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# Role of 5-HT1A receptors in the control of food intake in obese Zucker rats of different ages

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**Abstract**

The present study describes the role of 5-HT1A receptors in the serotonergic control of food intake in obese Zucker rats of different ages. In addition, serotonin (5-HT) and cholecystokinin (CCK) content and 5-HT turnover were determined in various brain regions. The 5-HT1A receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT; 100 μg/kg) stimulated food intake in 3-month-old lean control rats but inhibited feeding in obese Zucker rats (300 μg/kg). This pattern remained the same in 6-month-old rats. At 10 months of age, 8-OH-DPAT lost its inhibitory activity in the obese rats but still stimulated feeding in lean controls (300 μg/kg). 5-HT levels were higher in the hypothalamus and in the frontal and parietal cortices of 3-month-old obese Zucker rats and were associated with a lower cortical turnover. In the parietal cortex and the hypothalamus of 6-month-old rats, 5-HT levels were still higher, linked with a lower hypothalamic turnover. No differences were observed in 10-month-old rats. CCK content was not different between obese Zucker rats and lean rats. The persistently different feeding responses to 8-OH-DPAT in obese Zucker rats and lean controls may be related to changes in brain 5-HT metabolism in the obese Zucker rats. © 2002 Elsevier Science Inc. All rights reserved.

*Keywords:* Zucker rat; Serotonin metabolism; 5-HT1A receptor; 8-OH-DPAT; Feeding; CCK

## 1. Introduction

Serotonin (5-HT) is an important mediator of satiety. An increased serotonergic activity promotes satiety by mechanisms acting in the periphery and in the central nervous system (for review, see Halford and Blundell, 2000; Leibowitz and Alexander, 1998). This physiological role of 5-HT has also stimulated the investigation of central serotonergic mechanisms in obese Zucker rats. In general, previous studies performed in this animal model of obesity determined brain content of 5-HT and its major metabolite 5-hydroxyindoleacetic acid (5-HIAA). Some of these studies also focused on ontogenetic changes in brain 5-HT. In an early study, Finkelstein et al. (1982) found lower levels of the 5-HT precursor tryptophan in several brain regions of 13-week-old male obese Zucker rats. However, 5-HT content was lowered only in the mesencephalon. Tsujii et al. (1988) found increased 5-HIAA/5-HT ratios in different brain regions, including cortex and hypothalamus, of 12–14-week-old male Zucker rats, whether food deprived for 72 h or not. The putative effect of age on brain 5-HT metabolism in Zucker rats was addressed by Orosco et al. (1986) in a study with female Zucker rats at 5, 8, 12 and 16 weeks of age. At 5 weeks of age, no significant differences between obese and lean controls were found. At 8 weeks, 5-HIAA was reduced in the hypothalamus, striatum and cortex but not in the hippocampus of obese rats. In the striatum, this was accompanied by a reduction in 5-HT. Levels of 5-HT and 5-HIAA were lower in the hippocampus of 16-week-old obese Zucker rats, whereas hypothalamic 5-HT was increased in these rats.

Several more recent studies performed in vivo microdialysis in brain regions involved in feeding behaviour. In 4-month-old obese male Zucker rats, an augmented 5-HT release in response to a meal was found in the rostromedial hypothalamus (Orosco et al., 1995). However, this response to feeding declined with age and returned to the level of nonobese control rats in 12-month-old Zucker rats (Lemierre et al., 1998). A microdialysis study in the medial hypothal-

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amus of 10–14-week-old male lean and obese Zucker rats revealed that the net increase in extracellular 5-HT concentration was lower in the obese rats after a 50-Hz stimulation of the dorsal raphe nuclei, indicating a reduced capacity of serotonergic neurons to release 5-HT in obese Zucker rats (De Fanti et al., 2000).

