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Naloxone and Serotonin Receptor Subtype Antagonists: Interactive Effects Upon Deprivation-Induced Intake

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BECZKOWSKA, I. W. AND R. J. BODNAR. *Naloxone and serotonin receptor subtype antagonists: Interactive effects upon deprivation-induced intake.* PHARMACOL BIOCHEM BEHAV **38**(3) 605–610, 1991.—Whereas opiate receptor antagonists generally act to inhibit food intake under a variety of physiological conditions in rats, agonists of some serotonin (5-HT) receptor subtypes appear to stimulate intake, and others appear to inhibit intake. The present study evaluated the effects of the general 5-HT receptor antagonist, methysergide (1–5 mg/kg), the 5-HT_2 receptor antagonists, ketanserin (1–2.5 mg/kg) and ritanserin (1–2.5 mg/kg), and the 5-HT_3 receptor antagonist, ICS 205930 (1–5 mg/kg) upon deprivation (24 h)-induced intake themselves, and upon the hypophagic properties of the general opiate receptor antagonist, naloxone (1–5 mg/kg). Whereas the high doses of methysergide (0.5–4 h, 34%) and ketanserin (0.5 h, 28%) significantly decreased deprivation-induced intake themselves, ritanserin and ICS 205930 were without effect. Naloxone produced dose-dependent reductions in deprivation-induced intake (24–45%). Methysergide (1 mg/kg) significantly potentiated naloxone (5 mg/kg) hypophagia after 0.5 h. Significant potentiations of hypophagia occurred following pairing the 1 mg/kg ketanserin dose with the 1 and 5 mg/kg naloxone doses at 2 and 4 h respectively, and pairing the 2.5 mg/kg ketanserin and 1 mg/kg naloxone doses at 0.5 and 2 h. Whereas the 1 mg/kg dose of ritanserin eliminated naloxone (1 mg/kg) hypophagia over a 2-h time course, ritanserin failed to exert further effects in other dose conditions. The differences between ketanserin and ritanserin in their effects upon deprivation-induced feeding and naloxone hypophagia suggest that the former's antagonistic actions upon alpha-adrenergic receptors may be responsible for its effects. Significant potentiations of hypophagia occurred following pairing the 1 mg/kg ICS 205930 dose with the 1 mg/kg naloxone dose for up to 4 h, and pairing the 5 mg/kg ICS 205930 dose with both naloxone doses for up to 4 h. These data implicate the 5-HT_3 receptor in modulating endogenous opioid effects upon intake, and demonstrate the heterogeneous responsivity of 5-HT receptor subtypes in ingestive behavior.

Naloxone hypophagia Serotonin receptor subtypes Methysergide Ketanserin Ritanserin ICS 205930 Food intake

THE endogenous opioids and serotonin (5-HT) appear to play opposite roles in the mediation of food intake. Whereas agonists of opiate receptor subtypes generally stimulate food intake, opiate receptor antagonists inhibit food intake under a variety of conditions [see reviews, (35,41)]. In contrast, whereas 5-HT or its reuptake inhibitors inhibit food intake [see reviews, (3,4)], both antagonists and depletors of 5-HT stimulate food intake (6, 8, 47). Distinct 5-HT receptor subtypes [see reviews, (9,44)] have been subdivided into the 5-HT_{1A} [e.g., (42)], 5-HT_{1B} [e.g., (43)], 5-HT_{1C} [e.g., (25)], 5-HT_{1D} (23), 5-HT_2 (45) and 5-HT_3 (44) receptors. Some of these subtypes have been evaluated for their role in feeding behavior. Agonists of the 5-HT_{1A} receptor stimulate food intake, presumably through activation of 5-HT autoreceptors (11–13, 19, 27, 28). In contrast, agonists of the 5-HT_{1B} and the 5-HT_{1C} receptors inhibit food intake (26, 31, 32, 48). Methysergide, a nonselective 5-HT antagonist, reverses the inhibition of feeding elicited by 5-hydroxytryptophan (5-HTP) without affecting deprivation-induced feeding (14). However, methysergide has been shown to stimulate feeding in well-satiated rats (10,16). Ritanserin, a very potent and selective 5-HT_2 antagonist (36) reversed systemic 5-HT and quipazine hypophagia without altering food intake itself (40,52), but stimulated food intake in well-satiated rats [(16), but see (10)]. Ketanserin, a 5-HT_2 (35) and alpha$_1$-adrenoceptor (17,29) antagonist reversed fenfluramine anorexia, but failed to alter food intake itself (10, 24, 32).

