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Naltrexone, Dopamine Receptor Agonists and Antagonists, and Food Intake in Rats: 1. Food Deprivation

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HOBBS, D. J., J. E. KOCH AND R. J. BODNAR. *Naltrexone, dopamine receptor agonists and antagonists, and food intake in rats. 1. Food deprivation.* PHARMACOL BIOCHEM BEHAV **49**(1) 197–204, 1994.—Different forms of food intake are reduced by both agonists and antagonists of dopamine D_1 and D_2 receptors as well as general opioid antagonists. The present study evaluated whether deprivation (24 h)-induced food intake was altered following systemic administration of either the D_1 agonist, SKF-38393, the D_1 antagonist, SCH-23390, the D_2 agonist, quinpirole, or the D_2 antagonist, haloperidol, alone or in combination with the general opioid antagonist, naltrexone. Both SKF-38393 (5–10 mg/kg) and SCH-23390 (100–200 μg/kg) significantly and dose dependently reduced deprivation-induced intake. Whereas quinpirole (0.5–1 mg/kg) failed to alter deprivation-induced intake, haloperidol increased deprivation-induced intake at low (50 μg) doses and decreased intake at higher (100–500 μg/kg) doses. Naltrexone (2.5–10 mg/kg) significantly inhibited deprivation-induced intake. When naltrexone was paired with behaviorally ineffective doses of either SCH-23390 (2.5–100 μg/kg), quinpirole (0.01–1 mg/kg), or haloperidol (50 μg/kg), the degree of reduction of deprivation-induced intake was significantly greater than that produced by naltrexone alone. Pairing naltrexone with SKF-38393 produced reductions of deprivation-induced intake comparable to that of naltrexone alone.

Food deprivation Naltrexone SKF-38393 SCH-23390 Quinpirole Haloperidol Opioids D_1 Receptor D_2 Receptor

THE general opioid antagonists, naloxone and naltrexone, reduce different forms of food intake [see review (32)]. These reductions can be pharmacologically modulated by pairing opioid antagonists with other bioactive drugs such as serotonin receptor antagonists. For instance, greater reductions in hyperphagia following food deprivation occur following cotreatment with naloxone and 5-hydroxytryptophan relative to naloxone alone (18). Further, greater reductions in hyperphagia following either food deprivation or 2-deoxy-D-glucose occur following cotreatment of the 5-HT_3 antagonist, ICS 205930, and general opioid antagonists relative to opioid antagonism alone (9,10). Cotreatment of either general serotonergic or 5-HT_2 antagonists with opioid antagonists failed to produce such effects. Moreover, cotreatment of naltrexone with either 5-HT_2 or 5-HT_3 antagonists produced greater reductions in insulin hyperphagia relative to naltrexone alone (27). In contrast, whereas naltrexone inhibited either sucrose or maltose dextrin intake itself, this effect was eliminated or delayed when naltrexone was paired with the 5-HT_2 antagonist, ritanserin (25).

The effects of dopamine and dopaminergic receptor agonists and antagonists in feeding behavior have generated somewhat conflicting results. Both general dopamine receptor agonists and antagonists decrease food intake (3,8,11,23, 35,38,39,50,52,53). The existence of multiple dopamine receptor subtypes [e.g., (26,46)] allowed their evaluation in food intake, particularly the D_1 and D_2 receptor subtypes. The D_1 agonist, SKF-38393 [see review (15)] significantly decreased spontaneous food intake, palatable intake, and deprivation-induced food intake without appreciably altering deprivation-induced water intake (21,31,37). Alterations in intake following D_2 agonists are not as clear. The D_2 agonist, N-0437,

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significantly decreased palatable intake (36) which was additive with D_1 agonist administration (37). The D_2 agonist RU-24926 significantly decreased deprivation-induced food intake which was additive with D_1 agonists as well (29). Another D_2 agonist, (+)-4-propyl-9-hydroxynapthoxazine decreased intake of a sweet milk solution, but stimulated food intake of pellets that was blocked by both D_1 and D_2 antagonists (31). Finally, the D_2 agonist, lisuride, decreased deprivation-induced food intake in a home cage, but enhanced operant responding for food in a maze (19). The D_1 antagonist, SCH-23390 (24) significantly decreases deprivation-induced food intake (28) and sucrose intake in both sham-feeding (42,43) and developing (48) rats. The D_2 antagonist, haloperidol (12) decreases food intake in food-deprived rats in a way that suggests disruptions in activational aspects of food-motivated behavior in addition to motor deficits (35,38–40). The reductions in food intake by other D_2 antagonists such as YM-09151-2 and raclopride are produced by reductions in feeding rate and enhancements in meal size (16). D_1 and D_2 antagonists each reduce schedule-induced polydipsia and sucrose intake, but only the latter reduces intake of a corn-oil solution (47,49). Sucrose intake in sham-feeding rats displays an additive inhibition of D_1 and D_2 antagonists as well (44).

