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Effects of MCH and a MCH1-receptor antagonist on (palatable) food and water intake

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Abstract

Melanin concentrating hormone (MCH) is a regulator of ingestive behavior, but several issues regarding its effects on specific components of ingestive behavior remain to be elucidated. Therefore, we injected, in the 3rd ventricle of male Wistar rats, saline, MCH (5 μg), MCH (5 μg) together with a MCH1-R antagonist (A, 10 μg) and the antagonist alone (A, 10 μg). Our results show that (1) central administration of MCH stimulates food intake (lab chow and medium high fat diet) and this can be blocked by a MCH1-R antagonist; (2) the MCH-induced increase in food intake is mediated through increased meal number, meal duration and meal size; (3) the MCH1-R antagonist is able to significantly reduce the intake of a highly palatable food (condensed sweet milk) and is more effective in blocking MCH-induced food intake when rats are fed a palatable medium high fat food; and (4) MCH stimulated water intake independently from and disproportionately to food intake. In conclusion, our results point to an involvement of endogenous MCH in the enhanced intake of palatable food. Furthermore, they confirm that MCH stimulates not only food intake but also water intake.

1. Introduction

The melanin concentrating hormone (MCH), first isolated from salmon pituitaries and implicated in the regulation of melanin pigment aggregation in the melanocytes, has now clearly been established as a neuropeptide involved in the control of food intake and energy metabolism [19,24]. Central administration of MCH stimulates food intake [10,20] and chronic i3vt infusion of MCH leads to hyperphagia and obesity [15]. Mice lacking MCH are hypophagic and lean [25].

Two MCH receptor subtypes have been identified, the MCH1 receptor (MCH1-R, originally named SLC-1) and the MCH2-R, but only the MCH1-R is found in rodents [6,21,28]. The MCH1-R is expressed in numerous areas of the brain [3], and mediates the orexigenic actions of MCH in rodents. MCH1-R knock out mice are lean, hyperphagic, hyperactive, have an increased metabolism and are resistant to diet induced obesity (DIO) [7,17].

In the recent years, several MCH1-R antagonists such as T-226296 [27], SNAP-7941 [4] or the antagonist characterized by Bednarek et al. [1], Shearman et al. [23] and Mashiko et al. [18] have been developed. These drugs significantly reduce MCH-induced increase in food intake when MCH is injected centrally and the antagonist is given

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orally (T-226296, [27]), intraperitoneally (SNAP-7941, [4]) or intracerebroventrically [18,23].

Several questions addressing the role of MCH in ingestive behavior remain to be answered. First, there is controversy regarding the effect of MCH on water intake. Shearman et al. [23] showed that MCH influences food intake without affecting water intake while Clegg et al. [9] demonstrated that central injections of MCH into the third ventricle stimulated both food intake and water intake. In the latter studies, when food was not available, MCH still stimulated water intake.

The role of endogenous MCH in food intake is also still a subject of discussion. Chronic treatment with an MCH1-R antagonist alters appetite, body weight and adiposity in Sprague–Dawley rats [23] and in diet-induced obese (DIO) mice [18]. In addition, Borowsky et al. [4] showed that the MCH1-R antagonist SNAP-7941 injected intraperitoneally would block the intake a highly palatable food (sweet condensed milk). However, there are no data available on an acute effect of MCH1-R antagonists on normal lab chow intake. Taken together, these data suggest a role for endogenous MCH in the intake of palatable food, though Clegg et al. [8] demonstrated that rats injected MCH centrally failed to develop a preference for the high (more palatable) or the low (less palatable) fat diets in a choice paradigm.

The aim of the present experiments was to further characterize the effects of MCH on food and water intake. In the first series of experiments, we investigated, in rats given either lab chow or a medium high fat diet, whether feeding induced by central administration of MCH could be blocked by central injections of a MCH1-R antagonist peptide (corresponding to Compound 30 in Bednarek et al. [1] and to Compound B in Shearman et al. [23]). In the next series of experiments, we investigated whether the MCH1-R antagonist blocked MCH-induced water intake. In the third series of experiments, we assessed whether central injection of the MCH1-R antagonist would block the consumption of a highly palatable food. Finally, we determined how MCH influences meal size, meal number, meal duration and rate of ingestion, by analyzing in detail the meal patterns of rats after injection of MCH and/or the MCH1-R antagonist.

2. Materials and methods

2.1. Animals and diets

All methods and experiments were approved by the Animal Care Committee of the University of Groningen. Forty-one male Wistar rats weighing 280–300 g at the start of the experiments were included in the study. They were obtained from the breeding colony maintained at the University of Groningen. Animals were allowed 7–10 days to become habituated to the experimental conditions (individual housing in rooms with controlled humidity and temperature, 12/12 h dark/light cycle, lights on from 0.00 to 12.00).