Supraspinal opioid analgesia has been shown to be dependent upon the serotonergic bulbo-spinal system for its full expression [see reviews, (1,15)]. However, relatively little is known about the interaction between endogenous opioid and serotonergic systems upon food intake. Fernandez-Tome and co-workers (14) found that peripheral, but not central, coadministration of 5-HTP potentiated the hypophagic actions of naloxone and high doses of morphine in food-deprived rats. The present study evaluated possible interactions in food-deprived rats between the hypophagic actions of naloxone (5, 7, 18), a nonselective opiate receptor an-

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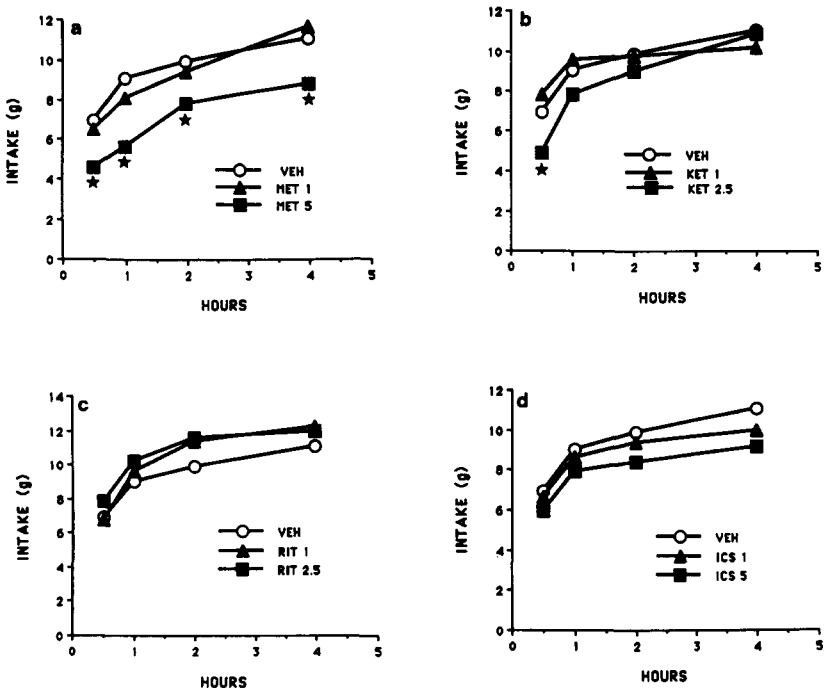

FIG. 1. Alterations in deprivation (24 h)-induced food intake following systemic administration of vehicle (VEH) and either a) methysergide (MET, 1 or 5 mg/kg), b) ketanserin (KET, 1 or 2.5 mg/kg), c) ritanserin (RIT, 1 or 2.5 mg/kg), or d) ICS 205930 (ICS, 1 or 5 mg/kg). The dark stars denote a significant difference in intake relative to the corresponding VEH condition in this and succeeding figures (Dunnett comparisons, $p<0.05$).

tagonist [see review, (49)], and the following serotonin antagonists: methysergide [general 5-HT, (44)], ketanserin [5-HT_2, (36)], ritanserin [5-HT_2, (37)] and ICS 205930 [5-HT_3, (46)].

METHOD

Forty adult male albino Sprague-Dawley rats (400–500 g; Charles River Laboratories, Wilmington, MA) were maintained individually in wire mesh cages on a 12-h light:12-h dark cycle with Purina rat chow and water available ad lib. In all experiments, rats were initially monitored daily for body weight and food intake over three days to establish normal intake patterns.

