Effects of \textit{m}-CPP and mesulergine on dietary choices in deprived rats: Possible mechanisms of their action

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Abstract

Although it has been well established that compounds that stimulate 5-HT$_{2C}$ and/or 5-HT$_{1B}$ receptors induce hypophagia by promoting satiety process, the relative role of these receptor subtypes in dietary choices remains to be fully determined. \textit{m}-CPP is considered a useful probe of 5-HT$_{2C}$ receptor function in vivo and its administration reduces food intake and appetite in humans and rats. Conversely, the non-selective 5-HT$_{2C}$ receptor antagonist mesulergine elicits feeding in rats. Food intake and dietary choices were measured in a food-deprivation experimental protocol employing male Wistar rats. Animals were given access for a 4-h period to a pair of isocaloric diets. These two diets were enriched in protein or carbohydrate proportions, respectively, but fat content was held constant. The mixed 5-HT$_{2C/1B}$ receptor agonist, \textit{m}-CPP, led to a dose-dependent hypophagia, due to substantial reduction in carbohydrate consumption while protein intake was spared (0.62, 1.25 and 2.50 mg/kg i.p., respectively). The non-selective 5-HT$_{2C}$ receptor antagonist and also D$_2$ agonist, mesulergine, on its own produced a significant dose-dependent increase in both protein and carbohydrate diets (1.0 and 3.0 mg/kg i.p., respectively). Combined treatment with \textit{m}-CPP, at its maximum effective dose, and mesulergine dose-dependently reversed \textit{m}-CPP-induced hypophagia, during the 4-h test period. In order to clarify the effects of mesulergine on dietary choices since it is simultaneously a dopamine agonist besides its antiserotonergic properties, the D$_2$ agonist apomorphine was also used. Apomorphine caused a dose-dependent increase in protein intake while carbohydrate and total food intake remained nearly unchanged (0.5 and 1.0 mg/kg i.p., respectively). It is concluded that the mesulergine-induced hyperphagic response on both diets is the expression of a dual mode of action, due to its 5-HT$_{2C}$ antagonist activity together with D$_2$ agonist properties. The results further indicate that the activation of hypothalamic 5-HT$_{2C}$ receptors may be involved in both protein sparing and carbohydrate suppressing effects of 5-HT (\textit{m}-CPP-like effect), whereas an important role in increase of protein consumption seems to have the dopaminergic system probably through D$_2$ receptors (apomorphine-like and mesulergine-like effects, respectively).

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Keywords: Apomorphine; Carbohydrate enriched diet; Dietary choices; Dopamine (DA) receptors; D$_2$; Food deprivation schedule; 5-Hydroxytryptamine (5-HT) receptors; 5-HT$_{2C}$; Isocaloric diets; \textit{m}-CPP; Mesulergine; Protein enriched diet

1. Introduction

The serotonergic system has an inhibitory role in appetite behaviour and has been the main target for drug development against obesity (Blundell and Halford, 1998; Brownell and Fairburn, 2002; Haldor and Blundell, 2000; Leibowitz, 1991; Simansky, 1996, 1998). Furthermore, there is a close relationship between satiety, dietary choices and serotonergic activities (Blundell, 1984, 1991; Curzon, 1990; Haldor et al., 2000; Leibowitz, 1990). Clinical and preclinical studies have shown that administration of compounds which enhance serotonergic neurotransmission (i.e., fenfluramine, fluoxetine and sertraline) induce hypophagia in both animals and humans (De Vry and...
Schreiber, 2000; Garattini et al., 1992; Hewitt et al., 2002; Kitchener and Dourish, 1994; Sargent et al., 1997; Simansky and Vaidya, 1990). Conversely, administration of serotonergic receptor antagonists reducing serotonin (5-HT) activity may increase food intake (Curzon et al., 1997; De Vry and Schreiber, 2000; Dourish et al., 1989; Fletcher, 1988).

Cloning and radioligand techniques have allowed the subdivision of serotonin (5-HT, 5-hydroxytryptamine) receptors into 7 distinct families, with each of 14 receptor subtypes that are recognized at present having its own properties (Hoyer et al., 2002). A variety of approaches have suggested that concurrent activation of 5-HT2C and 5-HT1B receptors located on hypothalamic sites leads to full expression of serotonergic satiety (De Vry et al., 2000, 2003; Simansky, 1996, 1998). Importantly, a confluence of evidence supports that 5-HT2C receptors contribute substantially to the serotonergic suppression of feeding (Giorgetti and Tecott, 2004).

