Pharmacology Biochemistry & Behavior, Vol. 32, pp. 907–911. © Maxwell Pergamon Macmillan plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

A Comparison of the Effects of Tryptamine and 5-Hydroxytryptamine on Feeding Following Injection Into the Paraventricular Nucleus of the Hypothalamus

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Received 27 July 1988

FLETCHER, P. J. AND I. A. PATERSON. *A comparison of the effects of tryptamine and 5-hydroxytryptamine on feeding following injection into the paraventricular nucleus of the hypothalamus.* PHARMACOL BIOCHEM BEHAV **32**(4) 907–911, 1989.—The effects of 5-hydroxytryptamine (5-HT) and tryptamine injected into the paraventricular nucleus of the hypothalamus (PVN) on food intake, and on noradrenaline- (NA) induced feeding were examined. In nondeprived rats, 12.5–100 nmol 5-HT reduced the intake of palatable wet mash diet over a 30-minute period. Tryptamine (50 and 100 nmol) was without effect in this paradigm. However, when tryptamine was injected into the PVN of rats pretreated with the monoamine oxidase inhibitor, pargyline, a strong anorectic effect was observed. The action of tryptamine in pargyline-treated rats was not affected by depletion of 5-HT levels in the PVN with PCPA. This indicates that the effect of tryptamine is not mediated by a release of endogenous 5-HT. Tryptamine injected into the PVN potentiated the effect of a low dose of 5-HT on food intake. This effect may be due to a prolongation of the activity of 5-HT resulting from tryptamine competing with 5-HT for the same reuptake system. Tryptamine and 5-HT attenauted the feeding response elicited by injection of 25 nmol NA into the PVN. Both tryptamine and 5-HT were more potent at attenuating the effects of NA than in reducing the intake of the palatable wet mash diet. Overall, the results suggest that tryptamine may act via the serotonergic system in the PVN to affect food intake, but it is a weaker compound than 5-HT in this respect.

Tryptamine 5-Hydroxytryptamine Paraventricular nucleus Feeding Rats

TRYPTAMINE is an indoleamine which occurs naturally in mammalian brain (24). Although it is present in small amounts the heterogenous distribution (24), subcellular localization (4) and rapid turnover rate (9) of tryptamine suggest a possible functional role in controlling neural activity. Several hypotheses concerning the nature of this functional role have been advanced (13).

In some studies it has been shown that tryptamine induces effects similar to those elicited by 5-hydroxytryptamine (5-HT) and 5-HT agonists. Examples of this include hyperactivity and the 5-HT syndrome in rats (20,21), a behavioural syndrome consisting of caudally directed biting and scratching in mice (17), myoclonus in guinea pigs (18), changes in cardiovascular function (16), reduced food intake (7), conditioned taste aversion (11) and impaired avoidance responding (12). These results show that in some instances tryptamine appears to act as a 5-HT agonist. Other experiments have shown that tryptamine can enhance the effects of 5-HT and 5-HT agonists. Thus, tryptamine enhances the effects of 5-HT on neuronal firing rate (14), locomotor activity (8), the biting and scratching syndrome (17) and the behavioural syndrome elicited by tryptophan plus tranylcypromine (21). Such findings have led to the proposal that tryptamine may serve as a modulator of 5-HT function (13). However, the results of further studies indicate that tryptamine may function independently of 5-HT systems. Microinjection of tryptamine into the preoptic area of the hypothalamus induces hyperthermia, whereas 5-HT administered into the same area induces hypothermia (5,6). These thermic responses were found to respond differently to pretreatment with 5-HT receptor antagonists (5), and the neurotoxin 5,7-dihydroxytryptamine (6). Further, 5-HT depleting electrolytic lesions of the midbrain raphe nuclei fail to alter tryptamine concentrations in the striatum, hypothalamus and hippocampus (15). These findings may indicate that tryptamine is a neurotransmitter in its own right, and this possibility is strongly supported by the demonstration of specific [^{3}H]-tryptamine binding sites in rat brain (1, 19, 23).

