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Resistance of male Sprague-Dawley rats to sucrose-induced obesity: effects of 18-methoxycoronaridine

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Abstract

Evidence suggests that the development of obesity in males and females might be mediated by distinct mechanisms, warranting different treatment approaches. In previous studies from this laboratory, a high sucrose diet induced excessive weight gain in female Sprague-Dawley rats and administration of a selective antagonist of $\alpha 3\beta 4$ nicotinic receptors, 18-methoxycoronaridine (18-MC), prevented this form of obesity. In the present study similar parameters were studied in male rats by using an identical experimental protocol. The effects of repeated administration of 18-MC on body weight gain, deposition of fat, consummatory behavior and biochemical markers of obesity in male rats were also assessed. In contrast to females, males consuming *ad libitum* quantities of sucrose solution (30%) in combination with normal chow did not become obese; they did not gain excessive weight nor show excessive fat deposition. Repeated administration of 18-MC (20 mg/kg, i.p.) attenuated weight gain in both sucrose-consuming and control animals without altering food or fluid intake. The present results indicate that males and females are differentially responsive to high carbohydrate-diet obesity. Such gender disparities could be secondary to sex-specific alterations in cholinergic mechanisms of feeding and body weight regulation.

Keywords

sucrose diet; weight gain; nicotinic receptors; sex difference

Introduction

Obesity is a major healthcare concern in the United States and other industrialized countries. Currently, about 30% of the US population is obese [1]. The widespread accessibility and consumption of highly palatable foods with a high glycemic index but low nutritive value lead to excessive calorie intake and trigger neurochemical responses similar to those observed in other addictive states [2;3]. Thus, many obese patients require pharmacological interventions; however, few effective anti-obesity agents are available.

Obesity rates are higher among women than in men [4]; however, only a few studies have assessed sex-specific alterations in neurochemistry or behavior of obese patients. Although

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the end-points of chronic energy excess, i.e., increased insulin resistance and morbidity, are similar in males and females [for review, [5;6]], some metabolic, neuroendocrine, and cognitive responses to the same diets have been shown to be sex-specific [7]. This suggests that some treatments developed for females may not be applicable for males or vice versa.

The interactions between dopaminergic and cholinergic systems in regulating food intake are attracting increasing attention in the literature [8]. For example, an increase in the levels of acetylcholine in the nucleus accumbens has been recently demonstrated to occur in parallel with a feeding-induced increase in extracellular dopamine in the same area, suggesting that accumbal acetylcholine is important for the initiation of feeding [9]. On the other hand, nicotinic receptors in the VTA have been shown to mediate ghrelin-induced increases in dopamine release in the mesolimbic pathway [10]. These studies suggest that nicotinic receptors could be a suitable target for appetite-suppressive and anti-obesity agents. Although the above phenomena were reported only in male rats, other aspects of dopamine and acetylcholine interactions during feeding have been assessed for both sexes. For example, dopamine and acetylcholine-sensitive neurons in the globus pallidus of both male and female primates were shown to be involved in regulating plasma glucose and feeding [11;12].

18-Methoxycoronaridine, a congener of the naturally occurring alkaloid ibogaine and a selective antagonist of $\alpha 3\beta 4$ nicotinic receptors, has been previously shown to reduce sucrose reward and prevent the development of sucrose-induced obesity in female rats [13]. The latter effect was achieved by a reduction in sucrose consumption without alterations in intake of normal chow. Since $\alpha 3\beta 4$ nicotinic receptors are not expressed in the ventral tegmental area or the nucleus accumbens [14], the latter effects were thought to be due to 18-MC's action at other brain sites known to be involved in eating behavior. The proposed sites could include the nucleus of the solitary tract, the area postrema, and parasympathetic ganglia of the gastrointestinal tract [15-18].