Receptor binding studies and functional models in rats have demonstrated that m-CPP has approximately 10-fold selectivity for the 5-HT2C over the 5-HT1B receptor subtype (Kennett, 1993; Vickers et al., 2003). Accordingly, m-CPP is considered a useful probe of 5-HT2C receptor function in both laboratory and clinic (Kennett and Curzon, 1988b; Sargent et al., 1997). In particular, studies using the mixed 5-HT2C/1B receptor agonist, m-CPP, indicated that its hypophagic effects in rats are primarily mediated via activation of 5-HT2C receptors and that stimulation of 5-HT1B receptors plays only a minor role in m-CPP-induced hypophagia (De Vry and Schreiber, 2000; Hewitt et al., 2002; Kennett and Curzon, 1988a, 1991). Moreover, the use of 5-HT receptor antagonists such as mianserin, metergoline and mesulergine, which show some selectivity for the 5-HT2C sites, strongly suggested that the 5-HT2C receptors were largely responsible for mediating the anorectic effects of m-CPP (De Vry and Schreiber, 2000; Kennett and Curzon, 1988a,b, 1991; Prinsen et al., 1996, 2000). The use of more selective 5-HT2C receptor antagonists in recent years, such as SB 200646 and SB 242084, which also caused a remarkable blockade of m-CPP-induced hypophagia in rats, have strengthened this argument (Bickerdike et al., 1999; Kennett et al., 1994, 1997; Vickers et al., 2003).

Assessment of the effects of serotonin (5-HT) receptor agonists and antagonists on feeding behaviour has been generally restricted to measurement of the consumption of solid standard food, i.e., pellets, whereas studies using macronutrient or diet selection have been scarce (De Vry and Schreiber, 2000). Unfortunately, diet selection paradigm studies are fraught with methodological problems that in turn result in a lack of definitive results. Contextual variables, such as quality of the test diets, form/type of macronutrient chosen, route of drug administration, acute or chronic treatment, respectively, nutritional state of the animals, deprivation or free feeding protocol, or even the isocaloric value of chosen diets among other things, could have a marked effect on any observed results (Halford et al., 2000; Leibowitz and Alexander, 1998). Although recent studies have shown that 5-HT drugs suppress carbohydrate and/or fat intake while sparing protein consumption, it is not yet fully clear that any specific 5-HT receptor subtype mediates the intake of a specific macronutrient (Halford et al., 2000; Meguid et al., 2000).

The objectives of the present study were threefold. First, to investigate the effects of both the mixed 5-HT2C/1B receptor agonist, m-CPP, and the non-selective 5-HT2C antagonist, mesulergine, on macronutrient selection. m-CPP is mentioned to be a 5-HT2C receptor ligand in vivo and its hypophagic effects are mainly, but not exclusively, mediated by agonistic activity at 5-HT2C receptors (De Vry and Schreiber, 2000; Kaplan et al., 1998; Kennett and Curzon, 1988b; Schreiber and De Vry, 2002; Vickers et al., 2003). Specifically, the hypophagic effects of m-CPP are thought to reflect a drug-induced acceleration of satiety processes at low doses (i.e., 0.1–3.0 mg/kg) and may also involve an inhibition of appetitive processes at the same dose range (De Vry and Schreiber, 2000; De Vry et al., 1999, 2003; Kitchener and Dourish, 1994). On the other hand, mesulergine has been reported to stimulate food intake in rats (De Vry and Schreiber, 2000; Dourish et al., 1989; Kaplan et al., 1998; Kennett and Curzon, 1988b; Schreiber and De Vry, 2002). Second, to assess the precise role of 5-HT2C receptors in macronutrient selection using combined treatment of m-CPP, at its highest effective dose, with mesulergine. A series of studies have revealed the marked, but not the complete, blockade of m-CPP-induced hypophagia by the non-selective 5-HT2C antagonist mesulergine. (De Vry and Schreiber, 2000; Kaplan et al., 1998; Kennett and Curzon, 1988b). Third, to clarify the effects of mesulergine on dietary choices given that this compound produced an unexpected increase in protein intake in rats according to our first findings. Consequently, we should try apomorphine, a dopamine agonist at D2 receptors, since mesulergine also possesses dopamine properties at D2 receptors besides its antagonist activity at 5-HT2C sites (Galanopoulou and Giannakopoulos, 1999; Giannakopoulos et al., 1998). It has been postulated that dopamine (DA) through D2 receptors located in the lateral hypothalamus and adjacent areas inhibits markedly or even completely feeding behaviour (Inoue et al., 1995; Parada et al., 1988; Schwartz et al., 2000; Yang et al., 1997). Systemic administration of D2 agonists (i.e., apomorphine, lisuride) that reduce dopaminergic neurotransmission led to a substantial hypophagic effect (Ferrari et al., 1992; Inui, 2000; Muscat et al., 1986; Treit and Berridge, 1990). Particularly, dopamine (DA) receptors have been related to the preference of protein and/or fat ingestion (Leibowitz, 1991, 1992). A two-isocaloric diet paradigm was used. These two isocaloric diets were prepared in our laboratory (Paleologos, 1967; Patston et al., 1984). Experimental animals were treated under a food-deprivation schedule (16 h deprivation and consequently 32 h free access to food) in order to increase feeding motivation (Blundell and Latham, 1979; De Vry and Schreiber, 2000).

