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Effects of serotonin 5-HT_1 and 5-HT_2 Receptor Agonists in a Conditioned Taste Aversion Paradigm in the Rat

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DE VRY, J., G. ECKEL, E. KUHL AND R. SCHREIBER. *Effects of serotonin 5-HT_1 and 5-HT_2 receptor agonists in a conditioned taste aversion paradigm in the rat.* PHARMACOL BIOCHEM BEHAV **66**(4) 797–802, 2000.—Although 5-$HT_{1/2}$ receptor agonists can inhibit ingestive behavior, it remains unclear whether this effect is confounded by drug-induced "malaise." The present study assessed the potential of such compounds to induce conditioned taste aversion (CTA), a possible correlate of aversive stimulus properties. Male Wistar rats were tested in a two-bottle saccharin versus water choice paradigm. DOI [5-$HT_{2A/2C}$ receptor agonist; ED_{50} (95% confidence limits) in mg/kg, IP: 0.29 (0.14–0.63)], m-CPP [5-$HT_{2C/1B}$; 1.69 (0.96–2.99)], TFMPP [5-$HT_{1B/2C}$; 2.45 (1.46–4.11)], ORG 37684 [5-HT_{2C}; 2.96 (1.17–7.52)], BW 723C86 [5-HT_{2B}; 3.49 (1.29–9.47)], CP-94,253 [5-HT_{1B}; 3.74 (1.54–9.08)], and ipsapirone [5-HT_{1A}; 20.15 (11.25–36.09)] dose dependently suppressed saccharin preference, with potencies that correlated with their previously reported potencies to inhibit ingestive behavior in operant- and free feeding paradigms. Although these results did not necessarily imply that such hypophagic effects result from a drug-induced "malaise," it can be hypothesized that they involve, at least partly, the same physiological mechanism/substrate underlying CTA. As the hypophagic effects of serotonergic compounds have been ascribed to their effects on satiety processes and generally occur at doses that are lower than those inducing CTA, it is speculated that weak activation of this substrate results in satiety, whereas strong activation will result in aversive effects, or drug-induced "malaise." © 2000 Elsevier Science Inc.

BW 723C86 CP-94,253 DOI 5-Hydroxytryptamine (5-HT) receptors 5-HT_{1A} 5-HT_{1B} 5-HT_{2A} 5-HT_{2B} 5-HT_{2C} Ingestive behavior Ipsapirone m-CPP ORG 37684 TFMPPr

ALTHOUGH it is now well established that serotonin (5-HT) receptor agonists with high to moderate affinity for the different subtypes of the 5-HT_1 and/or 5-HT_2 receptor families affect ingestive behavior, the precise role of these receptors (i.e., 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C}) in the control of ingestive behavior, as well as the physiological, neuroanatomical, and behavioral mechanisms underlying the hypophagic effects of these compounds are not yet fully understood [for reviews, see (4,7,9,21,29,34,39)]. Typically, hypophagic effects of these compounds are investigated in free-feeding paradigms, using nondeprived or food-deprived rats, and such effects have generally been ascribed to a drug-induced acceleration of satiety processes (2,3). Thus, by means of the behavioral satiety sequence paradigm, or by using paradigms that analyse the macro- and microstructure of ingestive behavior, a number of research groups have suggested that compounds which stimulate 5-HT_{2C} and/or 5-HT_{1B} receptors specifically enhance the state of satiety in rats [e.g., (6,19,25, 34,40)]; whereas 5-HT_{2A} receptor agonists have been hypothesized to induce hypophagia by disrupting the behavioral satiety sequence or continuity of ingestive behavior [(19,25,40); but see (34)]. Recently, it was found that compounds with agonist properties at the subtypes of the 5-HT_1 and/or 5-HT_2 receptor families potently suppressed operant food intake, as assessed in a limited access paradigm using food-deprived rats (9,10). Because attenuation of operant food intake generally occurred at lower doses than those inducing hypophagia during a comparable time interval in a free-feeding paradigm using food-deprived rats (37), it was suggested that a drug-induced suppression of motivational processes contributed to

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the mechanism(s) of action underlying the hypophagic effects of these compounds (9,10).

