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CCK_A and 5-HT_3 Receptors Interact in Anorectic Responses to Amino Acid Deficiency

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AJA, S. M., J. A. BARRETT AND D. W. GIETZEN. *CCK_A and 5-HT_3 receptors interact in anorectic responses to amino acid deficiency.* PHARMACOL BIOCHEM BEHAV **62**(3) 487–491, 1999.—Serotonin$_3$ (5-HT_3) receptors in the periphery mediate anorectic responses to the amino acid deficiency, which occurs after eating amino acid-imbalanced diets (IMB). However, other neurochemical systems, notably cholecystokinin (CCK), are known to affect food intake. We pretreated rats systemically with tropisetron, a 5-HT_3 receptor antagonist, alone and combined with antagonists of CCK_A and CCK_B receptors, and measured intake of an IMB. Devazepide, a CCK_A receptor antagonist, appeared to interact with tropisetron in the anorectic responses to IMB, blunting the usual remediation of IMB anorexia by tropisetron. The CCK_B receptor antagonist, L-365, 260, increased intake of both IMB and an amino acid-balanced basal diet (BAS) and did not interact with tropisetron. Our data suggest that activation of CCK_A receptors is interactive with 5-HT_3 receptor activity in mediating IMB anorexia in the aminoprivic feeding model. © 1999 Elsevier Science Inc.

Amino acid imbalance Rat Nutrition Food intake Tropisetron Devazepide L-365,260
Serotonin$_3$ receptor CCK_A receptor CCK_B receptor

THE use of amino acid imbalanced diets (IMB) is a nutritional model for establishing a selective essential amino acid deficiency in animals (17,24,25). Rats demonstrate their recognition of the deficient state by a rapid reduction of IMB intake. The anorectic response is rapid, reaching significance within a few hours, depending on the degree of amino acid disproportionality and the prefeeding regimen (13,25). Serotonin (5-HT) appears to be involved in the reduced intake of IMB (14), an effect selective for the 5-HT_3 receptor (16,20,34). Ondansetron, a highly selective 5-HT_3 antagonist, injected into the anterior piriform cortex, increases IMB intake (15,34), suggesting a central site for 5-HT in the response to IMB. Systemic injections of the 5-HT_3 antagonist, [1H]-indole-3-carbonic acid-tropine-ester hydrochloride, also known as tropisetron (TROP, formerly ICS 205-930), or its quaternized form, attenuate the anorectic response equally (19). In addition, both total subdiaphragmatic vagotomy and capsaicin blunt the antianorectic effect of TROP on IMB [(36); Dixon et al., unpublished]. Thus, peripheral 5-HT_3 receptors are likely to be involved in the depressed consumption of IMB, as well. The finding that pretreatment with TROP only increases IMB intake to 80–85% of a baseline basal diet (BAS) intake (16) prompted us to ask whether the 5-HT_3 receptor acts alone in the responses to IMB, or whether other systems may be involved. Since the early recognition of the importance of serotonin in feeding control [reviewed in (3)], considerable research has demonstrated potential interactions between serotoninergic activity and that of other systems.

Cholecystokinin (CCK) has been well-studied as a satiety agent. Exogenous CCK-8 decreases food intake in rats (12), monkeys (11), and humans (22). Antagonism of CCK_A receptors in the periphery (29), but not CCK_B receptors in the brain (33), blocks the anorectic response to intraperitoneal (IP) CCK-8 in fasted rats. However, in sated rats, blockade of CCK_B receptors has been shown to be more potent than antagonism of CCK_A receptors for increasing feeding and postponing onset of satiety (10). Capsaicin-sensitive vagal afferents have been implicated as a link between CCK activities in the gastrointestinal system and the brain for mediating satiety (37). As noted above, the full effect of TROP is dependent on an intact vagus as well (36). 5-HT_3 and CCK receptors coexist at many sites in both central and peripheral feeding–control

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pathways (2,4,6,7,18,21,23,30,32), and thus may interact in the control of feeding. Moreover, evidence has been presented suggesting that 5-HT and CCK interact to induce satiety (7,8).