Relationships between dopaminergic and opioid systems have been proposed for food intake [see review (17)]. Opioid agonists stimulate food intake when administered into such dopamine-rich cell and terminal regions as the ventral tegmental area (14,22,33) and nucleus accumbens (6,7,30,33). Microinjections of haloperidol into the latter site also stimulate food intake (5). The present and following studies examined whether coadministration of either D_1 or D_2 receptor agonists or antagonists with naltrexone would alter the latter's inhibitory effects upon different forms of food intake. Because naltrexone significantly reduces the hyperphagia following food deprivation [e.g., (12,13,20)], this initial study examined food intake in rats deprived of food for 24 h following SKF-38393 (D_1 agonist) (15), SCH-23390 (D_1 antagonist) (24), quinpirole (D_2 agonist (1,4), and haloperidol (D_2 antagonist) (2) pretreatment alone and in combination with naltrexone. The following study assesses these effects upon food intake following 2-deoxy-D-glucose glucoprivation (41).

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-3839315, and the D_1 antagonist, SCH-23390 (Research Biochemicals, Natick, MA), were dissolved in water and administered intraperitoneally. The D_2 agonist, quinpirole HCl (1,4) (Research Biochemicals), was dissolved in water and administered SC. These drugs are highly selective for their respective receptor subtypes. The D_2 antagonist, haloperidol (Research Biochemicals), administered IP, was dissolved in DMSO. Although haloperidol is quite selective for D_2 sites at low doses (2), it can also act at serotonergic and sigms receptor sites at higher doses. Each drug's route of injection was chosen for its maximal effectiveness in producing behavioral effects based upon the previously cited studies.

Protocols

At weekly intervals, four independent groups of ten rats each were deprived of food, but not water for 24 h prior to food reintroduction at 7 h into the light cycle. Intake was determined by weighing food pellets prior to and after each condition and adjusting for spillage at 30, 60, and 120 min after reintroduction of food. A period of 20 min elapsed between the first and second injections, and food was reintroduced immediately after the last injection. Table 1 summarizes the subsets of injection conditions for each group. Vehicle control injections were interspersed among other injection conditions to determine whether any long-term changes in intake occurred over the testing period. Animals were, thus, exposed to 12–15 weekly conditions. Significant differences in deprivation-induced intake failed to occur among these vehicle conditions; therefore, these values were pooled for each animal to derive an overall vehicle score.

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 food deprivation or naltrexone/food deprivation treatments.

RESULTS

D_1 and D_2 Agonists and Antagonists and Deprivation-Induced Intake

Significant differences in deprivation-induced intake were noted following vehicle and SKF-38393 treatments after 30, $F(2, 27) = 19.74$, $p < 0.0001$, 60, $F = 23.58$, $p < 0.0001$, and 120, $F = 4.50$, $p < 0.021$, min. The D_1 agonist, SKF-38393, significantly reduced deprivation-induced intake across the 120 min time course following the 10, but not the 5 mg/kg dose (Fig. 1A).

Significant differences in deprivation-induced intake were noted following vehicle and SCH-23390 treatments after 30, $F(2, 27) = 7.60$, $p < 0.002$, and 60, $F = 8.67$, $p < 0.001$, min, but not after 120 min, $F = 1.78$. The D_1 antagonist, SCH-23390, significantly reduced deprivation-induced intake at 30 and 60 min following the 200, but not the 100 μg/kg dose (Fig. 1B).

Significant differences in deprivation-induced intake failed to occur following vehicle and the D_2 agonist, quinpirole (0.5–1 mg/kg), treatments after 30, $F(2, 26) = 1.77$, 60, $F = 0.27$, and 120, $F = 0.67$, min (Fig. 1C).

Significant differences in deprivation-induced intake were noted following vehicle and haloperidol treatments after 30, $F(4, 45) = 17.15$, $p < 0.0001$, 60, $F = 33.95$, $p < 0.0001$, and 120, $F = 30.52$, $p < 0.0001$, min. The D_2 antagonist, haloperidol, significantly increased deprivation-induced intake across the 120 min time course following the 50 μg/kg dose, but significantly decreased deprivation-induced intake across the 120 min time course following doses of 100, 250, and 500 μg/kg (Fig. 1D).