In addition to the hypothesized effects of serotonergic compounds on satiety and motivational processes related to ingestive behavior, it remains possible that the observed hypophagic effects of 5-HT_1 and 5-HT_2 receptor agonists are, to a certain extent, confounded by drug-induced "malaise" (1,11,12). Although it may be difficult to ascertain the occurrence of drug-induced "malaise" in rodents, a possible correlate of this phenomenon is offered by the assessment of the ability of a drug to induce conditioned taste aversion (CTA). Demonstration of the capacity of a drug to induce CTA not necessarily implies that aversive stimulus properties of a drug underlie this phenomenon, nor that it is due to activation of emetic mechanisms, but it offers at least the possibilty that this might be the case [for discussion, see (8,16,17,33)]. Therefore, it was the aim of the present study to investigate whether (relatively) selective 5-$HT_{1/2}$ receptor agonists were able to induce a CTA, and to compare the potency of this effect with the reported potencies to induce hypophagia in free-feeding or operant paradigms. Rats were tested with the following 5-HT receptor agonists in a standardized CTA paradigm: ipsapirone [5-HT_{1A}; (41)], CP-94,253 [5-HT_{1B}; (26)], TFMPP [5-$HT_{1B/2C}$; (14)], m-CPP [5-$HT_{2C/1B}$; (13)], ORG 37864 [5-HT_{2C}; (30)]; BW 723C86 [5-HT_{2B}; (24)] and DOI [5-$HT_{2A/2C}$; (38)]. These compounds were selected for their 5-HT receptor subtype selectivity and/or their well-described effects in free-feeding and operant paradigms, both in nondeprived and food deprived rats (5,10,15,22,24–27,35–37,42).

METHOD

Animals

Male Wistar rats (Harlan–Winkelmann, Hsd/cpb: WU, Borchen, Germany), with body weights between 220–230 g upon arrival at the laboratory, were maintained in groups of two per cage throughout the studies (Macrolon® type 3). Room temperature was held constant at 22–23°C and a normal 12 L:12 D regime (lights on at 0700 h) was operative. The animals were allowed to adapt to the laboratory conditions for 1 week prior to the experimental sessions. Food (standard pellets; Ssniff Spezialdiäten GmbH, Soest, Germany) and tap water were supplied ad lib during the adaptation period. The procedure followed the guidelines for the use of animals, as given by the German government, and was approved by the local authorities.

Conditioned Taste Aversion (CTA) Procedure

In general, the method described by de Beun et al. (8) was followed. Thus, 24 h before the first session the animals were water deprived and fluid access was from then on restricted to daily experimental sessions of 15 min, which took place individually in a Macrolon® type 3 test cage. After each session, the animals returned to their respective home cages. Food was freely available in the home cages throughout the procedure, but was not available during the sessions. For a given subject, all six sessions required to complete a CTA took place in the same test cage, and the cages were not cleaned between sessions. Animals designated to the same experimental group ($n = 8$ per group) were run in parallel. During the first four sessions, both bottles contained plain tap water. This phase of the procedure gave the animals the opportunity to learn to drink a reasonable amount of water in a short period of time and to establish a relatively stable baseline value of water intake. For the fifth session (conditioning session), both bottles were filled with a novel fluid (i.e., a 0.1% w/v saccharin solution), and immediately after completion of this session the animals were injected with either the appropriate vehicle or the test drug. The following drugs were tested (doses in mg/kg, IP): ipsapirone (0, 10, 20, 30), CP-94,253 (0, 1, 3, 10), TFMPP (0, 0.3, 1, 3, 10), m-CPP (0, 0.3, 1, 3), ORG 37684 (0, 1, 3, 10), BW 723C86 (0, 3, 10, 30), and DOI (0, 0.1, 0.3, 1). Per animal, only one dose of a particular drug (or the corresponding vehicle) was tested. Between the conditioning session and the final test session for CTA, the animals were left undisturbed for about 72 h (washout period), and during the first 48 h of this period they had free access to tap water in their home cages until they were again deprived of water. During this last session, one bottle contained the saccharin solution used for conditioning and the other bottle was filled with tap water. To control for location bias, the saccharin solution was presented in the left bottle for half of the animals in each group and in the right bottle for the other half. By measuring the amount of fluid consumed from both bottles separately, drug-induced CTA could be determined by comparison of the relative saccharin intake in the drug treated groups and their vehicle-treated controls.

