$) antagonist ICS-205,930. Interactions between naloxone and either the general 5-HT antagonist methysergide or the 5-HT$_2$ antagonist ritanserin or ketanserin produced smaller effects. The present study evaluated whether 2-deoxy-D-glucose (2DG, 400 mg/kg) hyperphagia was affected by methysergide (0.5-5 mg/kg), ritanserin (0.25-2.5 mg/kg), or ICS-205,930 (0.5-5 mg/kg) alone or in combination with naltrexone (0.25 and 2.5 mg/kg). Only ICS-205,930 stimulated spontaneous intake for up to 4 h in the light cycle. Only ritanserin (1.25 mg/kg) transiently reduced 2DG hyperphagia. The dose-dependent decreases in 2DG hyperphagia by naltrexone were significantly enhanced by the dose range of ICS-205,930. The inhibition of 2DG hyperphagia by the low naltrexone dose was enhanced by methysergide (5 mg/kg) and ritanserin (1.25 mg/kg). These data suggest that the 5-HT$_3$ receptor primarily interacts with opioid systems to modulate 2DG hyperphagia and that one possible locus of interaction is in the caudal brainstem.

2-Deoxy-D-glucose hyperphagia Naltrexone Serotonin receptors Methysergide
Ritanserin ICS-205,930 Rats

THE inhibitory effects of serotonin (5-HT) and its reuptake inhibitors upon food intake are well known [see reviews: (7,8,)]. Multiple 5-HT receptors [see reviews: (48,49)] have been classified into 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1C}$, 5-HT$_{1D}$, 5-HT$_2$, and 5-HT$_3$ subtypes. Whereas 5-HT$_{1A}$ receptor agonists stimulate feeding through activation of 5-HT autoreceptors (15, 16,29,30), 5-HT$_{1B}$, 5-HT$_{1C}$, and 5-HT$_2$ receptor agonists inhibit intake (28,34,54,58,59). 5-HT receptor antagonists do not produce such consistent effects. Methysergide, a nonselective 5-HT antagonist, marginally reduces deprivation-induced feeding (4,18) and actually stimulates intake in well-satiated rats (14,19). Whereas the 5-HT$_2$ antagonists ritanserin and ketanserin typically fail to alter spontaneous intake [(14,24, 34,43,57), but see (19)], the latter marginally reduces deprivation-induced feeding (4). The 5-HT$_3$ antagonist ICS-205,930 failed to affect deprivation-induced feeding (4), but blocked anorexia induced by amino acid imbalance (22).

Both general (10,11,20) and specific [μ: (3); μ_1: (60); κ: (1,40) opioid receptor antagonists reduce spontaneous and deprivation intake. Recent studies (4,18) examined interactions between 5-HT and opioid systems in modulating food intake because: a) 5-HT and opioid antagonists each decrease fat consumption (33,42); b) medial and paraventricular hypothalamic nuclei mediate both 5-HT and naloxone hypophagia (39,56,66,68); and c) both opioid and 5-HT effects are most pronounced in the dark cycle (5,39). Peripheral 5-hydroxytryptophan significantly potentiated naloxone hypophagia in food-deprived rats (18). Our laboratory found that the 5-HT$_3$ antagonist ICS-205,930 potentiated naloxone hypophagia in food-deprived rats more potently than ritanserin, ketanserin, and methysergide (4).

The above studies suggest that 5-HT antagonist effects upon ingestive behavior appear to depend upon intake condition. Animals will overeat following glucoprivation induced by the antimetabolic glucose analog 2-deoxy-D-glucose (2DG). 2DG prevents glycolysis (27,67) and its hyperphagic effects are thought to be due to diminished glucose utilization (61,62), which activates brain glucoreceptors even in the absence of hyperglycemia (17,51,52). Opioid control of 2DG hyperphagia has been inferred by observations of reductions in this re-

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

sponse following general (41) and specific [μ: (3); κ: (1)] opioid antagonists.

The present study extended the potential interactions between opioid and 5-HT antagonists upon food intake by examining antagonist effects of methysergide (general), ritanserin (5-HT_2), and ICS-205,930 (5-HT_3) upon: a) spontaneous feeding in the light cycle; b) 2DG hyperphagia; and c) naltrexone's inhibition of 2DG hyperphagia. The following study (37) examines interactive effects of opioid and 5-HT receptor subtype antagonists upon hyperphagia induced by insulin glucoprivation.

METHOD

Adult, male, albino Sprague-Dawley rats (300-550 g; Charles River Laboratories, Wilmington, MA) were maintained individually in wire mesh cages on a 12 L : 12 D cycle with Purina Rat Chow and water available ad lib. In all experiments, rats were initially monitored for daily body weight and food intake over 3 days to establish normal intake patterns. The protocols described in this experiment were approved by the Queens College Institutional Care and Use Committee.

