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Naltrexone, Dopamine Receptor Agonists and Antagonists, and Food Intake in Rats: 2. 2-Deoxy-D-Glucose

LYNN A. SCHAEFER,* JAMES E. KOCH† AND RICHARD J. BODNAR*[1]

*Neuropsychology Doctoral SubProgram, Department of Psychology, Queens College, CUNY, 65-30 Kissena Blvd., Flushing, NY 11367
†Department of Pharmacology, Mount Sinai School of Medicine, New York, NY 10029

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SCHAEFER, L. A., J. E. KOCH AND R. J. BODNAR. *Naltrexone, dopamine receptor agonists and antagonists, and food intake in rats. 2. 2-Deoxy-*D-glucose. PHARMACOL BIOCHEM BEHAV **49**(1) 205-211, 1994. — Significantly greater inhibition of deprivation-induced food intake occurs following cotreatment with naltrexone and either the D_1 antagonist, SCH-23390, the D_2 agonist, quinpirole, or the D_2 antagonist, haloperidol, relative to naltrexone alone. Cotreatment with the D_1 agonist, SKF-38393, failed to alter naltrexone's inhibition of deprivation-induced intake. The present study evaluated whether each of these D_1 and D_2 agonists and antagonists altered hyperphagia following 2-deoxy-D-glucose (2DG) themselves or in combination with naltrexone. Neither SKF-38393 (1-10 mg/kg) nor SCH-23390 (25-200 μg/kg) altered 2DG hyperphagia. Quinpirole (0.025-0.5 mg/kg) dose dependently decreased 2DG hyperphagia. 2DG hyperphagia was respectively increased and decreased by low (50 μg/kg) and high (500 μg/kg) doses of haloperidol. Cotreatment of SKF-38393 (0.1-1 mg/kg) and naltrexone potently enhanced the inhibition of 2DG hyperphagia relative to naltrexone alone. In contrast, cotreatment of naltrexone and either SCH-23390 (100-200 μg/kg) or quinpirole (0.025-0.05 mg/kg) inhibited 2DG hyperphagia in a manner similar to that of naltrexone alone. Finally, cotreatment of haloperidol (5-50 μg/kg) and naltrexone transiently enhanced the inhibition of 2DG hyperphagia relative to naltrexone alone.

2-Deoxy-D-glucose Naltrexone SKF-38393 SCH-23390 Quinpirole Haloperidol Opioids D_1 Receptor D_2 Receptor

RELATIONSHIPS between dopaminergic and opioid systems have been proposed for food intake [see review (14)]. In exploring such potential relationships, our laboratory (18) examined whether deprivation-induced food intake was differentially altered by cotreatment with the general opioid antagonist, naltrexone, and either D_1 receptor agonists (SKF-38393) (12) or antagonists (SCH-23390) (19) or D_2 receptor agonists (quinpirole) (1) or antagonists (haloperidol) (2). Both SKF-38393 and SCH-23390 significantly reduced deprivation-induced intake as indicated previously (21,22,29). Whereas quinpirole failed to affect deprivation-induced intake in the accompanying study, other D_2 agonists (lisuride and CQ 32-084) have reduced this form of intake previously (15). Finally, haloperidol exerted biphasic effects upon deprivation-induced intake, increasing the response at low doses and decreasing the response at higher doses. The former response correlates well with the dose range at which haloperidol acts as a specific D_2 antagonist (2). The latter response has been previously explained by disruptions in activational processes as well as motor deficits (27,30-32). The accompanying study (18) also found that naltrexone's inhibition of deprivation-induced food intake was enhanced by cotreatment with either the D_1 antagonist, SCH-23390, the D_2 agonist, quinpirole, or the D_2 antagonist, haloperidol.

The hyperphagic response following administration of 2-deoxy-D-glucose (2DG) (36) is reduced by both opioid (24) and dopaminergic (8) antagonists. There are some qualitative and quantitative differences in opioid modulation of hyperphagia following food deprivation and 2DG. First, general opioid antagonists typically produce greater degrees of inhibition of

[1] To whom requests for reprints should be addressed.

2DG hyperphagia relative to deprivation-induced intake at lower effective antagonist doses [e.g., (6,7,10,11,16,24)]. Second, different opioid receptor subtypes appear to modulate each of these responses. Deprivation-induced intake is potently reduced by mu and mu_1 opioid receptor antagonists (5,35), marginally reduced by kappa opioid antagonists (23), and unaffected by delta opioid antagonists (4). In contrast, both kappa and mu opioid receptor antagonism potently inhibited 2DG hyperphagia, while delta and mu_1 opioid antagonists are without effect (3-5,20,35).