Naltrexone, SKF-38393, and Deprivation-Induced Intake

Significant differences in deprivation-induced intake were noted at each test interval following vehicle, SKF-38393, and

TABLE 1

PROTOCOLS OF DOPAMINE AGONIST AND ANTAGONIST EFFECTS AND OPIOID ANTAGONIST EFFECTS UPON DEPRIVATION-INDUCED INTAKE

First Injection (mg/kg)	Second Injection (mg/kg)
A. D_1 Agonist: SKF-38393	
Vehicle	Vehicle
SKF-38393 5.0	Vehicle
SKF-38393 10.0	Vehicle
Vehicle	Naltrexone 2.5
Vehicle	Naltrexone 10.0
SKF-38393 1.0	Naltrexone 2.5
SKF-38393 5.0	Naltrexone 2.5
SKF-38393 1.0	Naltrexone 10.0
SKF-38393 5.0	Naltrexone 10.0
B. D_1 Antagonist: SCH-23390	
Vehicle	Vehicle
SCH-23390 0.1	Vehicle
SCH-23390 0.2	Vehicle
Vehicle	Naltrexone 2.5
Vehicle	Naltrexone 10.0
SCH-23390 0.0025	Naltrexone 2.5
SCH-23390 0.025	Naltrexone 2.5
SCH-23390 0.1	Naltrexone 2.5
SCH-23390 0.025	Naltrexone 10.0
SCH-23390 0.1	Naltrexone 10.0
C. D_2 Agonist: Quinpirole	
Vehicle	Vehicle
QUIN 0.5	Vehicle
QUIN 1.0	Vehicle
Vehicle	Naltrexone 2.5
Vehicle	Naltrexone 5.0
Vehicle	Naltrexone 10.0
QUIN 0.5	Naltrexone 2.5
QUIN 1.0	Naltrexone 2.5
QUIN 1.0	Naltrexone 5.0
QUIN 0.01	Naltrexone 10.0
QUIN 0.1	Naltrexone 10.0
QUIN 1.0	Naltrexone 10.0
D. D_2 Antagonist: Haloperidol	
Vehicle	Vehicle
HAL 0.05	Vehicle
HAL 0.1	Vehicle
HAL 0.25	Vehicle
HAL 0.5	Vehicle
Vehicle	Naltrexone 0.5
Vehicle	Naltrexone 2.5
Vehicle	Naltrexone 10
HAL 0.05	Naltrexone 0.5
HAL 0.01	Naltrexone 2.5
HAL 0.05	Naltrexone 2.5

naltrexone treatments at naltrexone doses of 2.5 [30, $F(3, 36) = 9.05, p < 0.0001$, 60, $F = 13.47, p < 0.0001$, and 120, $F = 11.84, p < 0.0001$, min] and 10 [30, $F(3, 36) = 19.83, p < 0.0001$, 60, $F = 22.60, p < 0.0001$, and 120, $F = 12.08, p < 0.0001$, min] mg/kg. Naltrexone's (2.5 mg/kg) significant reductions in intake across the time course were generally unaffected by SKF-38393 coadministration, except for a transient (30 min) reduction in inhibition following cotreatment of SKF-38393 (1 mg/kg) and naltrexone (Fig. 2A). Naltrexone's (10 mg/kg) significant reductions in intake across the time course were generally unaffected by SKF-38393 coadministration, except for a transient (30 min) enhancement in inhibition following cotreatment of SKF-38393 (1 mg/kg) and naltrexone (Fig. 2B).

Naltrexone, SCH-23390, and Deprivation-Induced Intake

Significant differences in deprivation-induced intake were noted at each test interval following vehicle, SCH-23390, and naltrexone treatments at naltrexone doses of 2.5 [30, $F(4, 45) = 20.81, p < 0.0001$, 60, $F = 25.19, p < 0.0001$, and 120, $F = 18.69, p < 0.0001$, min] and 10 [30, $F(4, 42) = 23.80, p < 0.0001$, 60, $F = 32.12, p < 0.0001$, and 120, $F = 20.71, p < 0.0001$, min] mg/kg. Naltrexone's (2.5 mg/kg: 60–120 min) significant reductions in intake were significantly less than inhibition produced by cotreatment of naltrexone and SCH-23390 at doses of 2.5 (30–120 min), 25 (60 min), and 100 (30–120 min) μg/kg (Fig. 3A). The 2.5 and 25 μg/kg doses failed to differ from each other in exerting these effects. Naltrexone's (10 mg/kg: 60–120 min) significant reductions in intake were significantly less than inhibition produced by cotreatment of naltrexone and SCH-23390 at doses of 25 (30–120 min) and 100 (30–120 min) μg/kg (Fig. 3B).