Both male and female rats prefer sweet solutions to water [19;20]; however, female rats have been shown to display stronger preferences for both nutritive and non-nutritive sweet solutions than male rats [21]. Furthermore, female but not male rodents were shown to use sugary treats as a "comfort food" during periods of experimentally-induced stress [22]. Previous studies in this laboratory demonstrated that female rats allowed unlimited access to a highly caloric 30% sucrose solution became obese within a short period of time (i.e., two weeks) [13]. The present experiments were conducted to examine if male rats are equally susceptible to the development of obesity under the same experimental conditions. In addition, the role of cholinergic mechanisms in the regulation of body weight and sucrose intake in males was assessed by exposing animals to repeated (every 24 h for 2 weeks) doses of 18-MC (20 mg/kg, i.p.).

Methods

2.1 Animals

Naïve male Sprague-Dawley rats (250-275g; Taconic, Germantown, NY) were housed individually in food monitor chambers and maintained on a normal 12 h light cycle (light

on/off at 7 a.m./ 7 p.m.) in the colony room. Animal groups were matched by weight with appropriate water-drinking control rats and with the groups of female rats assessed in the previous study [13]. The experiments were conducted in accordance with the “Guide for the Care and Use of Laboratory Animals” (National Academy of Sciences, 1996) and were approved by the Institutional Review Committee for the use of Animals at Albany Medical College.

Drugs

18-MC (Albany Molecular Research, Albany, NY) was dissolved in 0.01 M NaH₂PO₄ (vehicle). Sucrose (30%, wt/vol, MP Biomedicals, Inc., Solon, OH) was dissolved in water.

Sucrose-induced weight gain paradigm

The four groups of male rats were matched by weight and were assigned the following treatments: access to both sucrose and water (i.e., sucrose-water groups) and injections of 18-MC; access to both sucrose and water and injections of vehicle; access to water only (i.e., water-water groups) and injections of 18-MC; and access to water only and injections of vehicle. The experimental paradigm utilized in the present study was identical to that previously described in female rats [13]. We have used the following four experimental groups of male rats: Specifically, the rats were individually housed in cages equipped with a food intake monitor system (BioDAQ, Research Diets, New Brunswick, NJ) and custom-made cage tops (see above); then were allowed to acclimate for three days while consuming normal chow and water. The normal chow and water remained available for the entire four weeks of the study. On the first day of the study rats in two groups received an additional bottle containing 30% sucrose solution or water, respectively. To control for possible side preferences, the left-right positions of the bottles were switched daily. Animals not preferring sucrose to water were excluded from the analysis. After a week of baseline measurements, animals were injected daily with 18-MC (20 mg/kg i.p.) or vehicle for two weeks, creating four groups. After the last injection, rats were monitored in the chambers for an additional week. Body weights of rats were recorded daily for four weeks.

Total food intake, and both sucrose and water consumption were measured for a 23-h period six days a week for the entire four weeks. The food intake monitor was comprised of a custom-modified cage connected to a central controller. A peripheral sensor was coupled to a food hopper, which was weighed approximately 50 times per second; the mean and standard deviation of the mean were generated each second by a computer. A feeding bout was recorded when more than 0.15 g of food was removed from the hopper; the end of the bout was defined as a lack of weight fluctuation for 5 sec.

Assessment of trunk blood composition and fat depot mass

Upon completion of the experiment, animals were euthanized in CO₂ chambers and decapitated. The trunk blood was collected and analyzed for serum glucose, cholesterol and triglycerides levels at the clinical biochemistry laboratory of Albany Medical Center; the tests were run in duplicates. The fully automated assays to determine serum levels of glucose (by means of oxidation) or serum levels of cholesterol and triglycerides (by means of spectrophotometry) were performed on a UniCel DxC Clinical System (Beckman Coulter

Inc, CA). Necropsies were performed to remove periovarian (or epididymal), perirenal and inguinal fat pads, and the combined fat tissue was weighed. The experimenter was blinded as to the treatment status of the animals.