The present experiments were designed to examine further the behavioural effects of tryptamine, and to compare them with those induced by 5-HT. Specifically, the effects of tryptamine on food intake following microinjection into the paraventricular nucleus of the hypothalamus (PVN) were examined. This particular paradigm

was chosen for several reasons. Firstly, relatively high levels of tryptamine are found in the hypothalamus (24). Secondly, the hypothalamus may be especially sensitive to exogenously applied tryptamine since hyperthermia was elicited by injecting a low dose of tryptamine (6.2 nmol) into this region (5). Thirdly, it is known that 5-HT plays an important role in the control of food intake (3). Recent evidence has suggested that the PVN may be an important brain region in this respect since 5-HT injected into the PVN reduces food intake induced by deprivation, and by the PVN administration of noradrenaline (25,26).

METHOD

Subjects

Adult male Sprague-Dawley rats weighing 270–310 g at the time of surgery served as subjects. Animals were individually housed in hanging wire mesh cages in a temperature controlled room (22 ± 2°C) with a 12-hour light-dark cycle (lights on at 8:00 a.m.) Food and water were available at all times.

Surgery

Rats were anaesthetised with 50 mg/kg sodium pentobarbital and placed in a stereotaxic frame with the incisor bar set 3.3 mm below the interaural line. A 22-gauge stainless steel guide cannula (Plastic Products, Roanoke, VA) was aimed to end 4 mm above the left paraventricular nucleus according to the coordinates AP −1.3, L +0.4, V −4.0 mm (22). The cannula was secured in place by 4 stainless steel screws and dental cement. A 28-gauge stainless steel stylet was used to keep each cannula patent. Animals were allowed at least one week recovery time before drug testing.

General Test Procedures

Two test procedures were used to assess the effects of 5-HT and tryptamine on food intake. In the first paradigm the effects of these amines on the consumption of a palatable wet mash diet (100 g powdered lab chow + 15 g sucrose + 120 ml water) were examined. Prior to drug testing animals were habituated to eating this diet for 1 hr a day for at least 7 days. Standard lab chow was available at all other times. Immediately after drug delivery (see below) animals were placed in the home cage together with a glass petri dish containing a weighed amount of food. Food intake was determined at 15 min and/or 30 min postinjection by reweighing the remaining food plus spillage. In the second paradigm the effects of 5-HT and tryptamine on the intake of standard lab chow were examined. Immediately after drug delivery animals were replaced in the home cage together with a weighed amount of standard laboratory chow. Food intake was determined 1 hr later by reweighing the remaining food plus spillage. This paradigm was used also to test the responsiveness of all animals to an injection of NA into the PVN. The purpose of this test was to help in the verification of cannulae placements.

Drugs were dissolved in sterile saline, and delivered into the PVN in a volume of 0.4 μl by means of an ultra-fine glass microinjection needle (2) connected to a 5 μl Hamilton syringe via a length of plastic tubing. The glass needle was housed in a length of 28-gauge stainless steel tubing, which ended flush with the cannula; the glass needle protruded 4 mm beyond the tip of the cannula, into the PVN. The solution was injected over a period of 1 minute, and the needle was left in situ for a further 30 seconds.

Experiment 1

Eleven animals were used to examine the effects of 12.5, 25, 50 and 100 nmol 5-HT (5-hydroxytryptamine bimaleate, Sigma Chemical Co., St. Louis, MO) and saline on consumption of the wet mash diet. Each animal was tested under every dose of 5-HT and saline. Doses were administered in a semi-randomized order, and at least 3 drug-free days intervened between successive tests. A further group of 11 animals was used to examine the effects of 50 and 100 nmol tryptamine HCl (Sigma Chemical Co., St. Louis, MO) on the intake of the wet mash diet. Doses were administered in a mixed order at least 3 days apart.

A further 22 animals were injected (IP) with 50 mg/kg pargyline HCl (Sigma). Twenty-four hours later the animals were assigned to three groups matched for the intake of the wet mash diet on the preceding day. One group was injected with 0.4 μl saline (n = 7), one received 50 nmol tryptamine (n = 7) and one received 100 nmol tryptamine (n = 8). Food intake was measured 30 minutes later.

Experiment 2

This experiment examined the effects of 5-HT depletion in the PVN (achieved by injecting 0.5 mg PCPA ethyl ester in 1 μl into the PVN) on the effect of tryptamine in pargyline-pretreated rats, using the wet mash as the test diet. Four groups of animals were used (n = 7 each). Two groups received PCPA, and two groups received saline 4 days prior to testing. Twenty-four hours prior to testing all rats were injected (IP) also with 50 mg/kg pargyline. On the test day one saline group and one PCPA group were microinjected with saline into the PVN. The remaining saline and PCPA groups were microinjected with 100 nmol tryptamine.