Naltrexone, Quinpirole, and Deprivation-Induced Intake

Significant differences in deprivation-induced intake were noted at each test interval following vehicle, quinpirole, and naltrexone treatments at naltrexone doses of 2.5 [30, $F(3, 35) = 5.94, p < 0.002$, 60, $F = 12.72, p < 0.0001$, and 120, $F = 10.32, p < 0.0001$, min], 5 [30, $F(2, 27) = 168.48, p < 0.0001$, 60, $F = 140.25, p < 0.0001$, and 120, $F = 214.43, p < 0.0001$, min], and 10 [30, $F(4, 45) = 108.13, p < 0.0001$, 60, $F = 102.32, p < 0.0001$, and 120, $F = 102.60, p < 0.0001$, min] mg/kg. Naltrexone's (2.5 mg/kg) significant reductions in intake across the time course were unaffected by cotreatment with quinpirole and naltrexone (Fig. 4A). Naltrexone's (5 mg/kg) significant reductions in intake across the time course was dramatically enhanced by cotreatment with quinpirole (1 mg/kg) and naltrexone (Fig. 4B). Naltrexone's (10 mg/kg) significant reductions in intake across the time course was dramatically and dose dependently enhanced by cotreatment with quinpirole at doses of 0.01, 0.1, and 1 mg/kg and naltrexone (Fig. 4C).

Naltrexone, Haloperidol, and Deprivation-Induced Intake

Significant differences in deprivation-induced intake were noted at each test interval following vehicle, haloperidol, and naltrexone treatments after 30, $F(6, 61) = 13.42, p < 0.0001$, 60, $F = 23.03$, $p < 0.0001$, and 120, $F = 26.45$, $p < 0.0001$, min. Naltrexone (0.5, 2.5, 10 mg/kg) significantly reduced intake across the time course following food reintroduction. Cotreatment of naltrexone (2.5 mg/kg) and haloperidol (10 and 50 ug/kg) produced significantly greater inhibition of deprivation-induced intake across the time course relative to naltrexone alone. In contrast, inhibition of deprivation-induced intake failed to differ following cotreatment of naltrexone (0.5 mg/kg) and haloperidol (50 ug/kg) relative to naltrexone alone (Fig. 5).

DISCUSSION

The D_1 agonist, SKF-38393, and antagonist, SCH-23390, significantly reduced deprivation-induced intake in a dose-dependent manner. These D_1-mediated effects are selective

