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Feeding and 8-OH-DPAT-Related Release of Serotonin in the Rat Lateral Hypothalamus

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VOIGT, J.-P., F. KIENZLE, R. SOHR, A. REX AND H. FINK. *Feeding and 8-OH-DPAT-related release of serotonin in the rat lateral hypothalamus.* PHARMACOL BIOCHEM BEHAV **65**(1) 183–189, 2000.—Based on the different effects of somatodendritic 5-HT_{1A} agonist 8-OH-DPAT on food intake whether given to food-deprived rats or freely feeding rats, we hypothesized that the effects of 8-OH-DPAT on extracellular serotonin (5-HT) in the lateral hypothalamus (LH) will interfere with different feeding states, eventually resulting in different patterns of 5-HT release. In a microdialysis study we measured extracellular 5-HT in the LH after 8-OH-DPAT under four experimental conditions, i.e., in freely feeding rats with no food available, freely feeding rats with access to food, in food-deprived rats with no food available, and in food-deprived rats with good available after treatment. The results show a significant decrease of 5-HT release after 300 μg/kg 8-OH-DPAT (IP) in freely feeding rats. This effect is not seen when food is provided after drug treatment. In contrast, the same dose of 8-OH-DPAT has no effect on 5-HT release in food-deprived rats. In addition, providing food after drug treatment does not change the release pattern significantly in food-deprived rats, suggesting more complexity in the underlying mechanisms. The present study describes the effects of 8-OH-DPAT on 5-HT release in the LH, depending on feeding conditions and feeding-related behavioral states. © 1999 Elsevier Science Inc.

Feeding Microdialysis Lateral hypothalamus Rat Serotonin 5-HT_{1A} receptor 8-OH-DPAT

FEEDING behavior is under control of mechanisms acting in the central nervous system as well as in the periphery. From the many neurotransmitters and peptides involved in these processes, serotonin (5-HT) plays a significant role (7,8,12, 35,36). Serotonin increases the rate of satiation and prolongs the state of satiety (47).

Drugs that enhance serotonergic activity usually reduce food intake, whereas drugs attenuating serotonergic activity may increase food intake (7). Serotonergic effects on food intake and satiety are mediated both by peripheral and central mechanisms (46,47). Serotonin receptors are classified into seven major classes with various subtypes (27,28). There is experimental evidence for the involvement of several of these 5-HT receptor subtypes in the effects of serotonin on food intake. These subtypes mediate also different aspects of satiety. The 5-HT_{1B} receptor subtype (in nonrodent species and human 1D) promotes seronergic enhancement of the satiating effect of food, whereas the 5-HT_{2C} receptor mediates inhibition of eating rate. Stimulating 5-HT_{2A} receptors has an effect on intermeal intervals [see (47) for review].

However, 5-HT agonists acting at the somatodendritic 5-HT_{1A} autoreceptor, for example 8-OH-DPAT, reduce serotonergic activity in the brain. Given systemically (16,17,19,31), but also directly into the raphe (4,13,22,29), 8-OH-DPAT and other 5-HT_{1A} agonists [see (20) for review] induced feeding in rats. The stimulation of food intake by 8-OH-DPAT is a phenomenon seen only in freely feeding rats but not in food-deprived rats, and is interpreted as disinhibition of feeding (18). In food-deprived rats (17,21), and also in rats adapted to daytime feeding (3), 8-OH-DPAT inhibited food intake. In

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rats, hypophagic after exercise, 8-OH-DPAT had no effect on nocturnal food intake (10). Diurnal variations in the feeding response to 8-OH-DPAT have been also observed at various times throughout the nocturnal cycle (13). There are several in vivo studies comparing the effects of 8-OH-DPAT on 5-HT release across different brain regions. Hjorth and Sharp (26) used brain microdialysis to measure 5-HT release in hippocampus, globus pallidus, frontal cortex, nucleus accumbens, and medial septum after systemic administration of 8-OH-DPAT to anesthetized rats. They found an overall decreased 5-HT release with only little regional differences. The inhibition of 5-HT release was less marked in the globus pallidus compared to the other brain regions studied. Casanovas et al. (9) found reduced extracellular 5-HT after treatment with 8-OH-DPAT that was more regionally selective, but also depending on the dose. These authors found a reduction in extracellular 5-HT to 32% of baseline in the striatum and to 69% in the dorsal hippocampus. Adell et al. (1) measured decreased extracellular 5-HT in the raphe and in the hippocampus after systemic injection of 8-OH-DPAT.