Four groups of ten rats each were exposed to ten injection conditions at weekly intervals. Each rat was deprived of food, but not water, for 24 h prior to food reintroduction during the first hour of the light cycle. Intake was determined by weighing food pellets prior to and after each condition and adjusting for spillage at 0.5, 1, 2 and 24 h after reintroduction of food. Body weight was determined prior to, and then 24 and 48 h after food deprivation. The first and tenth conditions were always pairs of vehicle injections to determine whether any long-term changes in intake occurred over the testing period. Significant differences in deprivation-induced intake failed to occur between the two vehicle conditions; therefore, these values were pooled for each animal to derive a vehicle score. The first group of rats received the following intervening conditions according to an incompletely counterbalanced design: vehicle paired with naloxone hydrochloride (Sigma Chemical Company) at doses of 1 and 5 mg/kg, methysergide (Sandoz) at doses of 1 and 5 mg/kg paired with vehicle, methysergide at a dose of 1 mg/kg paired with each dose of naloxone, and methysergide at a dose of 5 mg/kg paired with each dose of naloxone. The above protocol was utilized in succeeding groups, except that either ketanserin (Group 2, Janssen) at doses of 1 and 2.5 mg/kg, ritanserin (Group 3, Janssen) at doses of 1 and 2.5 mg/kg or ICS 205930 (Group 4, Sandoz) at doses of 1 and 5 mg/kg was used in lieu of methysergide. An interval of 15 min elapsed between the first and second injections, and an interval of 15 min elapsed between the second injection and food reintroduction. All injections were administered in a 1 ml/kg volume with naloxone and methysergide dissolved in 0.9% normal saline and injected intraperitoneally. Ketanserin was dissolved in distilled water and injected intraperitoneally. Ritanserin was initially prepared in 100% methanol at a concentration of 10 mg/ml, and then titrated with 0.9% normal saline to concentrations of 1 and 2.5 mg/ml 0.5 h prior to subcutaneous administration. ICS 205930 was initially prepared in 100% DMSO at a concentration of 6 mg/ml and then titrated with 0.9% normal saline to concentrations of 1 and 5 mg/ml prior to subcutaneous administration. Comparable vehicle control solutions were made and administered by the same routes. Significant differences in deprivation-induced feeding failed to occur among the different vehicle conditions; therefore, these data were pooled. Split-plot analyses of variance assessed significant effects upon individual intake points and body weights. Dunnett comparisons were used to discern differences between vehicle and individual drug treatments. Dunn comparisons were used to discern differences between naloxone and different 5-HT antagonist/naloxone treatments.

RESULTS

5-HT Receptor Antagonists and Deprivation-Induced Feeding

Figure 1 illustrates the short-term effects of the four 5-HT receptor subtype antagonists upon food intake following 24 h of food deprivation. The high (5 mg/kg) dose of methysergide sig-