Although the data are still fragmentary, they nevertheless clearly indicate ontogenetic changes as well as differences in brain 5-HT metabolism between obese Zucker rats and lean controls. Despite these reports on brain 5-HT metabolism, only few pharmacological studies investigated the effects of anorectic serotonergic drugs in obese Zucker rats. These available studies used the anorectic 5-HT releaser and reuptake inhibitor fenfluramine or fluoxetine. Overall, there were no significantly different effects when obese Zucker rats and lean controls were compared (Orosco et al., 1984; Grinker et al., 1980; Dryden et al., 1996). A similar anorectic effect in obese Zucker rats and their lean littermate controls was observed after acute administration of the putative 5-HT1B/2C receptor agonist trifluoromethylphenyl-piperazine (TFMPP; Koulu et al., 1990). In addition, the hypophagic response to the 5-HT2A/2C receptor agonist 1-(4-iodo-2,5-dimethoxyphenyl)-2-aminopropan (DOI) was of identical amplitude in lean and obese rats (Chaouloff et al., 1995).

In contrast to fenfluramine, 5-HT agonists acting at the somatodendritic 5-HT1A autoreceptor, as for example 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), reduce serotonergic activity in the brain and induce feeding in freely feeding rats. The effect of 5-HT1A agonists, however, is sensitive to experimental conditions and dose dependent and may turn even into hypophagia (for review, see Dourish, 1992; De Vry and Schreiber 2000).The reason for this dual mode of action has been subject of discussion. Changes in 'general' serotonergic activity, in particular synthesis and release, may account for the different effects of the agonist. Since brain 5-HT metabolism in obese Zucker rats is changed as outlined before, it is likely that 8-OH-DPAT acts differently on food intake in obese Zucker rats compared to lean controls.

At least in nonobese rats, 5-HT interacts with cholecystokinin (CCK), another important satiety factor, to control food intake, and the 5-$HT_{1A}$ receptor subtype is involved in this interaction (Poeschla et al., 1992; Voigt et al., 1995). Obese Zucker rats show a decreased sensitivity to the hypophagic effect of CCK (McLaughlin and Baile, 1980; Niederau et al., 1997).Therefore, not only the serotonergic system may be affected in obese Zucker rats but also brain CCK content.

In the current study, we investigated the effect of the 5-HT1A agonist 8-OH-DPAT on food intake in freely feeding obese Zucker rats and lean controls. We tested 3-, 6- and 10-month-old male rats. In addition, we determined 5-HT, 5-HIAA and CCK in different brain regions in order to investigate whether the differences in behavioural responses could be due to altered levels of these satiety factors.

## 2. Methods

### 2.1. Animals

Experiments were carried out in male obese (*fa/fa*) and lean (*Fa/?*) Zucker rats (IFA Credo, France). The rats were kept under standardised conditions with an artificial 12-h dark/light cycle (lights on 06:00–18:00 h). They had free access to a standard rat laboratory diet (Altromin 1326, Altromin, Germany) and water. For the experiments, independent groups of rats of different ages were used: 3, 6 and 10 months.

The experimental protocol was approved by the Institutional Review Committee for the Use of Animal Subjects (Authority for labour protection, occupational health and technical safety for the state and city of Berlin, Germany).

### 2.2. Drug

8-OH-DPAT (Research Biochemicals) was dissolved in 0.9% saline. 8-OH-DPAT was administered subcutaneously (sc). The application volume was 1 ml/kg body weight. All control animals received an equivalent volume of 0.9% saline.

### 2.3. Feeding experiments

All feeding experiments were performed between 09:00 and 13:00 h. 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. The doses chosen for treatment are based on previous experiments in our laboratory. In addition, the schedule of the experiments was planned according to earlier studies (Voigt et al., 1995, 2000). Group size was between 10 and 15 rats per group.