In contrast to these studies, the present article focuses on the comparison of 5-HT release within one single brain region—the lateral hypothalamus (LH)—but takes into account different behavioral states in relation to pharmacological treatment.

The role of 5-HT in the control of food intake by the LH was recently reviewed (6). This review discusses the effects of numerous transmitters, hormones, and appetite depressants, and describes a specific function of hypothalamic 5-HT for the coordination of food intake, and also for the selection of macronutrients. The lateral hypothalamus receives its main serotonergic innervation from the median raphe (48), a brain region where local administration of 8-OH-DPAT also acts to induce feeding (5,13,29).

Previous microdialysis studies showed an increase in extracellular 5-HT during feeding in the hypothalamus (39,42,43,49). During nocturnal feeding, an increased 5-HT metabolism was observed in the lateral hypothalamus (LH). This was paralleled by an increasing activity of 40% of LH neurons; 23% decreased and 37% of the neurons showed no change (2). Hypophagic doses of the satiety mediating peptide CCK also facilitate 5-HT release in the LH (49).

Based on the different effects of 8-OH-DPAT on food intake whether given to food-deprived rats or freely feeding rats, we hypothesized that the effects of 8-OH-DPAT on intracellular 5-HT in the LH will interfere with different feeding states, eventually resulting in different pattern of 5-HT release.

METHOD

Animals

Experiments were carried out in male Wistar rats (Harlan-Winkelmann, Germany) weighing 220–280 g. The rats were kept under standardized conditions, with an artificial 12 D:12 L cycle (lights on 0600–1800 h). They had free access to a standard rat laboratory diet (Altromin 1326, Altromin, Germany) and water.

The experimental protocol was approved by an Institutional Review Committee for the use of Animal Subjects (LAGetSi Berlin).

Drug

8-Hydroxy-2-(di-n-propylamino)tetralinHBr (8-OH-DPAT, Research Biochemicals Incorporated) was dissolved in 0.9% saline. 8-OH-DPAT was administered intraperitoneally (IP). The application volume was 1 ml/kg body weight. All control animals received an equivalent volume of 0.9% saline.

Feeding Experiments Without Microdialysis

These pilot studies were performed to determine the appropriate dosage of 8-OH-DPAT to be used in the microdialysis experiments later on. Experiments were performed in 16-h food-deprived rats in comparison to freely feeding rats. 8-OH-DPAT was administered in doses of 100 and 300 μg/kg 20 min prior to a 2-h test meal of the same laboratory diet the rats were accustomed to.

Locomotor Activity

This experiment was performed to investigate the possibility that differences in drug effects on 5-HT release in freely feeding rats compared to food-deprived rats are related to differences in locomotor activity. In this independent experiment, rats of the same age were single housed under the very same conditions as described below for the microdialysis experiments. One half of the animals was food deprived for 16 h, the other half received food until the beginning of the experiment. Both groups were treated with 300 μg/kg 8-OH-DPAT (IP) and locomotor activity was monitored individually. Cages were placed on an Animex (LKB, Sweden). Activity measures were obtained counting the disruptions of a vertical electrical field emitted by the Animex unit. The sensitivity of the meter was adjusted so that only gross movements were detected. Readings were done at 20-min intervals starting 1 h before treatment and were continued for 2 more h following drug administration.

Microdialysis Experiments

Surgery. Rats were anesthetized with sodium pentobarbitone (45 mg/kg IP) and placed in a stereotaxic frame to allow the implantation of a microdialysis guide canula (CMA, Sweden). The coordinates were AP −2.5 mm, L 1.6 mm, from bregma, and 5.5 mm from the skull surface, according to the atlas of Paxinos and Watson (40). The guide canula was fixed to the skull with stainless steel screws and cold curing resin (Technovit, Kulzer, Germany). Rats were allowed at least 1 week of postoperative recovery before starting the microdialysis experiments. During this time the rats were kept individually in cylindrical cages allowing also to perform the microdialysis experiments.

