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Naltrexone, Serotonin Receptor Subtype Antagonists, and Carbohydrate Intake in Rats

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ISLAM, A. K., T. DOUGHERTY, J. E. KOCH AND R. J. BODNAR. *Naltrexone, serotonin receptor subtype antagonists, and carbohydrate intake in rats.* PHARMACOL BIOCHEM BEHAV **48**(1) 193–201, 1994. – Functional interactions between serotonergic (5-HT) and opioid drugs have been observed with 5-HT_3 receptor antagonism enhancing the inhibitory actions of naloxone and naltrexone in both food-deprived and glucoprivic rats; 5-$HT_{2A/C}$ receptor antagonism enhanced naltrexone's inhibition of insulin hyperphagia. The present study examined whether pretreatment with either general 5-HT (methysergide: 0.5–5 mg/kg), 5-$HT_{2A/C}$ (ritanserin: 0.25–2.5 mg/kg), or 5-HT_3 (ICS 205930: 0.5–5 mg/kg) antagonists altered the pattern and magnitude of ad lib intake of simple (sucrose: 10%) or more complex (maltose dextrin: MD, 10%) carbohydrate solutions, or naltrexone's (0.25–2.5 mg/kg) inhibition of these forms of intake. Methysergide significantly increased the pattern and magnitude of sucrose intake at low (0.5–2.5 mg/kg) doses, and transiently delayed the pattern of MD intake at high (5 mg/kg) doses. Ritanserin significantly accelerated the pattern, but not the magnitude of sucrose intake at low (0.25–1.25 mg/kg) doses without affecting MD intake. ICS 205930 reduced the magnitude of sucrose intake at the highest (5 mg/kg) dose, and transiently reduced MD intake. Naltrexone dose dependently altered the pattern and magnitude of both sucrose and MD intake. Coadministration of ritanserin and naltrexone either eliminated or delayed the pattern of opioid antagonist inhibition of both sucrose and MD intake. Methysergide and ICS 205930 pretreatment produced minor changes in the pattern of naltrexone-induced inhibition. These data indicate that 5-HT receptor subtypes differentially modulate the pattern of carbohydrate intake, and indicate differential ingestive interactions between 5-HT and opioid antagonists under challenge and palatable conditions.

Sucrose Maltose dextrin Naltrexone Methysergide Ritanserin ICS 205930 Carbohydrate intake

A ROLE for serotonin (5-HT) in activating satiety [e.g., (5,6,10)] has been a prevailing view in ingestive behavior, and is supported by the anorectic actions of the 5-HT reuptake inhibitor, fenfluramine [see review (47)]. The identification of 5-HT receptor subtypes and the development of selective subtype agonists and antagonists [see review (22)] have allowed analysis of their effects in ingestive behavior. Administration of the general 5-HT antagonist methysergide stimulates food intake in well-sated rats (11,16), marginally reduces deprivation-induced feeding (1,14), and fails to alter glucoprivic hyperphagia elicited by either 2-deoxy-D-glucose (2DG) or insulin (3,34). Whereas 5-HT_{1A} agonists stimulate intake (12,13,19,24,25), 5-HT_{1B} and 5-$HT_{2A/C}$ receptor agonists inhibit intake [e.g., 23,27–29,48,49,56,57)]. 5-$HT_{2A/C}$ antagonists fail to alter spontaneous intake (11,20,29,41,55), reduce hyperphagia following deprivation (1), 2DG (3), and insulin (34), but stimulate intake in sated rats (16). 5-HT_3 antagonists fail to affect deprivation or 2DG hyperphagia (1,3), but stimulate insulin hyperphagia (34).

Functional interactions between 5-HT and opioid drugs in modulating food intake include the observation that peripheral 5-hydroxytryptophan significantly potentiated naloxone hypophagia in food-deprived rats (14). Further, the hyperphagia induced by 5-HT_{1A} agonists is inhibited by naloxone (17). Pretreatment with the 5-HT_3 antagonist, ICS 205930, potentiated the hypophagic properties of naloxone and naltrexone in food-deprived rats and in rats treated with either 2DG or insulin (1,3,34). Whereas the 5-$HT_{2A/C}$ antagonist ritanserin enhanced naltrexone's inhibition of insulin hyperphagia, it produced less consistent effects upon opioid antagonist inhibition

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of deprivation-induced and 2DG hyperphagia. Finally, methysergide inconsistently affected these forms of opioid modulation (1,3,34).

Naloxone and naltrexone inhibit different forms of food intake [see reviews (37,43)], including carbohydrate intake: sucrose (32,33,46,58) and maltose dextrin [MD (4)]. Sucrose and MD intake are both inhibited by mu antagonists, while the former is only inhibited by kappa antagonists (2,4). Both general (4,30–33) and specific (2,4) opioid antagonists produce a delayed pattern of inhibition upon sucrose and MD intake, indicating alterations in the maintainance rather than the initiation of palatable intake.

Because previous studies of functional interactions between opioid and 5-HT antagonists upon food intake were limited to challenge situations (1,3,14,34), the present study examined alterations in these two forms of palatable intake following methysergide (general), ritanserin (5-$HT_{2A/C}$) and ICS 205930 (5-HT_3) pretreatment alone and in combination with naltrexone. Because opioid antagonists delay the patterns of sucrose and MD intake, the two forms of intake were monitored cumulatively at 5 min intervals over a 60 min time course to determine whether these serotonergic antagonists altered patterns as well as magnitude of intake.

METHOD

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 IACUC.

Drugs

Methysergide (Sandoz, East Hanover, NJ) was dissolved in 0.9% normal saline and administered intraperitoneally. Ri-

TABLE 1

SUMMARY OF PROTOCOLS FOR SEROTONERGIC AND OPIOID ANTAGONIST EFFECTS UPON SUCROSE AND MALTOSE DEXTRIN INTAKE

A. Serotonergic Antagonists Alone

Condition (mg/kg)	Sucrose Intake (*n*)	MD Intake (*n*)
Vehicle	21	19
Methysergide (0.5)	9	10
Methysergide (2.5)	9	10
Methysergide (5.0)	9	10
Ritanserin (0.25)	7	5
Ritanserin (1.25)	7	8
Ritanserin (2.50)	6	8
ISC205930 (0.5)	7	7
ICS205930 (2.5)	7	7
ICS205930 (5.0)	7	7