The present studies were designed to evaluate potential interactions between TROP and activity at CCK_A and CCK_B receptors in the IMB feeding model, using peripheral injections of selective antagonists of the receptors in question.

METHOD

Animals

Sprague–Dawley male rats (Simonsen Labs, Gilroy, CA) were naive to diet and drug treatments. Animals were housed individually in hanging wire cages in a controlled environment maintained at 22 ± 2°C, on a 12L:12D cycle, with the onset of the dark phase at noon. Animal protocols were approved by the University's Animal Use and Care Committee. Purified L-amino acid diets (Table 1) and water were available ad lib. The rats were allowed at least 10 days to adjust to a powdered low-protein isoleucine (ile) basal (BAS) diet (Table 1), housing conditions and the food intake protocol. After at least 2 days of baseline food intake measurements on the BAS diet, the animals were weighed and randomly assigned to experimental groups having equal mean body weights. On the first experimental day (ED1), food cups were removed and replaced with fresh cups of either ile-BAS or ile-IMB diet (Table 1). The rats were given IP injections of the drugs or equal volumes of the appropriate vehicles 10–45 min before the onset of the dark cycle, at which time preweighed cups containing the test diets were placed in the cages. Food intake, in g/interval, represents the difference between food cup weights before and after the interval, corrected for spillage. In preliminary trials, there were no differences in either control or test diets after injection of vehicles that were used in these studies (data not shown). Food intake measurements were taken at 3-h intervals during the dark cycle, with a 12-h measurement of feeding during the light cycle. Subsequent food intake measurements were continued daily for 3 days after the injections. Specific food intake protocols are described for each experiment.

Diets

Purified diets, with L-amino acids as the sole protein source (Ajinomoto, USA, Inc., Teaneck, NJ) and ile as the growth-limiting amino acid, were used in the experiments. The amino acid-imbalanced diet (IMB) was prepared by adding indispensable amino acids, except ile, to the low protein BAS diet (Table 1). These diets have been described in detail previously (16).

TABLE 1

COMPOSITION OF DIETS USED IN EXPERIMENTS
% OF DIET BY WEIGHT

Ingredients	BAS	IMB
Dispensable amino acid mixture	7.53	7.53
Indispensable amino acid mixture	3.77	3.77
Imbalanced amino acid mixture		9.10
Vitamin mixture	1.00	1.00
Salt mixture	5.00	5.00
Corn oil	5.00	5.00
Sucrose	25.87	22.83
Cornstarch	51.73	45.67
Choline chloride	0.10	0.10
Total	100.00	100.00

Isoleucine was the growth limiting amino acid in both diets. BAS, ile-basal diet; IMB, ile-imbalanced diet. All ingredients have been described previously in detail (16).

Drugs

TROP was a gift from Sandoz Research Institute (East Hannover, NJ). 3S-(−)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1, 4-benzodiazepin-3-yl)-1H-indole-2-carboxamide (Devazepide, DEV, formerly L-364,718 or MK-329) and 3R-(+)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H-1,4-benzodiazepin-3-yl)-N1-(3-methylphenyl)-urea (L-365,260, L) were gifts of Merck, Sharp and Dohme Research Laboratories (West Point, PA). TROP was prepared in 0.9% NaCl (Sal) and administered IP at a dose of 9 mg/kg body weight. This has been shown to be the optimal dose of TROP for ameliorating IMB-induced anorexia in previous dose–response studies (16,20). DEV and L-365,260 were dissolved in 4% ethanol(EtOH) and given at 0.1 mg/kg. Each drug or vehicle was injected IP in a volume of 1 ml/kg. Both DEV and L-365,260 were tested in dose–response trials on BAS, using 0, 0.01, 0.1, and 1.0 mg/kg of each drug, as recommended in (29), to determine the optimal dose, and to assure that the drugs and vehicles did not decrease BAS intake, indicating malaise.