Free Feeding

At 1-3 h into the light cycle, rats received a vehicle injection (1 ml/kg, n = 39) in 1 week and either methysergide (5 mg/kg, IP, Sandoz Labs, East Hanover, NJ, n = 13), ritanserin (2.5 mg/kg, SC, Janssen, Beerse, Belgium, n = 13), or ICS-205,930 (5 mg/kg, SC, Sandoz, Basle, Switzerland, n = 13) in a second test week. Intake of preweighed food pellets, adjusted for spillage, was measured at 2, 4, and 6 h after injection. Methysergide was dissolved in 0.9% normal saline. Ritanserin was initially prepared in 100% methanol at a concentration of 10 mg/ml and then titrated with 0.9% normal saline to its desired concentration 0.5 h prior to treatment. ICS-205,930 was initially prepared in 100% dimethyl sulfoxide (DMSO) at a concentration of 10 mg/ml and then titrated with 0.9% normal saline to its desired concentration 0.5 h prior to treatment. Vehicle injections for each group consisted of their respective solute and injection route; these treatments failed to differ from each other, and were pooled. The doses and injection intervals were chosen in this and subsequent protocols on the basis of these antagonist effects upon deprivation-induced feeding itself and their interaction with naloxone upon deprivation-induced feeding (4).

2DG Feeding

At 1-3 h into the light cycle, rats received subsets of the following injection conditions, summarized in Table 1 (section A). In each condition, food intake was determined with preweighed food pellets at 2, 4, and 6 h after the second injection. Rats received a maximum of five pairs of injections at 15-min intervals according to an incompletely counterbalanced design with a minimum of 1 week elapsing between different experimental conditions. The 2DG dose (Sigma Chemical Co., St. Louis, MO, 400 mg/kg, IP) was chosen to elicit a significant although submaximal hyperphagia to allow observation of any potential antagonist-induced increases or decreases in 2DG hyperphagia.

Serotonin Antagonist/Naltrexone Interactions upon 2DG Feeding

At 1-3 h into the light cycle, rats received subsets of the following injection conditions, summarized in Table 1 (section B). Food intake was determined with preweighed food pellets at 2, 4, and 6 h after the last injection. In this paradigm, rats received a maximum of 10 triads of injections at 15-min intervals according to an incompletely counterbalanced design with a minimum of 1 week elapsing between different experimental conditions. A previous study (4) indicated that long-term changes in intake over a 10-week interval does not occur in young, although mature, rats. Further, repeated administration fails to alter the magnitude of 2DG hyperphagia (9). Naltrexone doses (Sigma, 0.25 and 2.5 mg/kg, SC) were chosen to produce partial antagonism of 2DG hyperphagia to allow potential antagonist-induced increases or decreases in opioid effects.

TABLE 1

PROTOCOLS OF SEROTONIN ANTAGONIST EFFECTS AND SEROTONIN ANTAGONIST-OPIOID ANTAGONIST EFFECTS UPON 2DG HYPERPHAGIA

A. Serotonin Antagonists and 2DG Hyperphagia

First Injection (mg/kg)	Second Injection	n
Vehicle	Vehicle	26
Vehicle	2DG	26
Methysergide 0.5	2DG	6
Methysergide 5.0	2DG	8
Methysergide 10	2DG	6
Ritanserin 0.25	2DG	7
Ritanserin 1.25	2DG	7
Ritanserin 2.5	2DG	9
ICS-205,930 0.5	2DG	7
ICS-205,930 2.5	2DG	7
ICS-205,930 5.0	2DG	9

B. Naltrexone, Serotonin Antagonists, and 2DG hyperphagia

First Injection (mg/kg)	Second Injection (mg/kg)	Third Injection	n
Vehicle	Vehicle	Vehicle	21
Vehicle	Vehicle	2DG	21
Vehicle	Naltrexone 0.25	2DG	21
Vehicle	Naltrexone 2.5	2DG	21
Methysergide 0.5	Naltrexone 0.25	2DG	7
Methysergide 2.5	Naltrexone 0.25	2DG	7
Methysergide 5.0	Naltrexone 0.25	2DG	6
Methysergide 0.5	Naltrexone 2.5	2DG	7
Methysergide 2.5	Naltrexone 2.5	2DG	7
Methysergide 5.0	Naltrexone 2.5	2DG	7
Ritanserin 0.25	Naltrexone 0.25	2DG	6
Ritanserin 1.25	Naltrexone 0.25	2DG	7
Ritanserin 2.5	Naltrexone 0.25	2DG	7
Ritanserin 0.25	Naltrexone 2.5	2DG	7
Ritanserin 1.25	Naltrexone 2.5	2DG	7
Ritanserin 2.5	Naltrexone 2.5	2DG	7
ICS-205,930 0.5	Naltrexone 0.25	2DG	7
ICS-205,930 2.5	Naltrexone 0.25	2DG	7
ICS-205,930 5.0	Naltrexone 0.25	2DG	7
ICS-205,930 0.5	Naltrexone 2.5	2DG	7
ICS-205,930 2.5	Naltrexone 2.5	2DG	7
ICS-205,930 5.0	Naltrexone 2.5	2DG	7

Statistical Analyses

Split-plot analyses of variance (ANOVAs) assessed significant effects upon individual intake points. Dunnett and Dunn

comparisons were used to discern respective differences between vehicle and drug treatments and between serotonin antagonists and either 2DG or naltrexone/2DG treatments.

RESULTS

Serotonin Receptor Subtype Antagonists and Free Feeding

Significant differences in intake were observed among groups after 2, $F(3, 74) = 4.15$, $p < 0.009$, and 4, $F = 3.50$, $p < 0.02$, h, but not after 6 ($F = 1.74$) h. Whereas methysergide and ritanserin failed to alter spontaneous intake across this time course, ICS-205,930 significantly stimulated food intake after 2 (142%) and 4 (92%) h (Fig. 1).