All compounds and the combined treatment were given immediately prior to a 4-h refeeding period. It has been reported that the effects of acute administration of a compound on ingestive behaviour may be more pronounced during this short time interval (De Vry and Schreiber, 2000).
2. Methods

2.1. Animals

Male Wistar rats 2 months ±10 days of age and mean body weight 210 ± 5 g were used. Rats were randomly assigned to treatment groups (usually n = 6–8/group) and individually housed in a quiet environment under a normal 12-h light/dark period (light on at 8:00 a.m.). Room temperature was maintained at 21 ± 1°C and relative humidity at 50 ± 15%. Animals were allowed free access to a pair of isocaloric diets enriched in protein or carbohydrate, respectively, and had ad libitum access to water.

All animal experiments were reviewed and approved by the local committee and all studies have been carried out in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) revised 1996. Effects were made in order to use the minimal amount of rats and reduce their suffering.

2.2. Drugs

m-CPP (1-[3-chlorophenyl]piperazine) was obtained from Research Biochemicals International (Natick, MA). Mesulergine hydrochloride and apomorphine hydrochloride were purchased from Sandoz Pharma Company, Basle, Switzerland. All compounds were dissolved in 0.9% saline and were administered via the intraperitoneal route in a volume of 1 ml/kg body weight. The doses of all drugs were based on our previous tests (unpublished data) and published studies of the others (Clark et al., 1988; De Vry and Schreiber, 2000; De Vry et al., 2003; Dourish et al., 1989; Hewitt et al., 2002; Schreiber and De Vry, 2002; Treit and Berridge, 1990).

2.3. Preparation of isocaloric diets

Animals were singly housed in cages, supported by two feeders. They were supplied with the following pair of powdered isocaloric diets prepared in our laboratory (Paleologos, 1967). These two diets in their protein and carbohydrate content but fat content was held constant. Specifically, protein enriched diet (PED) in feeder A contained 80% casein, whereas carbohydrate enriched diet (CED) in feeder B contained 80% D-glucose with starch (Patston et al., 1984). The precise proportions of the components in both diets are shown in Table 1. Feeders were alternated daily to minimize place preference development.

2.4. Experimental procedure

Experimental study was performed according to food-deprivation schedule which consists of 16-h food deprivation and consequently free access to food for the next 32 h (Blundell and Latham, 1979). A maximum of six groups (usually n = 6–8 per group) was tested in parallel, always including control group(s) treated with the corresponding vehicle of the particular drug(s) tested. Rats were once tested. Before testing animals were acclimatized to 3 periods of deprivation-refeeding and received a single injection of vehicle (0.9% saline) at times corresponding to subsequent drug administration. On the day of the experiment, rats received a single injection of a particular dose of a given drug or its vehicle 15 min before the refeeding period. When cotreatment was used, the antagonist was given 30 min before testing, i.e., 15 min before the second injection (agonist or saline). Then, animals were given a simultaneous free access to each pair of isocaloric diets. Feeders, which contained preweighed food, were removed 4 h after the last injection. Finally, protein (PED) and carbohydrate enriched diet (CED) selected by animals were measured and total food intake (TFI) was calculated too.

All testing was conducted during the light phase of the cycle between 9:00 a.m. and 14:00 p.m. (Dourish et al., 1989; Kennett and Curzon, 1988b, 1991).