### 2.4. Dissection of the brains and homogenisation procedures

Groups of obese and lean Zucker rats were decapitated at the age of 3, 6 and 10 months. These rats were decapitated under the same feeding conditions and during the same time of day as feeding experiments were performed. The brains were rapidly removed, immediately frozen on dry ice and stored at −80 °C until use. Various brain areas including hypothalamus, hippocampus, striatum, frontal cortex and parietal cortex were dissected from the frozen brain on a cold plate (−10 °C; König and Klippel, 1970). The tissue samples from the right hemisphere were weighed and stored at −80 °C until homogenisation. The tissue samples of the left hemisphere were weighed and immediately homogenised by Ultraturax after adding 800-μl boiling distilled water. After homogenisation, boiling was continued in a water bath for 8 min. After centrifugation (12,000 × *g*), the supernatants were stored at −20 °C. Sample size was between 7 and 10 per brain region.

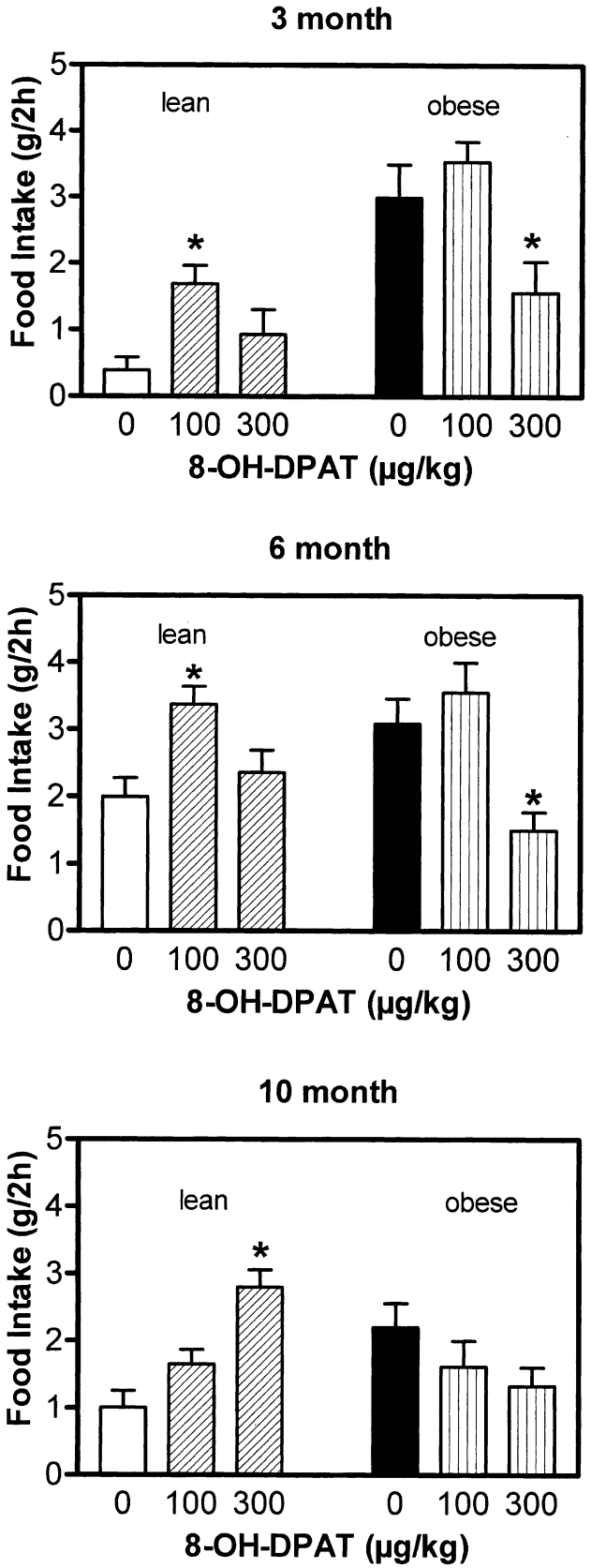


Fig. 1. Effect of 8-OH-DPAT (subcutaneous) on 2-h food intake in obese and lean Zucker rats. Food intake was measured in 3-, 6- and 10-month-old rats. $n = 10-15$ rats per group. Mean + S.E.M. * $P < .05$ vs. lean controls. ANOVA followed by Dunnett's test.