Methysergide and 2DG Hyperphagia

Significant differences in intake were observed among groups after 2, $F(4, 67) = 17.33$, $p < 0.001$, 4, $F = 21.21$, $p < 0.0001$, and 6, $F = 14.11$, $p < 0.0001$, h. Methysergide failed to alter the significant increases in intake induced by 2DG across the 6-h time course (Fig. 2A).

Ritanserin and 2DG Hyperphagia

Significant differences in intake were observed among groups after 2, $F(4, 70) = 14.40$, $p < 0.0001$, 4, $F = 18.71$, $p < 0.0001$, and 6, $F = 10.38$, $p < 0.0001$, h. Ritanserin failed to alter 2DG hyperphagia except for a transient (2 h) reduction (51%) induced by the highest ritanserin dose (Fig. 2B).

ICS-205,930 and 2DG Hyperphagia

Significant differences in intake were observed among groups after 2, $F(4, 70) = 12.45$, $p < 0.0001$, 4, $F = 17.71$, $p < 0.0001$, and 6, $F = 11.79$, $p < 0.0001$, h. ICS-205,930 failed to alter 2DG hyperphagia over the 6-h time course (Fig. 2C).

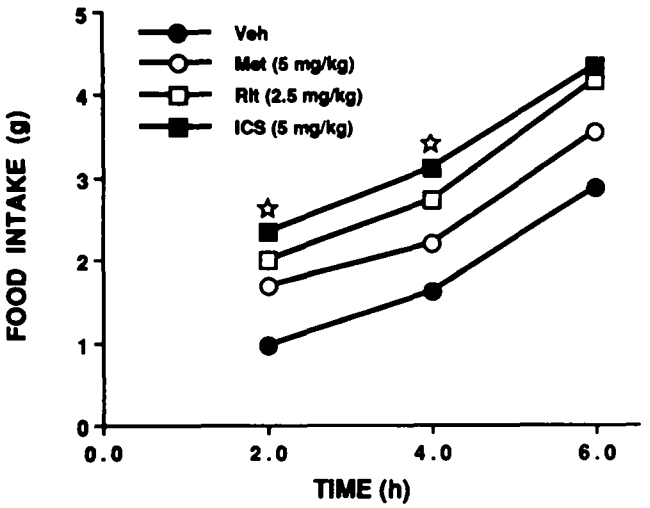

FIG. 1. Alterations in spontaneous food intake following systemic administration of vehicle (Veh), methysergide (Met), ritanserin (Rit), and ICS-205,930 (ICS). (☆) significant increases in food intake relative to the corresponding Veh condition (Dunnett comparisons, $p < 0.05$).

Methysergide, 2DG Hyperphagia, and Naltrexone (0.25 mg/kg)

Significant differences in intake were observed among groups after 2, $F(5, 77) = 7.36$, $p < 0.0001$, 4, $F = 15.18$, $p < 0.0001$, and 6, $F = 23.82$, p , 0.0001, h. Whereas naltrexone (0.25 mg/kg) significantly inhibited 2DG hyperphagia by 36% after 2 h (Fig. 3, upper panel), methysergide (5 mg/kg) significantly enhanced (78%) this inhibition. 2DG hyperphagia after 4 h was unaffected by either naltrexone alone or naltrexone paired with methysergide. In contrast, 2DG hyperphagia was significantly potentiated after 6 h by naltrexone alone (87%) and by naltrexone paired with methysergide doses of 0.5 (67%) and 5 (115%) mg/kg.

Naltrexone (2.5 mg/kg). Significant differences in intake were observed among groups after 2, $F(5, 78) = 13.19$, $p < 0.0001$, 4, $F = 13.18$, $p < 0.0001$, and 6, $F = 15.53$, $p < 0.0001$, h. The significant inhibition (67%) of 2DG hyperphagia by naltrexone (2.5 mg/kg) after 2 h was not affected by methysergide (Fig. 3, lower panel). Naltrexone alone or naltrexone paired with methysergide failed to alter 2DG hyperphagia at 4 h. However, methysergide (2.5 mg/kg) paired with naltrexone (2.5 mg/kg) significantly potentiated 2DG hyperphagia by 53% at 6 h.

Ritanserin, 2DG Hyperphagia, and Naltrexone (0.25 mg/kg)

Significant differences in intake were observed among groups after 2, $F(5, 77) = 8.51$, $p < 0.0001$, 4, $F = 16.05$, $p < 0.0001$, and 6, $F = 18.15$, $p < 0.0001$, h. Naltrexone's (0.25 mg/kg, 36%) inhibition of 2DG hyperphagia after 2 h was significantly enhanced by the intermediate (1.25 mg/kg) dose of ritanserin 95% (Fig. 4, upper panel). Naltrexone failed to alter 2DG hyperphagia after 4 h either in the presence or absence of ritanserin. However, naltrexone (0.25 mg/kg) paired with the low (0.25 mg/kg) ritanserin dose potentiated 2DG hyperphagia (74%) after 6 h.