Statistical Analysis

The animal weight, water consumption and food intake for groups of male rats consuming sucrose and water or water and water were analyzed using two-way ANOVA, with treatment and time as main factors; the body weights on day 1 were compared in a separate one-way ANOVA. The sucrose consumption for the groups consuming sucrose and water was analyzed similarly. Post-hoc comparison tests (Fisher LSD tests) were conducted when appropriate. The fat depot data for male rats were analyzed by two-way ANOVA with the diet and treatment as the main factors. The metabolic data for the same animals were analyzed separately for each biochemical marker, i.e. sucrose, cholesterol and triglycerides by two-way ANOVA with diet and treatment as the two main factors. In addition, in order to access the effect of sucrose consumption on weight gain in vehicle-treated control groups of male rats, the body weights of those consuming sucrose and water vs. water only were compared using two-way ANOVA with diet and time as main factors.

Results

3.1 The unlimited intake of 30% sucrose solution does not increase weight gain in male rats

The effect of 30% sucrose diet on body weights of both vehicle-treated males and vehicle-treated females is shown in Fig.1 (insert; data from [13]). Prior to the beginning of treatment, the average weights of male rats on day 1 (baseline) in groups consuming sucrose-water and water-water were as follows ($g \pm SEM$): 291.0 ± 7.7 and 281 ± 4.5 , respectively; there was no significant difference between the two diet groups. As apparent from Fig. 1, both groups of male rats displayed similar rates of weight gain throughout the entire course of the experiment, suggesting that a high sucrose diet does not induce obesity in male rats (Diet $\times$ Time interaction: $F(22, 242)=0.46$, $p>0.98$). In contrast, as previously demonstrated, female rats consuming 30% sucrose displayed a significant weight gain compared to water-consuming controls of the same sex (Group $\times$ Time interaction: $F(19, 228)=2.02$, $p<0.008$; post-hoc tests; Fig.1, insert).

3.2 18-MC reduces weight gain but not fat deposition in male rats consuming a high sucrose diet

To determine if a selective antagonist of $\alpha 3\beta 4$ nicotinic receptors could inhibit weight gain in male rats, animals were injected daily for two weeks with 18-MC (20 mg/kg, i.p. or vehicle), while being allowed unlimited access to sucrose and water (Fig. 2A) or water only (Fig. 2A; insert). Prior to the beginning of 18-MC treatment, the average weights of rats ($g \pm SEM$) on day 1 in vehicle-assigned and 18-MC-assigned groups consuming sucrose and water were as follows, respectively: 291.0 ± 7.7 and 284.4 ± 5.8 ; there was no significant difference between the two treatment groups. Both groups demonstrated similar rates of weight gain during the baseline week; however, after the initiation of treatment, weight gain was significantly lower in the 18-MC-treated group, as compared to the vehicle-treated

group. The latter effect was apparent beginning the fifth day of injections and remained significant until the end of the study (Group $\times$ Time interaction: $F(22, 198) = 1.97, p < 0.008$; post-hoc tests; Fig. 2A).

On the first day of the experiment, the average weights ($g \pm SEM$) of male rats in vehicle-assigned and 18-MC assigned groups consuming water were as follows, respectively: 281 ± 4.5 and 287.1 ± 3.4 (Fig. 2A; insert). There was no significant difference between the weights in the two treatment groups on day 1 and during the baseline week (days 1-6). After initiation of treatment, 18-MC-treated rats demonstrated significantly slower weight gain compared to the vehicle-treated controls; the latter effect was present at all time points beginning on the fourth day of treatment (Group $\times$ Time interaction: $F(22, 264) = 7.70, p < 0.0001$; post-hoc tests; Fig. 2A; insert).