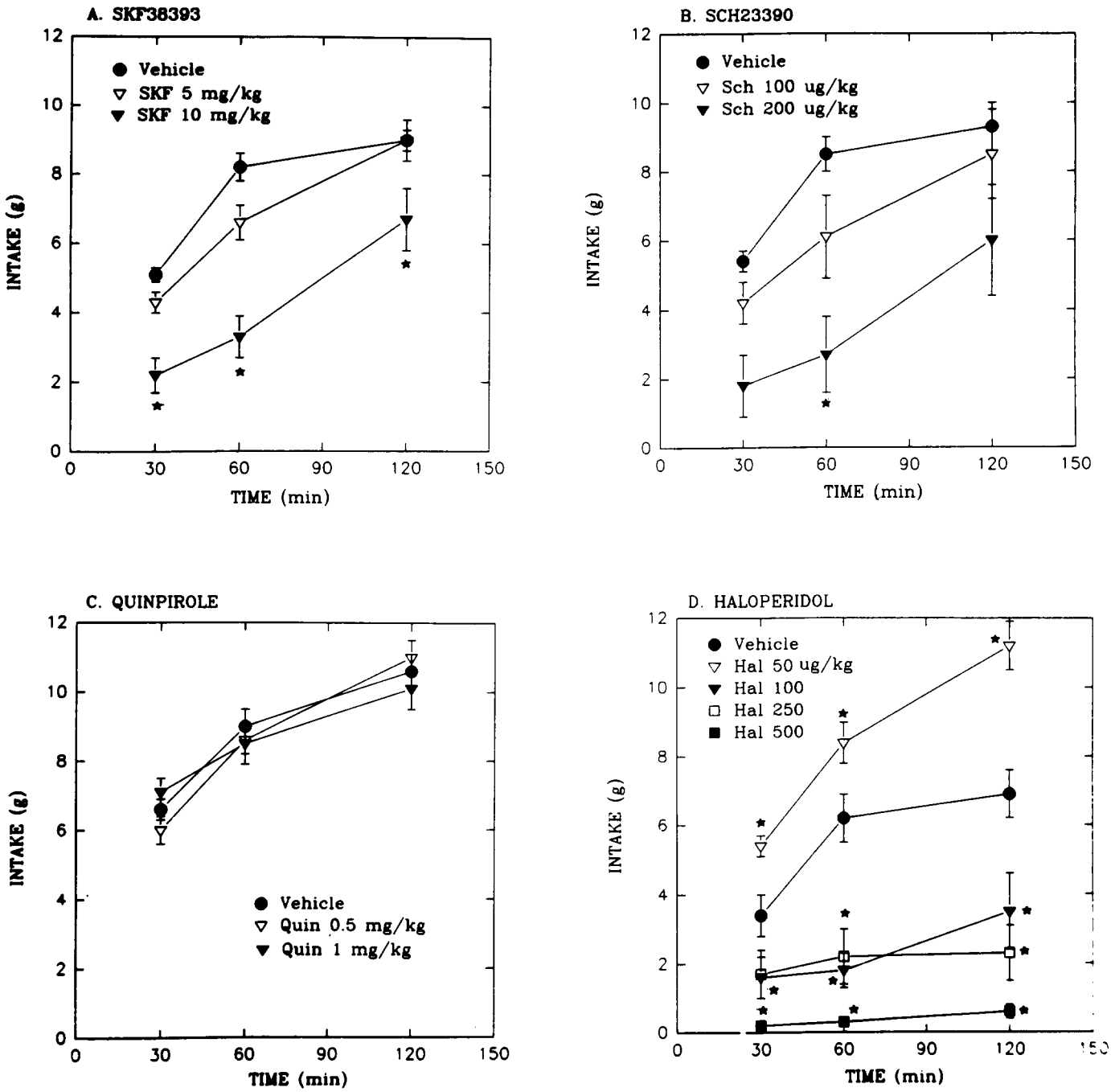

FIG. 1. Alterations in deprivation-induced food intake (g, SEM) following administration of either the D_1 receptor agonist, SKF 38393 (upper left), the D_1 receptor antagonist, SCH 23390 (upper right), the D_2 receptor agonist, quinpirole (lower left), and the D_2 receptor antagonist, haloperidol (lower right). The solid stars indicate significant effects relative to vehicle treatment in this and subsequent figures (Dunnett comparison, $p < 0.05$).

given the affinities of the drugs employed (15,24) and are consistent with previous reports of decreased intakes following either SKF-38393 (21,31,37) or SCH-23390 (28,42,43,48). The D_2 agonist, quinpirole, failed to alter deprivation-induced intake, Given quinpirole's selectivity for the D_2 receptor site (1,4), its failure to alter deprivation-induced intake provides further evidence for this receptor's inconsistent intake effects. D_2 agonists alternatively decrease palatable intake (31,36), decrease, or fail to affect deprivation-induced food intake (19,29), yet stimulate spontaneous pellet intake (31) and operant responding for food in a maze (19). Haloperidol produced biphasic effects upon deprivation-induced intake, increasing intake following low doses and decreasing intake following higher doses. The decreased intake by high doses of haloperidol is consistent with previous findings, suggesting disruptions in activational aspects of food-motivated behavior