B. Serotonergic-Opioid Antagonist Interactions:

First Injection (mg/kg)	Second Injection (mg/kg)	Sucrose Intake (*n*)	MD Intake (*n*)
Vehicle	Vehicle	21	19
Vehicle	Naltrexone (0.25)	10	–
Methysergide (5.0)	Naltrexone (0.25)	7	–
Ritanserin (0.25)	Naltrexone (0.25)	7	–
Ritanserin (2.50)	Naltrexone (0.25)	7	–
ICS205930 (5.0)	Naltrexone (0.25)	7	–
Vehicle	Naltrexone (1.0)	9	10
Methysergide (0.5)	Naltrexone (1.0)	–	7
Methysergide (5.0)	Naltrexone (1.0)	7	7
Ritanserin (0.25)	Naltrexone (1.0)	7	7
Ritanserin (2.50)	Naltrexone (1.0)	7	7
ICS205930 (0.5)	Naltrexone (1.0)	–	7
ICS205930 (5.0)	Naltrexone (1.0)	7	7
Vehicle	Naltrexone (2.5)	–	7
Methysergide (0.5)	Naltrexone (2.5)	–	7
Methysergide (5.0)	Naltrexone (2.5)	–	7
Ritanserin (0.25)	Naltrexone (2.5)	–	7
Ritanserin (2.50)	Naltrexone (2.5)	–	7
ICS205930 (0.5)	Naltrexone (2.5)	–	7
ICS205930 (5.0)	Naltrexone (2.5)	–	7

tanserin (Janssen, Beerse, Belgium), administered subcutaneously (SC), 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 205930 (Sandoz, Basle, Switzerland), administered SC, was initially prepared in 100% dimethyl sulfoxide 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. Naltrexone (Sigma, St. Louis, MO), administered SC, was dissolved in 0.9% normal saline. The serotonergic antagonist doses were chosen for their effectiveness upon other forms of intake (1,3,34), while the naltrexone doses were chosen for their effectiveness upon sucrose (2,30–33,46,58) and MD (4) intake.

Preliminary Testing

Rats were initially water deprived for 24 h, and then given 1 h access to either a 10% sucrose (Sigma) or a 10% MD (Bio-Serv) solution in a sipper tube (Lab Products, 55 ml, 1 ml gradations). Three ad lib tests occurred in the presence of both the test solution (front of the cage) and the automatic watering system (rear of the cage). Cumulative intakes were assessed at 5 min intervals for up to 1 h. A criterion intake (10 ml over 1 h) of the test solution was necessary for the animal to proceed in antagonist testing. Because rats sampled water infrequently during testing, only intake of the test solutions were evaluated.

Sucrose Intake Protocol

A group of 21 naive rats were initially tested for sucrose intake 15 min following vehicle administration. Subgroups of rats, matched for baseline sucrose intake, were exposed at weekly intervals to the conditions summarized in Table 1. Sucrose was introduced 15 min after serotonergic antagonist injections alone. In serotonergic-opioid combinations, the serotonergic antagonist was administered 15 min prior to the opioid antagonist, and the sucrose solution was introduced 15 min after the second injection. These injection intervals produced positive effects in previous studies of serotonergic and opioid ingestive effects (1,3,34). Intake of the 10% sucrose solution in tap water was assessed cumulatively at 5 min intervals for up to 1 h.

MD Intake Protocol

A group of 19 naive rats were initially tested for MD intake 15 min following vehicle administration. Subgroups of rats, matched for their baseline MD intake, were exposed at weekly intervals to the conditions summarized in Table 1. Injection intervals were identical to that described in the sucrose protocol. Intake of the 10% MD solution in tap water was assessed cumulatively at 5 min intervals for up to 1 h.

Statistical Analyses

The primary goals of this study were to determine if serotonergic and opioid antagonists, given alone or together, would: a) alter the magnitude of sucrose and MD intake, and b) alter the temporal pattern of intake over a time course. These data could be assessed in one of two ways: a) intakes at each of the 12 5-min intervals could be recorded individually and subjected to a split-plot analysis of variance with interval as a repeated measure, or b) intakes over the 12 intervals could

TABLE 2

SUMMARY OF SEROTONERGIC ANTAGONIST EFFECTS UPON SUCROSE INTAKE

Injection (mg/kg)	Time (min)											
	5	10	15	20	25	30	35	40	45	50	55	60
Veh	2.4	4.5	6.2	8.5	10.1	11.0	11.8	12.3	13.2	14.8	15.2	16.4
SEM	0.4	0.6	0.8	0.8	0.9	0.8	0.8	0.8	0.8	0.7	0.7	0.8
Met-0.5	3.3	8.1*	12.8*	14.6*	15.8*	17.3*	18.0*	18.2*	19.2*	20.1*	20.9*	21.4*
SEM	0.3	0.5	0.7	0.8	1.0	0.9	0.7	0.9	1.0	1.1	1.2	1.2
Met-2.5	2.8	6.3	9.1	11.1	12.4	13.6	14.3	15.9	17.9	19.1	19.9*	21.4*
SEM	0.6	0.8	1.1	1.3	1.4	1.3	1.3	1.3	1.1	0.8	0.5	0.7
Met-5.0	2.7	5.4	6.8	9.9	11.2	13.0	13.9	14.8	15.3	16.6	17.2	18.1
SEM	0.7	1.3	1.7	2.0	2.1	2.1	2.2	2.0	2.0	1.9	2.0	2.1
Rit-0.25	4.7	9.3*	12.1*	12.7	14.3	14.4	15.0	16.1	16.4	17.0	17.6	18.7
SEM	0.8	0.8	0.8	1.1	1.1	1.1	1.1	1.2	1.3	1.2	1.4	1.3
Rit-1.25	3.7	6.4	8.9	11.7	14.3	15.7	17.3*	18.0*	18.7*	19.9*	20.3*	20.9
SEM	0.4	0.4	0.6	1.1	0.9	1.3	1.7	1.6	1.7	1.7	1.6	1.4
Rit-2.50	3.8	6.3	9.3	9.9	11.1	11.6	11.7	11.7	12.3	12.7	13.1	13.4
SEM	0.6	1.0	1.5	1.5	1.6	1.7	1.7	1.7	1.7	1.7	1.6	1.5
ICS-0.5	3.6	7.3	10.0	11.3	12.6	13.4	14.1	14.9	15.6	16.9	17.0	17.7
SEM	0.7	1.0	1.5	1.6	1.4	1.2	0.7	1.0	1.1	1.3	1.3	1.4
ICS-2.5	1.3	3.7	7.3	9.0	11.6	12.1	13.1	14.4	14.9	15.1	15.1	15.4
SEM	0.6	1.2	2.1	1.8	2.1	2.2	1.6	1.1	1.3	1.3	1.3	1.4
ICS-5.0	1.4	2.3	4.0	6.1	6.3	6.7	7.0	7.9	8.6	9.0*	9.1*	10.4*
SEM	0.7	1.3	1.3	1.7	1.7	1.7	1.6	2.2	2.2	2.3	2.3	2.4