Naltrexone (2.5 mg/kg). Significant differences in intake were observed among groups after 2, $F(5, 78) = 11.39$, $p < 0.0001$, 4, $F = 12.20$, $p < 0.0001$, and 6, $F = 10.00$, $p < 0.0001$, h. Ritanserin failed to alter any changes in 2DG hyperphagia induced by the higher dose of naltrexone (Fig. 4, lower panel).

ICS-205,930, 2DG Hyperphagia, and Naltrexone (0.25 mg/kg)

Significant differences in intake were observed among groups after 2, $F(5, 78) = 13.18$, $p < 0.0001$, 4, $F = 14.91$, $p < 0.0001$, and 6, $F = 18.22$, $p < 0.0001$, h. Naltrexone's (0.25 mg/kg, 36%) inhibition of 2DG hyperphagia after 2 h was significantly enhanced by the 0.5 (76%), 2.5 (99%), and 5 (99%) doses of ICS-205,930 (Fig. 5, upper panel). Naltrexone failed to alter 2DG hyperphagia after 4 h either in the presence or absence of ICS-205,930. However, 2DG hyperphagia was significantly potentiated at 6 h by naltrexone (0.25 mg/kg) paired with ICS-205,930 doses of 0.5 (69%), 2.5 (102%), and 5 (86%) mg/kg.

Naltrexone (2.5 mg/kg). Significant differences in intake were observed among groups after 2, $F(5, 78) = 17.83$, $p < 0.0001$, 4, $F = 9.77$, $p < 0.0001$, and 6, $F = 9.72$, $p < 0.0001$, h. Naltrexone's (2.5 mg/kg, 67%) inhibition of 2DG hyperphagia after 2 h was significantly potentiated by pretreatment with ICS-205,930 doses of 2.5 (92%) and 5 (94%) mg/kg (Fig. 5, lower panel). Further, whereas this naltrexone dose failed to alter 2DG hyperphagia after 4 h (10% inhibi-