### 2.5. Determination of 5-HT, 5-HIAA and CCK

At the day of the determination of 5-HT and 5-HIAA, each frozen tissue sample of the various brain areas dissected from the right hemisphere was homogenised by ultrasonication in 10–20 volumes of 0.1-N perchloric acid containing 0.4-mM $NaHSO_3$ and centrifuged at 25,000 × $g$ for 10 min at 4 °C. The supernatant was used for the measurement of 5-HT and 5-HIAA. 5-HT and 5-HIAA were analysed as described previously using high-performance liquid chromatography (HPLC) with electrochemical detection (Sperk, 1982). In the stored supernatants obtained from the left hemisphere, CCK was determined by a radioimmunoassay described previously. A rabbit antibody (K4) raised against CCK-8 (carrier ovalbumine) produced by Schade et al. (1988) was used. Sample size was between 7 and 10 per brain region.

### 2.6. Statistical analyses

All data are expressed as means ± S.E.M. Statistical analysis of the data from the feeding experiments was performed using one-way ANOVA followed by Dunnett's test. All other data were analysed by two-tailed Student's $t$ test. A probability level of $P < .05$ was regarded as significant.

## 3. Results

### 3.1. Feeding experiments

At the age of 3 months, saline-treated obese Zucker rats consumed 2.9 ± 0.5 g compared to 0.4 ± 0.2 g in the lean control group during the 2-h daytime testing. 8-OH-DPAT (100 µg/kg) stimulated food intake in nonobese control rats [$F(2,27) = 5.11$, $P < .01$]. The same dose had no significant effect on food intake in obese Zucker rats and a higher dose

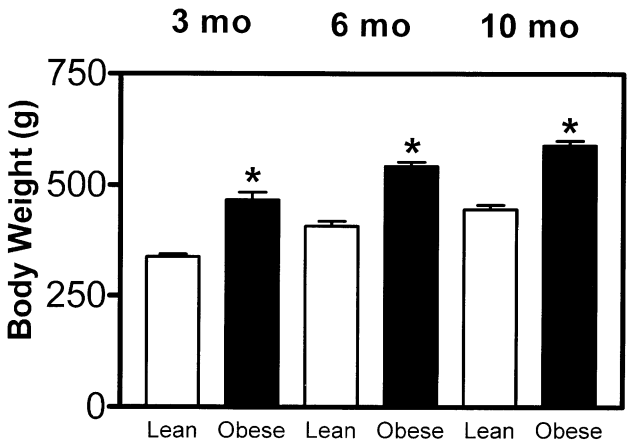


Fig. 2. Body mass of obese and lean Zucker rats as determined at the age of 3, 6 and 10 months. $n = 10-15$ rats per group. Mean + S.E.M. * $P < .05$ vs. lean controls. Two-tailed Student's $t$ test.