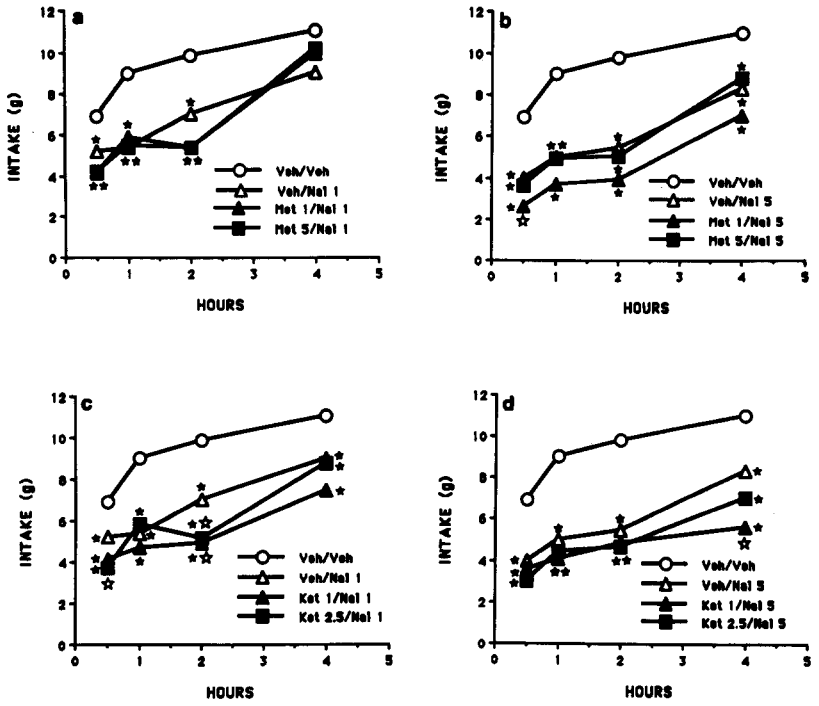

FIG. 2. Alterations in deprivation-induced intake following systemic administration of either vehicle (Veh) or naloxone (NAL; 1 mg/kg: left panels; 5 mg/kg: right panels) in rats pretreated with either methysergide (Met: a and b) or ketanserin (Ket: c and d). The open stars denote a significant difference in intake relative to the corresponding Veh/Nal condition in this and succeeding figures (Dunn comparisons, $p<0.05$).

nificantly decreased intake by 34% across a 4-h time course (Fig. 1a). The high (2.5 mg/kg) dose of ketanserin significantly decreased deprivation-induced intake by 28% only after 0.5 h (Fig. 1b). Deprivation-induced intake failed to be affected by either ritanserin (Fig. 1c) or ICS 205930 (Fig. 1d) treatment.

Methysergide/Naloxone Interactions

Naloxone significantly reduced deprivation-induced intake by 25–40% over 2 h following the 1 mg/kg dose, and by 24–45% over 4 h following the 5 mg/kg dose. Pairing either dose of methysergide with the 1 mg/kg dose of naloxone failed to alter the latter's inhibition of deprivation-induced feeding (Fig. 2a). Pairing the lower (1 mg/kg), but not the higher (5 mg/kg) dose of methysergide with the 5 mg/kg dose of naloxone significantly increased the latter's inhibition of deprivation-induced feeding from 43% to 62% only after 0.5 h (Fig. 2b).

Ketanserin/Naloxone Interactions

The inhibition of deprivation-induced feeding induced by a 1 mg/kg dose of naloxone was significantly increased from 29% to 51% 2 h following its pairing with the 1 mg/kg dose of ketanserin (Fig. 2c). Pairing the higher (2.5 mg/kg) dose of ketanserin with the 1 mg/kg dose of naloxone also significantly increased the latter's inhibition of deprivation-induced feeding at 0.5 (25% to 38%) and 2 (29% to 47%) h after injection (Fig. 2c). The inhibition of deprivation-induced feeding induced by the 5 mg/kg dose of naloxone was significantly increased from 24% to 49% 4 h following its pairing with the 1 mg/kg dose of ketanserin, but was unaffected by the higher ketanserin dose (Fig. 2d).

Ritanserin/Naloxone Interactions

The significant 25–40% inhibition of deprivation-induced feeding induced over 2 h by a 1 mg/kg dose of naloxone was eliminated following its pairing with the 1 mg/kg dose of ritanserin (Fig. 3a). However, this reduction in naloxone's hypophagic actions was not noted following either the pairing of the 2.5 mg/kg dose of ritanserin with the 1 mg/kg dose of naloxone, or the pairings of the 1 and 2.5 mg/kg doses of ritanserin with the 5 mg/kg dose of naloxone (Fig. 3a, b).

ICS 205930/Naloxone Interactions

Pairing the 1 mg/kg dose of ICS 205930 with the 1 mg/kg dose of naloxone significantly increased the latter's inhibition of deprivation-induced feeding at 1 (40% to 49%), 2 (29% to 53%) and 4 (19% to 51%) h after injection (Fig. 3c). Pairing the 5 mg/kg dose of ICS 205930 with the 1 mg/kg dose of naloxone significantly increased the latter's inhibition of deprivation-induced feeding at 1 (40% to 54%), 2 (29% to 59%) and 4 (19% to 50%) h after injection (Fig. 3c). Pairing the 5 mg/kg dose of ICS 205930 with the 5 mg/kg dose of naloxone significantly increased the latter's inhibition of deprivation-induced feeding at 1 (45% to 86%), 2 (45% to 85%) and 4 (24% to 76%) h after injection (Fig. 3d).