Experiment 3

Eleven animals were used to examine the effect of 12.5 and 50 nmol 5-HT and saline in the absence or presence of 100 nmol tryptamine on consumption of the wet mash diet. Thus, each animal was tested twice with each dose of 5-HT and saline, once combined with 100 nmol tryptamine, and once without tryptamine. At least 3 drug-free days separated successive test days.

Experiment 4

The fourth experiment used 9 animals to examine the impact of 5-HT and tryptamine on the eating of laboratory chow elicited by 25 nmol noradrenaline bitartrate (Sigma). Each animal was tested five times, with noradrenaline alone, noradrenaline combined with 12.5 and 25 nmol 5-HT, and noradrenaline combined with 50 and 100 nmol tryptamine. At least 3 drug-free days separated successive test days.

Verification of Cannula Placements

Following completion of the experiments rats were anaesthetised with sodium pentobarbital, injected with 0.4 μl fast green dye into the PVN, and perfused intracardially with 4% formaline. The brain was removed and standard histological procedures were used to determine the injection sites. The data from animals with injection sites outside the PVN were not used in the analysis of the behavioural effects. In addition, all animals were screened for their eating response (of standard laboratory chow) to an injection of 25 nmol noradrenaline into the PVN. Any rat eating less than 1 g of food following this injection of NA was excluded from the experiments.

RESULTS

Experiment 1

Figure 1 shows the effects of increasing doses of 5-HT injected

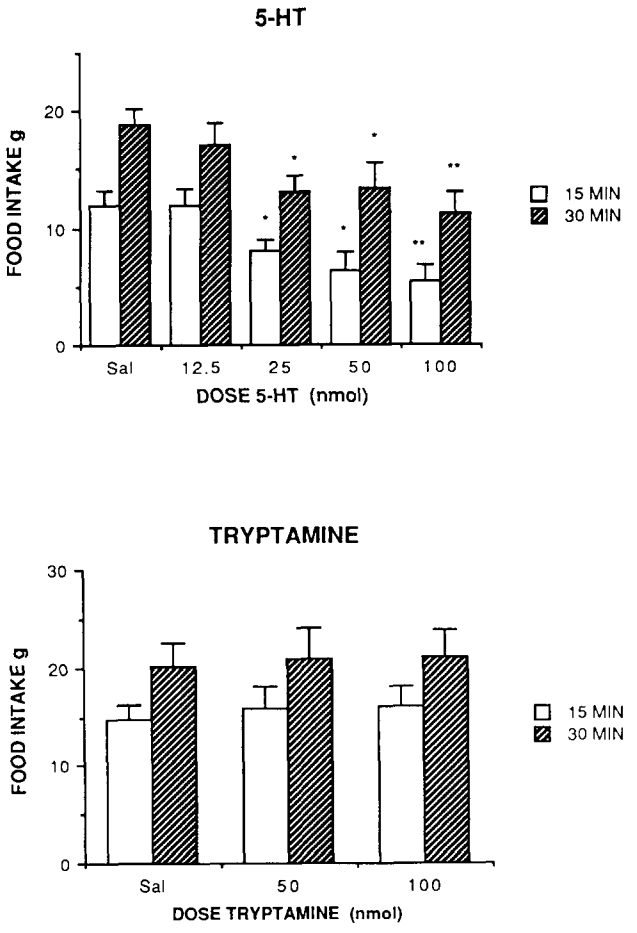

FIG. 1. The effects of various doses of 5-HT and tryptamine injected into the PVN on the cumulative intake of a wet mash diet. Values are the mean (±SEM) food intakes of 11 animals in each experiment. *$p<0.05$, **$p<0.01$, compared to saline treatment.

into the PVN on the intake of the wet mash diet. One-way analysis of variance revealed that 5-HT significantly reduced food intake at 15 minutes, $F(4,40)=7.4$, $p<0.001$, and 30 minutes, $F(4,40)=5.4$, $p<0.01$, postinjection. Comparisons against the mean intake under saline injection (Dunnett's test, $\alpha=0.05$) showed that the reductions in intake were significant at a dose of 25 nmol and higher. It can be seen also in Fig. 1 that tryptamine failed to alter the food intake at 15 minutes, $F(2,20)=0.1$, $p>0.1$, and 30 minutes, $F(2,20)=0.1$, $p>0.1$, postinjection.