Microdialysis. The microdialysis membranes (CMA 10) were 3 mm long, with an outer diameter of 0.5 mm and 20,000 molecular weight cutoff. According to our in vitro calibration test, the relative recovery was around 20% for 5-HT. The microdialysis probe was perfused (1 μl/min) with artificial CSF (125 mM NaCl, 2.5 mM KCl, 27 mM $NaHCO_3$, 0.5 mM NaH_2PO_4 H_2O, 2.4 mM NA_2HPO_4 $2H_2O$, 0.5 mM Na_2SO_4, 1 mM $MgCl_2$ 6 H_2O, 1 mM $CaCl_2$ $2H_2O$, pH 7.4). The flow rate (1 μl/min) allowed the collection of 20 μl samples every 20 min into microvials.

Analysis of dialysates. Dialysates were analyzed by reverse-phase high-performance liquid chromatography with electrochemical detection (HPLC-EC). Samples were injected directly into a valve with a 20-μl loop (Rheodyne, USA). The sample was separated by a 125-mm (Megapharm ODS-5 i.d. 1 mm; BAS) column. The mobile phase contained 0.1 M NaH_2PO_4, 1 mM EDTA, 0.7 mM OSA, 5% isopropanol at pH 5.4. The mobile phase was delivered by a pump

(Gynkotek, Germany) with an external pulse dampener at a flow rate of approximately 200 μl/min. Serotonin was oxidized at 0.650 V (a LKB electrochemical cell and an EC-30 electrochemical detector, Gynkotek, Germany).

Experimental design. The dialysis probe was inserted through the guide canula at 1600 h the day before the experiment. After establishing a stable baseline of three consecutive samples (sampling interval: 20 min) 8-OH-DPAT was administered, and collecting samples was continued for another 2 h. Experiments were performed between 0900 and 1400 h.

Experiment 1. The experiment was performed in freely feeding rats. However, to exclude any interference with 5-HT release, food was removed immediately before drug treatment (100 and 300 μg/kg 8-OH-DPAT), and was not returned before the experiment was finished. Control animals were treated with saline. 8-OH-DPAT and saline, respectively, were administered immediately following the third baseline sample.

Experiment 2. The experiment was performed in 16-h food-deprived rats, and there was no food available at any time during the experiment. 8-OH-DPAT was administered in the dose of 300 μg/kg, which was found effective in Experiment 1. Control animals were treated with saline. 8-OH-DPAT and saline, respectively, were administered immediately following the third baseline sample.

Experiment 3. This experiment was performed as described under Experiment 1, except that only one dose of 8-OH-DPAT (300 μg/kg) was administered, and good was also provided during the last 2 h of the experiment immediately following drug administration.

Experiment 4. The experiment was performed as described under Experiment 2, except that food was provided for 2 h after treatment.

Histology

At the end of the microdialysis experiment, the brain was removed and frozen on the stage of a cryomicrotome. The brain was cut into serial coronal sections at 30 μm. The localization of the microdialysis probe was verified under a microscope by an observer unaware of the experimental data.

Statistical Analysis

Feeding experiments. Data are presented as mean ± SEM. Data were analyzed by one-way ANOVA followed by Dunnett's test, or, when normality test failed by Kruskal–Wallis test, followed by Dunn's test.

Locomotor activity. Between-group comparisons were made by Mann–Whitney *U*-test.

Microdialysis experiments. Baseline release rates of 5-HT showed interindividual differences. Therefore, data from each animal were expressed as percentages. Data from three dialysates before treatment or feeding, respectively, were averaged, and the mean set as 100%; all individual values were calculated accordingly.

Between-group comparisons were made either by one-way ANOVA followed by Dunnett's test (Experiment 1) or by Student's *t*-test, or, where normality test failed, by nonparametric Mann–Whitney *U*-test (Experiments 2 through 4).

A probability level of $p < 0.05$ was regarded as significant.