Long-Term 5-HT/Naloxone Interactions

Table 1 summarizes the significant changes in food intake and

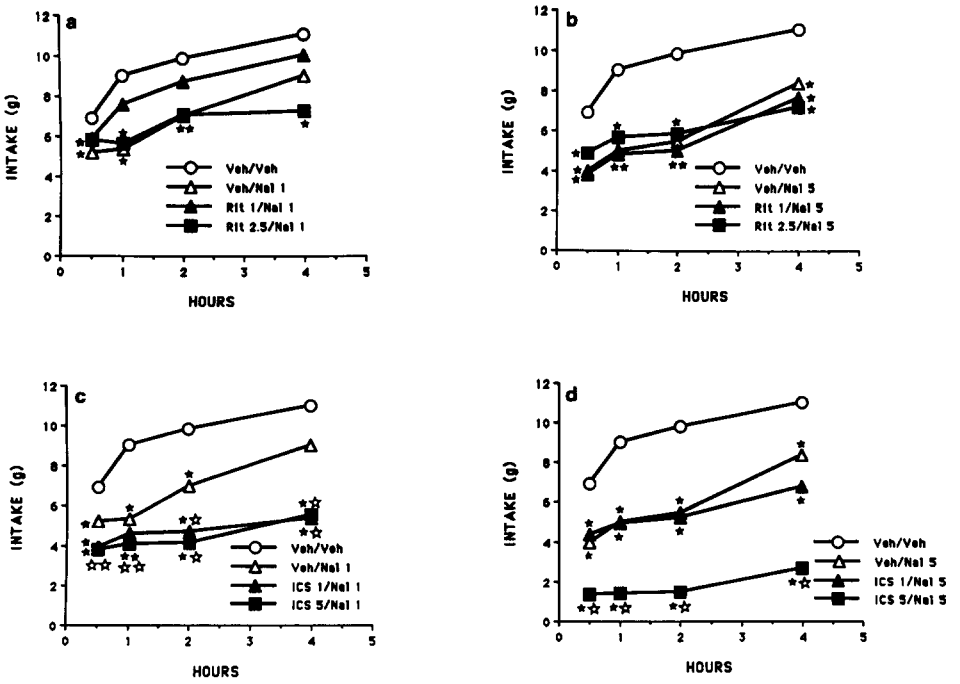

FIG. 3. Alterations in deprivation-induced intake followed systemic administration of either Veh or NAL in rats pretreated with either ritanserin (Rit: a and b) or ICS 205930 (ICS: c and d).

body weight recovery 24 h after reintroduction of food to food-deprived rats after paired and separate naloxone and 5-HT antagonist treatments. Naloxone failed to alter food intake or body weight recovery 24 h after injection. Both methysergide doses significantly retarded body weight recovery, but failed to alter 24-h intake. The low dose of ketanserin significantly increased 24-h intake without altering body weight recovery. The high dose of ritanserin significantly retarded body weight recovery without altering 24-h intake. The high dose of ICS 205930 significantly reduced 24-h intake without altering body weight recovery. A significant reduction in 24-h intake occurred only following the pairing of the high naloxone and low methysergide dose. Significant retardation of body weight recovery occurred following the pairing of both methysergide doses with the low naloxone dose, but a significant facilitation of body weight recovery occurred following the pairing of the high methysergide and naloxone doses. Both doses of ketanserin when paired with the low naloxone dose significantly reduced 24-h intake and retarded body weight recovery. Pairing the low ketanserin and high naloxone doses significantly retarded body weight recovery. The pairing of both doses of either ritanserin or ICS 205930 with both doses of naloxone significantly reduced 24-h intake. In contrast, pairing the high dose of either ritanserin or ICS 205930 with the low naloxone dose significantly facilitated body weight recovery. The above changes in long-term food intake and body weight recovery across treatments failed to correlate with one another ($r = .068$), nor was there any consistent correspondence between short-term and long-term effects upon intake within treatments.