Injection of 25 nmol NA into the PVN of animals in the 5-HT group increased the intake of standard laboratory chow to 3.6 ± 0.6 g from 0.5 ± 0.2 g following saline injection, $t(9)=3.8$, $p<0.001$. Similarly, for the tryptamine group, 25 nmol NA elicited an eating response of 2.8 ± 0.5 g compared to 0.4 ± 0.2 g following saline treatment, $t(10)=5.0$, $p<0.001$. These results confirm that injection sites were situated in the PVN.

In contrast to the lack of effect of typtamine alone, tryptamine injected into animals pretreated with MAOI pargyline significantly decreased wet mash intake 30 minutes postinjection, $F(2,19)=4.3$, $p<0.01$. The mean ± SEM food intakes for the three groups of animals in this experiment were 10.8 ± 1.7 g (saline), 5.3 ± 1.9 g (50 nmol tryptamine) and 3.5 ± 1.2 g (100 nmol tryptamine). Both doses of tryptamine significantly reduced food intake. It should be noted that pargyline + saline appeared to suppress 30-minute food intake from 20.5 ± 1.6 g immediately prior to pargyline injection, to 10.8 ± 1.7 g 24 hr after pargyline treatment.

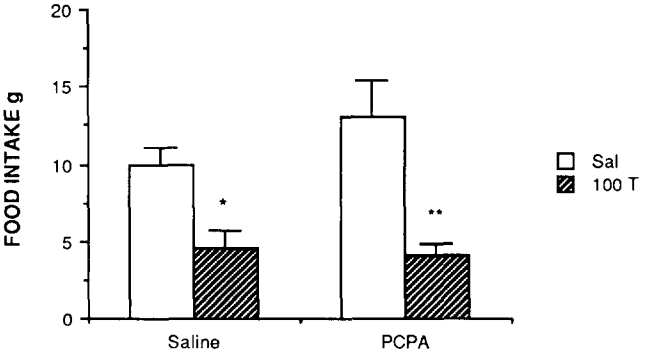

FIG. 2. The effects of 100 nmol tryptamine (T) and saline (Sal) injected into the PVN on food intake in rats pretreated with 0.5 mg PCPA (1 μl in the PVN, 4 days previously) or saline. Values are the mean (±SEM) food intakes (g) at 30 minutes postinjection. *$p<0.05$, **$p<0.01$, compared to appropriate saline- (Sal) treated group.

Experiment 2

Figure 2 illustrates the effects of PCPA injected into the PVN on the anorectic action of 100 nmol tryptamine in pargyline-pretreated rats. Two-way analysis of variance (with dose of PCPA and dose of tryptamine as factors) of these data revealed a significant main effect of tryptamine dose, $F(1,24)=28.9$, $p<0.001$. Neither the main effect of PCPA, $F(1,24)=0.8$, $p>0.1$, nor the PCPA × tryptamine interaction, $F(1,24)=0.2$ $p>0.1$, were significant. Thus, tryptamine again significantly reduced food intake in pargyline-treated animals, but this effect was not altered by 5-HT depletion with PCPA.

Experiment 3

The effects of 100 nmol tryptamine on the action of various doses of 5-HT are shown in Fig. 3. Two-way analysis of variance (using dose of 5-HT and dose of tryptamine as factors) revealed a significant main effect of 5-HT dose after 15 minutes, $F(2,20)=573$, $p<0.001$. Post hoc comparisons (Tukey's test, $\alpha=0.05$) showed that the anorectic action of 5-HT was confined to the highest dose only; 12.5 nmol 5-HT did not significantly reduce food intake. A significant 5-HT × tryptamine interaction was found, $F(2,20)=3.9$, $p<0.04$. Tests of simple main effects on this interaction revealed that animals treated with tryptamine and 12.5 nmol 5-HT consumed significantly less food than animals treated with saline and 12.5 nmol 5-HT, $F(1,10)=6.1$, $p<0.04$. The effect of tryptamine at the higher dose of 5-HT was not significant, $F(1,10)=3.2$, $p>0.1$.