2.5. Statistical analysis

For data presentation, food intake was expressed in grams per 4 h of refeeding period and means and S.E.s were calculated for all animal groups. For agonist testing (Experiments 1 and 3), data were analysed by a one-way ANOVA with the factor dose and the dependent variable macronutrient intake. For antagonist testing (Experiment 2), data were analysed by a two-way ANOVA with the factors agonist and antagonist and the dependent variable macronutrient intake. The Tukey HSD test was done for post hoc multiple comparisons with P < .05 considered to indicate statistical significance.

3. Results

3.1. Effects of m-CPP on feeding and dietary choices in rats under food-deprivation schedule

Administration of all three doses of m-CPP (Experiment 1) led to a dose-dependent hypophagia (Fig. 1). Specifically, protein consumption was spared while carbohydrate and total food intake were significantly suppressed in a dose-dependent manner. All doses of m-CPP were effective in this test. Accordingly, 2.50 mg/kg of m-CPP (maximum effective dose) was selected for the subsequent antagonist study with mesulergine. ANOVA showed a significant effect for agonist on carbohydrate consumption, F(3, 29) = 2.237, P < .001; total food intake, F(3, 29) = 14.146, P < .001. The protein consumption was unaffected by m-CPP, F(3, 29) = 0.824, P < 1.0.
3.2. Effects of serotonin antagonist mesulergine on m-CPP-induced hypophagia and dietary choices in rats under food-deprivation schedule

The results for this experimental testing (Experiment 2) are presented in Table 2. The dose of 2.5 mg/kg of m-CPP induced a significant reduction in carbohydrate and total food intake, respectively whereas protein intake remained unchanged again.

Pretreatment with the non-selective 5-HT2C antagonist mesulergine, dose-dependently reversed m-CPP-induced hypophagia during the 4-h test period. In great detail, protein consumption was significantly increased while the hypophagic effects induced by m-CPP on carbohydrate and total food intake were blocked by pretreatment with mesulergine in a dose-dependent manner.

Interestingly, mesulergine treatment on its own caused a significant dose-dependent hyperphagia, since a substantial increase in both protein and carbohydrate intakes were found with significant increase of total food intake as a consequence.

ANOVA indicated a significant interaction effect between the factors agonist and antagonist on protein ingestion, \(F(5, 42) = 23.740, P < .001\); carbohydrate ingestion, \(F(5, 42) = 21.110, P < .001\); and total food intake, \(F(5, 42) = 32.340, P < .001\).

3.3. Effects of dopamine agonist apomorphine on feeding and dietary choices in rats under food-deprivation schedule

The results for this experimental testing (Experiment 3) are presented in Fig. 2. Apomorphine, a selective D2 agonist, caused a dose-dependent increase in protein intake whereas carbohydrate and total food intake remained nearly unchanged.

Treatment with mesulergine produced the expected feeding behaviour. According to our findings, mesulergine led to a significant hyperphagia, due to an increased intake of both protein and carbohydrate enriched isocaloric diets.

ANOVA gave a significant effect for Agonist on Protein intake, \(F(3, 21) = 11.410, P < .001\). The carbohydrate and total food intake were unaffected by apomorphine.