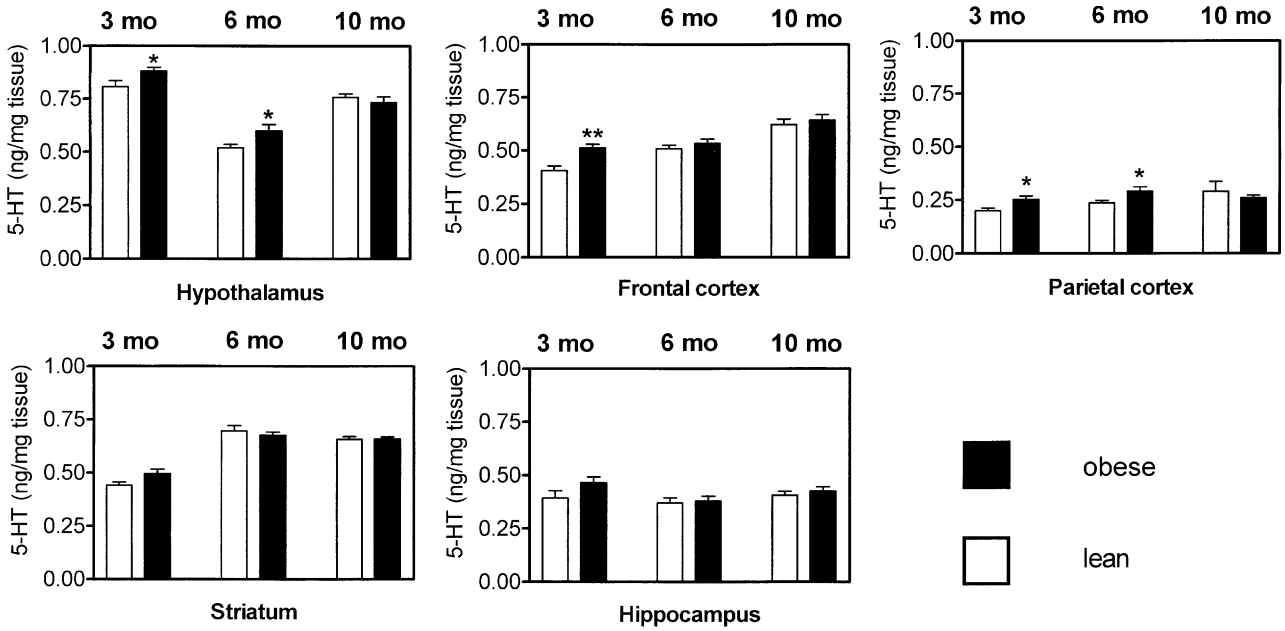


Fig. 3. Tissue levels of 5-HT in various brain areas of obese and lean Zucker rats at the age of 3, 6 and 10 months. The black columns represent the levels of obese Zucker rats and the white columns those of the lean rats. $n = 7–10$ rats per group. Mean + S.E.M. ng/mg tissue. * $P < .05$, ** $P < .001$ versus lean controls. Two-tailed Student's $t$ test.

(300μg/kg) even inhibited feeding in these rats [$F(2,27) = 5.12$, $P < .01$] but had no effect in the lean controls (Fig. 1). A similar pattern was seen in 6-month-old rats [obese: $F(2,42) = 8.45$, $P < .001$; lean: $F(2,42) = 5.83$, $P < .01$; Fig. 1]. When the rats reached the age of 10 months, 8-OH-DPAT had no effect in obese Zucker rats [$F(2,42) = 1.67$, $P > .05$] but still stimulated food intake in lean controls as seen after a dose of 300 μg/kg [$F(2,42) = 13.88$, $P < .001$]. Although not significant, a tendency to reduce food intake remained, however, also after 300-μg/kg 8-OH-DPAT in the obese group (Fig. 1). Obese Zucker rats had a significantly higher body weight when compared to the control rats at all age periods (Fig. 2).

Table 1
Molar ratio of 5-HIAA/5-HT in various brain areas of obese and lean Zucker rats of different ages

| Brain area | Rats | 3 months | 6 months | 10 months |
|---|---|---|---|---|
| Hypothalamus | Obese | 0.747 ± 0.027 | 1.281 ± 0.071 * | 0.933 ± 0.040 |
| | Lean | 0.816 ± 0.038 | 1.479 ± 0.064 | 0.835 ± 0.030 |
| Frontal cortex | Obese | 0.643 ± 0.045 ** | 0.541 ± 0.023 | 0.424 ± 0.020 |
| | Lean | 0.959 ± 0.059 | 0.564 ± 0.022 | 0.404 ± 0.020 |
| Parietal cortex | Obese | 0.856 ± 0.035 * | 0.724 ± 0.050 | 0.593 ± 0.030 |
| | Lean | 1.168 ± 0.074 | 0.844 ± 0.048 | 0.538 ± 0.040 |
| Hippocampus | Obese | 1.190 ± 0.096 | 1.060 ± 0.090 | 0.814 ± 0.050 |
| | Lean | 1.570 ± 0.172 | 1.130 ± 0.067 | 0.882 ± 0.070 |
| Striatum | Obese | 1.260 ± 0.037 | 0.893 ± 0.038 | 0.704 ± 0.090 |
| | Lean | 1.390 ± 0.039 | 0.859 ± 0.029 | 0.717 ± 0.090 |