Veh: vehicle; Ntx: naltrexone; Met: methysergide; Rit: ritanserin; ICS: ICS205930. *Denotes significant difference relative to Veh (Dunnett comparison, $p < 0.01$).

be recorded cumulatively with each of the resultant 12 data points evaluated in separate analyses of variance. Although the former option is preferable statistically because it controls for the occurrence of Type I errors, it does not reflect the temporal pattern of intake over the time course. Indeed, evaluation of each form of intake following vehicle treatment revealed significant declines over the time course for both sucrose, $F(11, 220) = 6.60$, $p < 0.001$, and MD, $F(11, 198) = 58.39$, $p < 0.001$, intakes. These time-dependent patterns of sucrose and MD intakes in vehicle-treated rats render temporal patterns of drug effects meaningless. In contrast, analyses of cumulative intake more clearly reflects any temporal changes in the time course. Although these cumulative analyses evaluate separate values at each time point, a more conservative criterion for Dunnett comparisons ($p < 0.01$) was employed to assess significant effects, and caveats regarding interpretation of isolated significant effects appear in the discussion section.

RESULTS

Serotonin Antagonists and Sucrose Intake

Significant differences in cumulative sucrose intake were observed from 10–60 min following vehicle and methysergide treatments, $F(3, 44) = 3.65$–7.56, $p < 0.02$–0.0003. Sucrose intake was significantly stimulated by the methysergide dose of 0.5 mg/kg from 10 to 60 min, and to a lesser degree by the 2.5 mg/kg dose at 55 and 60 min (Table 2). These methysergide doses significantly increased the overall magnitude of sucrose intake by 30%. Significant differences in cumulative sucrose intake were observed across the time course following vehicle and ritanserin treatments, $F(3, 38) = 3.29$–7.64, $p < 0.03$–0.0004. Sucrose intake was significantly stimulated by the ritanserin dose of 1.25 mg/kg from 35 to 55 min and, to a lesser degree, by the 0.25 mg/kg dose at 10 and 15 min (Table 2). The dose range of ritanserin failed to significantly alter the overall magnitude of sucrose intake (18% reduction–25% increase). Significant differences in cumulative sucrose intake were observed at 10–15 and 25–60 min following vehicle and ICS 205930 treatments, $F(3, 38) = 2.91$–5.67, $p < 0.047$–0.003. Sucrose intake was significantly reduced by the ICS 205930 dose of 5 mg/kg at 50 to 60 min with a reduction in the overall magnitude of the effect of 37% (Table 2).

Serotonin Antagonists and MD Intake

Significant differences in cumulative MD intake were observed at 5–55 min following vehicle and methysergide treatments, $F(3, 36) = 2.89$–5.19, $p < 0.049$–0.004. MD intake was significantly reduced by the methysergide dose of 5 mg/kg at 10 to 15 min (Table 3). The dose range of methysergide failed to significantly alter the overall magnitude of MD intake (8–32% reductions). Significant differences in cumulative MD intake failed to occur at any interval following vehicle and ritanserin treatments (1% reduction–11 % increase, Table 3). Significant differences in cumulative MD intake were observed across the time course following vehicle and ICS 205930 treatments, $F(3, 24) = 3.14$–12.05, $p < 0.044$–0.0001. MD intake was significantly increased by the 0.5 mg/kg dose of ICS 205930 and reduced by the 5 mg/kg dose of ICS 205930 only at the 5 min intake interval (Table 3), and

TABLE 3

SUMMARY OF SEROTONERGIC ANTAGONIST EFFECTS UPON MALTOSE DEXTRIN INTAKE

Injection (mg/kg)	Time (min)											
	5	10	15	20	25	30	35	40	45	50	55	60
Veh	5.3	9.2	11.4	12.3	12.9	13.5	13.9	14.4	14.5	15.1	15.4	15.8
SEM	0.5	0.5	0.5	0.4	0.5	0.5	0.6	0.6	0.5	0.6	0.6	0.6
Met-0.5	5.2	8.8	11.2	12.5	13.5	13.6	13.7	13.9	14.0	14.6	14.6	14.6
SEM	0.7	0.8	0.9	0.9	1.1	1.2	1.2	1.3	1.3	1.5	1.5	1.5
Met-2.5	3.9	5.9	7.4	8.8	9.6	9.8	9.9	10.8	11.1	11.4	11.8	12.2
SEM	0.9	1.2	1.3	1.4	1.4	1.5	1.5	1.3	1.3	1.2	1.2	1.2
Met-5.0	2.3	4.9*	6.6*	7.5	8.6	9.1	9.3	9.4	9.7	9.9	10.4	10.8
SEM	0.6	0.8	1.3	1.3	1.3	1.4	1.5	1.4	1.4	1.5	1.6	1.7
Rit-0.25	4.8	10.0	12.0	12.6	13.2	13.4	14.2	15.2	15.4	15.6	15.6	15.6
SEM	1.0	1.5	1.9	2.2	2.0	2.0	1.9	1.9	1.9	1.8	1.8	1.8
Rit-1.25	5.8	9.8	12.6	13.8	14.8	15.8	15.9	16.3	16.3	16.3	16.4	16.5
SEM	0.6	0.7	1.0	1.0	1.2	1.3	1.3	1.2	1.2	1.2	1.3	1.4
Rit-2.50	6.5	11.5	14.3	15.3	15.9	16.5	17.0	17.0	17.0	17.4	17.4	17.4
SEM	1.1	1.4	1.5	1.5	1.4	1.4	1.5	1.5	1.5	1.6	1.6	1.6
ICS-0.5	7.6*	12.0	15.4	16.1	16.4	16.7	17.1	17.1	17.6	18.4	18.7	19.3
SEM	0.8	0.8	1.4	1.6	1.5	1.5	1.4	1.4	1.4	1.7	2.0	2.1
ICS-2.5	5.4	9.1	12.9	14.4	15.3	15.7	15.9	15.9	15.9	16.9	17.0	17.6
SEM	0.8	1.4	1.7	1.9	1.8	1.7	1.7	1.7	1.7	1.5	1.4	1.6
ICS-5.0	2.3*	6.0	7.3	8.9	10.1	10.6	10.7	11.1	11.4	11.6	12.1	12.4
SEM	0.4	0.9	1.2	1.4	1.2	1.3	1.3	1.6	1.5	1.5	1.3	1.3

Veh: vehicle; Ntx: naltrexone; Met: methysergide; Rit: ritanserin; ICS: ICS205930. *Denotes significant difference relative to Veh (Dunnett comparison, $p < 0.01$).

overall magnitudes of intake failed to differ from vehicle (22% reduction–22% increase).