DISCUSSION

Serotonin, its precursor, and drugs that either increase its release, or inhibit its metabolism all inhibit food intake (3,4). These data would suggest that 5-HT antagonists would stimulate food intake themselves, and might prevent anorectic actions of other systems. The present data indicate that this schema is incorrect,

TABLE 1

FOOD INTAKE (FI: g, SEM) AND BODY WEIGHT CHANGE RELATIVE TO PREDEPRIVATION LEVELS (BW: g, SEM) 24 h AFTER FOOD REINTRODUCTION IN FOOD-DEPRIVED RATS TREATED WITH NALOXONE (NAL) AND/OR DIFFERENT SEROTONIN RECEPTOR ANTAGONISTS

		Treatment		
Pretreatment		Vehicle	NAL (1 mg/kg)	NAL (5 mg/kg)
Vehicle	FI	33.2 (0.5)	33.6 (0.7)	32.4 (0.6)
	BW	−5.6 (0.8)	−5.1 (1.0)	−3.7 (1.7)
Methysergide				
1.0 mg/kg	FI	32.9 (0.8)	35.0 (1.2)	28.3 (0.7)*
	BW	−9.8 (1.6)*	−9.4 (2.0)	−6.5 (1.8)
5.0 mg/kg	FI	33.4 (2.0)	35.0 (1.4)	33.2 (0.6)
	BW	−8.6 (1.3)*	−14.2 (2.0)*	+17.7 (1.4)†
Ketanserin				
1.0 mg/kg	FI	37.1 (1.3)†	27.7 (0.8)*	31.0 (1.0)
	BW	−7.1 (2.3)	−15.0 (2.3)*	−9.8 (2.3)*
2.5 mg/kg	FI	34.1 (1.2)	27.0 (0.8)*	30.1 (1.3)
	BW	−7.3 (1.5)	−17.4 (4.8)*	−7.4 (2.5)
Ritanserin				
1.0 mg/kg	FI	31.4 (1.0)	29.5 (1.4)*	28.1 (1.1)*
	BW	−6.5 (2.0)	−9.6 (2.0)*	−6.7 (1.9)
2.5 mg/kg	FI	31.5 (1.3)	29.0 (0.8)*	28.5 (1.0)*
	BW	−11.7 (1.5)*	−3.5 (1.4)†	−6.9 (1.4)
ICS 205930				
1.0 mg/kg	FI	33.3 (0.6)	30.3 (0.9)*	29.1 (0.9)*
	BW	−5.7 (2.1)	−5.0 (1.6)	−5.3 (1.9)
5.0 mg/kg	FI	29.5 (0.6)*	28.8 (1.2)*	26.7 (0.8)*
	BW	−6.1 (1.8)	−2.3 (2.0)†	−7.4 (0.9)

Note: Significant reductions (*) and increases (†) in food intake and in body weight change relative to predeprivation levels are evaluated for each treatment relative to vehicle/vehicle treatments (Dunnett Comparisons, $p<0.05$).

and that rather, 5-HT receptor subtypes play differential and, in some cases mutually antagonistic roles, upon food intake and its relationship to opioid systems. The general 5-HT antagonist, methysergide dose-dependently reduced deprivation-induced feeding with the higher 5 mg/kg dose reducing intake by 34%. The previous failure to observe differences in deprivation-induced feeding following methysergide utilized chronic limited-access feeding schedules rather than acute deprivation (14). The 5-HT_2 receptor antagonist, ketanserin transiently reduced deprivation-induced intake by 28%; this mild, short-term effect is consistent with the relative inability of ketanserin to affect free feeding (10,24). Neither ritanserin, a 5-HT_2 receptor antagonist, nor ICS 205930, a 5-HT_3 receptor antagonist, altered deprivation-induced feeding themselves; these effects are also consistent with previous studies in other feeding models (10, 40, 52).

Naloxone and each of the four 5-HT receptor antagonists utilized in the present study are short-acting, and have reversible effects at their respective receptors [see reviews, (9, 44, 49)]. Therefore, it seems surprising that both intake 24 h after food reintroduction and body weight recovery were affected by some of the above manipulations. Two points need to be made. First, a consistent correspondence between changes in long-term intake and body weight recovery failed to occur, suggesting that these changes were sporadic and not linked. Second, the relationship between short-term and long-term intake changes were not consistently observed within treatments. These points suggest that the longer-term effects could be due to other factors as they relate to either body weight recovery (e.g., metabolism) or long-term intake (e.g., pharmacokinetics); the present study cannot distinguish between the different possibilities at this time.