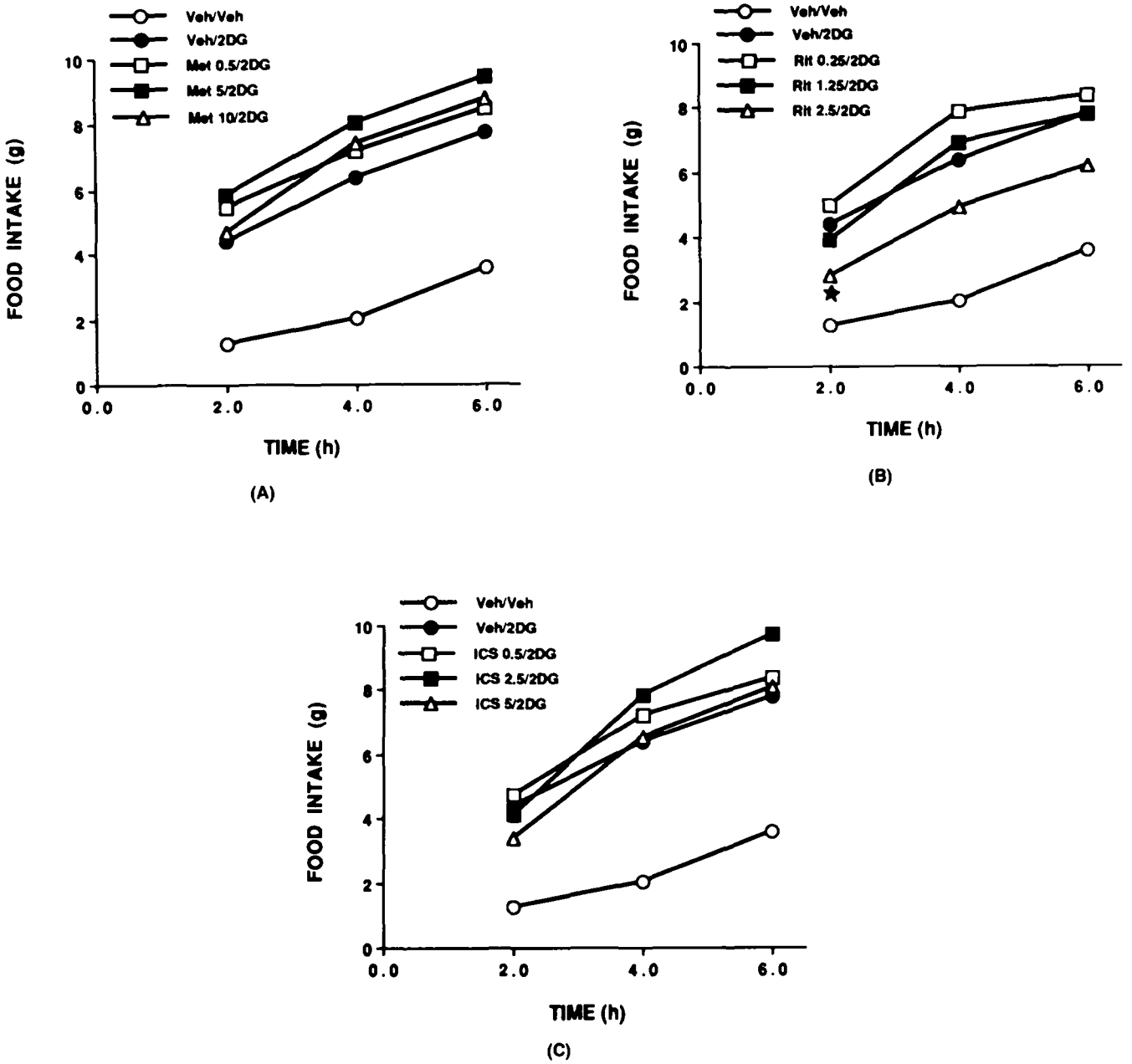

FIG. 2. Alterations in food intake in vehicle (Veh) and 2-deoxy-D-glucose (2DG)-treated rats following pretreatment with methysergide (Met: 0.5–5 mg/kg, A), ritanserin (Rit: 0.25–2.5 mg/kg, B) and ICS-205,903 (ICS: 0.5–5 mg/kg, C). 2DG produced significant hyperphagia across the 6-h time course. (★) significant reductions in 2DG hyperphagia relative to the corresponding veh pretreatment (Dunett comparisons, $p < 0.05$).

tion) pairing naltrexone with the high (5 mg/kg) dose of ICS-205,930 significantly reduced 2DG hyperphagia by 37% at this interval. The significant 2DG hyperphagia at 6 h failed to be affected by naltrexone and ICS-205,930 pretreatments.

DISCUSSION

The following major findings were observed in the present study. First, the 5-HT_3 receptor antagonist ICS-205,930 significantly stimulated spontaneous food intake during the light cycle for up to 4 h after administration. Increased intake following either the general 5-HT receptor antagonist methysergide or the 5-HT_2 receptor antagonist ritanserin failed to differ significantly from vehicle pretreatment. Second, 2DG hyperphagia was significantly, but only transiently (2 h), reduced following the highest dose of ritanserin. Neither methysergide nor ICS-205,930 altered 2DG hyperphagia themselves. Third, naltrexone produced significant dose-dependent decreases in 2DG hyperphagia after 2 h, but significantly increased 2DG hyperphagia after 6 h following pretreatment with a low (0.25 mg/kg) naltrexone dose. Fourth, naltrexone's inhibition of 2DG hyperphagia after 2 h was significantly enhanced by all