Drugs

Ipsapirone (BAY q 7821), CP-94,253 {(3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3,2-b]pyridine}, ORG 37684 {(S)-3-[(2,3-dihydro-5-methoxy-1*H*-inden-4-yl)oxy]-pyrrolidine hydrochloride} and BW 723C86 (1-[5-(2-thienylmethoxy)-1H-3-indoyl]propan-2-amine hydrochloride) were synthesized by the Chemistry Departments of Bayer AG, Germany, or Bayer Corporation, West Haven, CT. m-CPP (1-[3-chlorophenyl]piperazine), TFMPP (1-[3-(trifluoromethyl)phenyl]piperazine) and DOI (1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane) were obtained from RBI, Natick, MA. Compounds were dissolved in the following vehicles: distilled water (ipsapirone and DOI); 5% V/V Solutol HS (12-hydroxystearic acid ethoxilate, BASF, Ludwigshafen, Germany), 5% v/v pure ethanol and 90% v/v distilled water (CP-94,253), 0.9% saline and a few drops of $NaHCO_3$ (BW 723C86), and 0.9% saline (other compounds). Saccharin (2,3-dihydro-3-oxobenz-isosulfonazole sodium salt) was purchased from the Sigma Chemical Company (St. Louis, MO) and dissolved in tap water in a concentration of 0.1% w/v. All compounds were injected IP in a volume of 5 ml/kg.

Statistical Analysis

Individual saccharin preference values were calculated as the ratio of saccharin consumption divided by total fluid consumption, as obtained on the test session. For each drug, saccharin preference values were analyzed by ANOVA; followed, where appropriate, by a post hoc Tukey test. In the case of TFMPP, additional tests with particular doses (and the corresponding vehicle) were needed to obtain the complete dose–response curve. In that case, data obtained with vehicle were pooled (as there was no evidence for a statistical difference between the first and second test with vehicle) for data analysis and graphical presentation. The lowest dose that resulted in a statistically significant ($p < 0.05$) reduction of saccharin preference compared with vehicle was considered to be the minimal effective dose (MED). For calculation of the effective $dose_{50}$ (ED_{50}) values and the corresponding 95% confidence limits, data obtained with each dose of a particular test drug were expressed as percentage reduction compared

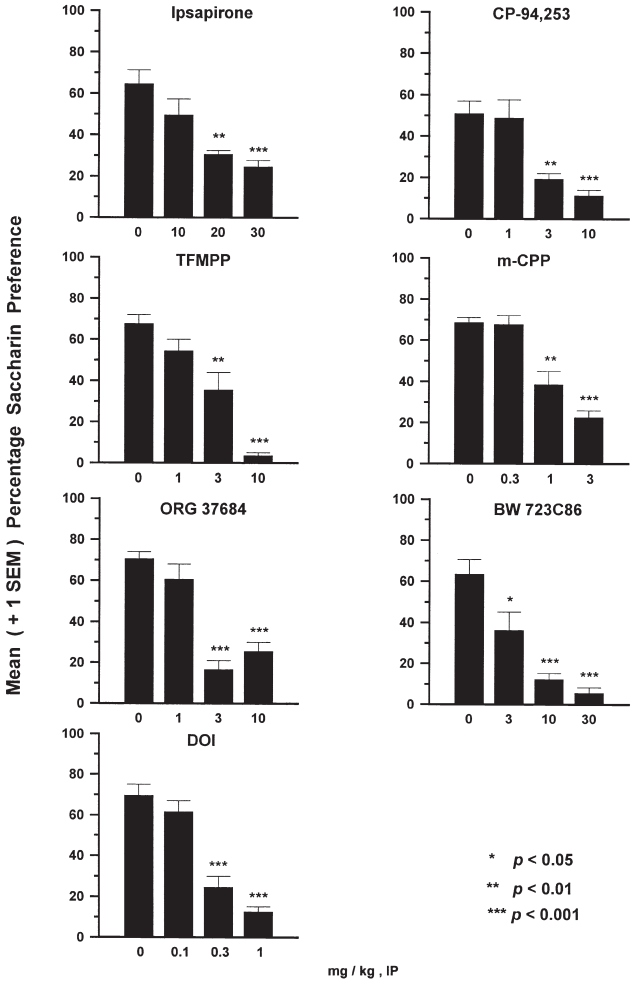

FIG. 1. Effects of 5-HT receptor agonists with differential selectivity for the 5-HT_1 and 5-HT_2 receptor families in a conditioned taste aversion (CTA) paradigm. Saccharin preference was expressed as the ratio of saccharin intake divided by total fluid intake, multiplied by 100, during the test session for CTA. Compounds were administered IP, 72 h before the 15-min test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared to vehicle control. n = 8–16 per treatment. Only the minimal effective dose range is shown (in the case of TFMPP leading to the omission of doses lower than the no-effect dose).