Serotonin-Opioid Antagonists and Sucrose Intake

Significant differences in cumulative sucrose intake were observed following vehicle, naltrexone, and serotonergic antagonist treatments, $F(3, 46) = 3.60–17.00$, $p < 0.02–0.0001$. Sucrose intake was significantly reduced the 0.25 mg/kg dose of naltrexone only at 60 min, resulting in a 32% reduction in the overall magnitude of intake. The 1 mg/kg dose of naltrexone significantly reduced sucrose intake from 25 to 60 min, resulting in a 63% reduction in the overall magnitude of intake (Table 4). The patterns of naltrexone's inhibition of sucrose intake were altered by 5-HT antagonists. Animals treated with methysergide (5 mg/kg) and naltrexone exhitited only transient (5 min) delays in the pattern of both doses of naltrexone's inhibition of sucrose intake (Table 4). Animals treated with ritanserin (0.25 mg/kg) and naltrexone (1 mg/kg) failed to display any inhibitory effects upon sucrose intake, while animals treated with ritanserin (1.25 mg/kg) and naltrexone (1 mg/kg) exhibited a 20 min delay (45–60 min) in the pattern of naltrexone's inhibition of sucrose intake (Table 4). Less pronounced effects were observed for ritanserin's interaction with the lower naltrexone dose. Animals treated with ICS 205930 (5 mg/kg) and naltrexone (0.25 mg/kg) only exhibited a transient (10 min) acceleration in the pattern of naltrexone's inhibitory effects upon sucrose intake (Table 4).

Serotonin-Opioid Antagonists and MD Intake

Significant differences in cumulative MD intake were observed following vehicle, naltrexone, and serotonergic antagonist treatments, $F(2, 24) = 4.27–62.20$, $p < 0.026–0.0001$. MD intake was significantly reduced by both naltrexone doses from 10 to 60 min with respective reductions in overall magnitudes of intake of 61% and 68% for the 1 and 2.5 mg/kg doses (Table 5). Animals treated with methysergide (5 mg/kg) and naltrexone (1 mg/kg) only exhibited a transient (10 min) delay in the pattern of naltrexone's inhibitory effects upon MD intake (Table 5). Animals treated with either ritanserin (0.25 mg/kg) and naltrexone (1 mg/kg) or ritanserin (2.5 mg/kg) and naltrexone (2.5 mg/kg) failed to display any inhibitory effects upon MD intake, while animals treated with ritanserin (2.5 mg/kg) and naltrexone (1 mg/kg) exhibited a 20 min delay (30–60 min) in the pattern of naltrexone's inhibition of MD intake (Table 5). Animals treated with ICS 205930 and naltrexone failed to alter the pattern of naltrexone's inhibitory effects upon MD intake, except for a transient 5 min acceleration at the highest doses of each antagonist.

DISCUSSION

The present study found that low doses of methysergide significantly accelerated the pattern of sucrose intake across a 1 h time course and increased its magnitude by 30%. In contrast, high doses of methysergide transiently (10–15 min) decreased MD intake. Low doses of ritanserin significantly ac-

TABLE 4

SUMMARY OF SEROTONERGIC AND OPIOID ANTAGONIST EFFECTS UPON SUCROSE INTAKE

First Injection (mg/kg)	Second Injection (mg/kg)	Time (min)											
		5	10	15	20	25	30	35	40	45	50	55	60
Veh	Veh	2.4	4.5	6.2	8.5	10.1	11.0	11.8	12.3	13.2	14.8	15.2	16.4
SEM		0.4	0.6	0.8	0.8	0.9	0.8	0.8	0.8	0.8	0.7	0.7	0.8
Veh	Ntx-0.25	2.9	5.2	6.9	7.3	8.6	8.9	9.6	10.0	10.0	10.6	11.0	11.2*
SEM		0.7	1.2	1.2	1.3	1.3	1.2	1.2	1.1	1.1	1.1	1.1	1.1
Met-5.0	Ntx-0.25	2.4	5.6	5.9	7.9	9.0	10.6	11.7	12.3	12.4	12.9	14.0	14.1
SEM		0.6	1.3	1.7	1.9	2.0	1.6	1.5	1.3	1.1	1.0	1.2	1.3
Rit-0.25	Ntx-0.25	5.4*	7.4	8.4	8.9	9.1	9.6	10.3	10.7	10.9	12.0	13.0	13.1
SEM		0.8	0.8	1.0	0.9	0.8	0.7	0.6	0.6	0.6	0.8	1.4	1.4
Rit-2.50	Ntx-0.25	6.1*†	8.1	8.4	8.7	8.7	8.9	8.9	9.0	9.0	9.0*	9.0*	9.0*
SEM		0.3	0.5	0.5	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
ICS-5.0	Ntx-0.25	2.9	4.1	5.4	7.1	8.1	8.4	8.7	9.1	9.3	10.0*	10.0*	10.3*
SEM		0.6	0.7	0.9	0.9	1.0	1.2	1.3	1.2	1.1	1.3	1.3	1.5
Veh	Ntx-1.0	0.9	2.8	3.4	3.8	4.3*	4.6*	4.7*	4.7*	4.9*	5.6*	5.6*	6.1*
SEM		0.5	0.8	1.1	1.2	1.1	1.1	1.2	1.1	1.1	1.2	1.2	1.3
Met-5.0	Ntx-1.0	3.3	4.4	5.1	5.3	5.6	5.9*	6.0*	6.3*	7.4*	7.9*	8.9*	9.6*
SEM		0.7	0.6	0.7	0.7	0.8	0.9	0.9	1.0	1.1	1.0	1.0	1.0
Rit-0.25	Ntx-1.0	7.6*†	9.7*†	11.0†	11.4†	12.1†	13.1†	13.1†	13.6†	13.9†	14.3†	14.3†	14.3†
SEM		1.3	1.7	2.0	1.8	1.5	1.0	1.0	1.0	1.0	1.2	1.2	1.2
Rit-2.50	Ntx-1.0	5.4*†	6.4	7.0	7.3	7.7	7.9	7.9	8.1	8.1*	8.1*	8.4*	8.4*
SEM		0.5	0.4	0.4	0.4	0.5	0.6	0.6	0.6	0.6	0.6	0.7	0.7
ICS-5.0	Ntx-1.0	3.3	3.7	3.7	4.0	4.7*	4.9*	4.9*	4.9*	5.4*	5.7*	5.9*	7.3*
SEM		1.2	1.5	1.5	1.5	1.4	1.5	1.5	1.5	1.5	1.6	1.6	1.5

Veh: vehicle; Ntx: naltrexone; Met: methysergide; Rit: ritanserin; ICS: ICS205930. *Denotes significant difference relative to veh/veh (Dunnett comparison, $p < 0.01$). †Denotes significant difference relative to veh/ntx (Dunnett comparison, $p < 0.01$).