The weights of fat tissue from the rat carcasses examined upon completion of experiment (i.e., on day 8 after the last 18-MC injection) are shown in Fig. 2B. A two-way ANOVA with diet and treatment as the two main factors revealed no significant effect of diet or diet $\times$ treatment interaction (Diet: $F(1, 21) = 0.82, p > 0.38$; Diet $\times$ Treatment interaction: $F(1, 21) = 0.48, p > 0.50$), but a significant effect of treatment (Treatment: $F(1, 21) = 9.26, p < 0.006$; Fig. 2B). Thus, 18-MC reduced fat deposition in both diet groups.

3.3 18-MC does not affect consumption of water or sucrose in male rats

The effect of 18-MC on total 23h intake of water in groups having access to both sucrose and water or water only is shown in Fig. 3. In sucrose-water groups, the consumption of water ($ml \pm SEM$) in the vehicle and 18-MC groups on day 1 was 4.2 ± 0.7 and 7.4 ± 2.9 , respectively; there was no significant difference between the two groups (Fig. 3). 18-MC did not affect intake of water (Group $\times$ Time interaction: $F(22, 198) = 1.02, p > 0.44$; Fig. 3).

In rats consuming only water the total intake of water ($ml \pm SEM$) in vehicle and 18-MC groups on day 1 was 20.71 ± 5.3 and 29.71 ± 2.48 , respectively; there was no significant difference between the two groups. Repeated administration of 18-MC did not alter the intake of water (Group $\times$ Time interaction: $F(22, 264) = 0.99, p > 0.48$; Fig. 3, insert).

The effects of 18-MC on the total intake of sucrose in 23h in rats having access to both sucrose and water is shown in Fig. 4. All animals from vehicle and 18-MC groups preferred sucrose to water (see above) and their sucrose consumption ($ml \pm SEM$) on day 1 was 30.7 ± 2.5 and 24.4 ± 6.9 , respectively. There was no significant difference between the two groups either on day 1 or during the baseline period (days 1-6). 18-MC did not significantly alter the intake on sucrose (Group $\times$ Time interaction: $F(22, 198) = 1.35, p > 0.14$; Fig. 4).

3.4 18-MC does not alter chow intake in male rats

To determine how 18-MC may affect different aspects of feeding behavior in rats consuming sucrose and water or water only, the total food intake as well as frequency of feeding bouts and bout sizes were assessed for each 23h period (Figs. 5, 6). The average intakes of chow ($g \pm SEM$) in vehicle and 18-MC groups consuming sucrose and water on day 1 were as follows, respectively: 14.1 ± 0.9 and 12.8 ± 1.7 ; there was no significant difference between the two groups (Fig. 5). On the same day, the average numbers of bouts

in the same groups were as follows 124.5 ± 13.5 and 129.0 ± 15.9 (Fig. 6A), while the average bout sizes ($g \pm SEM$) were 0.12 ± 0.01 and 0.08 ± 0.02 (Fig. 6B), respectively. There was no significant difference in either the numbers of bouts or bout sizes between the two treatment groups at the beginning of the experiment. 18-MC did not alter total food intake nor did it affect the frequency of bouts or bout size in rats consuming high sucrose diet (for total food intake: Group $\times$ Time interaction: $F(22, 198) = 1.06$, $p > 0.39$; Fig. 5; for number of bouts: Group $\times$ Time interaction: $F(22, 198) = 0.50$, $p > 0.97$; Fig. 6A; for bout size: Group $\times$ Time interaction: $F(22, 198) = 1.06$, $p > 0.40$; Fig. 6B).

The average food intake ($g \pm SEM$) on day 1 in vehicle and 18-MC groups of rats consuming water only was as follows, respectively: 16.0 ± 3.5 and 15.0 ± 2.5 . Assessed on the same day, the average numbers of bouts in the same groups were 124.5 ± 11.0 and 134.6 ± 18.6 while the average bout sizes ($g \pm SEM$) were 0.14 ± 0.03 and 0.12 ± 0.03 , respectively. There was no significant difference between the two treatment groups in either total food intake, numbers of bouts or bout sizes on the first day of the experiment. 18-MC did not affect total food intake, numbers of bouts, or bout sizes in rats consuming water and normal chow [for total food intake: Group $\times$ Time interaction: $F(22, 264) = 0.68$, $p > 0.86$; Fig. 5 (insert); for number of bouts: Group $\times$ Time interaction: $F(22, 264) = 0.41$, $p > 0.99$; Fig. 6A (insert); for bout size: Group $\times$ Time interaction: $F(22, 264) = 0.75$, $p > 0.79$; Fig. 6B (insert)].