to vehicle control, and these percentages were transfomed by log-probit analysis before submission to least-square analysis. ED_{50} values with nonoverlapping 95% confidence limits were considered to be significantly different.

RESULTS

Each compound induced a dose-dependent and pronounced CTA. Thus, ipsapirone, $F(3, 28) = 9.90$, $p < 0.001$, CP-94,253, $F(3, 27) = 11.67$, $p < 0.001$, TFMPP, $F(3, 44) = 18.37$, $p < 0.001$, m-CPP, $F(3, 28) = 19.38$, $p < 0.001$, ORG 37684, $F(3, 28) = 21.80$, $p < 0.001$, BW 723C86, $F(3, 28) = 16.20$, $p < 0.001$, and DOI, $F(3, 28) = 27.35$, $p < 0.001$, reduced saccharin preference during the test session (Fig. 1). The magnitude of the CTA effect, as indicated by the percentage reduction of saccharin preference compared to vehicle control, was considered to be relatively strong; with maximal levels ranging between 63% (ipsapirone) to 95% (TFMPP). Because the maximal level of effect exceeded 50% for each compound, ED_{50} values could be calculated (MED and ED_{50} values in Table 1). Thus, as estimated by the respective ED_{50} values and 95% confidence limits, the following order of potency was obtained: DOI (m-CPP < TFMPP ⩽ ORG 37684 ⩽ BW 723C86 ⩽ CP-94-253 < ipsapirone (Fig. 2). As indicated by the occurrence of ED_{50} values with nonoverlapping 95% confidence limits, DOI was considered to be significantly more potent than the other compounds. There was no statistical evidence for a difference in potency between TFMPP, m-CPP, ORG 37864, BW 723C86, and CP-94,253, whereas ipsapirone was significantly less potent than the other compounds.

TABLE 1

SUMMARY OF RESULTS OBTAINED IN A CONDITIONED TASTE AVERSION PARADIGM

Compound	5-HT Receptor Subtype(s)	MED	ED_{50} (95% Confidence Limits)
Ipsapirone	5-HT_{1A}	20	20.15 (11.25–36.09)
CP-94,253	5-HT_{1B}	3	3.74 (1.54–9.08)
TFMPP	5-$HT_{1B/2C}$	3	2.45 (1.46–4.11)
m-CPP	5-$HT_{2C/1B}$	1	1.69 (0.96–2.99)
ORG 37684	5-HT_{2C}	3	2.96 (1.17–7.52)
BW 723C86	5-HT_{2B}	⩽3	3.49 (1.29–9.47)
DOI	5-$HT_{2A/2C}$	0.3	0.29 (0.14–0.63)

MED = minimal effective dose (lowest dose that resulted in a statistically significant reduction of saccharin preference, compared with vehicle control, $p < 0.05$), ED_{50} = effective $dose_{50}$; all doses in mg/kg, IP.

DISCUSSION

Compounds that activate different subtypes of 5-HT_1 and/or 5-HT_2 receptors decrease food intake in operant and free-feeding paradigms (for reviews, see Introduction). Although it has been argued that the hypophagic effects of some of these compounds (i.e., m-CPP, TFMPP, and CP-94,253) result from specific drug-induced effects on satiety [e.g., (6,19,25,40)], other behavioral mechanisms, such as drug-induced effects on motivational processes [e.g., (6,9,10)], or drug-induced disruption of the feeding cascade [as has been