TABLE 5

SUMMARY OF SEROTONERGIC AND OPIOID ANTAGONIST EFFECTS UPON MD INTAKE

First Injection (mg/kg)	Second Injection (mg/kg)	Time (min)											
		5	10	15	20	25	30	35	40	45	50	55	60
Veh	Veh	5.3	9.2	11.4	12.3	12.9	13.5	13.9	14.4	14.5	15.1	15.4	15.8
SEM		0.5	0.5	0.5	0.4	0.5	0.5	0.6	0.6	0.5	0.6	0.6	0.6
Veh	Ntx-1.0	3.2	4.3*	4.6*	4.7*	4.7*	5.0*	5.0*	5.1*	5.4*	5.5*	5.8*	6.1*
SEM		0.6	0.6	0.6	0.6	0.6	0.5	0.5	0.5	0.6	0.6	0.6	0.7
Met-0.5	Ntx-1.0	3.6	4.6*	4.7*	5.0*	5.0*	5.0*	5.0*	5.0*	5.3*	5.4*	5.9*	5.9*
SEM		0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.7	0.7	0.9	0.9
Met-5.0	Ntx-1.0	3.6	4.9	5.6	5.9*	6.0*	6.0*	6.1*	6.6*	6.9*	6.9*	6.9*	7.1*
SEM		0.3	0.5	0.7	0.7	0.6	0.6	0.6	0.5	0.6	0.6	0.6	0.5
Rit-0.25	Ntx-1.0	6.6	8.4	8.7	9.0	9.3	9.7	9.9	10.0	10.0	10.0	10.6	10.6
SEM		0.9	0.7	0.8	0.8	0.8	0.6	0.8	0.7	0.7	0.7	0.8	0.8
Rit-2.50	Ntx-1.0	5.0	7.3	7.9	7.9	7.9	7.9*	8.0*	8.1*	8.3*	8.3*	8.6*	9.1*
SEM		0.4	1.0	1.2	1.2	1.2	1.2	1.2	1.3	1.3	1.3	1.2	1.2
ICS-0.5	Ntx-1.0	3.9	5.0	5.7	5.7*	5.7*	5.7*	5.9*	5.9*	5.9*	6.1*	6.1*	6.1*
SEM		0.7	1.2	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.6	1.6	1.6
ICS-5.0	Ntx-1.0	3.4	3.9*	4.1*	4.1*	4.1*	4.1*	4.3*	4.7*	5.1*	5.1*	5.3*	5.4*
SEM		0.8	1.1	1.2	1.2	1.2	1.2	1.2	1.3	1.4	1.4	1.4	1.4
Veh	Ntx-2.5	3.0	3.3*	3.3*	3.6*	3.7*	3.7*	3.9*	4.3*	4.4*	5.0*	5.1*	5.1*
SEM		0.4	0.4	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.8	0.8	0.8
Met-0.5	Ntx-2.5	3.4	3.4*	3.7*	3.9*	4.0*	4.4*	4.4*	4.6*	4.6*	4.9*	5.3*	5.3*
SEM		1.0	1.0	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.8	1.0	1.0
Met-5.0	Ntx-2.5	2.1*	2.9*	2.9*	2.9*	3.4*	3.6*	3.9*	4.0*	4.0*	4.1*	4.3*	4.3*
SEM		0.8	1.0	1.0	1.0	0.9	0.8	1.0	1.1	1.1	1.0	1.1	1.1
Rit-0.25	Ntx-2.5	3.1	3.3*	3.7*	3.9*	4.1*	4.3*	4.4*	4.4*	4.4*	4.9*	5.3*	5.3*
SEM		0.4	0.5	0.7	0.8	0.7	0.7	0.8	0.8	0.8	1.0	1.1	1.1
Rit-2.50	Ntx-2.5	5.0	6.7	7.1	7.7	8.0	8.0	8.0	8.3	8.3	8.3	8.3	8.6
SEM		0.9	1.2	1.2	1.3	1.4	1.4	1.4	1.5	1.5	1.5	1.5	1.3
ICS-0.5	Ntx-2.5	3.0	4.3*	4.4*	4.6*	4.6*	4.9*	5.0*	5.0*	5.1*	5.1*	5.1*	5.4*
SEM		0.6	0.9	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
ICS-5.0	Ntx-2.5	1.0*	1.0*	1.0*	1.6*	1.6*	1.6*	1.6*	1.6*	1.9*	1.9*	1.9*	1.9*
SEM		0.5	0.5	0.5	0.8	0.8	0.8	0.8	0.8	1.0	1.0	1.0	1.0

Veh: vehicle; Ntx: naltrexone; Met: methysergide; Rit: ritanserin; ICS: ICS205930. *Denotes significant difference relative to veh/veh (Dunnett comparison, $p < 0.01$).

celerated the pattern of sucrose intake without significantly affecting overall intake magnitude. In contrast, ritanserin failed to alter MD intake. High doses of ICS 205930 significantly reduced the overall magnitude of sucrose intake by 37% without altering its temporal pattern. ICS 205930 transiently (5 min) reduced MD intake. Serotonergic antagonist effects appeared behaviorally specific because they each altered one form of intake without affecting a second form of intake delivered in the same manner over the same time course. Naltrexone produced significant dose-dependent reductions in both sucrose and MD intake with inhibition appearing after 25 and 10 min, respectively. These delayed effects are similar to that observed previously (2,4,30–33), and suggests that opioid antagonists decrease palatable intake by interfering with the maintainance rather than the initiation of intake. When animals were coadministered ritanserin, naltrexone's inhibitory effects upon sucrose and MD intakes were either delayed or even eliminated. When animals were coadministered either methysergide or ICS 205930, naltrexone's inhibitory effects upon sucrose and MD intakes were minimally affected. These data are discussed in terms of: a) 5-HT antagonist effects upon carbohydrate intake, and b) functional interactions between 5-HT and opioid antagonists upon carbohydrate intake.