At 30 minutes postinjection a significant main effect of 5-HT was observed, $F(2,20)=28.5$, $p<0.001$, which was due to the anorectic action of the higher dose of 5-HT. The interaction term was not significant, $F(2,20)=0.5$, $p>0.1$. The main effect of tryptamine treatment was significant, $F(1,10)=12.8$, $p<0.01$, however, multiple comparison tests (Tukey's test, $\alpha=0.05$) did not reveal any significant effects of tryptamine at each dose level of 5-HT. Nevertheless, the combination of tryptamine plus 12.5 nmol 5-HT significantly reduced food intake relative to the saline control condition.

Experiment 4

Figure 4 illustrates the effects of 5-HT and tryptamine injected

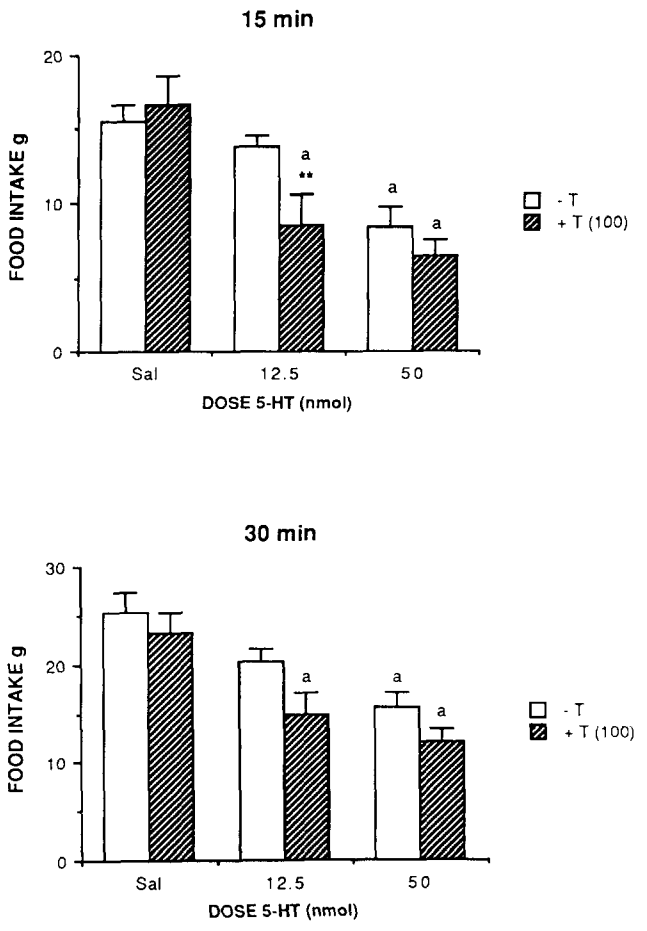

FIG. 3. The effects of saline, 12.5 and 50 nmol 5-HT injected into the PVN, in the absence of (−T) or presence (+T, 100) of 100 nmol tryptamine, on mean (±SEM) food intake (g) at 15 and 30 minutes postinjection. $^{a}p<0.05$, compared to saline (−T) treatment; $^{**}p<0.01$, compared to 12.5 nmol 5-HT (+T) treatment.

into the PVN on the eating of laboratory chow induced by PVN injection of 25 nmol NA. One-way analysis of variance showed a significant effect of treatments, $F(4,32)=9.3$, $p<0.001$. Multiple comparison tests (Dunnett's $\alpha=0.05$) showed that the eating response of 3.5 ± 0.4 g induced by NA was attenuated by 12.5 and 25 nmol 5-HT, and by 100 nmol tryptamine.

A comparison of these results with those illlustrated in Fig. 1 shows that both 5-HT and tryptamine were apparently more potent in suppressing the NA-induced feeding than in reducing the intake of the wet mash diet.

DISCUSSION

The results of the first experiment showed that 5-HT injected into the PVN reduced the intake of a palatable wet mash diet. This finding confirms previous reports that 5-HT injected into the PVN exerts an anorectic action (25,26). The dose response curve obtained with 5-HT was shallow, with a dose of 100 nmol 5-HT inducing only a slightly greater anorectic action than a dose of 25 nmol. As noted previously (26), 5-HT at doses higher than 25 nmol induced apparent sedation. In contrast to the anorectic action of 5-HT, tryptamine failed to affect food intake at doses up to 100