Data Analysis

Food intake data were subjected to analysis of variance (ANOVA), using a general linear model (GLM) with type III sums of squares (version 6.04, SAS, Carey, NC). Diet and drug were the independent variables; interactions among diets and drugs were also examined. Food intake, the dependent variable, was expressed as g/interval/rat. Least-significant difference tests were performed to compare group means after a significant overall ANOVA (Fischer's protected LS mean). Significance was assumed at $p \leqslant 0.05$.

Experiment 1: 5-HT_3 and CCK_A Receptor Interactions

Tropisetron and Devazepide. TROP, a selective 5-HT_3 receptor antagonist, which is active in our model after IP injection (16,19,20), and DEV, a CCK receptor antagonist predominantly at the level of the gastrointestinal tract (CCK_A), were used to evaluate possible interactions between these two systems in the anorectic response to IMB. Rats (total $n = 144$ rats) weighed 150–200 g at the beginning of each experiment. A 4 × 2 factorial design was used, with TROP, DEV, and their vehicles (Sal and EtOH) as the four drug conditions, and with BAS and IMB diets as the two diet conditions. In Experiment 1, six animals were assigned to each of the following groups: BAS:EtOH+Sal, BAS:EtOH+TROP, BAS:DEV+Sal, BAS:DEV+TROP, IMB:EtOH+Sal, IMB:EtOH+ TROP, IMB:DEV+Sal, and IMB:DEV+TROP. Baseline BAS intake was measured for the last 2 prefeeding days. Rats were injected with drugs and vehicles before introduction of the test diets on ED1, and test diet intake was monitored for 3 days. In preliminary trials, the groups were either divided into two runs with intake measured 3, 6, 9, 12, and 24 h on all days, or eight additional groups were studied at 24 h only. In Experiment 1, all eight groups, naive rats, were used simultaneously and intake was measured at 3, 6, 9, 12, and 24 h on ED1, followed by 24-h measurements on ED2 and ED3.

Experiment 2: 5-HT_3 and CCK_B Receptor Interactions

Tropisetron and L-365,260. An antagonist at the CCK_B receptor, found chiefly in the brain (27) was used in conjunction with TROP to investigate potential interactions between the CCK_B and 5-HT_3 systems. The 4 × 2 factorial design of Experiment 1 was repeated, substituting the CCK_B antagonist, L-365,260 (L), for the CCK_A antagonist. Rats received injections of the Sal and EtOH vehicles at the beginning of each of 3 days of baseline BAS intake measurement, prior to ED1. On ED1 rats were given drugs and vehicles prior to introducing the test diets, and food intake was again measured at 3, 6, 9, 12, and 24 h intervals for 3 days.

RESULTS

Confirming previous findings (16,19,20), rats treated with both vehicles (double-vehicle group) responded to IMB with reduced intake, relative to their BAS baseline intake ($p < 0.0001$). The anorectic response was significant by 3 h ($p = 0.0001$). Pretreatment with TROP attenuated the anorexia by the 3-h measurement in Experiment 1 (TROP effect, $p = 0.002$), and in Experiment 2 ($p < 0.006$). In all cases, the TROP effect in ameliorating the anorectic responses to IMB continued throughout at least ED1 ($p < 0.0001$).

Experiment 1: 5-HT_3 and CCK_A Receptors

The food intake data for ED1 were highly significant for each interval, as well as cumulatively ($p \leq 0.001$), as shown in Fig. 1. None of the drug injections altered BAS intake at any time, when compared with the BAS + double-vehicle controls. Also, as can be seen in the figure, DEV alone had no effect on the intake of either IMB or BAS throughout ED1, compared with double vehicle controls for the appropriate diet.