5-HT Antagonists and Carbohydrate Intake

Serotonergic drugs appear to affect food intake through a number of mechanisms. The serotonin reuptake inhibitor fluoxetine increases intake latency, decreases meal size and feeding rate, and produces a more rapid satiety sequence from eating to sleeping (9,35,59). The serotonin antagonist, metergoline, blocked fluoxetine's increased latency to feed, yet potentiated the reduction in overall food intake. However, metergoline blocks fenfluramine-induced reductions in feeding rate and numbers of meals in food-deprived rats (8). The differential pattern of serotonergic drugs upon different parameters of feeding was observed in the present study as well.

Methysergide's stimulation of the pattern and magnitude of sucrose intake may be acting through the 5-$HT_{2A/C}$ receptor subtype because : a) ritanserin accelerated the pattern of sucrose intake, and b) both 5-HT_3 and 5-HT_{1A} (15,42) receptor subtype drugs failed to affect sucrose intake. In contrast, serotonergic antagonists produced small and transient changes in MD intake. Thus, the particular time interval to assess intake magnitude and the analysis of intake patterns emerge as critical variables in evaluating serotonergic drug effects.

That 5-HT and 5-$HT_{2A/C}$ antagonists stimulate sucrose but not MD intake has implications for proposed 5-HT mediation of macronutrient intake. Wurtman and co-workers (21,60–62) found that agents that enhance 5-HT transmission reduce carbohydrate consumption, while 5-HT_{1A} agonists stimulate carbohydrate intake (38–40). Indeed, increased carbohydrate consumption noted during the first meal of the dark cycle is selectively reduced by serotonin administration into the hypothalamic paraventricular nucleus (36). Further, when rats were provided with a high-protein and a high-carbohydrate diet, medial hypothalamic administration of either serotonin or *dl*-norfenfluramine significantly and selectively reduced carbohydrate intake (54). The specificity of sertonergic modulation of carbohydrate intake has been questioned. Chronic administration of fenfluramine reduced intake and body weights of rats exposed to either a high-carbohydrate or a high-fat diet, and it was not more potent in reducing the carbohydrate-supplemented diet (7). Further, if the animals were provided a choice of protein, carbohydrate, and fat, fenfluramine reduced both carbohydrate and fat intake (54). 5-HT agonists also reduce fat intake in food-deprived rats (26,44). Finally, because learning of texture cues and sensory characteristics of different macronutrients may be a determinant of 5-HT modulation, it was found that fenfluramine failed to alter the selection of protein-paired or carbohydrate-paired odors in rats (18). A simple model of 5-HT-induced modulation of carbohydrate intake would suggest that both general 5-HT and selective antagonists would potently increase both sucrose and MD intake. That methysergide and ritanserin increase sucrose, but not MD intake, argues for the importance of the type of ingested carbohydrate, and suggests that the 5-HT system may modulate ingestion of more complex carbohydrates in a different way than simple carbohydrates.

An alternative proposal is that the intakes of sucrose and MD are related to palatability which is supported by the stable, ad lib intake noted in nondeprived rats. Sclafani (61) has proposed the existence of two distinct taste systems, sugar-sensitive and starch-sensitive. The selective facilitatory effects of 5-HT antagonists upon sucrose intake suggest that 5-HT may act to inhibit the sugar-sensitive system, yet fail to generally alter the starch-sensitive system. The relative sweetness of sucrose relative to MD is difficult to ascertain in animal models, but the threshold for MD and other complex carbohydrates to elicit a preference in rats are significantly lower than that for sucrose and other simple carbohydrates (45,50–53). It must be noted that only one concentration (10%) of sucrose and MD was employed in the present study, and any definitive explanations of the role of 5-HT antagonists upon sweetness preference must await an analysis of sucrose and MD intake at different concentrations.

5-HT-Opioid Effects Upon Carbohydrate Intake

Naltrexone's inhibition of both sucrose and MD intake through interference with the maintainance rather than the initiation of sucrose and MD intake supports previous findings (2,4,30–33,46,58). Opioid mediation of sucrose intake occurs through kappa and mu_2 receptors, while opioid mediation of MD intake occurs through mu_2 receptors (2,4). The interaction between 5-HT receptor antagonists and naltrexone appears to be markedly different for sucrose and MD intake as compared to hyperphagia following either food deprivation, 2DG, or insulin. First, the 5-HT_3 antagonist ICS 205930 significantly enhanced the hypophagic effects of general opioid antagonists in food-deprived rats or in rats treated with either 2DG or insulin (1,3,34). In contrast, ICS 205930 failed to alter naltrexone's inhibition of sucrose or MD intake. Second, the 5-$HT_{2A/C}$ antagonist, ritanserin significantly enhanced the hypophagic effects of naltrexone in insulin-treated rats (34), yet ritanserin cotreatment either delayed or eliminated naltrexone's inhibition of both sucrose and MD intake. Third, whereas methysergide generally failed to alter opioid antagonist inhibition of deprivation-induced and glucoprivic intake (1,3,34), methysergide coadministration transiently delayed naltrexone's inhibition of both sucrose and MD intake. It should be noted that such nonspecific effects as sedation of hypoactivity cannot account for the differential patterns of these 5-HT antagonist effects. Thus, whereas cotreatment of 5-HT_3 antagonists acts to enhance opioid antagonist inhibition of those forms of intake related to challenge situations, cotreatment of 5-$HT_{2A/C}$ antagonists acts to delay or eliminate opioid antagonist inhibition of two forms of intake related to palatable or taste qualities. It is imperative to note that because this was a systemic pharmacological study, one cannot ascertain as to whether the 5-HT antagonists acted to alter the opioid system, whether the opioid antagonist acted to alter the 5-HT system, or whether each class of drugs altered the pharmacokinetics or pharmacodynamics of the other class. In any case, it is clear that these functional interactions between 5-HT and opioid antagonists exert differential effects upon challenge and palatable intake situations.