Naloxone produced its expected, dose-dependent reduction in deprivation-induced intake as previously described [e.g., (5, 7, 18)]. The low, but not the high dose of methysergide transiently potentiated hypophagia induced by the high, but not the low dose of naloxone. Methysergide has very high affinity for the 5-HT_{1C} and 5-HT_2 receptors, and moderate affinity for the 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors (44). Given the stimulation of food intake by 5-HT_{1B} and 5-HT_{1C} agonists (26, 31, 32, 48), it would appear that methysergide antagonism at multiple 5-HT receptor subtypes might act to cancel out the different physiological actions of 5-HT at these sites.

The two 5-HT receptor antagonists, ketanserin and ritanserin, respectively potentiated and reduced the magnitude of naloxone hypophagia. Both doses of ketanserin potentiated the hypophagia induced by the 1 mg/kg dose of naloxone, but failed to affect the more pronounced hypophagia induced by the 5 mg/kg dose of naloxone. In contrast, ritanserin reduced the effectiveness of the 1 mg/kg dose of naloxone to produce hypophagia without affecting the hypophagic actions of the 5 mg/kg dose of naloxone. It should be noted, however, that this action of ritanserin was not dose-dependent. Both ketanserin and ritanserin are 5-HT_2 receptor antagonists with the latter considered more potent in binding affinity (36,37). However, ketanserin at these doses also possesses affinity for alpha-adrenoceptors (17,29). Therefore, the ability of ketanserin to potentiate naloxone hypophagia and transiently reduce deprivation-induced feeding itself might be attributable to its interactions with the alpha-adrenergic receptor subtype [e.g., (21)].

Naloxone hypophagia was most markedly and consistently affected by pretreatment with the 5-HT_3 receptor antagonist, ICS 205930. Both doses of ICS 205930 potentiated the hypophagic actions of the 1 mg/kg dose of naloxone across a 4-h time course. The higher dose of ICS 205930 produced pronounced potentiations of the hypophagic actions of the 5 mg/kg dose of naloxone across the 4-h time course transforming a 42–45% inhibition of intake by naloxone alone to a 80–86% inhibition of intake. The interaction of naloxone and ICS 205930 is quite marked since ICS 205930 itself failed to alter deprivation-induced intake. The 5-HT_3 receptor was initially isolated in the periphery (44), however, more recent studies have demonstrated the existence of central 5-HT_3 receptors in the central nervous system (20,33). Since the present study utilized systemic routes of injection, we cannot determine at present whether the interaction between ICS 205930 and naloxone occurs at central or peripheral receptors. However, it should be noted that the modulation of food intake by endogenous opioid and serotonergic systems have been presumed to be centrally mediated (3, 4, 35, 41).

Serotonin and the endogenous opioid system appear to share some similarities in their control of food intake. Fat consumption is selectively decreased by receptor antagonists of serotonin (30) and opioids (39), yet is increased by the opiate agonist, morphine (38,50). Second, the medial hypothalamus, particularly the hypothalamic paraventricular nucleus, appears to mediate in part the hyperphagic properties of endogenous opioids [e.g., (22, 53, 55)], the hypophagic properties of naloxone (55), and the hypophagic properties of serotonin (34, 51, 54). Third, the hyperphagic properties of the endogenous opioids and the hypophagic properties of serotonin appear most pronounced at the onset of the dark cycle (2,34). In its pronounced potentiation of naloxone hypophagia, the 5-HT_3 receptor antagonist, ICS 205930 is acting similarly to 5-HTP (14). This would suggest that a potent and selective agonist of the 5-HT_3 receptor should stimulate feeding and reduce naloxone hypophagia; the present lack of such a selective agonist precludes this experimental test. These data indicate that 5-HT anorexia is not mediated through the 5-HT_3 receptor, and supports the emerging evidence from pharmacological studies that 5-HT receptor subtypes play diverse and antagonistic roles in food intake.

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