For drug effects on IMB during the first 3 h, TROP, with or without DEV, brought IMB intake up to the level of BAS intake seen in the double vehicle control group, although the DEV+TROP group ate less of IMB than the group having the same drug combination ate of BAS. IMB intake by DEV+TROP treated rats was significantly greater than IMB intake by rats treated with DEV only ($p = 0.017$), which was not different from the low IMB intake by double vehicle controls. In the 0–6-h and 0–9-h intake of IMB, the DEV+TROP and TROP groups fell significantly below BAS intake levels, but remained higher than the DEV and vehicle groups eating IMB. Further, the DEV+TROP group IMB intake decreased to those of vehicle-injected groups in the 0–12-h and 0–24-h measurements, while TROP maintained an elevated IMB intake throughout ED1.

Experiment 2: 5-HT_3 and CCK_B Receptors

Data from ED1 are in Fig. 2 [at 3 h, the overall $F(7, 40) = 10.01$, $p=0.0001$]. L-365,260 alone significantly increased IMB intake when compared with the double-vehicle treatment ($p = 0.039$), but also increased BAS intake similarly ($p = 0.041$). The increase in BAS and IMB intakes by L was clear at 0–6 h, as well, with a significant main effect of L ($p = 0.021$). During 0–3 h, TROP remediated the IMB-induced anorexia similarly in the presence ($p =0.0007$) or absence of L-365,260 ($p = 0.0001$), compared with double-vehicle controls. Intake of IMB by the L+TROP group did not differ significantly from either IMB:L+Sal or IMB:EtOH+TROP, but the L+TROP combination tended to be less effective than TROP alone for attenuating IMB-anorexia ($p = 0.086$).

By 24 h, $F(7, 40) = 52.12$, $p = 0.0001$, L-365,260 alone did not affect intake of IMB. IMB:L+TROP was significantly greater than IMB:L+Sal ($p = 0.0001$), but not significantly different from IMB intake with TROP alone. BAS intake by EtOH+TROP-treated rats was elevated when compared with double-vehicle controls ($p = 0.0001$).

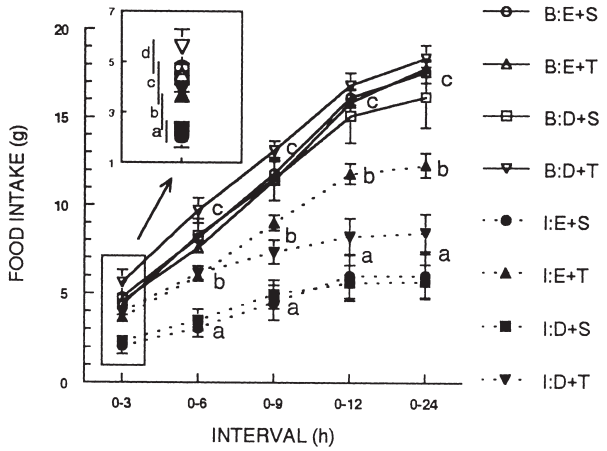

FIG. 1. Experiment 1: food intakes on experimental day 1. Values are means ± SE; $n = 6$ animals/group. Data are expressed in grams of diet eaten. Diets: B, ile-basal diet; I, ile-imbalanced diet. Drugs and vehicles: E, 4% ethanol vehicle (1 ml/kg); S, 0.9% NaCl vehicle (1 ml/kg); the 5-HT_3 antagonist, T, tropisetron (9 mg · ml^{-1} · kg^{-1}) in Sal; the CCK_A receptor antagonist, D, devazepide (0.1 mg · ml^{-1} · kg^{-1} in 4% ethanol). Groups, identified in the legend, having differing superscript letters are significantly different ($p \leq 0.05$). Inset is an enlargement of the data for 0–3 h. For clarification within the inset, the B:E+S and B:E+T groups are similar and are designated "cd." Likewise, "c" is assigned to both B:D+S and I:D+T.