4. Discussion

A number of studies have demonstrated that the administration of the mixed 5-HT2C/1B receptor agonist, m-CPP, causes a significant hypophagia through a clear serotonin-type action (Hewitt et al., 2002; Kennett and Curzon, 1988b). The results obtained in the present food-deprivation protocol replicated the hypogastic effects of m-CPP in a dose-dependent manner. Particularly, a substantial decrease in carbohydrate ingestion was noted without any important influence on protein intake.
consumption. However, it is well known that serotonin (5-HT) and compounds which enhance serotonergic neurotransmission, like fenfluramine and fluoxetine, induce a reduction in caloric intake attributed to a decrease in carbohydrate and/or fat consumption, while protein intake remains relatively unaffected (Halford et al., 2000; Meguid et al., 2000). The hypophagic effects of \( m \)-CPP are predominantly mediated by agonistic activity at 5-HT2C receptors (De Vry and Schreiber, 2000; Kaplan et al., 1998; Kennett and Curzon, 1988b; Schreiber and De Vry, 2002; Vickers et al., 2003). A bulk of studies have recommended a role of 5-HT2C and a lesser extend 5-HT1B receptors in the control of ingestive behaviour (De Vry and Schreiber, 2000; De Vry et al., 2003; Hewitt et al., 2002). It has also been suggested that 5-HT2C knockout mice (mutant mice lacking functional 5-HT2C receptors) are less sensitive to the hypophagic effects of \( m \)-CPP, supporting the suggestion that 5-HT2C receptors are involved in the hypophagic effect of \( m \)-CPP (Hewitt et al., 1998, 2002; Tecott et al., 1995). Particular attention has focused on the hypothalamus as the locus of serotonergic effects on feeding. Systemic administration of indirect agonists such as \( \alpha \)-fenfluramine and fluoxetine increases extracellular hypothalamus serotonin (5-HT) levels and suppresses food intake in animals (Giorgetti and Tecott, 2004; Vickers et al., 2001). Microinjections of serotonin into the paraventricular nucleus (PVN) of hypothalamus have been found to suppress feeding by reducing meal size and feeding rate (Hutson et al., 1988; Schwartz et al., 1989; Shor-Posner et al., 1986). Similar effects were also observed with microinjection of serotonin into the ventromedial (VMN) and dorsomedial (DMN) nuclei of the hypothalamus (Leibowitz et al., 1988). Local perfusion of \( m \)-CPP into ventromedial hypothalamic nucleus but not into lateral area of hypothalamus (LHA) or frontal cortex, inhibits intake in rats (Hikiji et al., 2004). 5-HT2C receptors are expressed in these hypothalamic regions— principally in ventromedial hypothalamic nucleus (VMN)— implicated in the regulation of energy balance (Giorgetti and Tecott, 2004; Hoffman and Mezey, 1989; Kaplan et al., 1998; Wright et al., 1995). According to our findings in the present study, 5-HT2C receptor activation seems to make the major contribution to the hypophagic actions of \( m \)-CPP. Regarding the pharmacological mechanisms underlying \( m \)-CPP-induced hypophagia in the rats, it has been reported that \( m \)-CPP has little affinity for dopamine (DA) receptors and does not produce significant alterations to dopaminergic system (Invernizzi et al., 1981; Kennett and Curzon, 1988b), which is also in agreement with our neurochemical findings (unpublished data). The above data and results indicate that hypophagic effects of \( m \)-CPP is mainly mediated by 5-HT2C receptors, especially in carbohydrate suppressing and protein sparing effect of serotonin (5-HT).

In addition, it is generally accepted that non-selective 5-HT2C receptor antagonists, such as mianserin, metergoline and mesulergine appear to induce a dose-dependent hyperphagia (De Vry and Schreiber, 2000; Dourish et al., 1989; Kennett and
Curzon, 1991; Prinsen et al., 1996, 2000). Consequently, only hyperphagic response on carbohydrate isocaloric diet could be explained as a single antagonist activity of mesulergine at hypothalamic 5-HT2C receptors. On the contrary, the mesulergine-induced increase in protein consumption ought to be further clarified.

4.1. Agonism study with apomorphine

Our previous suggestion is based on the fact that although apomorphine, produced a weak reduction in total food intake, it caused a dose-dependent significant enhancement of protein intake. In fact, a decrease in carbohydrate almost equal to the increase in protein intake was observed. This could imply a role of dopaminergic function in regulating the ratio of protein to carbohydrate intake. It has recently been postulated using microdialysis and pharmacological approaches, that the ventrolateral striatum is closely involved in the motor control of oral activity and feeding behaviour (Inoue et al., 1995; Salamone et al., 1993). Furthermore, dopaminergic system through D2 receptors located in the lateral hypothalamus (LHA) and the adjacent area of ventrolateral striatum inhibits feeding behaviour at a wide range (Inoue et al., 1995; Parada et al., 1988; Schwartz et al., 2000; Yang et al., 1997), and the above mentioned receptors are implicated in the preference of protein and/or fat ingestion (Leibowitz, 1991, 1992). Mesulergine is considered a dopamine (DA) agonist at D2 sites besides its affinity at 5-HT2C receptors (Galanopoulou and Giannakopoulos, 1999) and this dual mode of its action is in line with our neurochemical results (unpublished data). So, a possible explanation is that activation of D2 receptors underlies the potency of mesulergine in increasing protein intake. The results in this study are consistent with our previous findings in free feeding rats treated with mesulergine. Those animals were fed two diets, differing in protein and carbohydrate content, but not isocaloric, where, a dose dependent increase of PED and total food intake was observed 4 h after its administration (Giannakopoulos et al., 1998). Therefore, it is possible that both food intake and diet selection elicited by mesulergine in the present study can be also explained as an interaction between D2 and 5-HT2C receptors located, at least in part, in adjacent hypothalamic areas. Indeed, the use of apomorphine was determinant in explaining the effects of mesulergine on protein consumption as well.