RESULTS

Feeding Experiments Without Microdialysis

In freely feeding rats, 8-OH-DPAT stimulated food intake as expected, with an significant effect at 300 μg/kg, $F(2, 43) = 3.435$, $p = 0.0413$. During the 2-h test meal control rats fed 0.62 ± 0.17 g, and rats treated with 300 μg/kg 8-OH-DPAT fed 1.46 ± 0.26 g. In contrast, the very same dose significantly inhibited feeding in rats previously food deprived for 16 h, $H(2) = 8.008$, $p = 0.018$. Food-deprived control-rats fed 7.7 ± 0.45 g during the subsequent 2-h test meal. This amount was reduced to 4.71 ± 0.85 g in rats treated with 300 μg/kg 8-OH-DPAT (Fig. 1).

Locomotor Activity

In contrast to food intake, however, the effect of 300 μg/kg 8-OH-DPAT on locomotor activity was not significantly different in food-deprived and satiated rats. The only significant difference was observed during the 20-min interval immediately before treatment. Activity reading was higher in the food-deprived group ($p = 0.0159$) at this time point (Fig. 2).

Microdialysis Experiments

Experiment 1. In the first microdialysis experiment, performed in freely feeding rats, 100 or 300 μg/kg 8-OH-DPAT was injected intraperitoneally, and intrahypothalamic 5-HT release was monitored in comparison to saline-injected rats. There was no significant between-group difference during baseline, i.e., at any of the three time points before treatment. Twenty minutes after treatment a single intraperitoneal injection of 300 μg/kg 8-OH-DPAT resulted in a significant decrease in hypothalamic 5-HT release compared to saline treated controls, $F(2) = 0.31$, $p = 0.258$. The difference to the control was also significant at 40 min, $H(2) = 6.14$, and 60 min $F(2) = 6.10$, $p = 0.010$, after drug treatment (Fig. 3).

Experiment 2. In contrast to Experiment 1, there was no between-group difference between saline and 300 μg/kg 8-OH-DPAT, when rats were food deprived for 16 h (Fig. 4).

Experiment 3. When food was available to freely feeding rats after drug treatment, 8-OH-DPAT induced food intake in the microdialysis experiment as also seen in the behavioral experiments, resulting in a significantly attenuated effect on 5-HT release of a drug compared to the nonfood condition. In fact, 40 min ($t = 3.892$, $p = 0.005$) and 60 min ($t = -3.571$, $p =$

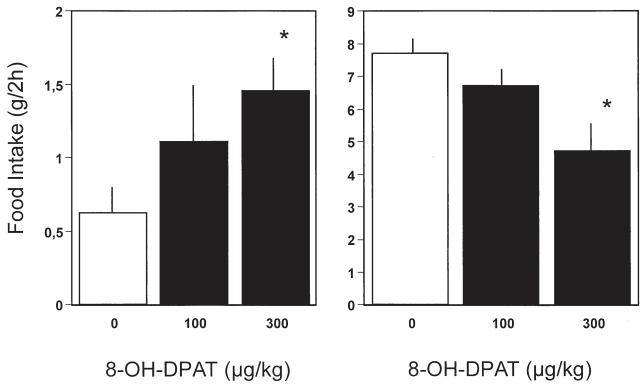

FIG. 1. Effect of 8-OH-DPAT on food intake in freely feeding rats (left panel) and 16-h food-deprived rats (right panel). Control animals received saline. 8-OH-DPAT (300 μg/kg, IP) stimulated food intake significantly in freely feeding rats, but had the opposite effect in formerly food-derived rats. Food intake was measured over 2 h. $n =$ 10–18 animals per group. Mean ± SEM. *$p < 0.05$ vs. control. ANOVA followed by Dunn's test.

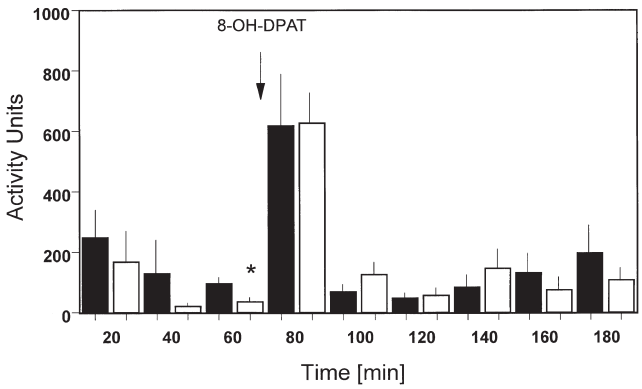

FIG. 2. Effect of 300 μg/kg 8-OH-DPAT (IP) on locomotor activity as measured by ANIMEX, in freely feeding rats (white columns) and 16-h food-deprived rats (black columns). Locomotor activity as expressed in counts was significantly different between groups only within the 20-min interval immediately before treatment. $n = 4$–5 animals per group. Mean ± SEM. $^*p < 0.05$ vs. control. Mann–Whitney *U*-test.