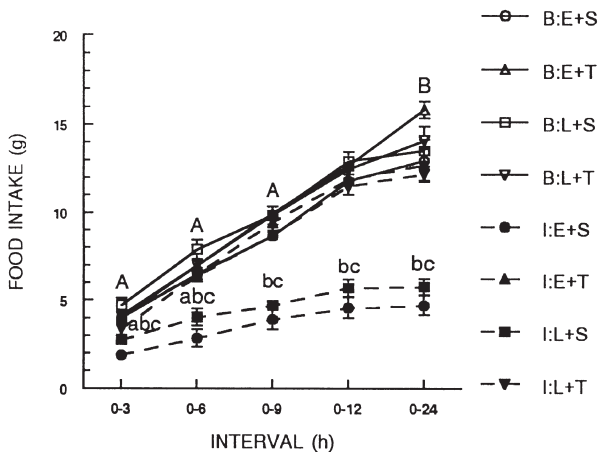

FIG. 2. Experiment 2: food intakes on experimental day 1. Conditions are the same as in Fig. 1 except for the CCK antagonist, which was L-365,260, selective for the CCK_B receptor, abbreviated "L," in place of devazepide. Superscript letters indicate significant differences from the respective vehicle control as follows: capital letters, differences within BAS diet groups: (A) L-365,260 greater than control, (B) TROP greater than control. Lower case letters indicate significant difference from vehicle control in the IMB groups for: (a) L-365,260, (b) TROP, (c) the combination of both drugs ($p < 0.05$).

24 h Data From ED1–ED3 in Both Experiments

Daily 24-h IMB intakes over the 3 days subsequent to drug or vehicle treatment showed only the effects of the IMB diet, along with residual effects from the TROP injections, extending to the end of ED2. On ED2, IMB intakes of both TROP-treated groups remained significantly higher than those of the non-TROP groups in both experiments ($p \leq 0.012$ in Experiment 1 and 0.0002 in Experiment 2). By ED3, all IMB groups had similar food intake values (p = ns). Food intakes of groups eating BAS remained near 100% of pretreatment control throughout all of the trials (data not shown).

DISCUSSION

The 5-HT_3 receptor plays an important role in the mechanisms underlying the reduced intake of essential amino acid-imbalanced diets. This effect of 5-HT_3 receptors appears to be selective for IMB-induced anorexia, because the reduced feeding seen after serotonergic treatments in animals eating balanced diets does not appear to be mediated by TROP-sensitive receptors (31). Yet, pretreatment of rats with TROP yields IMB intakes that are only 80–85% of BAS baseline (16). CCK has been shown to decrease food intake as well, an effect mediated, at least in part, in the periphery (12). The aim of this study was to evaluate potential involvement of CCK_A and CCK_B receptors in aminoprivic feeding, and possible interactions with the 5-HT_3 system in this model. We designed the present studies to discriminate between independent effects of CCK and 5-HT_3 systems on IMB feeding, and interactions between these systems. Our results indicated that activities at CCK_A and 5-HT_3 receptors may interact to mediate anorectic responses to IMB. The DEV–TROP interaction resulted in a decreased response with TROP later in ED1, as seen at 12 and 24 h (Fig. 1). Because vagotomy and capsaicin also decrease the antianorectic effect of TROP [(36); Dixon et al., unpublished], the CCK_A–5-HT_3 interaction suggested by the present results may modulate activity of vagal afferents.

5-HT_3 Receptors

TROP pretreatment increases intake of IMB reliably [(16, 19,20,34,36); present results: Figs. 1 and 2], although no such evidence has yet been produced regarding 5-HT_3 receptor involvement in models of satiety using balanced diets. Indeed, ondansetron, a selective 5-HT_3 antagonist, has been shown to decrease intake of highly palatable food in nondeprived rats (35) at doses higher than we used to increase IMB intake (20); we have rarely seen a significant effect of 5-HT_3 antagonists on control diet intake, including the present results (Figs. 1 and 2).