3.5 18-MC does not alter serum biochemical markers of obesity in male rats consuming high sucrose diet

The average levels of glucose, cholesterol and triglycerides in the serum of trunk blood of rats consuming high sucrose diet and control diet are shown in Fig. 7. Serum levels ($mg/dl \pm SEM$) of glucose in the vehicle- and 18-MC-treated groups of rats consuming sucrose and water or water only were as follows: 173.42 ± 9.94 , 160.90 ± 7.51 , 160.93 ± 6.90 , and 153.57 ± 8.28 , respectively. A two-way ANOVA with diet and treatment as the two main factors did not reveal any significant effects, indicating that neither the sucrose diet nor 18-MC treatment altered glucose levels in trunk blood (Diet: $F(1, 21) = 1.41$, $p > 0.25$; Treatment: $F(1, 21) = 1.42$, $p > 0.25$; Diet $\times$ Treatment interaction: $F(1, 21) = 0.1$, $p > 0.76$).

Serum levels ($mg/dl \pm SEM$) of cholesterol in the vehicle- and 18-MC-treated groups consuming high sucrose diet and control diet were as follows: 61.83 ± 2.77 , 64.30 ± 5.44 , 54.57 ± 3.85 , and 49.0 ± 3.90 . Although an ANOVA revealed a significant effect of diet, there was no significant diet $\times$ treatment interaction, indicating that 18-MC treatment did not alter cholesterol levels in either diet group (Diet: $F(1, 21) = 7.86$, $p < 0.01$; Treatment: $F(1, 21) = 0.15$, $p > 0.70$; Diet $\times$ Treatment interaction: $F(1, 21) = 1.0$, $p > 0.33$).

Serum levels ($mg/dl \pm SEM$) of triglycerides in the vehicle- and 18-MC-treated groups of rats consuming sucrose and water or water only were as follows: 135.75 ± 24.94 , 100.20 ± 8.72 , 176.86 ± 29.95 , and 117.79 ± 11.03 , respectively. The ANOVA of triglyceride data revealed no significant main effect of diet or diet $\times$ treatment interaction, but a significant effect of treatment (Diet: $F(1, 21) = 1.76$, $p > 0.20$; Treatment: $F(1, 21) = 4.58$, $p < 0.04$; Diet $\times$ Treatment interaction: $F(1, 21) = 0.28$, $p > 0.60$). These results indicate that 18-MC reduced triglyceride levels in both diet groups.

Discussion

The present studies were designed to assess weight gain and food intake in male Sprague-Dawley rats consuming a high sucrose diet and to compare them with previously described data from female rats [13]. In these experiments, male Sprague-Dawley rats were fed a high-sucrose (30%) diet for 28 days. While this regimen caused an excessive weight gain in female rats [13], males on the same diet did not gain excessive weight or become obese. Additional studies were also carried out to examine the potential role of $\alpha\beta4$ nicotinic receptors in feeding behavior of male rats. These experiments revealed that the administration of a selective antagonist of $\alpha\beta4$ nicotinic receptors, 18-MC, reduced weight gain, fat deposition and serum triglyceride levels in both sucrose-drinking and control male rats without altering their food or water intake. Although there was a trend towards the reduction of sucrose intake by 18-MC the effect did not reach statistical significance. Taking collectively, these data suggests that $\alpha\beta4$ nicotinic receptors may participate in the metabolic regulation of body weight regardless of dietary conditions.