$n = 7–10$. Mean ± S.E.M. versus lean control rats. Two-tailed Student's $t$ test.
* $P < .05$.
** $P < .01$.

### 3.2. 5-HT brain content and 5-HIAA/5-HT ratio

At the age of 3 months, 5-HT levels were significantly higher in the hypothalamus, the frontal cortex and the parietal cortex of obese Zucker rats compared to lean controls. In the hypothalamus and the parietal cortex, this difference continued to exist up to 6 months of age, whereas no significant differences were observed in 10-month-old rats. No significant differences were observed in the hippocampus and the striatum (Fig. 3).

The turnover of 5-HT as expressed by the 5-HIAA/5-HT ratio was significantly lower in the cortex (frontal and parietal) of 3-month-old obese Zucker rats. At the age of 6 months, the only significant difference was observed in the hypothalamus, where obese Zucker rats had a lower

Table 2
Tissue levels of CCK in various brain areas of obese and lean Zucker rats of different ages

| Brain area | Rat | 3 months | 6 months | 10 months |
|---|---|---|---|---|
| Hypothalamus | Obese | 84.3 ± 3.0 | 90.5 ± 4.6 | 51.2 ± 5.3 |
| | Lean | 89.1 ± 5.0 | 84.8 ± 5.1 | 56.0 ± 3.8 |
| Frontal cortex | Obese | 403.5 ± 27.9 | 385.4 ± 21.9 | 284.3 ± 18.4 |
| | Lean | 310.4 ± 34.5 | 386.6 ± 29.0 | 291.6 ± 26.0 |
| Parietal cortex | Obese | n.e. | 242.1 ± 13.1 | 203.4 ± 10.6 |
| | Lean | n.e. | 262.3 ± 12.5 | 176.9 ± 10.6 |
| Hippocampus | Obese | 122.5 ± 15.1 | 128.7 ± 9.3 | 87.5 ± 6.5 |
| | Lean | 117.2 ± 7.7 | 135.1 ± 8.2 | 71.7 ± 11.3 |
| Striatum | Obese | 203.8 ± 7.6 | 213.7 ± 10.6 | 97.4 ± 29.7 |
| | Lean | 199.7 ± 4.6 | 219.4 ± 8.3 | 103.9 ± 10.0 |

$n = 7–10$. Mean ± S.E.M. fmol/mg tissue.

turnover. No significant differences occurred in 10-month-old rats (Table 1).

### 3.3. CCK brain content

CCK contents were not different in obese Zucker rats and lean control rats in any of the five brain areas and at any age period investigated (Table 2).

## 4. Discussion

This study describes the effects of the 5-HT1A receptor agonist 8-OH-DPAT on food intake in obese Zucker rats of different ages. In addition, brain content has been determined for 5-HT, 5-HIAA and CCK.