CCK Receptors

Our data do not support an independent role for CCK_A receptors in mediating anorectic responses to IMB, because DEV alone did not alter IMB intake at any time point (Fig. 1). The BAS:DEV+Sal intake was the highest BAS intake of any measured in Experiments 1 and 2, and we did see small (not significant) increases in BAS intake at 0.01 and 0.1 mg/kg doses at 3 h in our earlier dose–response trials. DEV has been shown to increase intake of ground rat chow in 3 h, but not at 2 h, at the dose used in our study (29). Only higher doses of 0.3 and 1.0 mg/kg significantly increase intake at 21 h (29); this is consistent with the present data, and our dose–response trials on the BAS diet.

Blockade of CCK_B receptors with L-365,260 alone resulted in 3 h intake of both BAS and IMB diets that was greater than that of the vehicle controls, but was not sustained by 24 h, as expected given the short half-life of this drug (5). Thus, the CCK_B antagonist may have had a generalized short-term orexigenic effect by inhibiting the well-known satiety effects of CCK (12). There appeared to be no selective effect on intake of the IMB diet, leading us to suggest that the mechanisms underlying the responses to amino acid deficiency do not involve the CCK_B receptor.

CCK and 5-HT_3 Receptors

A model has been proposed, in which increased activity of both 5-HT and CCK are required for full expression of satiety, and antagonism of one component would hinder the effectiveness of the other in reducing food intake (7). Although the model is based on evidence involving other 5-HT receptor types, interactions between CCK and 5-HT_3 receptors have been reported (28). DEV inhibits the anorectic effects of fenfluramine in some situations (7,8), suggesting that elevated 5-HT activity may lead to enhanced CCK_A activity and thus contribute to expression of satiety. However, this finding has not been observed under some experimental conditions (26). Our data suggest an interaction between CCK_A and 5-HT_3 activity in the mediation of IMB-anorexia. Intake of IMB by the TROP+DEV group was significantly lower than that of the TROP alone group by 12 h, and this observation extended to the end of ED1 (Fig. 1). There was no such effect on the BAS diet with the DEV–TROP interaction.

Total subdiaphragmatic vagotomy (36), capsaicin (Dixon et al., unpublished) and DEV (Fig. 1) all blunted the antianorectic effect of TROP on IMB similarly, and at approximately the same time (6–12 h), on ED1. We, therefore, propose that, in the untreated rat, activation of CCK_A receptors associated with capsaicin-sensitive vagal afferents may be important for at least part of the 5-HT_3 receptor-mediated reduction of IMB intake. Because, unlike vagotomy and capsaicin [(36); Dixon et al., unpublished], DEV does not increase IMB intake, there are probably mechanisms contributing to IMB anorexia, which involve capsaicin-sensitive vagal afferents, but not CCK_A receptors.

5-HT enhancement of CCK release from synaptosome preparations of cerebral cortex and nucleus accumbens, sites where CCK_B receptors exist, is antagonized by the 5-HT_3 receptor blockers, TROP and ondansetron, but not by 5-HT_1 or 5-HT_2 receptor blockade with methiothepin (28). The present study does not indicate involvement of CCK_B–5-HT_3 interactions in reduced intake of IMB, because IMB:L+TROP intake did not differ from IMB:EtOH+TROP intake (Fig. 2). Such an interaction is likewise not supported in the current 5-HT–CCK satiety model, because the CCK_B antagonist L-365,260 fails to antagonize the anorectic effect of *d*-fenfluramine (9).

CONCLUSIONS

In these experiments we have again confirmed involvement of 5-HT_3 receptors in the aminoprivic feeding model for investigating the responses to acute amino acid deficiency. The short-term orexigenic effect of L-365,260 was not specific to IMB feeding, the drug failed to alter IMB-anorexia seen later in ED1, and did not alter the remediating effect of

TROP on IMB intake. Thus, in terms of the mechanisms underlying the normal reduction in IMB intake, CCK_B receptors are not likely to be a major influence, either independently or in functional interaction with 5-HT_3 receptors.

We have determined that activity at CCK_A receptors does not alter rats' normal responses to IMB independently. However, a CCK_A–5-HT_3 interaction in mediating responses to amino acid deficiency is suggested by our data. Such an interaction may involve vagal afferent function.

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