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REFERENCES

1. Beczkowska, I. W.; Bodnar, R. J. Naloxone and serotonin receptor subtype antagonists: Interactive effects upon deprivation-induced intake. Pharmacol. Biochem. Behav. 38:605–610; 1991.
2. Beczkowska, I. W.; Bowen, W. D.; Bodnar, R. J. Central opioid receptor subtype antagonists differentially alter sucrose and deprivation-induced water intake in rats. Brain Res. 589:291–301; 1992.
3. Beczkowska, I. W.; Koch, J. E.; Bodnar, R. J. Naltrexone, serotonin receptor subtype antagonists and glucorprivic intake: I. 2-Deoxy-d-glucose. Pharmacol. Biochem. Behav. 42:661–669; 1992.
4. Beczkowska, I. W.; Koch, J. E.; Bostock, M. E.; Leibowitz, S. F.; Bodnar, R. J. Central opioid receptor subtype antagonists differentially reduce intake of saccharin and maltose dextrin solutions in rats. Brain Res. 618:261–270; 1993.
5. Blundell, J. E. Is there a role for serotonin (5-hydroxytryptamine) on feeding? Int. J. Obes. 1:15–42; 1977.

6. Blundell, J. E.; Hill, A. J. Nutrition, serotonin and appetite: Case study in the evolution of a scientific idea. Appetite 8:183–194; 1987.
7. Blundell, J. E.; Hill, A. J. Do serotonergic drugs decrease energy intake by reducing fat or carbohydrate intake? Effect of *d*-fenfluramine with supplemented weight-increasing diets. Pharmacol. Biochem. Behav. 31:773–778; 1989.
8. Blundell, J. E.; Latham, C. J. Characterisation of adjustments to the structure of feeding behaviour following pharmacological treatment: Effects of amphetamine and fenfluramine and the antagonism produced by pimozide and metergoline. Pharmacol. Biochem. Behav. 12:717–722; 1980.
9. Clifton, P. G.; Barnfield, A. M. C.; Philcox, L. A behavioural profile of fluoxetine-induced anorexia. Psychopharmacology (Berlin) 97:89–95; 1989.
10. Dourish, C. T. 5-HT receptor subtypes and feeding behaviour. Adv. Bioscien. 85:179–202; 1992.
11. Dourish, C. T.; Clark, M. L.; Fletcher, A.; Iversen, S. D. Evidence that blockade of 5-HT-1 receptors elicits feeding in satiated rats. Psychopharmacology (Berlin) 97:54–58; 1989.
12. Dourish, C. T.; Hutson, P. H.; Curzon G. Characteristics of feeding induced by the serotonin agonist, 8-hydroxy-2(di-n-propylamino)tetralin (8-OH-DPAT). Brain Res. Bull. 15:377–384; 1985.
13. Dourish, C. T.; Hutson, P. H.; Curzon, G. Low doses of the putative serotonin agonist, 8-hydroxy-2(di-n-propylamino)tetralin (8-OH-DPAT) elicit feeding in the rat. Psychopharmacology (Berlin) 86:197–204; 1985.
14. Fernandez-Tome, M. P.; Gonzalez, Y.; DelRio, J. Interactions between opioid agonists or naloxone and 5-HTP on feeding behavior in food-deprived rats. Pharmacol. Biochem. Behav. 29: 387–392; 1988.
15. Fletcher, P. J. 8-OH-DPAT elicits gnawing and eating of solid but not liquid foods. Psychopharmacology (Berlin) 92:192–195; 1987.
16. Fletcher, P. J. Increased food intake in satiated rats induced by the 5-HT antagonists methysergide, metergoline and ritanserin. Psychopharmacology (Berlin) 96:237–242; 1988.
17. Fletcher, P. J. Opiate antagonists inhibit feeding induced by 8-OH-DPAT: Possible mediation in the nucleus accumbens. Brain Res. 560:260–267; 1991.
18. Gibson, E. L.; Booth, D. A. Fenfluramine and amphetamine suppress dietary intake without affecting learned preferences for protein or carbohydrate cues. Behav. Brain Res. 30:25–29; 1988.
19. Gilbert, F.; Dourish, C. T. Effects of the novel anxiolytics gepirone, buspirone and ipsapirone on free feeding and feeding induced by 8-OH-DPAT. Psychopharmacology (Berlin) 93:349–352; 1987.
20. Hewson, G.; Leighton, G. E.; Hill, R. G.; Hughes, J. Ketanserin antagonizes the anorectic effect of DL-fenfluramine in the rat. Eur. J. Pharmacol. 145:227–230; 1988.
21. Hirsch, J. A.; Goldberg, S.; Wurtman, R. J. Effect of (+)- or (−)-enantiomers of fenfluramine or norfenfluramine on nutrient selection by rats. J. Pharm. Pharmacol. 34:18–21; 1982.
22. Humphrey, P. P. A.; Hartig, P.; Hoyer, D. A proposed new nomenclature for 5-HT receptors. Trends Pharmacol. Sci. 14: 233–236; 1993.
23. Hutson, P. H.; Donohue, T. P.; Curzon, G. Infusion of the 5-hydroxytryptamine agonists RU24969 and TFMPP into the paraventricular nucleus of the hypothalamus causes hypophagia. Psychopharmacology (Berlin) 95:550–552; 1988.
24. Hutson, P. H.; Dourish, C. T.; Curzon, G. Neurochemical and behavioral evidence for mediation of the hyperphagic action of 8-OH-DPAT by 5-HT cell body autoreceptors. Eur. J. Pharmacol. 129:347–352; 1986.
25. Hutson, P. H.; Dourish, C. T.; Curzon, G. Evidence that the hyperphagic response to 8-OH-DPAT is mediated by 5-HT-1A receptors. Eur. J. Pharmacol. 150:361–366; 1988.
26. Kanarek, R. B.; Dushkin, H. Peripheral serotonin administration selectively reduces fat intake in rats. Pharmacol. Biochem. Behav. 31:113–122; 1988.
27. Kennett, G. A.; Curzon, G. Evidence that hypophagia induced by mCPP and TFMPP requires 5-HT-1B receptors and 5-HT-1C receptors: Hypophagia induced by RU24969 only requires 5-HT-1B receptors. Psychopharmacology (Berlin) 96:93–100; 1988.
28. Kennett, G. A.; Curzon, G. Evidence that mCPP may have behavioral effects mediated by central 5-HT-1C receptors. Br. J. Pharmacol. 94:137–147; 1988.
29. Kennett, G. A.; Dourish, C. T.; Curzon, G. 5-HT-1B agonists produce anorexia at a postsynaptic site. Eur. J. Pharmacol. 141: 429–435; 1987.
30. Kirkham, T. C.; Blundell, J. E. Dual action of naloxone on feeding revealed by behavioral analysis: Separate effects on initiation and termination of eating. Appetite 5:45–52; 1984.
31. Kirkham, T. C.; Blundell, J. E. Effects of naloxone and naltrexone on the development of satiation measured in the runway: Comparisons with *d*-amphetamine and *d*-fenfluramine. Pharmacol. Biochem. Behav. 25:123–128; 1986.
32. Kirkham, T. C.; Cooper, S. J. Attenuation of sham feeding by naltrexone is stereospecific: Evidence for opioid mediation of orosensory reward. Physiol. Behav. 43:845–847; 1988.
33. Kirkham, T. C.; Cooper, S. J. Naloxone attenuation of sham feeding is modified by manipulation of sucrose concentration. Physiol. Behav. 44:491–494; 1988.
34. Koch, J. E.; Beczkowska, I. W.; Bodnar, R. J. Naltrexone, serotonin receptor subtype antagonists and glucoprivic intake: II. Insulin. Pharmacol. Biochem. Behav. 42:671–680; 1992.
35. Lee, M. D.; Clifton, P. G. Partial reversal of fluoxetine anorexia by the 5-HT antagonist metergoline. Psychopharmacology (Berlin) 107:359–364; 1992.
36. Leibowitz, S. F.; Weiss, G. F.; Walsh, U. A.; Viswanath, D. Medial hypothalamic serotonin: Role in circadian patterns of feeding and macronutrient selection. Brain Res. 503:132–140; 1989.
37. Levine, A. S.; Grace, M.; Billington, C. J.; Portoghese, P. S. Nor binaltorphamine decreases deprivation and opioid-induced feeding. Brain Res. 534:60–64; 1990.
38. Li, E. T. S.; Luo, S. Buspirone-induced carbohydrate feeding is not influenced by route of administration and nutritional status. Brain Res. Bull. 30:547–550; 1993.
39. Luo, S.; Li, E. T. S. Food intake and selection pattern of rats treated with dexfenfluramine, fluoxetine and RU 24969. Brain Res. Bull. 24:729–733; 1990.
40. Luo, S.; Ransom, T.; Li, E. T. S. Selective increase in carbohydrate intake by rats treated with 8-hydroxy-2-(di-n-propylamino)tetralin or buspirone. Life Sci. 46:1643–1648; 1990.
41. Massi M.; Marini, S. Effect of the 5HT-2 antagonist ritanserin on food intake and on 5HT-induced anorexia in the rat. Pharmacol. Biochem. Behav. 26:333–340; 1987.
42. Montgomery, A. M. J.; Willner, P.; Muscat, R. Behavioral specificity of 8-OH-DPAT-induced feeding. Psychopharmacology (Berlin) 94:110–114; 1988.
43. Morley, J. E.; Levine, A. S.; Yim, G. K. W.; Lowy, M. T. Opioid modulation of appetite. Neurosci. Biobehav. Rev. 7:281–305; 1983.
44. Orthen-Gambill, N.; Kanarek, R. B. Differential effects of amphetamine and fenfluramine on dietary self-selection in rats. Pharmacol. Biochem. Behav. 16:303–309; 1982.
45. Ramirez, I. Thresholds for starch and polycose are lower than sucrose in rats. Physiol. Behav. 50:699–703; 1991.
46. Rockwood, G. A.; Reid, L. D. Naloxone modifies sugar-water intake in rats drinking with open gastric fistulas. Physiol. Behav. 29:1175–1178; 1982.
47. Rowland, N. E.; Carlton, J. Neurobiology of an anorectic drug: Fenfluramine. Prog. Neurobiol. 27:13–62; 1986.
48. Samanin, R.; Mennini, T.; Ferraris, A.; Bendotti, C.; Borsini, F.; Garattini, S. M-chlorophenylpiperazine: A central serotonin agonist causing powerful anorexia in rats. Naunyn Schmiedebergs Arch. Pharmacol. 308:159–163; 1979.
49. Schechter, L. E.; Simansky, K. J. 1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropame (DOI) exerts an anorexic action that is blocked by 5-HT-2 antagonists in rats. Psychopharmacology (Berlin) 94:342–346; 1988.