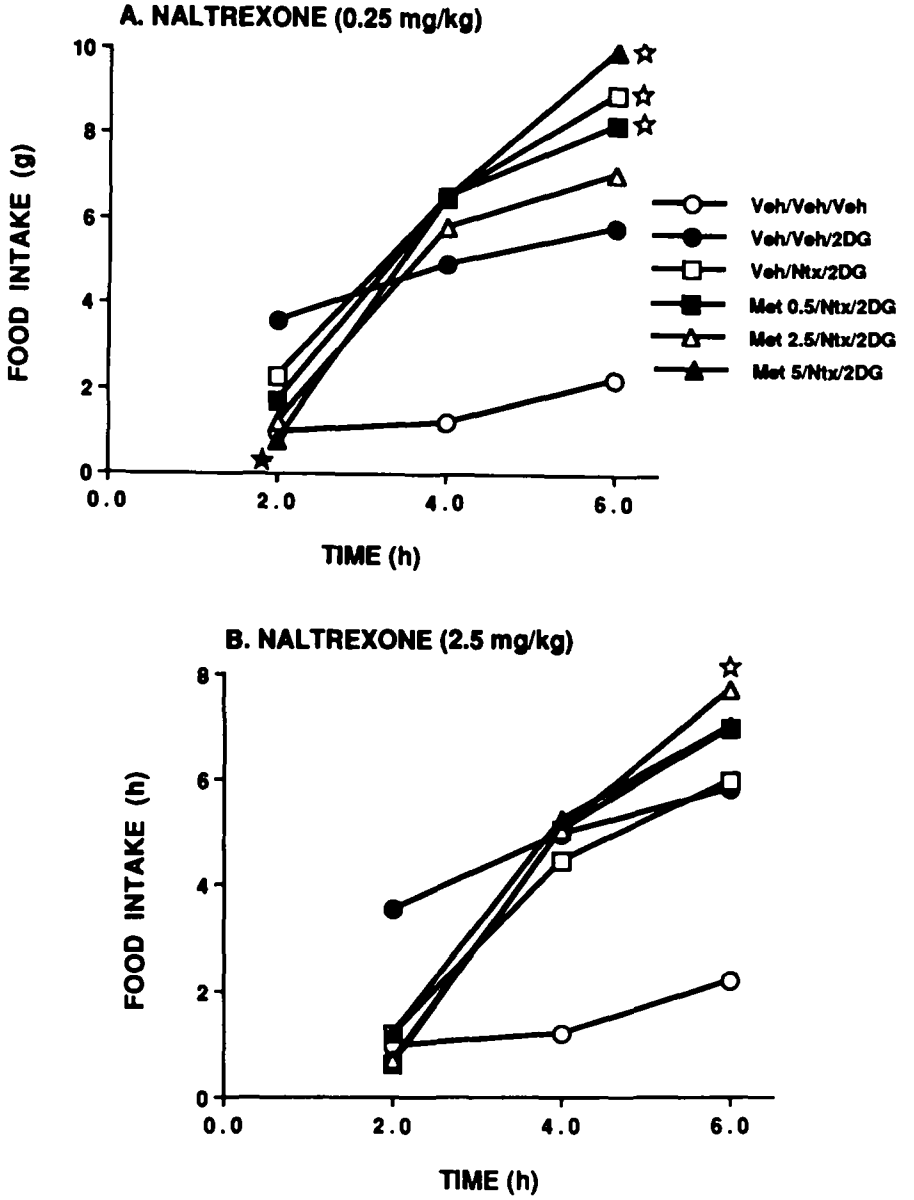

FIG. 3. Alterations in food intake in 2DG-treated rats following paired pretreatment with naltrexone (Ntx) and methysergide (Met: 0.5-5 mg/kg). 2DG produced significant hyperphagia across the 6-h time course. Naltrexone doses of 0.25 mg/kg (top panel) and 2.5 mg/kg (bottom panel) significantly inhibited 2DG hyperphagia by 36 and 67%, respectively, after 2 h. (★) significant enhancement of naltrexone's inhibition of 2DG hyperphagia by 5-HT receptor subtype antagonists in this and subsequent figures (Dunnett comparisons, $p < 0.05$). (☆) significant increases in 2DG hyperphagia after 6 h following naltrexone alone or naltrexone paired with 5-HT receptor subtype antagonists in this and subsequent figures (Dunnett comparisons, $p < 0.05$).

ICS-205,930 doses; cotreatment of the high naltrexone and ICS-205,930 doses also suppressed 2DG hyperphagia after 4 h. In contrast, cotreatment of the low naltrexone dose with either methysergide (5 mg/kg) or ritanserin (1.25 mg/kg) significantly enhanced naltrexone's inhibition of 2DG hyperphagia only after 2 h. Fifth, significant increases in 2DG hyperphagia occurred after 6 h in rats treated with the low naltrexone dose and either methysergide (0.5 and 5 mg/kg), ritanserin (0.25 mg/kg), or ICS-205,930 (0.5, 2.5, and 5 mg/kg). Taken together, it appears that whereas methysergide, ritanserin, and ICS-205,930 fail to appreciably alter 2DG hyperphagia themselves, they significantly potentiate the inhibitory effects of naltrexone upon 2DG hyperphagia. In this regard, the 5-HT_3 antagonist ICS-205,930 appears to possess the most profound effects.

The role of endogenous opioid systems in modulating 2DG hyperphagia has been confirmed based upon the ability of naloxone to inhibit this effect (41). Specific opioid receptor