4.2. Antagonism study with mesulergine—potential role for 5-HT2C receptors in diet selection

Pretreatment with mesulergine abolished the hypophagia induced by m-CPP. Such data provide further pharmacological support that activation of 5-HT2C receptors induces a suppression of total food intake due to a significant reduction in a carbohydrate ingestion, while protein intake is not altered. Interestingly, among the most remarkable findings from earlier antagonism studies are the marked blockade of m-CPP-induced hypophagia by the non-selective 5-HT2C receptor antagonists mianserin, metergoline and mesulergine (Curzon et al., 1997; De Vry and Schreiber, 2000; Kaplan et al., 1998; Kennett and Curzon, 1988b; Prinsen et al., 1996, 2000). In corroboration of this finding, the hypophagic effect of m-CPP is completely blocked by low doses of the selective receptor antagonists SB 20646 and SB 242084, respectively (Bickerdike et al., 1999; Hewitt et al., 2002; Kennett et al., 1994, 1997; Vickers et al., 2003).

The relationship between 5-HT and nutrient intake has been questioned. Unfortunately, diet selection paradigm studies are fraught with methodological problems that in turn end in a lack of definitive results. Contextual variables, such as form/type of macronutrient chosen, caloric value of chosen diet, acute or chronic treatment regime, central or peripheral administration of serotonergic drugs could have a noticeable effect on any observed results in animal studies (Halford et al., 2000). The differing paradigm methodology produced strikingly different results. Nonetheless, many studies employing the three-choice diet selection paradigm have shown uniformly that stimulation of serotonin activity, through either microinjection of 5-HT and 5-HT agonists (i.e., fluoxetine, d-fenfluramine) into the paraventricular nucleus of the hypothalamus or peripheral administration of 5-HT agonists and 5-HT antagonists (i.e., metergoline), leads to the selective suppression of carbohydrate consumption with no change in the consumption of protein or fat (Halford et al., 2000; Leibowitz et al., 1993; Weiss et al., 1991). In most cases, the effects of acute administration of a serotonergic compound on cumulative food consumption over a short time interval (i.e., 30 min–4 h) was measured in food-deprivation schedules than in free feeding rats (De Vry and Schreiber, 2000). In particular, the design of the studies contained a period of food deprivation, typically varying between 12 and 23 h, in order to increase feeding motivation. In our testing session, animals were treated with a food-deprivation protocol and had a 4-h period free access to a pair of isocaloric diets, which differed in protein or carbohydrate proportions but fat levels were held constant. Our results replicated and extended earlier findings got under similar experimental conditions.

It seems likely that hypothalamic 5-HT2C receptors play a dominant, but not the exclusive, role in hypophagic effects of m-CPP. Specifically, the activation of 5-HT2C receptors is associated with both protein sparing and carbohydrate suppressing effects of m-CPP. Although m-CPP is reported to be a potent 5-HT2C receptor ligand in vivo, it is finally a mixed 5-HT2C/1B receptor agonist. Therefore, it remains to be confirmed by studies using more selective 5-HT2C receptor agonists. The extend to which 5-HT2C receptors located in hypothalamic regions influence energy balance ought to be further investigated. Concerning hyperphagia induced by mesulergine, the blockade of 5-HT2C receptors produces a significant increase in carbohydrate increase, mesulergine led to a substantial enhancement of protein intake, attributed to its dopaminergic properties.

5. Conclusions

In the present study, results indicate that mesulergine, a serotonin (5-HT) antagonist at 5-HT2C sites and dopamine D2 agonist, leads to food intake and diet selection by a dual mode of action: due to the simultaneous antiserotonergic and
dopaminergic activity causes hyperphagia, which goes in parallel with an increase in CED and PED intake, respectively.

It is also suggested that the activation of hypothalamic 5-HT$_{2C}$ receptors may be involved in both protein sparing and carbohydrate suppressing effects of 5-HT ($m$-CPP-like effect). On the contrary, an important role in increase of protein consumption seems to possess the dopaminergic system probably through D$_2$ receptors (apomorphine-like and mesulergine-like effect, respectively).

In conclusion, hypothalamic 5-HT$_{2C}$ receptors play a dominant, not the exclusive, role in food intake and diet selection. These findings extend our understanding on neurobiological substrate of appetite and contribute to the studies related to new drugs against obesity, especially those referred to 5-HT$_{2C}$ compounds with agonistic properties (Bickerdike, 2003; Clifton et al., 2000; Hewitt et al., 2002; Vickers et al., 2003).

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