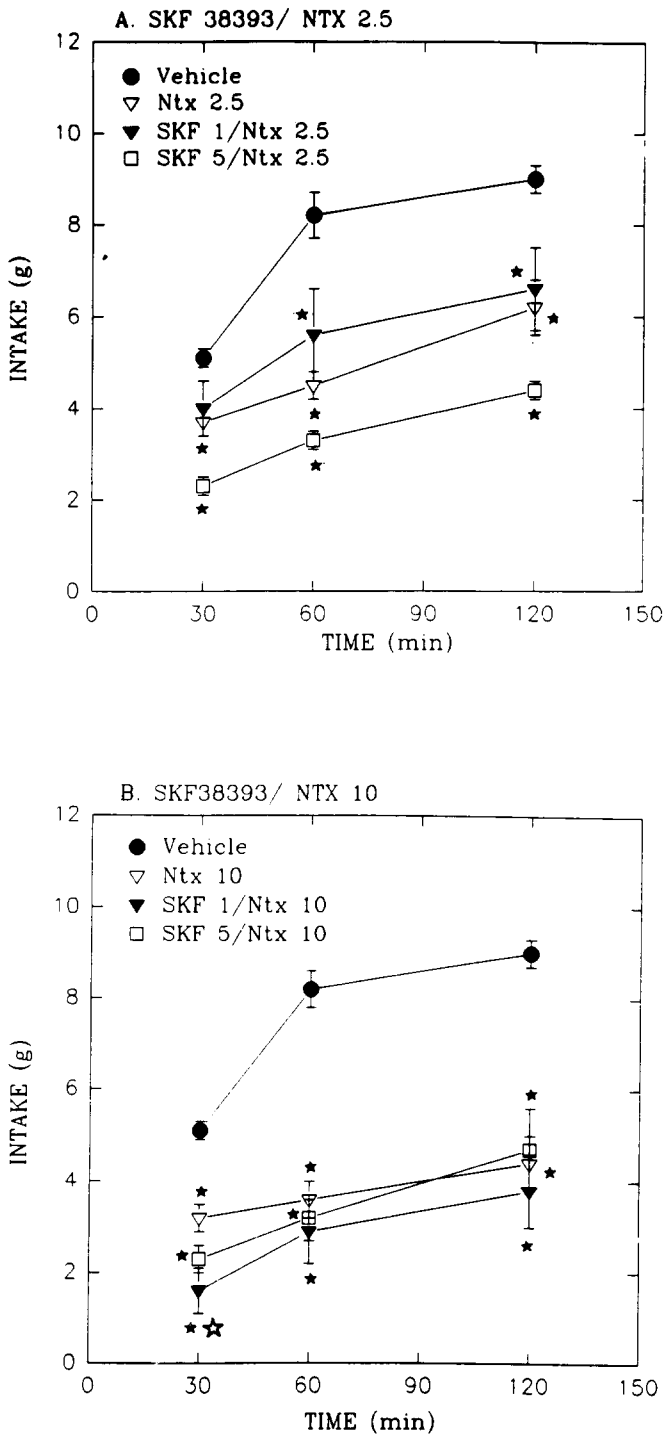

FIG. 2. Alterations in deprivation-induced food intake (g, SEM) following cotreatment of the D_1 agonist, SKF 38393, and naltrexone at doses of either 2.5 (upper panel) or 10 (lower panel) mg/kg. The open stars indicate significant effects relative to naltrexone treatment in this and subsequent figures (Dunn comparison, $p < 0.05$).

as well as motor deficits (16,35,38–40). It is conceivable that the stimulation of deprivation-induced intake by haloperidol at low doses was due to its selective actions at D_2 sites, although reduction of deprivation-induced intake by higher haloperidol doses was due to its less-selective actions at other receptors which include the D_2 receptor, the sigma receptor, and serotonergic receptors (2). That agonists and antagonists of a specific dopaminergic receptor subtype (e.g., D_1) produce similar directions of effects upon a given behavior suggests that they may be acting at different sites and/or different mechanisms of the behavior. Such views are consistent with

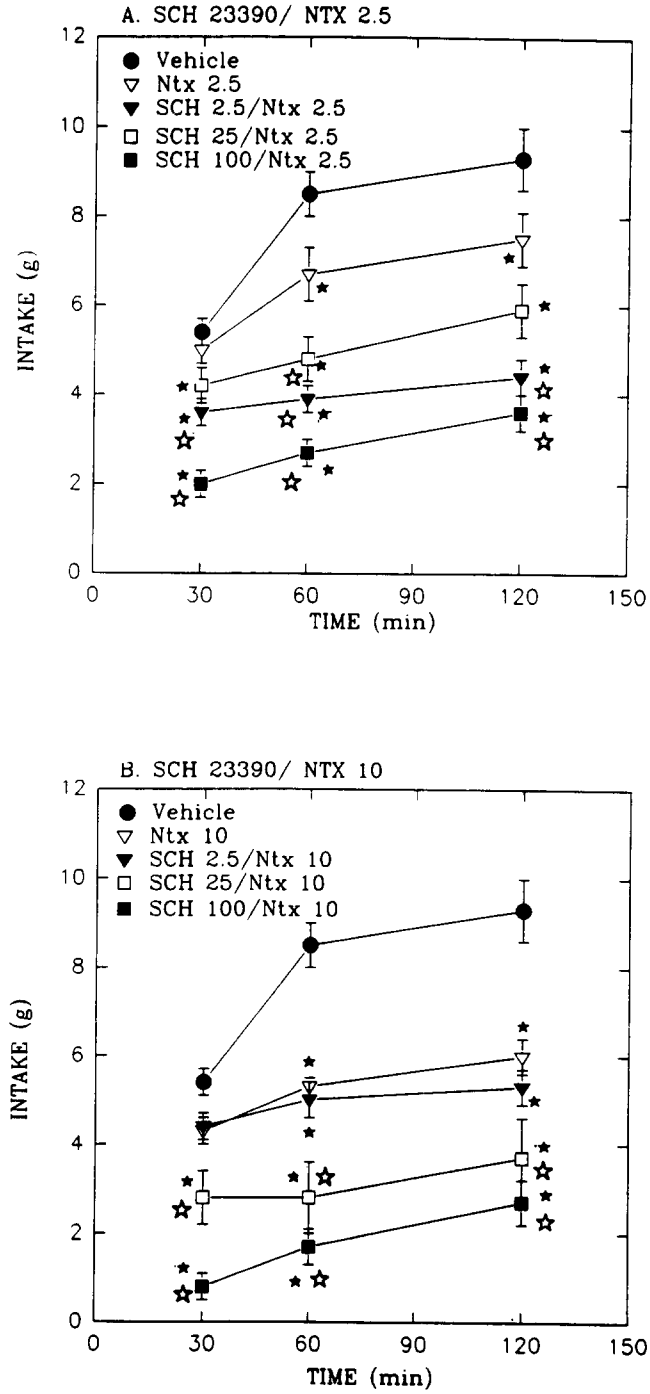

FIG. 3. Alterations in deprivation-induced food intake (g, SEM) following cotreatment of the D_1 antagonist, SCH 23390, and naltrexone at doses of either 2.5 (upper panel) or 10 (lower panel) mg/kg.