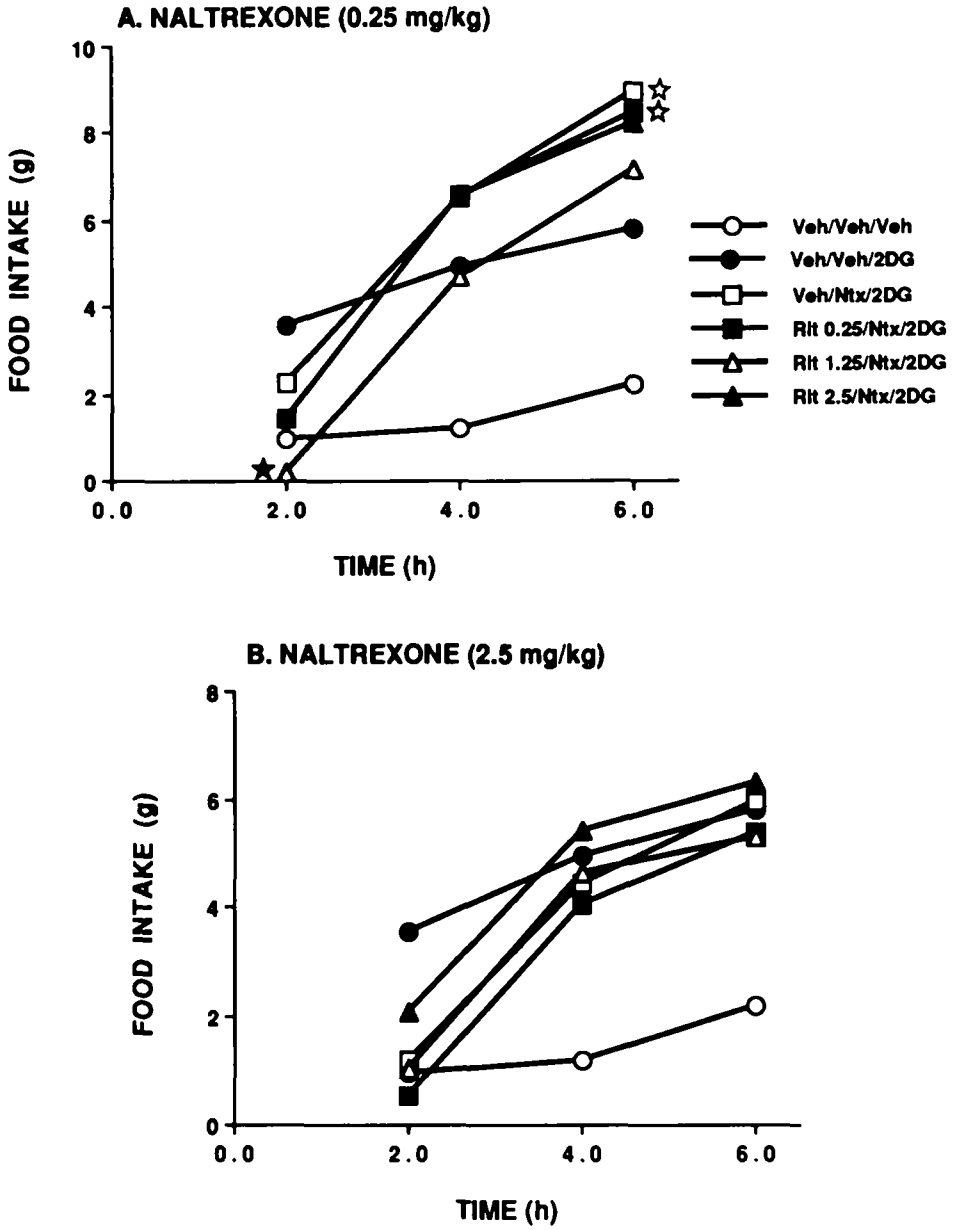

FIG. 4. Alterations in food intake in 2DG-treated rats following paired pretreatment with naltrexone (Ntx) and ritanserin (Rit: 0.25-2.5 mg/kg). Ritanserin significantly enhanced naltrexone's inhibition of 2DG hyperphagia after 2 h and potentiated 2DG hyperphagia after 6 h when paired with naltrexone. (★ and ☆) defined in Fig. 3.

subtypes have been assessed with 2DG hyperphagia inhibited by the μ-selective antagonist β-funaltrexamine and the κ-selective antagonist norbinaltorphamine, but not by the μ_1-selective antagonist naloxonazine or the δ-selective antagonist ICI174864 or [D-Ala^2,Leu^5,Cys^6]-enkephalin (1-3,32,60). These data suggest that κ and μ_2 opioid binding sites are responsible for these effects. The present study found that the low (0.25 mg/kg) dose of naltrexone produced biphasic effects upon 2DG hyperphagia, initially reducing intake after 2 h, failing to exert effects after 4 h, and potentiating 2DG hyperphagia after 6 h. These data suggest that 2DG hyperphagia was increased by a rebound response to the low dose of naltrexone. Such a response has not been observed in previous studies. Lowy and coworkers (41) initially observed reductions in 2DG hyperphagia following 1- to 10-mg/kg doses of naloxone after 3 h, but did not examine effects over a longer time course. Our laboratory (60) found that intravenous administration of naloxonazine (10 mg/kg) failed to alter 2DG hyperphagia after 2 h and significantly potentiated this response by 39% after 4 h. In contrast, central administration of either the μ-selective antagonist β-funaltrexamine or the κ-selective antagonist norbinaltorphamine reduced 2DG hyperphagia