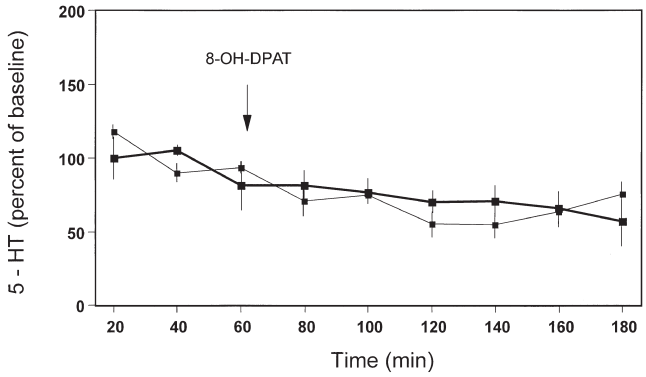

FIG. 4. Effect of 8-OH-DPAT (300 μg/kg, IP, thick line) and saline (thin line) on extracellular serotonin (5-HT) in LH in 16-h food-deprived rats. There was no difference between drug and saline-treated rats in 5-HT release. Data points are expressed as percent of baseline (mean of the first three samples set 100%). n = 6–7 animals per group. Mean ± SEM.

0.007) after treatment 5-HT release was higher when feeding occurred compared to the nonfood situation (Fig. 5). Under these conditions, rats consumed 2.54 ± 0.23 g/2 h.

Experiment 4. Performing the latter experiment in food-deprived rats also resulted in a weak increase in 5-HT release that was, however, at no time point significant compared to the control group (Fig. 6). Rats consumed 3.25 ± 0.28 g/2 h. During the first hour, they fed 2.8 ± 0.23 g compared to 4.68 ± 0.85 g (55) in untreated controls.

DISCUSSION

Since first shown in a study by Dourish et al. (16), many groups reported increased food intake after administration of the 5-HT_{1A} receptor agonist 8-OH-DPAT [see (20) for review]. This effect is mediated by somatodendritic autoreceptors (17,29,31). It is interesting to note, however, that the exogenic action of 8-OH-DPAT depends on experimental conditions. One important condition to allow 8-OH-DPAT–stimulated food intake is that rats are freely fed but not food deprived. In hungry rats, on the contrary, 8-OH-DPAT has either no effect, or even suppresses food intake (5,17,21). This different mode of action was also confirmed in our pilot experiments.

Bendotti and Samanin (5) proposed that in hungry rats 8-OH-DPAT may act more postsynaptically, resulting in a stronger serotonin syndrome, possibly interfering with feeding behavior. In rats, this syndrome includes reciprocal forepaw treading, hyperlocomotion head weaving, and flattened body posture (15,25,32). However, our data, although from a rather small sample, could not confirm that, but suggest the same effect of 8-OH-DPAT on locomotor activity, an increase within 20 min following injection, in satiated and food-deprived rats. The dose of 8-OH-DPAT used in the present experiment appears to be high, but the route of administration was, simply for technical reasons, related to the microdi-

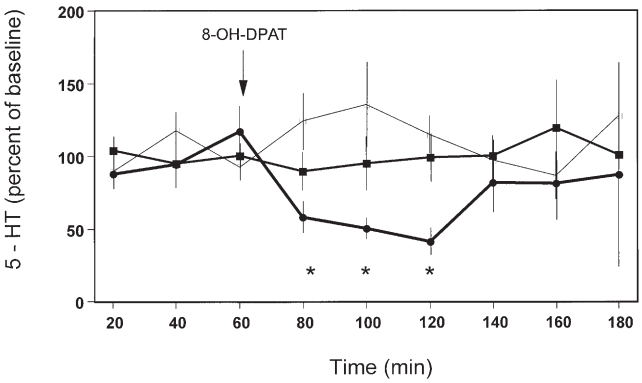

FIG. 3. Effect of 8-OH-DPAT (300 μg/kg, IP, thick line; 100 μg/kg intermediate line, and saline, thin line) on extracellular serotonin (5-HT) in LH in freely feeding rats. 8-OH-DPAT (300 μg/kg) significantly reduced 5-HT release. Data points are expressed as percent of baseline (mean of the first three samples set 100%) n = 5–8 animals per group. Mean ± SEM. $^*p < 0.05$ vs. control. ANOVA followed by Dunn's test.