Although selective D_1 and D_2 agonist and antagonist effects have been evaluated for food intake under spontaneous (25,27,31), deprivation (15,18,21,22,28,29), and palatable (25,29) conditions, dopamine receptor subtype effects upon 2DG hyperphagia have not been systematically evaluated except for reductions noted following haloperidol pretreatment (8). Therefore, the present study examined food intake in rats treated with 2DG following either SKF-38393, SCH-23390, quinpirole, or haloperidol alone and in combination with naltrexone.

METHOD

Forty adult, male albino Sprague-Dawley rats (approximately 250 g at the start of testing; 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 IACUC.

Drugs

Naltrexone (Sigma, St. Louis, MO) was dissolved in 0.9% normal saline and administered subcutaneously (SC). The D_1 agonist, SKF-38393, and the D_1 antagonist, SCH-23390 (Research Biochemicals, Natick, MA), were dissolved in water and administered intraperitoneally (IP). The D_2 agonist, quinpirole HCl (Research Biochemicals), was dissolved in water and administered SC. The D_2 antagonist, haloperidol (Research Biochemicals), was dissolved in DMSO and administered IP. 2DG (Sigma) was dissolved in 0.9% normal saline and administered IP. Each drug's route of injection was chosen for its maximal effectiveness in producing behavioral effects based upon the previously cited studies.

Protocols

At 5-7 h into the light cycle, four independent groups of 10 rats each received subsets of the following injection conditions at weekly intervals as summarized in Table 1. Intake was determined by weighing food pellets prior to and after each condition and adjusting for spillage at 2 and 4 h after the last injection. A 20-min interval elapsed between the first and second injections, and between the second and third injections. The preweighed food was introduced immediately after the third injection. The 2DG dose of 450 mg/kg was chosen to elicit a significant, though submaximal hyperphagia to allow observation of any potential drug-induced increases or decreases in 2DG hyperphagia. Vehicle-2DG injections were interspersed among other injection conditions to determine whether any long-term changes in hyperphagia occurred over the testing period. Animals were thus exposed to 12-15 weekly conditions. Significant differences in 2DG hyperphagia failed to occur among these vehicle conditions; therefore, these values were pooled for each animal to derive an overall vehicle-2DG score. These data agree with previous work (9) indicating that repeated 2DG administration fails to alter the magnitude of hyperphagia.

Within-subject analyses of variance assessed significant effects upon individual intake points. Dunnett and Dunn comparisons ($p < 0.05$) were used to discern respective differences between vehicle and drug treatments and between dopaminergic agonist/antagonist and either 2DG or naltrexone/2DG treatments.

RESULTS

D_1 and D_2 Agonists and Antagonists and 2DG Intake

Significant differences in intake were noted following vehicle, 2DG, and SKF-38393/2DG treatments after 2, $F(4, 45) = 6.99$, $p < 0.0002$, and 4, $F = 11.93$, $p < 0.0001$, h. 2DG significantly increased intake across the time course in all conditions. 2DG hyperphagia was unaffected by SKF-38393 (1-10 mg/kg; Fig. 1A).

Significant differences in intake were noted following vehicle, 2DG, and SCH-23390/2DG treatments after 2, $F(4, 45) = 4.36$, $p < 0.005$, and 4, $F = 8.51$, $p < 0.0001$, h. SCH-23390 dose dependently altered 2DG hyperphagia, reducing this response following the 200, but not the 25 or 100, μg/kg doses (Fig. 1B).

Significant differences in intake were noted following vehicle, 2DG, and quinpirole/2DG treatments after 2, $F(5, 53) = 9.91$, $p < 0.0001$, and 4, $F = 33.00$, $p < 0.0001$, h. Quinpirole significantly reduced 2DG hyperphagia after 2 h at lower (0.025-0.05 mg/kg) doses, and across the time course at higher (0.1-0.5 mg/kg) doses (Fig. 1C), despite the occurrance of high baseline intake responses in this group.