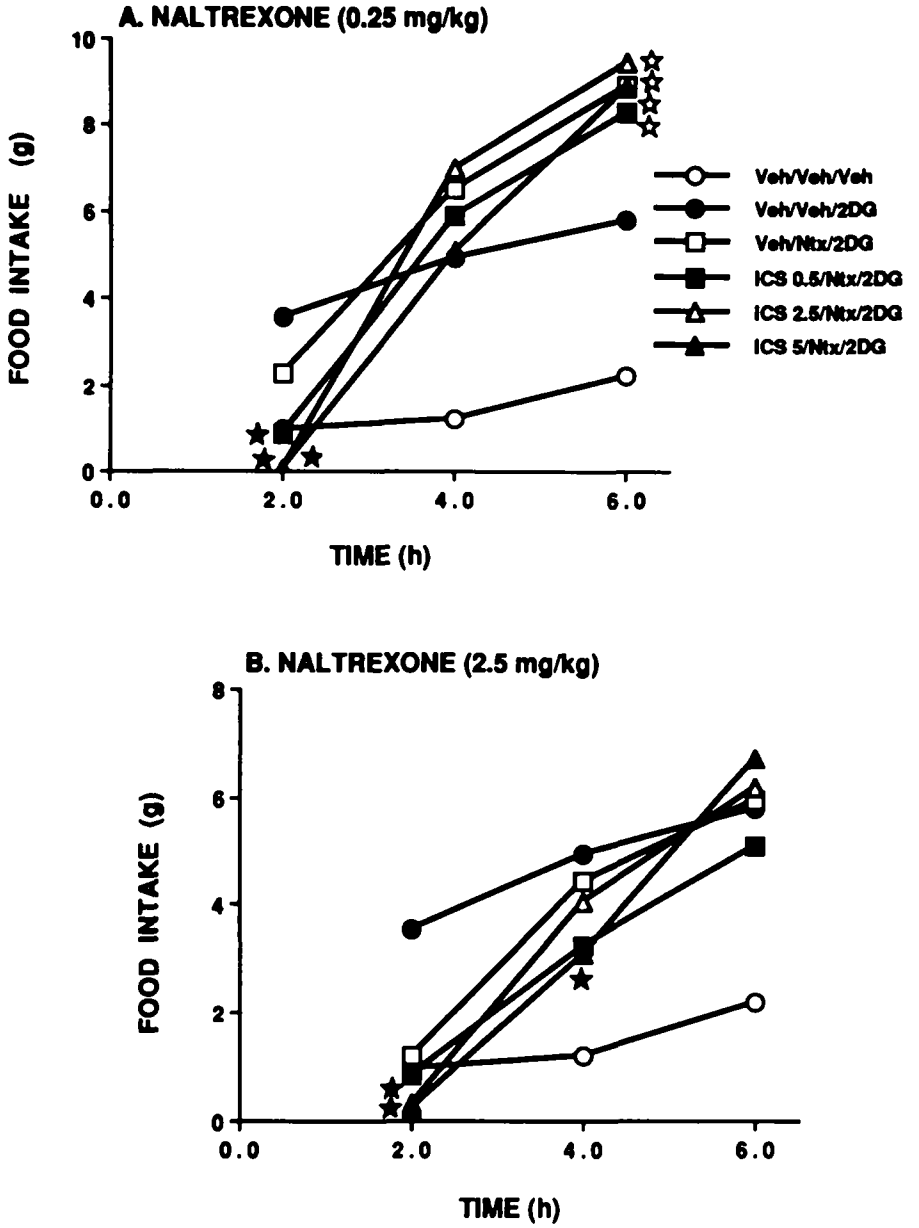

FIG. 5. Alterations in food intake in 2DG-treated rats following paired pretreatment with naltrexone (Ntx) and ICS-205,930 (ICS: 0.5–5 mg/kg). ICS-205,930 significantly enhanced naltrexone's inhibition of 2DG hyperphagia after 2 and 4 h and potentiated 2DG hyperphagia after 6 h when paired with naltrexone. (★ and ☆) defined in Fig. 3.

over a 6-h time course (1,3). Whether the presently observed increase in 2DG hyperphagia by a low dose of naltrexone represents either a rebound response following low levels of opioid receptor blockage or a specific effect of a particular opioid receptor subtype should be examined further.

The 5-HT_3 receptor antagonist ICS-205,930 significantly enhanced naltrexone's inhibition of 2DG hyperphagia without altering 2DG hyperphagia itself. These effects parallel the ability of ICS-205,930 to enhance naloxone's inhibition of hyperphagia following food deprivation without altering deprivation-induced feeding itself (4). Previous interactions between 5-HT_3 and opioid receptor systems include observations that ICS-205,930 significantly reduces antinociception induced by both the κ-receptor agonist U-50,488H (23,26) and 5-HT (21). The potentiations of opioid antagonist inhibition of 2DG hyperphagia by ICS-205,930 could be mediated through either central or peripheral processes. Although the observed interactions between 5-HT_3 and opioid antagonists occurred using systemic injections, the effects have been presumed to be centrally mediated for the following reasons. First, whereas the 5-HT_3 receptor was initially characterized in the periphery [see review: (50)], recent autoradiographic studies with highly selective 5-HT_3 ligands indicate that the highest density of 5-HT_3 receptors is localized to such areas as

the nucleus tractus solitarius (NTS), dorsal nucleus of the vagus, area postrema (AP), and substantia gelatinosa of the spinal trigeminal nucleus and the dorsal horn of the spinal cord (36,64,65). Second, general and specific opioid receptor antagonists produce hypophagic effects at low doses following central administration (1-3,40). Third, Carr and coworkers (12) recently demonstrated that microinjections of μ-selective, but not κ-selective, opioid receptor antagonists into the parabrachial region significantly reduce stimulation-induced feeding elicited from the lateral hypothalamus. The parabrachial area receives dense innervation from the NTS and AP (55,63), which contain high densities of 5-HT_3 receptors. Finally, the NTS, dorsal vagus, and AP are important sites for the induction of glucoprivic feeding (53), as well as for the maintenance of that response following AP lesions [(6,13), but see (31)].

The 5-HT_2 antagonist ritanserin and the general 5-HT antagonist methysergide also enhanced the inhibitory effects of naltrexone upon 2DG hyperphagia, although the magnitude and dose range of effects were more limited. These effects also parallel 5-HT and 5-HT_2 antagonist effects upon naloxone's suppression of deprivation-induced feeding (4). Interactions between general opioid and general serotonergic systems have been extensively studied in analgesic processes with brainstem and spinal serotonergic synapses participating in the expression of opiate analgesia [see reviews: (69,70)]. Interactions between 5-HT_2 receptors and opioid effects demonstrated that 5-HT_2 antagonists reduced both opiate and opioid-mediated forms of analgesia (25,35,45,46). Receptor autoradiography has revealed that 5-HT_2 biding sites are predominantly supraspinal and can be found in the frontal cortex, limbic system, basal ganglia, and dorsal raphe nucleus (38,44,47). Thus, one difference in the relative activities of 5-HT_3 and 5-HT_2 receptors in their interactions with opioid systems on deprivation and 2DG hyperphagia might be the site(s) at which they act. Given the high degree of selectivity of ritanserin and ICS-205,930 for 5-HT_2 and 5-HT_3 receptor sites, respectively [see review: (49)], it is unlikely that the effects of one of these antagonists was acting at the other's receptor site.

In conclusion, despite the relative inability of methysergide, ritanserin, and ICS-205,930 to alter 2DG hyperphagia these 5-HT antagonists significantly potentiated the hypophagic effects of naltrexone on this measure. As with the inhibitory 5-HT-opioid interactions observed for deprivation-induced intake (4), the 5-HT_3 antagonist ICS-205,930 displayed the largest and most potent interactive effects with naltrexone in inhibiting 2DG hyperphagia.

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