50. Sclafani, A. Carbohydrate taste, appetite and obesity: An overview. Neurosci. Biobehav. Rev. 11:131–153; 1987.
51. Sclafani, A.; Clyne, A. E. Hedonic response of rats to polysaccharide and sugar solutions. Neurosci. Biobehav. Rev. 11:173–180; 1987.
52. Sclafani, A.; Mann, S. Carbohydrate taste preferences in rats: Sucrose, maltose, fructose and Polycose compared. Physiol. Behav. 40:563–568; 1987.
53. Sclafani, A.; Nissenbaum, J. W. Taste preference thresholds for Polycose, maltose and sucrose in rats. Neurosci. Biobehav. Rev. 11:181–185; 1987.
54. Shor-Posner, G.; Grinker, J. A.; Marinescu, C.; Brown, O.; Leibowitz, S. F. Hypothalamic serotonin in the control of meal patterns and macronutrient selection. Brain Res. Bull. 17:663–671; 1986.
55. Shukla, R.; MacKenzie-Taylor, D.; Rech, R. H. Evidence for 5-HT-2 receptor mediation in quipazine anorexia. Psychopharmacology (Berlin) 100:115–118; 1990.
56. Simansky, K. J. Peripheral 5-carboxamidotryptamine (5-CT) elicits drinking by stimulating 5-HT-1-like serotonergic receptors in rats. Pharmacol. Biochem. Behav. 38:459–462; 1991.
57. Simansky, K. J.; Sisk, F. C.; Vaidya, A. H.; Eberle-Wang, K. Peripherally administered alpha-methyl-5-hydroxy-tryptamine and 5-carboxamidotryptamine reduce food intake via different mechanisms in rats. Behav. Pharmacol. 1:241–246; 1990.
58. Siviy, S. M.; Reid, L. D. Endorphinergic modulation of acceptability of putative reinforcers. Appetite 4:249–257; 1983.
59. Willner, P.; McGuirk, J.; Phillips, G.; Muscat, R. Behavioural analysis of the anorectic effects of fluoxetine and fenfluramine. Psychopharmacology (Berlin) 102:273–277; 1990.
60. Wurtman, J. J.; Wurtman, R. J. Fenfluramine and fluoxetine spare protein consumption while suppressing carbohydrate intake in rats. Science 198:1178–1180; 1977.
61. Wurtman, J. J.; Wurtman, R. J. Drugs that enhance central serotonergic transmission diminish elective carbohydrate consumption by rats. Life Sci. 24:895–904; 1979.
62. Wurtman, R. J.; Wurtman, J. J. Carbohydrate craving, obesity and brain serotonin. Appetite 7:99–103; 1986.