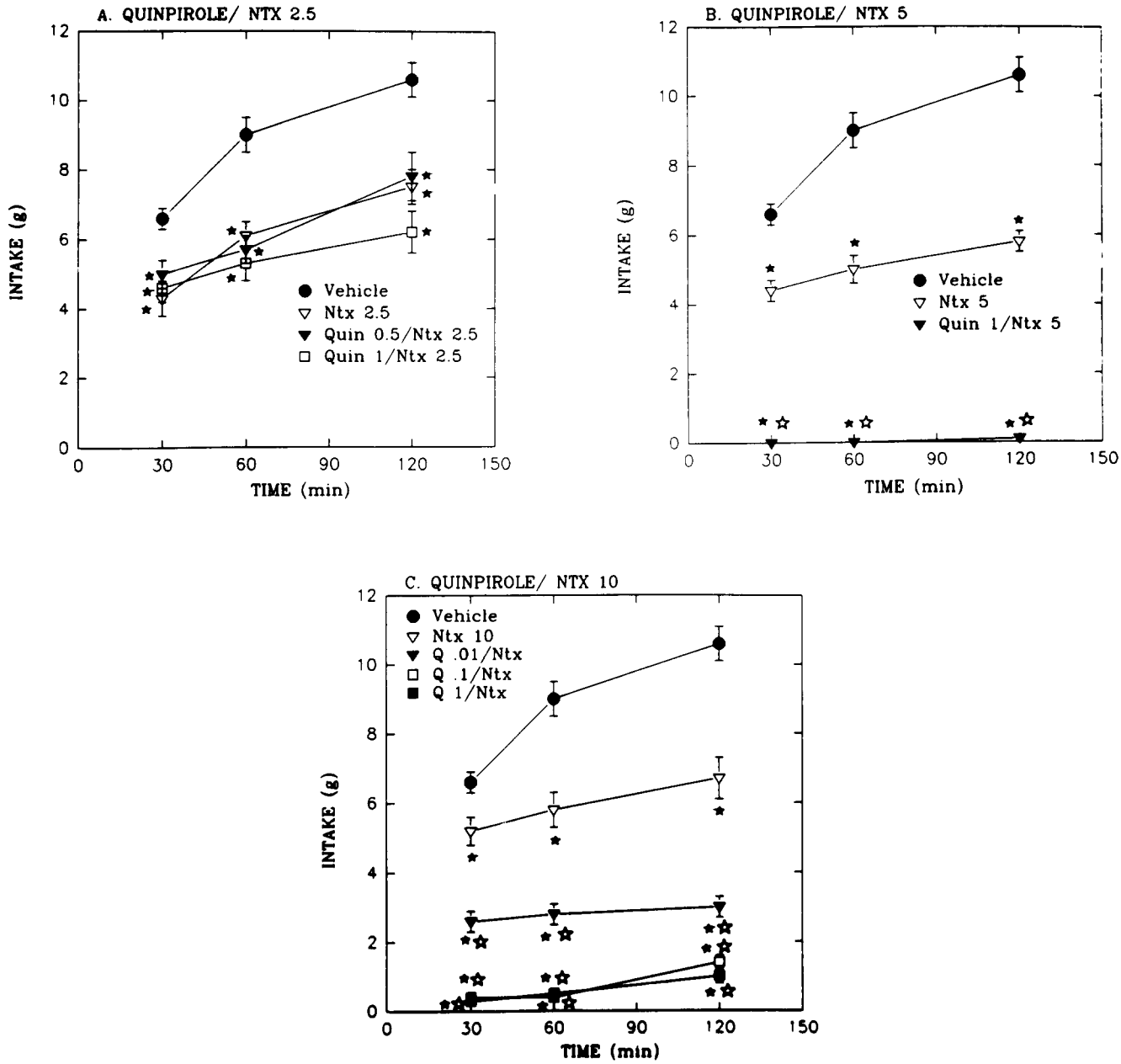

FIG. 4. Alterations in deprivation-induced food intake (g, SEM) following cotreatment of the D_2 agonist, quinpirole, and naltrexone at doses of either 2.5 (upper left panel), 5 (upper right panel), or 10 (lower panel) mg/kg.

roles for dopamine in the mediation of the negatively reinforcing aspects of addiction (51), the positively reinforcing aspects of addiction (45,51), and the incentive-sensitization theory of addiction (34). If these models applied to food intake, it would suggest that the agonist and antagonist effects might be acting at different sites along the neuraxis, and/or be acting on different components of the intake situation (e.g., deprivation state, motor acts, hedonics and palatability, conditioned and unconditioned learning cues).