Studies assessing the role of a high sucrose diet in inducing excessive weight gain in male rats have provided conflicting evidence, even in the same strain of rats (i.e., Sprague-Dawley) and with near identical diets [23-25]. For instance, an *ad libitum* diet of sucrose solution (32%) and chow induced excessive weight gain in 140-day old males after 70 days of treatment [23] and in 270-day old males after 40 days of treatment [26]. However, the same diet failed to induce excessive weight gain in young males followed from weaning until 70 days of age [25] or even until 110 days of age [27]. The results of our study, using 70-day old male rats for 28 days, are consistent with the latter finding.

One possibility for the lack of excessive weight gain in young sucrose-consuming rats is that the excess calories from the sucrose solution [27] could be stored in dense adipose tissue leading to the development of an obese phenotype in the absence of excessive weight gain [25]. However, in the present study the weights of fat depots of the two diet groups were not significantly different (Fig. 2B), indicating that the excess of calories was not deposited in fat of the rats on a high sucrose diet. The lack of a difference in the levels of serum triglycerides in the same groups (Fig.7) further confirms that metabolism of fat (i.e. lipolysis, triglyceride uptake and storage in adipose tissue) was not altered by the sucrose diet [28].

Another possible explanation for the lack of an obesogenic effect of high sucrose in male rats could be due to sucrose-drinking animals being more active than control male rats and compensating for excessive caloric intake with exercise [27]. Hirsch et al (1982) reported that sucrose-drinking male rats allowed access to a running wheel demonstrated daily increases in both activity and sucrose intake, while activity levels remained stable in chow-fed control rats [26]. Although no measurements of activity were performed in the present experiments, such an explanation is plausible.

In contrast to male rats whose excess weight and adiposity seemed to be eliminated with exercise, Hirsch et al. (1982), also reported that active female rats fed the same sucrose diet (32% solution) remained obese. However, other studies comparing patterns of carbohydrate-

induced obesity in male and female rats with normal activity revealed either no difference in weight gain [26] or more dramatic weight gain in females [29]. As described in the present study, female but not male Sprague-Dawley rats demonstrated excessive weight gain (Fig.1, insert) when fed a high sucrose diet. Despite the fact that female rats weighed less than male rats after the baseline week, their intakes of sucrose [13] were nearly the same. This suggests that females are more likely to exceed their caloric requirements when offered *ad libitum* access to sucrose than males. Exposure to sex steroids either during adult life or in the perinatal period could possibly contribute to male-female differences in food intake regulation [30;31]. Although the males in this study were slightly younger than females used in our previous study [13] (70 days vs. 80 days), the experimental conditions were virtually identical and comparisons between the two sexes are appropriate.

In the present study we also used male rats to re-examine a previously described weight-reducing effect of 18-MC in female rats [13]. Surprisingly, although 18-MC reduced weight gain and fat depot weights in male rats, it did not affect the consumption of sucrose in these animals. This was in contrast to female rats whose sucrose drinking was decreased by both acute and repeated administration of 18-MC [13]. Similar to female rats [13], male rats did not alter their patterns of chow intake in response to 18-MC treatment. 18-MC also had no effect on water consumption in these animals. 18-MC reduced weight gain, fat deposition and serum triglyceride levels in both sucrose-consuming and control groups of males. This suggests that 18-MC's effects were mediated by its action on metabolism of fat rather than on food intake. This could be accomplished via a direct effect on peripheral non-neuronal tissue or via altering hormonal signaling pathways in the hypothalamus [reviewed in [32]]. For example, 18-MC could inhibit lipoprotein lipase activity, decrease triglyceride uptake from the gut and reduce fat storage in adipose tissue [28]. In fact 18-MC might be acting similar to a high desensitizing dose of nicotine [33], which is known to promote leanness in animals [34] and protect against fat deposition in humans [35]. Alternatively, 18-MC could act in the nucleus of the solitary tract and disrupt cholinergic neurotransmission in the lateral hypothalamus without producing anorexic effect [36;37]. The present effects of 18-MC in both sucrose-consuming and control groups suggest that nicotinic receptors may be involved in the regulation of fat metabolism, regardless of caloric intake. Consistent with this premise, smokers have been shown to consume more sugar than non-smokers (reviewed in [38]). Notably, female smokers report more intense cravings for sweets than male smokers [39].