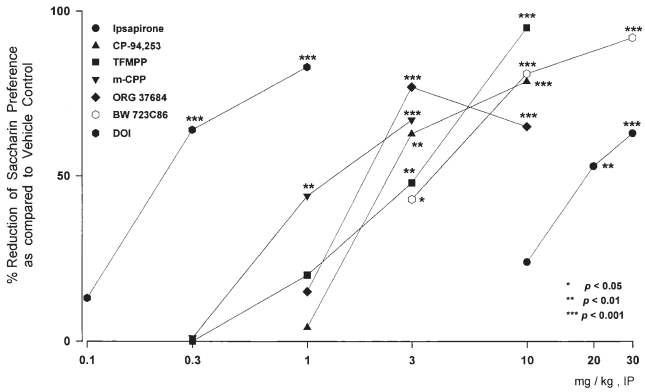

FIG. 2. Dose–response curves obtained with 5-HT receptor agonists with differential selectivity for the 5-HT_1 and 5-HT_2 receptor families in a CTA paradigm. For further details, see legend of Fig. 1.

suggested for DOI, (19,25,40)] have been proposed [for review on possible mechanisms, see (9)]. In addition to the above-mentioned behavioral mechanisms, it remains unclear as to what extent the observed hypophagia is the result of a drug-induced "malaise" (1,11). It was the aim of the present study to investigate the effects of a number of 5-$HT_{1/2}$ receptor agonists in a CTA paradigm, a possible correlate of drug-induced "malaise," and to compare the potency of these compounds to induce CTA with the reported potencies to induce hypophagia in free feeding and operant paradigms (10,37).

Each serotonergic compound tested in the present study dose dependently suppressed saccharin preference in a two-bottle saccharin vs. water choice paradigm; with the following order of potency: DOI < m-CPP ⩽ TFMPP ⩽ ORG 37684 ⩽ BW 723C86 ⩽ CP-94,253 < ipsapirone. These results appear consistent with those obtained in a recent preliminary study in which it was found that DOI, TFMPP, and m-CPP were able to reduce intake of a 2.5% sodium saccharin solution in a single-bottle CTA procedure using rats (1). In the present study, the maximal levels of CTA, as indicated by the percentage reduction of saccharin preference, were pronounced and relatively comparable within the tested dose ranges. Comparison of the present data obtained with ipsapirone with those reported earlier employing the same two-bottle procedure (8) indicates that they are very similar. Thus, in both studies a MED value of 20 mg/kg, IP, was found and maximal levels of efficacy of 63 and 55%, respectively, were obtained at 30 mg/kg, suggesting that, at least for ipsapirone, drug-induced CTA is a robust phenomenon.

The relative potencies of the presently tested compounds to induce CTA correlate reasonably well with their reported potencies to induce hypophagic effects. Thus, if the effects obtained with ipsapirone, CP-94,253, TFMPP, m-CPP, ORG 37684, BW 723C86, and DOI in the CTA paradigm were compared with those obtained in an operant food intake paradigm using the same strain of rats (10), the respective potencies correlated in a statistically significant manner ($r = 0.79$ and 0.81, $p < 0.05$; for correlation of ED_{50} and MED values, respectively). Similarly, a relatively strong correlation was obtained if the potencies of the same compounds were compared in the CTA paradigm and a free-feeding paradigm [again using the same strain of rats, (37)]. Thus, if potencies to inhibit food intake during the first h of a 12-h access paradigm were compared with potencies observed in the CTA paradigm, r values of 0.73, $p = 0.065$ and 0.80, $p < 0.05$ were obtained (comparison of ED_{50} and MED values, respectively). If such a comparison was made with respect to the first 2 h of the 12-h access period (37), respective correlations of 0.74 ($P = 0.059$) and 0.79 ($p < 0.05$) were obtained. Comparison of the absolute potencies to induce CTA with the absolute potencies to induce hypophagic effects in an operant feeding model (10) showed that CTA tended to be obtained at doses that were generally higher (two to six times) than those that induced hypophagia, except for DOI and BW 723C86, which were roughly equipotent in both assays. This potency difference was less pronounced if a comparison was made with the hypophagic effects assessed during relatively short intervals (i.e., first hour or first 2 h) of a 12-h access free-feeding paradigm (37). In fact, when considering the first hour of food intake, TFMPP was the only compound that was significantly more potent in the feeding paradigm than in the CTA paradigm. There was considerable overlap between the potencies to induce CTA and hypophagia as assessed during the first 2 h (or longer intervals) of food access.