Significant differences in intake were noted following vehicle, 2DG, and haloperidol/2DG treatments after 2, $F(5, 48) = 13.08$, $p < 0.0001$, and 4, $F = 16.55$, $p < 0.0001$, h. Haloperidol respectively increased and decreased 2DG hyperphagia at low (50 μg/kg) and high (500 μg/kg) doses (Fig. 1D).

Naltrexone, SKF-38393, and 2DG Intake

Significant differences in intake were noted following vehicle, 2DG, naltrexone/2DG, and SKF-38393/naltrexone/2DG treatments after 2, $F(8, 81) = 13.00$, $p < 0.0001$, and 4, $F = 7.86$, $p < 0.0001$, h. Naltrexone (0.05-0.5 mg/kg) significantly reduced 2DG intake at 2 h. Whereas the inhibition of 2DG hyperphagia failed to differ between naltrexone (0.05 mg/kg) and cotreatment with SKF-38393 and naltrexone (0.05 mg/kg) (Fig. 2A), cotreatment with SKF-38393 (0.1-10 mg/kg) and a higher (0.5 mg/kg) naltrexone dose produced significantly greater inhibition of 2DG hyperphagia than that dose of naltrexone alone (Fig. 2B).

Naltrexone, SCH-23390, and 2DG Intake

Significant differences in intake were noted following vehicle, 2DG, naltrexone/2DG and SCH-23390/naltrexone/2DG treatments after 2, $F(7, 72) = 10.01$, $p < 0.0001$, and 4, $F = 4.24$, $p < 0.0006$, h. Naltrexone (0.05-0.5 mg/kg) significantly reduced 2DG intake at 2 h. Cotreatment with SCH-23390 (100-200 μg/kg) and naltrexone (0.5 mg/kg) failed to differ from naltrexone alone in inhibiting 2DG intake, except for a transiently (4 h) greater inhibition of 2DG hyperphagia than naltrexone alone (Fig. 3).

TABLE 1

PROTOCOLS OF DOPAMINE AGONIST AND ANTAGONIST AND OPIOID ANTAGONIST EFFECTS UPON 2-DEOXY-D-GLUCOSE-INDUCED INTAKE

First Injection (mg/kg)	Second Injection (mg/kg)	Third Injection (mg/kg)
A. D_1 Agonist: SKF-38393		
Vehicle	Vehicle	Vehicle
Vehicle	Vehicle	2DG 450
SKF-38393 1.0	Vehicle	2DG 450
SKF-38393 5.0	Vehicle	2DG 450
SKF-38393 10.0	Vehicle	2DG 450
Vehicle	Naltrexone 0.05	2DG 450
Vehicle	Naltrexone 0.5	2DG 450
SKF-38393 1.0	Naltrexone 0.05	2DG 450
SKF-38393 10.0	Naltrexone 0.05	2DG 450
SKF-38393 0.1	Naltrexone 0.5	2DG 450
SKF-38393 1.0	Naltrexone 0.5	2DG 450
SKF-38393 10.0	Naltrexone 0.5	2DG 450
B. D_1 Antagonist: SCH-23390		
Vehicle	Vehicle	Vehicle
Vehicle	Vehicle	2DG 450
SCH-23390 0.025	Vehicle	2DG 450
SCH-23390 0.1	Vehicle	2DG 450
SCH-23390 0.2	Vehicle	2DG 450
Vehicle	Naltrexone 0.05	2DG 450
Vehicle	Naltrexone 0.5	2DG 450
SCH-23390 0.1	Naltrexone 0.05	2DG 450
SCH-23390 0.2	Naltrexone 0.05	2DG 450
SCH-23390 0.1	Naltrexone 0.5	2DG 450
SCH-23390 0.2	Naltrexone 0.5	2DG 450
C. D_2 Agonist: Quinpirole		
Vehicle	Vehicle	Vehicle
Vehicle	Vehicle	2DG 450
QUIN 0.025	Vehicle	2DG 450
QUIN 0.05	Vehicle	2DG 450
QUIN 0.1	Vehicle	2DG 450
QUIN 0.5	Vehicle	2DG 450
Vehicle	Naltrexone 0.05	2DG 450
QUIN 0.025	Naltrexone 0.05	2DG 450
QUIN 0.05	Naltrexone 0.05	2DG 450
D. D_2 Antagonist: Haloperidol		
Vehicle	Vehicle	Vehicle
Vehicle	Vehicle	2DG 450
HAL 0.05	Vehicle	2DG 450
HAL 0.1	Vehicle	2DG 450
HAL 0.25	Vehicle	2DG 450
HAL 0.5	Vehicle	2DG 450
Vehicle	Naltrexone 0.05	2DG 450
HAL 0.05	Naltrexone 0.005	2DG 450
HAL 0.005	Naltrexone 0.05	2DG 450
HAL 0.05	Naltrexone 0.05	2DG 450