In the present study, male rats from control the group increased their body weight by approximately 60% while the females from the control group [13] increased their weight by about 5%, suggesting that males were in the dynamic phase of body weight gain, while the females were not. Although it is possible that the difference in response to a high sucrose diet in male and female rats could be attributed to the different growth rates, our recent findings suggest that it is not likely to be the case. We have found that when female and male rats are compared in a high fat model of obesity, their responses are exactly opposite, i.e., the male rats become obese while female rats do not (unpublished data). The animals used in the high fat study had initial weights similar to those in the present study, and the duration of the high fat study (i.e., 34 days) was comparable to that in the present study.

Excessive ingestion of carbohydrates contributes to the development of obesity in humans, and such diets may affect females more notably than males [40;41]. There is evidence that sweet foods are strongly preferred by women [42] who also self-report carbohydrate cravings as a cause of obesity more often than males even when controlled for age and level of education [42;43]. The findings provided herein provide additional evidence for the previously recognized fact that the development of obesity is influenced by gender, and the treatment of obesity may require gender-specific approaches. Furthermore, $\alpha 3\beta 4$ nicotinic receptors appear to be involved in metabolic regulation of body weight regardless of the caloric state of the organism.

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Figure 1.

Effects of a high sucrose diet (30% solution) on weight gain in male rats (g, mean $\pm$ SEM). The insert (data from Taraschenko et al, 2008) shows the effects of a high sucrose diet (30% solution) on weight gain in female rats.

Figure 2.

(**A**). Effects of repeated administration of 18-MC (20 mg/kg, i.p. or vehicle for two weeks) on weight gain (g, mean $\pm$ SEM) in male rats having access to 30% sucrose solution and water or water only (insert); the bar represents the beginning and the end of treatment with 18-MC. (**B**) Effects of repeated administration of 18-MC (20 mg/kg, i.p. or vehicle for two weeks) on fat deposition in male rats having access to 30% solution and water or water only.

Figure 3.

Effects of repeated administration of 18-MC (20 mg/kg, i.p. or vehicle for two weeks) on total water consumption (ml, mean $\pm$ SEM) in 23 h in male rats having access to 30% sucrose solution and water or water only (insert); the bar represents the beginning and the end of treatment with 18-MC.

Figure 4.

Effects of repeated administration of 18-MC (20 mg/kg, i.p. or vehicle for two weeks) on total consumption (ml, mean $\pm$ SEM) of 30% sucrose solution in 23 h in male rats; the bar represents the beginning and the end of treatment with 18-MC.

Figure 5.

Effects of repeated administration of 18-MC (20 mg/kg, i.p. or vehicle for two weeks) on total food intake (g, mean $\pm$ SEM) in 23 h in male rats having access to 30% sucrose solution and water or water only (insert); the bar represents the beginning and the end of treatment with 18-MC.

Figure 6.

(A-B). Effects of repeated administration of 18-MC (20 mg/kg, i.p. or vehicle for two weeks) on average number of bouts per 23 h (A) and average bout size (B) in male rats having access to 30% sucrose solution and water or water only (insert). Bar represents the beginning and the end of treatment with 18-MC.

Figure 7. Average serum concentrations (mg/dl $\pm$ SEM) of glucose, cholesterol and triglycerides in trunk blood of male rats receiving repeated injections of 18-MC (20 mg/kg, i.p. or vehicle for two weeks) and having access to 30% sucrose solution and water or water only.