Several earlier studies in nonobese rats usually reported an induction of food intake after 8-OH-DPAT in freely feeding rats. 8-OH-DPAT was effective after both systemical administration but also when given directly into the raphe (Dourish et al., 1985a,b; Bendotti and Samanin, 1986; Hutson et al., 1986,1988; Fletcher and Davies, 1990). This was confirmed by the data obtained from the nonobese group of our study. Under certain conditions, however, an inhibitory effect on food intake was observed in normal weight rats. For example, 8-OH-DPAT inhibits food intake also in rats adapted to 4-h daytime feeding (Aulakh et al., 1988). Variations in the feeding response to 8-OH-DPAT have been observed at various times throughout the nocturnal cycle (Currie and Coscina, 1993). 8-OH-DPAT also inhibits food intake in food-deprived rats (Dourish et al., 1985b, Ebenezer 1992). At the age of 3 months, obese Zucker rats responded differently to the activation of 5-HT1A receptors as compared to lean controls. At the lower dose of 100 μ/kg, 8-OH-DPAT stimulated feeding in the lean control group as expected but was ineffective in the obese group. In contrast, a dose of 300-μg/kg 8-OH-DPAT inhibited food intake in freely feeding obese Zucker rats but had no effect in lean controls. Almost the same pattern of response to 8-OH-DPAT was observed at the age of 6 months. Later, at 10 months of age, 8-OH-DPAT did not change feeding behaviour significantly anymore in obese Zucker rats but still stimulated feeding in lean controls (300 μg/kg). The data indicate that the inhibitory effect of 8-OH-DPAT on food intake in freely feeding obese Zucker rats persisted for several months, at least up to 6 months of age, but was markedly attenuated in 10-month-old rats. Comparably, the increased 5-HT release in response to a meal in young obese Zucker rats as measured by intrahypothalamic microdialysis also returned to control levels in older (12 months) rats (Lemierre et al., 1998). However, our data on food intake are in contrast to the results of an earlier study by Chaouloff and Jeanrenaud (1988). These authors reported a similar feeding response to 8-OH-DPAT in lean and obese Zucker rats. They applied the high dose of 500 μg/kg to induce feeding. In addition, the rats used in the latter study, either obese or lean, had a similar basal food intake. This is also in contrast to our study, where obese rats fed significantly more than lean rats. In addition, the study by Chaouloff and Jeanrenaud has been performed in the afternoon, whereas our experiments were conducted in the morning.

Since 5-HT activity is disturbed in obese Zucker rats, one may also speculate that in consequence to the long-lasting decrease in serotonergic activity observed in these rats, the altered feeding response to 8-OH-DPAT might be explained by adaptive changes in the sensitivity of postsynaptic 5-HT1A receptors. In consequence to the long-lasting decrease in serotonergic activity observed in obese Zucker rats, an up-regulation of postsynaptic 5-HT receptors is likely to develop. Such a mechanism could also account for the parallel normalisation of serotonergic activity and the failure of 8-OH-DPAT to significantly inhibit food intake in 10-month-old obese Zucker rats. Moreover, it also has to be considered that 8-OH-DPAT has been shown to reduce hyperinsulinemia in up to 22-week-old obese Zucker rats after a single dose or during repeated administration (Chaouloff and Jeanrenaud, 1988; Pesonen et al., 1991).Inhibition of insulin secretion in obese rats could then produce beneficial metabolic effects influencing the hyperphagic behaviour.

Furthermore, 5-HT1A receptor expression may be affected by endocrine mechanism that may be differentially regulated or even disturbed in obese Zucker rats. For example, circulating glucose levels have been shown to regulate 5-HT1A receptor expression (Jhanwar-Uniyal et al., 1994). Obese Zucker rats are only slightly hyperglycaemic (Martin et al., 1978; Bray, 1977), but the insulin resistance occurring in these rats may reduce glucose availability in specific brain areas. In addition to glucose, 5-HT1A receptor expression depends also on adrenal hormones (Meijer and de Kloet, 1994; Le Corre et al., 1997). Obese Zucker rats have been found to have elevated serum corticosterone concentrations (Guillaume-Gentil et al., 1990). Corticosterone has been shown to suppress the expression of 5-HT1A receptor mRNA in the hippocampus (Meijer et al., 1998). In Zucker rats, adrenalectomy results in a generalised increase in brain 5-HT turnover although it does not prevent onset of obesity (Routh et al., 1995).