Although the compounds tested in the present study were selected for their ability to decrease feeding behavior in the rat, it is not for all compounds clear which 5-HT receptor subtypes mediate their hypophagic properties [for review, see (9)], or their ability to induce CTA. The hypophagic effects of ipsapirone and CP-94,253 are generally assumed to be mediated by activation of 5-HT_{1A} and 5-HT_{1B} receptors, respectively. Although some authors have argued that 5-HT_{2C} and 5-HT_{2A} receptors are predominantly responsible for the hypophagic effects of m-CPP (as well as TFMPP), and DOI, respectively (22,23,36), additional involvement of other 5-HT receptor subtypes cannot be excluded yet [for review, see (9)]. With respect to the receptor involvement in the case of CTA, Benvenga and Leander (1) showed that the selective 5-HT_{2A} receptor antagonist MDL 100,907 was able to block the effects of DOI, suggesting that the 5-HT_{2A} receptor subtype is responsible for the CTA-inducing effect of DOI. In addition, these authors report that pretreatment with this antagonist was less efficacious against m-CPP, and hypothesize that stimulation of 5-HT_{2C}, and possibly 5-HT_{2B} receptors may also result in CTA (1). Inasmuch as ORG 37684 and BW 723C86 are selective 5-HT_{2C} and 5-HT_{2B} receptor agonists, respectively, the present study supports this suggestion. Further work is clearly needed to characterize the relative contribution of the different 5-HT receptor subtypes to the CTA-inducing properties of 5-$HT_{1/2}$ receptor agonists, and to determine to what extent selective stimulation of these different receptor subtypes will result in different levels of separation between hypophagic properties and CTA-inducing properties.

It is still controversial whether demonstration of a drug-induced CTA necessarily implies that aversive stimulus properties of the drug are responsible for this phenomenon, and whether CTA is due to activation of emetic mechanisms [for discussion, see (8,16,17,33). In addition, it has been argued that there is no simple relationship between the ability of a compound to induce CTA and to decrease feeding [i.e., (12)]. Nevertheless, the finding that the presently tested compounds are able to induce a potent and marked CTA, and that this correlates and even coincides to a large extent with the previously reported hypophagic effects of these compounds, offers at least the possibility that the hypophagic effects of compounds with agonist properties at particular 5-$HT_{1/2}$ receptor subtypes result from a drug-induced "malaise" (9,11). It can be hypothesized that the hypophagic effects of particular 5-$HT_{1/2}$ receptor agonists involve, at least partly, the same physiological mechanism/brain substrate(s) than the one underlying CTA. As the hypophagic effects of serotonergic compounds have generally been ascribed to their effects on satiety processes (2,3), and, possibly, motivational processes (6,9,10), and hypophagic effects of at least some of these compounds can be demonstated at lower doses than those that induce CTA, it can be speculated that weak stimulation (produced by relatively low doses) of such brain substrate(s) results in satiety, whereas strong stimulation of this substrate (produced by high doses) will result in aversive effects. In the light of this hypothesis it is interesting to note that Kaplan et al. (20) suggested, based on studies in chronic decerebrate rats, that 5-HT receptors in the caudal brain stem are necessary and sufficient for the hypophagic effects of m-CPP. In addition, local injection of a low dose range of m-CPP, or CP-94,253, into the fourth ventricle was reported to induce a clear hypophagic effect (18,20). These findings suggest that 5-HT receptors located in the brain stem are involved in the hypophagic effects of 5-HT_{1B}/2C receptor agonists. Indeed, Lee et al. (28) recently reported that CP-93,129, a selective 5-HT_{1B} receptor agonist closely related to CP-94,253, was 50-fold

more potent in reducing food intake following injection into the parabrachial nucleus of the brain stem compared with local injection into the hypothalamus. This observation may be very important with respect to the mechanism underlying the hypophagic effects of 5-$HT_{1/2}$ receptor agonists, as the parabrachial nucleus has been shown to contain 5-HT_{1B} and, possibly, 5-HT_{2C} receptors (28,31), and this nucleus is thought to be critically involved in the development/expression of CTA (32). It would, therefore, be highly interesting to test whether local application of the (low) dose range of these compounds that has been demonstrated to affect ingestive behavior, is able to induce CTA.

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