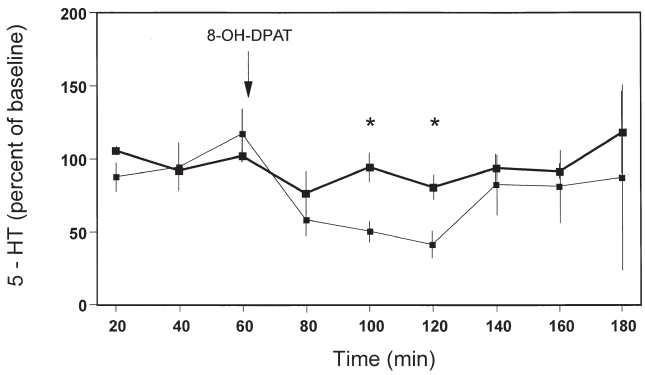

FIG. 5. Effect of 8-OH-DPAT (300 μg/kg, IP) on extracellular serotonin (5-HT) in LH when food is available to satiated rats after treatment (thick line) compared to the nonfood condition (thin line). Ingesting food led to an relative increase in 5-HT release. Data points are expressed as percent of baseline (mean of the first three samples set 100%). n = 6–8 animals per group. Mean ± SEM. $^*p < 0.05$ vs. nonfood condition. *t*-test.

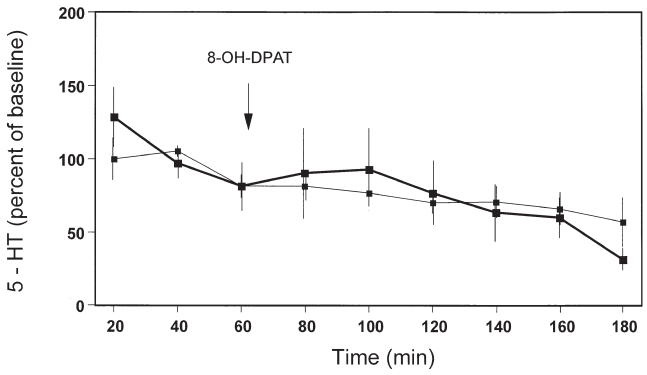

FIG. 6. Effect of 8-OH-DPAT (300 μg/kg, IP) on extracellular serotonin (5-HT) in LH when food is available to 16-h food deprived rats after treatment (thick line) compared to the nonfood condition (thin line). There was no difference between drug and saline-treated rats in 5-HT release. Data points are expressed as percent of baseline (mean of the first three samples set 100%). n = 6–8 animals per group. Mean ± SEM.

alysis procedure, intraperitoneal. The dose of 8-OH-DPAT used in the present experiment appears to be high, but the route of administration was, simply for technical reason related to the microdialysis procedure, intraperitoneal. This route of administration, however, results in lower levels of the compound in the brain compared to subcutaneous administration (41). 8-OH-DPAT is also more potent after subcutaneous administration compared to intraperitoneal administration (24). This may explain the absence of a clear 5-HT syndrome during the microdialysis experiments or during testing locomotor activity, respectively. So far, our data suggest, that differences in the effect of 8-OH-DPAT on 5-HT release in LH seen between hungry and satiated rats do not simply reflect differences in locomotor activity.