Our data on 5-HT and 5-HIAA levels in various brain areas provide further evidence supporting the blunted serotonergic activity in the brains of obese Zucker rats reported in earlier studies (Routh et al., 1994). We were able to demonstrate for the first time that the decrease in 5-HT turnover vanishes when obese Zucker rats grow older (10 months). Thus, the decrease in serotonergic function in obese Zucker rats is a transient and age-dependent phenomenon, which is not yet developed in the first days of life (Horwitz et al., 1998) and disappears in the later life as shown in the present study.

Microdialysis data presented by Orosco et al. (1995) further contributed to the interpretation of data on 5-HT and

5-HIAA brain levels and pharmacological responses. These authors found a similar profile of rostromedial hypothalamic 5-HT release in response to spontaneous feeding in obese Zucker rats and in Wistar rats. However, the magnitude of the release was significantly higher in the obese rats. More recently, De Fanti et al. (2001) studied medial hypothalamic 5-HT release in Zucker rats. The total net release in response to a meal was also higher in obese Zucker rats. The authors consider compensations for elevated orexigens for a reduced CCK activity or a functional resistance to 5-HT as explanation for their findings. Another study by Meguid et al. (2000) conducted in the ventromedial hypothalamus demonstrated differences in baseline levels in 5-HT between lean and obese rats, but the response to a meal was only slightly higher in the obese group. Orosco et al. (1995) interpret their data in terms of a large amount of 5-HT that is required to bring about satiety in obese Zucker rats, and Meguid et al. (2000) suggest an impaired postsynaptic monoaminergic action to produce an adequate metabolic response in obese Zucker rats. This would also be in line with the hypothesis mentioned before that postsynaptic 5-HT1A receptor density is regulated by circulating glucose levels. Since the stimulation of feeding is mediated by somatodendritic autoreceptors, we may hypothesise a modified interplay between pre- and postsynaptic sites in obese Zucker rats. Orosco et al. (1986) suggested that the changes they observed in the serotonergic system are secondary with respect to the development of obesity in Zucker rats. Similarly, based on their findings in neonate Zucker rats, Horwitz et al. (1998) concluded that the onset of increased adiposity induced by the *fa/fa* mutation does not require decreased VMH serotonergic activity. Our finding that the blunted serotonergic activity is no longer evident in older animals in spite of continued adiposity would provide further support for a secondary phenomenon. However, even if the serotonergic system has been changed as a result of developing obesity or in parallel to obesity, this change may have functional significance and therefore become a target for treatments to reduce food intake and fight obesity.

In contrast to 5-HT and 5-HIAA, there were no differences in brain CCK content between obese and lean Zucker rats. McLaughlin et al. (1985), however, reported different hypothalamic CCK content in obese and lean Zucker rats, but the changes in CCK content following feeding were the same. Nevertheless our data suggest a lower brain CCK content in 10-month-old rats of both groups. Under certain conditions, the responsivity to CCK may be diminished in aged rats (Voigt et al., 1996). This could affect 5-HT–CCK interactions and eventually lead to the reduced response to 8-OH-DPAT, with aging that is obvious in obese rats and also in lean rats. In the obese group, the inhibitory effect of 300-μg/kg 8-OH-DPAT lost its significance at 10 months. Also, in the lean group, a higher dose of 8-OH-DPAT is required to obtain the same stimulating effect seen in younger rats already after 100 μg/kg. So far, our data on CCK content need additional experimentation to study brain CCK release, since measures of peptide content reflect both synthesis and release. For example, De Fanti et al. (1998) could show a blunted hypothalamic CCK release in obese Zucker rats as measured by push–pull perfusion. In conclusion, the data indicate persistently different feeding responses to 8-OH-DPAT when obese Zucker rats and lean controls are compared. This finding may be related to changes in brain 5-HT metabolism in the obese Zucker rats and subsequently also to changes at pre- and/or postsynaptic 5-HT1A receptor sites.

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