Cotreatment of behaviorally ineffective doses of D_1 or D_2 receptor agonists or antagonists with naltrexone produced some selective effects upon deprivation-induced intake. Typically, cotreatment of the D_1 agonist, SKF-38393, with naltrexone produced similar inhibition of deprivation-induced intake relative to naltrexone alone, except for a transient reduction following naltrexone (2.5 mg/kg) and SKF-38393 (1 mg/kg) cotreatment, and a transient enhancement following naltrexone (10 mg/kg) and SKF-38393 (1 mg/kg) cotreatment. Cotreatment of the D_1 antagonist, SCH-23390 (2.5-100 μg/kg) with naltrexone produced significantly and dose dependently greater inhibition of deprivation-induced intake relative to naltrexone (2.5 and 10 mg/kg) alone. Thus, whereas both D_1 agonists and antagonists significantly reduced deprivation-induced intake themselves, only D_1 antagonists were effective

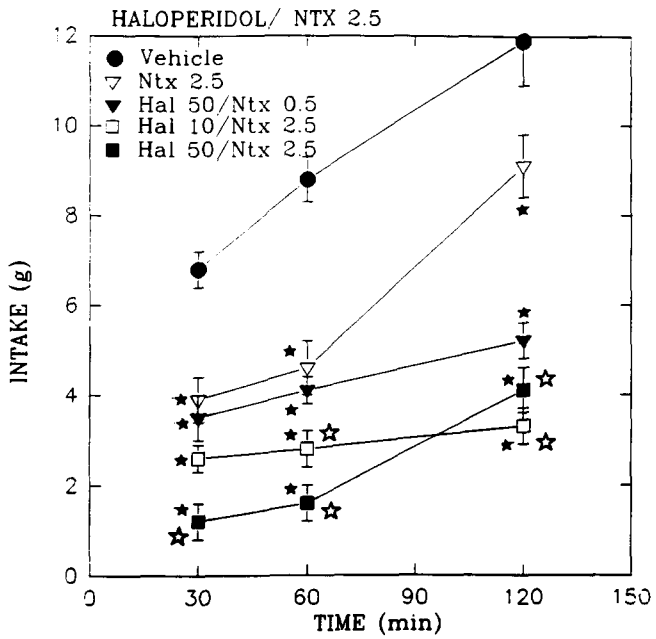

FIG. 5. Alterations in deprivation-induced food intake (g, SEM) following cotreatment of the D_2 antagonist, haloperidol, and naltrexone.

in producing greater magnitudes of inhibition following cotreatment with naltrexone relative to naltrexone alone. Moreover, those doses of SCH-23390 that were effective in enhancing naltrexone's inhibition of deprivation-induced intake following cotreatment, were ineffective in altering deprivation-induced intake per se.

Whereas the D_2 agonist quinpirole failed to alter deprivation-induced intake itself, cotreatment of quinpirole with naltrexone produced greater inhibition of deprivation-induced intake relative to naltrexone alone. This effect was dependent upon the naltrexone dose. Naltrexone produced comparable inhibition of deprivation-induced intake at doses of 2.5, 5, and 10 mg/kg. Cotreatment of quinpirole (0.01–1 mg/kg) and naltrexone produced significantly and dose dependently greater inhibition of deprivation-induced intake relative to naltrexone alone when the naltrexone dose was either 5 or 10 mg/kg, but not when it was 2.5 mg/kg. Finally, haloperidol doses (10–50 μg/kg), which significantly stimulated deprivation-induced intake when administered alone, produced significantly greater inhibition of deprivation-induced intake relative to naltrexone alone when these haloperidol doses were cotreated with naltrexone. Thus, both D_2 agonists and antagonists were effective in producing greater magnitudes of inhibition following cotreatment with naltrexone relative to naltrexone alone. Moreover, those doses of either quinpirole or haloperidol that were effective in enhancing naltrexone's inhibition of deprivation-induced intake following cotreatment were either ineffective in altering deprivation-induced intake per se or actually increased deprivation-induced intake.

The present study indicated that cotreatment of either D_1 antagonists, D_2 agonists or D_2 antagonists with naltrexone produced significantly greater inhibition of deprivation-induced intake realtive to naltrexone alone. It is imperative to note that because this was a systemic pharmacological study, one cannot ascertain as to whether the dopaminergic drugs acted upon their receptors to produce subsequent alterations in opioid functioning, whether the opioid antagonist acted upon its receptors to produce 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 an independent system. Further, the use of systemic administration cannot pinpoint the locus (peripheral or central) where these different classes of drugs produce these effects following cotreatment. Studies evaluating the links between dopaminergic and opioid systems in motivated behaviors have suggested central sites of action [e.g., (17,34,45,51)]. Because previous studies found that food intake is altered following microinjections of dopaminergic and opioid drugs into the ventral tegmental area and nucleus accumbens (5–7,14,22,30,33), further studies are currently in progress examining whether some of the present findings are mediated by these central sites.

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