Naltrexone, Quinpirole, and 2DG Intake

Significant differences in intake were noted following vehicle, 2DG, naltrexone/2DG, and quinpirole/naltrexone/2DG treatments after 2, $F(4, 45) = 9.55$, $p < 0.0001$, and 4, $F = 5.42$, $p < 0.001$, h. Naltrexone (0.05 mg/kg) significantly reduced 2DG intake across the time course. Cotreatment with quinpirole and naltrexone failed to differ from naltrexone alone in inhibiting 2DG intake, except for a transient (4 h) loss of inhibition following cotreatment of quinpirole (0.05 mg/kg) with naltrexone (0.05 mg/kg) (Fig. 4).

Naltrexone, Haloperidol, and 2DG Intake

Significant differences in intake were noted following vehicle, 2DG, naltrexone/2DG, and haloperidol/naltrexone/2DG treatments after 2, $F(6, 61) = 13.35$, $p < 0.0001$, and 4, $F = 12.19$, $p < 0.0001$, h. Naltrexone (0.05 mg/kg) significantly

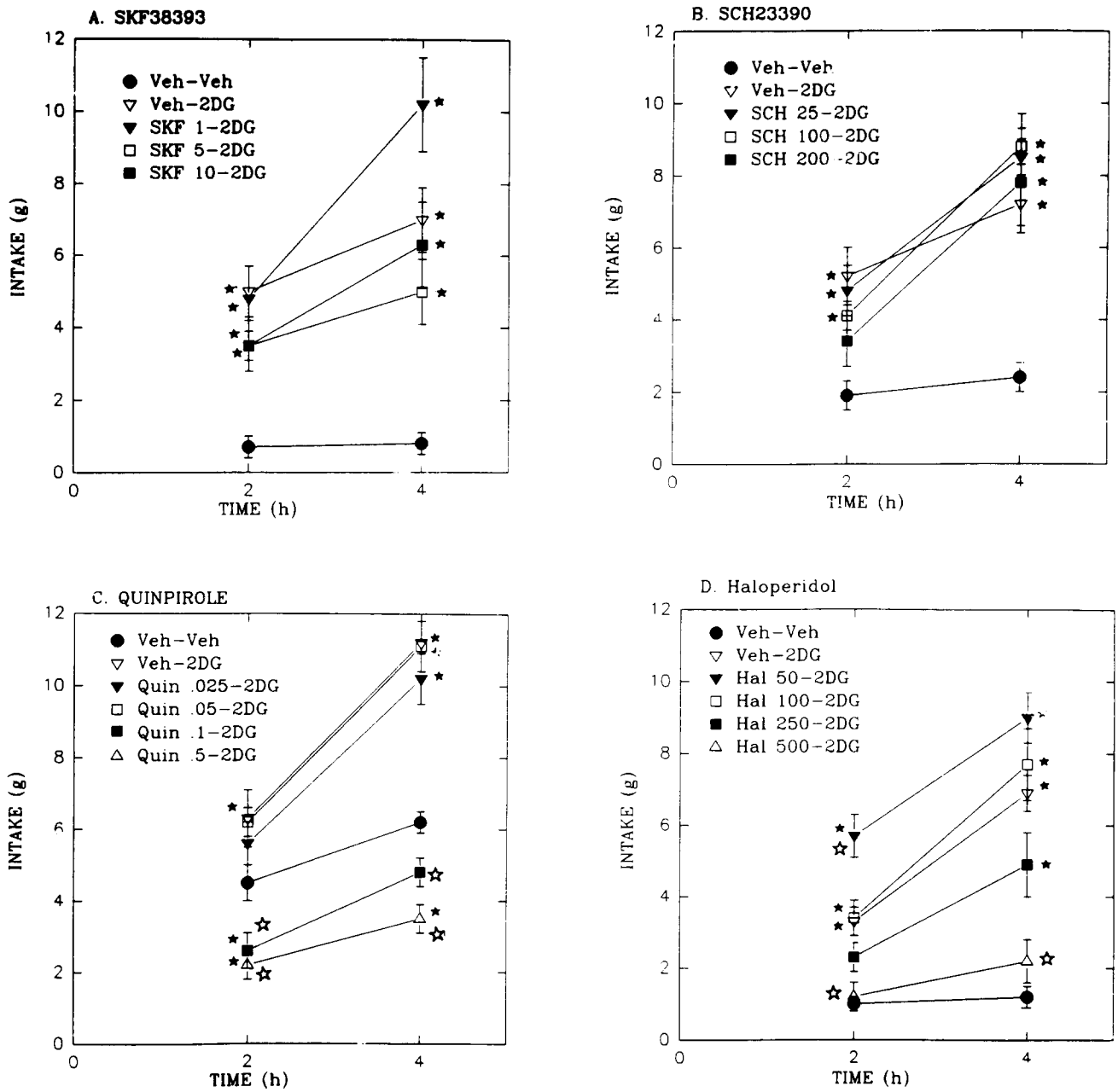

FIG. 1. Alterations in 2-deoxy-D-glucose (2DG) hyperphagia (g, SEM) following administration of either the D_1 receptor agonist, SKF 38393 (upper left), the D_1 receptor antagonist, SCH 23390 (upper right), the D_2 receptor agonist, quinpirole (lower left), and the D_2 receptor antagonist, haloperidol (lower right). The solid stars indicate significant increases in intake following 2DG relative to vehicle treatment in this and subsequent figures (Dunnett comparison, $p < 0.05$). The open stars indicate significant alterations in 2DG hyperphagia by dopaminergic or opioid drugs in this and subsequent figures (Dunn comparisons, $p < .05$).

reduced 2DG intake at 2 h. Cotreatment with haloperidol (50 μg/kg) and naltrexone (0.05 mg/kg) produced significantly greater inhibition of 2DG hyperphagia after 2 h than naltrexone alone (Fig. 5).

DISCUSSION

The present study clearly indicates that the patterns of D_1 and D_2 agonist and antagonist effects upon glucoprivic intake induced by 2DG differ relative to other intake situations. The D_1 agonist, SKF-38393, failed to alter the magnitude of 2DG hyperphagia, which is in marked contrast to the ability of this agonist to reduce intake under spontaneous, deprivation, and palatable intake conditions (17,18,25,29). The D_1 antagonist, SCH-23390, generally failed to alter the magnitude of 2DG hyperphagia, except when high SCH-23390 doses paired with 2DG failed to elicit significant increases in intake relative to vehicle treatment after 2 h. These minor alterations are in marked contrast to the ability of SCH-23390 to reduce deprivation-induced intake (18,21) and palatable intake (33,34,37)