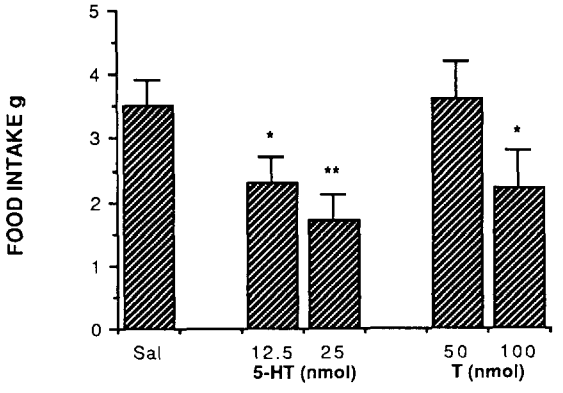

FIG. 4. The effects of 12.5 nmol 5-HT, 50 and 100 nmol tryptamine (T) and saline injected into the PVN on the food intake elicited by 24 nmol noradrenaline injected into the PVN. $^{*}p<0.05$, $^{**}p<0.01$, compared to saline treatment.

nmol. This is perhaps somewhat surprising in view of the demonstration that 6.2 nmol of tryptamine induced a hyperthermic effect which persisted for 30 minutes when injected into the preoptic anterior hypothalamus (5). However, when tryptamine was injected into the PVN of rats pretreated with pargyline, to retard the oxidative deamination of tryptamine, a strong suppression of food intake was observed. This effect appeared to be greater than that achieved with any dose of 5-HT. It is likely that this is due in part to monoamine oxidase inhibition per se, since the pargyline treatment alone affected food intake relative to baseline levels in animals injected with saline in the PVN. As with the higher doses of 5-HT, tryptamine in pargyline-treated rats induced a marked sedation, which undoubtedly interfered with the ability of the animals to feed normally.

This suppression of food intake induced by tryptamine (plus pargyline) was not affected by treatment with PCPA. Since PCPA depletes 5-HT levels by inhibiting tryptophan hydroxylase activity, it is unlikely that the anorectic effect of tryptamine occurs via an interaction with endogenous 5-HT.

In a variety of experiments tryptamine has been found to enhance the actions of 5-HT (8, 14, 17). Such an effect was demonstrated in the present study. A dose of 12.5 nmol of 5-HT injected into the PVN did not significantly reduce food intake, but when 100 nmol tryptamine was injected simultaneously a modest anorectic action was observed. Previously it was shown that in mice tryptamine enhanced a behavioural syndrome induced by intrathecal administration of 5-HT (17). The effects of 5-HT were also enhanced by the 5-HT reuptake inhibitor fluoxetine. However, fluoxetine did not enhance the behavioural effect of the combination of tryptamine and 5-HT. These findings suggested to the authors that tryptamine enhances the action of 5-HT by competing for the same reuptake site (17) so that the synaptic availability of 5-HT is prolonged. Such a mechanism could account for the effects of these indoleamines following PVN injection. This possible explanation is supported by the observation that tryptamine and 5-HT share a common uptake system (10), and by the finding that tryptamine increases the half-life of 5-HT when both amines are injected intraventricularly in mice (Orikasa and Sloley, personal communication).

Injection of NA into the PVN elicits feeding in satiated rats and this effect is antagonised by 5-HT injected into the same site (26). In fact, 5-HT is more effective at reducing feeding induced by NA than at reducing feeding induced by deprivation. A similar effect

was observed in the present experiments. A dose of 12.5 nmol 5-HT, which did not reliably reduce the intake of a wet mash diet, suppressed the feeding response of 25 nmol NA to 66% of the control condition. Further, as can be seen by comparing Figs. 1 and 4, 25 nmol 5-HT was considerably more effective against NA-induced feeding. In view of the increased potency of 5-HT at attenuating the action of NA it is interesting that 100 nmol tryptamine significantly reduced NA-induced feeding, even though the intake of the wet mash diet was unaffected by this dose of tryptamine. It is likely, therefore, that tryptamine and 5-HT act through the same mechanism to suppress NA-induced feeding. In view of this, and the observation that tryptamine reduces food intake only after MAO inhibition, an effect which cannot be explained in terms of an interaction with endogenous 5-HT, it appears that tryptamine injected into the PVN acts as a weak 5-HT agonist.

ACKNOWLEDGEMENTS

P. J. Fletcher and I. A. Paterson are in receipt of Postdoctoral Fellowships from Saskatchewan Health Research Board.

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