8-OH-DPAT, by acting at somatodentritic autoreceptors, reduces extracellular 5-HT in the hypothalamus as shown in the present study and before by other groups (37,43). With our second microdialysis experiment, however, we could also demonstrate that 8-OH-DPAT had no effect on extracellular 5-HT compared to controls, when rats were 16-h food deprived. Several studies already addressed the issue of mechanisms responsible for the different effects of 8-OH-DPAT, depending on satiety state. Serotonin synthesis depends on the supply of its precursor tryptophan and serotonin release into synapses, and also depends on tryptophan availability. In the brain, the level of tryptophan increases following starvation (14,45). An increased 5-HT turnover (expressed as increase in 5-HIAA/5-HT ratio) in the lateral hypothalamus and other brain regions has been reported in fasted rats (23,34,38). Fuenmayor et al. (23) suggested that an increased turnover of 5-HT in the hypothalamus appears to be accompanied by an increased neuronal release. Schwartz et al. (44) found in a microdialysis study that a peripheral tryptophan load can elevate hypothalamic 5-HT more effectively in food-deprived rats than in food-replete rats. Hutson et al. (30) found decreased ratios 5-HIAA/5-HT, i.e., a decreased turnover, after 60 μg/kg 8-OH-DPAT in different brain regions, including the hypothalamus. Therefore, it appears possible that one process may compensate the other functionally in food-deprived rats, finally resulting in an unchanged extracellular level of 5-HT after treatment with the 5-HT_{1A} agonist, as seen in our study in food-deprived rats.

Chalouff et al. (11) hypothesesized a desensitization of 5-HT_{1A} autoreceptors in food-deprived rats because of a fasting-related increase in the firing rate of serotonergic cells. However, fasting neither affected 8-OH-DPAT–induced inhibition of midbrain 5-HT synthesis—indicating no change in 5-HT_{1A} autoreceptor sensitivity—nor [^{3}H]-8-OH-DPAT binding at 5-HT_{1A} autoreceptors. Fasting increased brain tryptophan levels in rats to the same extent whether treated with saline or 8-OH-DPAT before. Therefore, the authors concluded that food deprivation does not affect 5-HT_{1A} autoreceptors.

In contrast, the involvement of postsynaptic 5-HT_{1A} receptors in regulation of food intake is less clear. A study by Jhanwar et al. (33) proposed that presynaptically mediated 8-OH-DPAT–induced hyperphagia may require specific circulating levels of insulin and glucose, which in turn, are regulated via postsynaptic hypothalamic 5-HT_{1A} receptors. Jhanwar et al. found increased 5-HT_{1A} receptor density in the medial but not the lateral hypothalamus after treatment with the hypoglycemic compound tolbutamide. Therefore, different circulating levels of glucose or insulin in satiated and fasted rats may also contribute to different effects of 8-OH-DPAT on food intake and 5-HT release. Taken together, these studies suggest that the missing effect of 8-OH-DPAT on 5-HT release in fasted rats may depend on complex serotonergic mechanisms rather than only on changes at the somatodendritic autoreceptor site.

Because food intake leads to an increase in extracellular 5-HT in the LH, this may have also been expected in the third microdialysis experiment, where food was provided after administering 8-OH-DPAT. However, as shown in this experiment, the release pattern obtained from analysis of microdialysis samples also reflects interferences of a drug-induced decrease in extracellular 5-HT, with a feeding induced increase in 5-HT release. In the fourth microdialysis experiment, we expected an increase in extracellular 5-HT due to the food intake. There are several reasons why the release pattern appears less clear in the fourth experiment. First, the activity of the serotonergic system or other neurotransmitter systems may be different in hungry rats, as already discussed for the second experiment. Second, food intake is reduced after 8-OH-DPAT compared to saline-treated controls, as also shown in the feeding experiments without microdialysis. Comparing food intake under microdialysis condition during the first hour after 8-OH-DPAT as determined in Experiment 4 with untreated but also hungry rats (49) also revealed a drug-induced reduction. In that previous study from our laboratory, the feeding-induced increase in extracellular 5-HT was about 164% from baseline. Therefore, the possibility exists that the relatively low food intake in the fourth experiment is not sufficient to induce a significant increase in 5-HT release.

Taken together, the present microdialysis study describes different effects of 8-OH-DPAT on 5-HT release in the LH, depending on feeding conditions. In freely feeding rats, hypothalamic 5-HT release after treatment with the 5-HT_{1A} agonist 8-OH-DPAT depends on food intake at the same time. These data further suggest that different feeding-related behavioral states influence 5-HT release in the lateral hypothalamus.

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