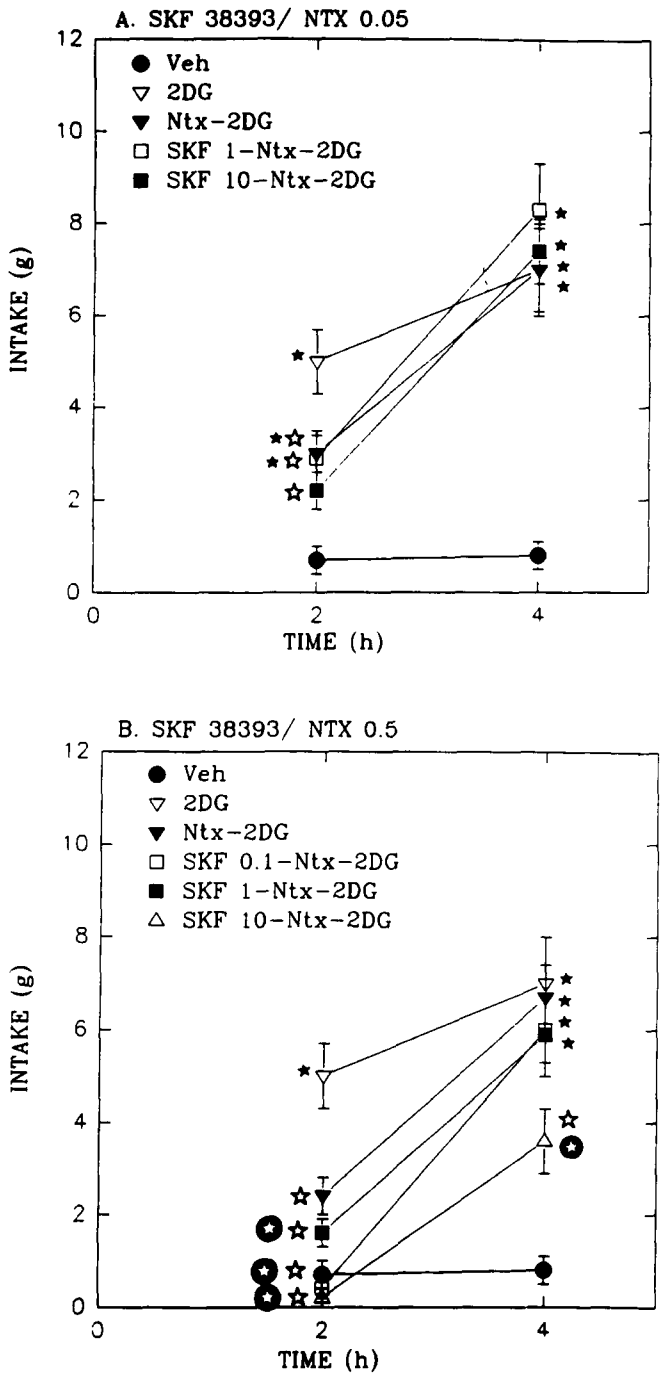

FIG. 2. Alterations in 2DG hyperphagia (g, SEM) following cotreatment of the D_1 agonist, SKF-38393, and naltrexone at doses of either 0.05 (upper panel) or 0.5 (lower panel) mg/kg. The enclosed stars indicate significant effects relative to naltrexone treatment in this and subsequent figures (Dunn comparisons, $p < 0.05$).

rats. The D_2 agonist, quinpirole (1) dose dependently decreased 2DG hyperphagia, effects that occurred despite high baseline intake and which were similar to D_2 agonist-induced decreases in palatable (25,30) and deprivation [(15,22), but see (18)] intake. The abilities of low (50 μg/kg) doses of haloperidol to increase 2DG hyperphagia and high (500 μg/kg) doses of haloperidol to decrease 2DG hyperphagia are similar to the pattern observed following food deprivation (18). Although the former response may be due to haloperidol's selective D_2 antagonism at this dose range (2), the latter response may be due to effects at other receptors (e.g., sigma, serotonergic) and disruptions in activational aspects of food-motivated behavior as well as motor deficits (13,27,30-32).

The effects of cotreatment of naltrexone with either D_1 or D_2 agonists or antagonists upon 2DG hyperphagia also differed from such cotreatment effects upon food deprivation

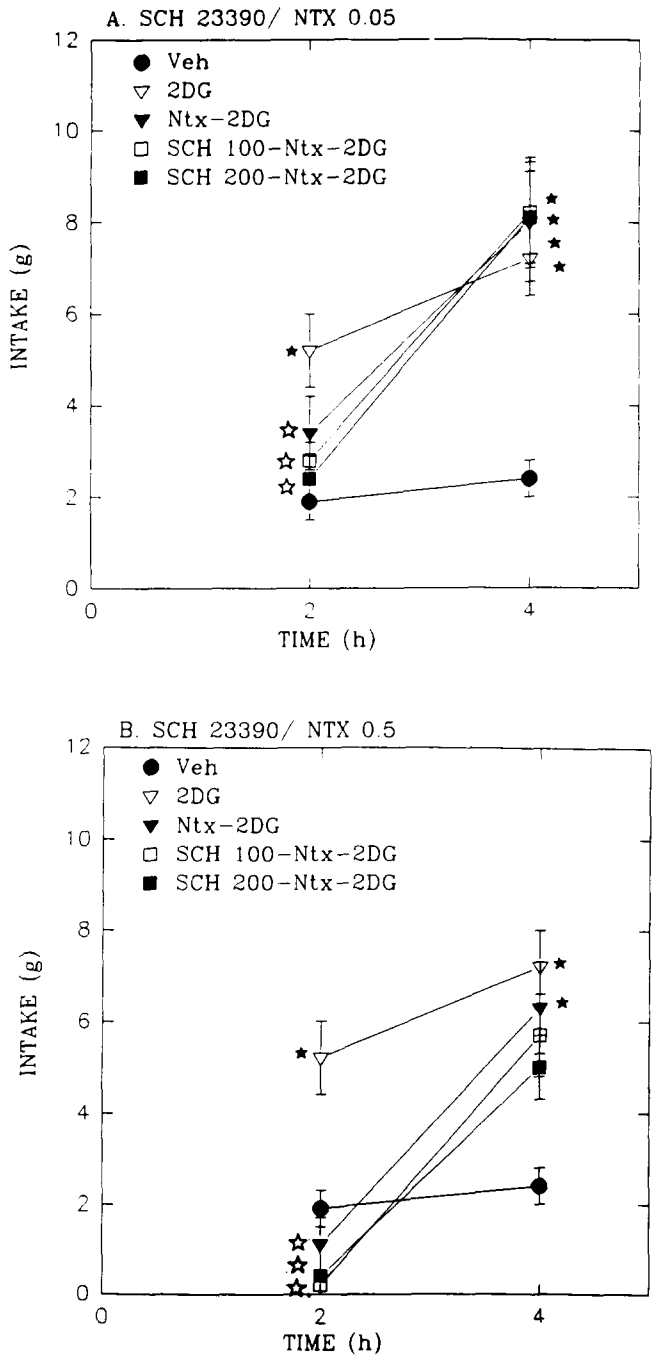

FIG. 3. Alterations in 2DG hyperphagia (g, SEM) following cotreatment of the D_1 antagonist, SCH 23390, and naltrexone at doses of either 0.05 (upper panel) or 0.5 (lower panel) mg/kg.

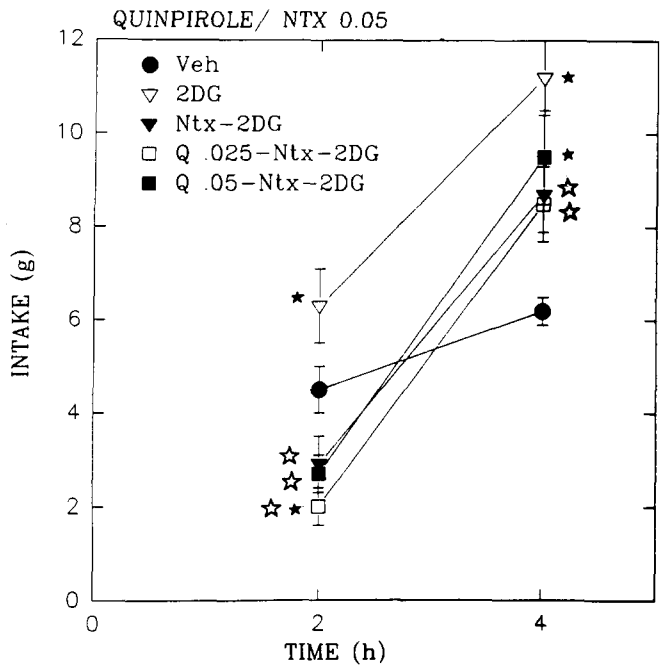

FIG. 4. Alterations in 2DG hyperphagia (g, SEM) following cotreatment of the D_2 agonist, quinpirole, and naltrexone at doses of either 0.05 (upper panel) or 0.5 (lower panel) mg/kg.

(18). First, as indicated previously [e.g., (6,7,10,11,16,24,35)], lower doses of naltrexone produced significantly greater inhibition of 2DG hyperphagia relative to deprivation-induced intake. Second, cotreatment with the D_1 agonist, SKF-38393, and naltrexone only transiently enhanced inhibition of deprivation-induced intake relative to naltrexone alone, yet potently enhanced the inhibition of 2DG hyperphagia relative to naltrexone alone. The inhibitory effects upon 2DG hyperphagia occurred at far lower SKF-38393 (0.1–1 mg/kg) and naltrexone (0.5 mg/kg) doses than those SKF-38393 (5 mg/kg) and naltrexone (10 mg/kg) doses used to inhibit deprivation-induced intake. Again, such cotreatment effects occurred at SKF-38393 doses that were ineffective in altering 2DG hyperphagia themselves. Third, whereas cotreatment with the D_1 antagonist, SCH-23390 (2.5–100 μg/kg) and naltrexone (2.5–10 mg/kg) produced greater inhibition of deprivation-induced intake relative to naltrexone alone, cotreatment of SCH-23390 and naltrexone generally failed to alter naltrexone's inhibition of 2DG hyperphagia. Fourth, whereas cotreatment with the D_2 agonist, quinpirole (0.01–1 mg/kg) and naltrexone (5–10 mg/kg) potently enhanced inhibition of deprivation-induced intake relative to naltrexone alone, cotreatment of quinpirole and naltrexone again generally failed to alter naltrexone's inhibition of 2DG hyperphagia. Finally, haloperidol (50 μg/kg) stimulated both deprivation-induced intake and 2DG hyperphagia itself, yet its cotreatment with naltrexone produced significantly greater inhibition of both forms of intake relative to naltrexone alone.

In the accompanying study (18), we indicated that because these were systemic pharmacological analyses, one could not ascertain as to whether the dopaminergic drugs acted upon their receptors to provide subsequent alterations in opioid functioning, whether opioid antagonists acted upon their receptors to provide subsequent alterations in dopaminergic functioning, or whether each class of drugs altered the respective pharmacokinetics or pharmacodynamics of their receptors to produce subsequent alterations in and independent system. The differential effects of D_1 and D_2 agonists alone and in combination with naltrexone upon deprivation-induced intake and 2DG hyperphagia argue against the idea that these treatment and cotreatment paradigms are producing effects in a nonspecific manner. Hence, while D_1 agonists and antagonists potently suppress deprivation-induced intake, the same dose ranges of SKF-38393 and SCH-23390 failed to alter 2DG hyperphagia. In contrast, although the D_2 agonist, quinpirole, significantly reduced 2DG hyperphagia, the same dose range failed to appreciably alter deprivation-induced intake. However, haloperidol produced similar biphasic effects upon both 2DG hyperphagia and deprivation-induced intake, stimulating both responses at low doses and decreasing both responses at higher doses. Further, the cotreatment paradigms indicated that when either D_1 antagonists, D_2 agonists, or D_2 antagonists were paired with naltrexone, greater inhibitory effects upon deprivation-induced intake occurred relative to naltrexone alone. In contrast, pairing either D_1 agonists, or, to a lesser degree, D_2 antagonists with naltrexone produced greater inhibitory effects upon 2DG hyperphagia relative to naltrexone alone. Therefore, these individual and cotreatment effects suggest that selective relationships between opioid antagonists and dopaminergic receptor subtype agonists and antagonists are observed for different forms of food intake. Two additional areas of study are necessary to examine these relationships further. The first area is to assess whether these relationships are mediated through central or peripheral sites of action; further studies are underway examining the roles of the ventral tegmental area and nucleus accumbens in these responses. Because the present studies merely used the amount of food intake over proscribed periods of time to examine drug effects, it will be necessary to generalize these findings

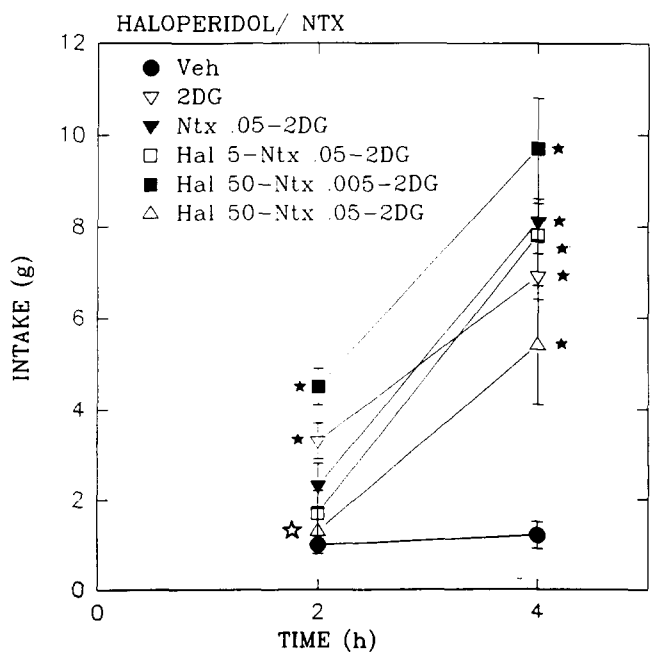

FIG. 5. Alterations in 2DG hyperphagia (g, SEM) following cotreatment of the D_2 antagonist, haloperidol, and naltrexone.

to other domains of ingestive behavior such as meal pattern analyses, behavioral satiety sequences, sensory-motor integration, and hedonic, appetitive, and motivational factors [see reviews (14,26,38)].

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