After habituation, rats were implanted stereotaxically with a 22-gauge stainless steel guide cannula (Plastics One, Roanoke, VA) into the third cerebral ventricle (i3vt) under O_2/N_2O-isoflurane anesthesia. Finadyne® (1 g/kg BW, Schering-Plough, Maarssen, The Netherlands) was given to reduce surgery stress and the rats were allowed to recover for 5–7 days. After recovery, correct placement of the cannula was confirmed by injection of 10 ng of angiostensin II through an injector placed in the guide cannula. Only the rats that drank more than 6 ml of water within 30 min after the injection were used in the subsequent experiments.

Rats were fed regular lab chow (RMH-B, Hope Farms, Woerden, The Netherlands; 3.8 kcal/g). In Experiment 1b, a 42% fat diet (Medium high fat-MHF-diet, Purified High Fat diet with lard, 4031.09, Arie Block BV, Woerden, The Netherlands; 4.7 kcal/g) was also used.

2.2. Chemicals

MCH was purchased from Bachem (Weil am Rhein, Germany). The MCH1-R antagonist peptide was synthesized at Bachem (Weil am Rhein, Germany) and it consists of the amino acid sequence Acetyl-Arg-Cys-Met-5-amino-pentanoyl-Arg-Val-Tyr-5-aminopentanoyl-Cys-NH2. This peptide sequence has previously been characterized in vitro and in vivo by Bednarek et al. ([1], "Compound 30"), Shearman et al. ([23]; "Compound B") and Mashiko et al. [18]. The antagonist peptide was shown to exhibit a high affinity for the MCH1-R with a K_i value of 9.9 nM. It showed an antagonistic activity in a functional assay with an IC50 value of 15 nM [18].

2.3. Experiments

2.3.1. Experiment 1: effects of i3vt administration of MCH and the MCH1-R antagonist (A) on food intake

Rats were injected with either saline (4 μl), MCH (5 μg in 4 μl saline), MCH and the MCH1-R antagonist (5 μg + 10 μg, respectively, in 4 μl saline) or the MCH1-R antagonist alone (10 μg in 4 μl of saline) through an injector ending 1 mm lower than the guide cannula. This dose of antagonist was chosen because it was shown to be effective by Shearman et al. [23]. The study was done following a cross-over design, each rat being submitted to the 4 conditions with a week between each i3vt injection. The injections were performed 30 min before lights went off. Food hoppers were weighed at the onset of dark and then 1, 2, 3, 4, 6 and 24 h later.

Two studies were performed in Experiment 1. In experiment 1a, rats were kept on normal lab chow, and in experiment 1b, the MHF diet was given for the duration of the experiment. The rats in the second group were allowed to get accustomed to the MHF diet several times in the week prior to the experiment. Typically, they were given 1–2 pellets of the MHF diet every day in their cage. Animals would avidly eat that food.

2.3.2. Experiment 2: effects of i3vt administration of MCH and MCH1-R antagonist (A) on water intake

The same design as described in Experiment 1 was used in this experiment, except that the experiment was shortened to 6 h. Rats were allowed ad libitum food and water access prior to the experiment. Food was removed at the time of the injection and was returned after 6 h to allow assessment of water intake independently of food intake.

2.3.3. Experiment 3: meal pattern analysis after i3vt administration of MCH and MCH1-R antagonist (A)

Rats were injected with saline, MCH, MCH + MCH1-R antagonist or the MCH1-R antagonist alone 30 min before the start of the dark phase, following the same procedure as described in Experiment 1. Each rat was successively submitted to each condition in a cross-over design, with 7 days between each i3vt injection. Food intake was then recorded for 24 h using a TSE Drinking and Feeding Monitor (TSE Systems GmbH, Bad Hamburg, Germany). Food was weighed at 10 s intervals. Meal number, meal duration (s), meal size (g) and ingestion rate (g/min) were then determined. The food intake signal was analyzed as follows: a meal needed to be larger than 0.1 g and longer than 10 s and two distinct meals needed to be separated by an Inter Meal Interval (IMI) of 10 min [2,5,13]. We evaluated the data using different IMI (between 1 and 10 min) and this did not appreciably change the results (data not shown).

2.3.4. Experiment 4: sweet condensed milk intake after i3vt administration of a MCH1-R antagonist in satiated rats

The protocol used in this experiment was adapted from Borowsky et al. [4]. Four hours after the start of the dark phase (i.e., at 16.00), food was removed from the rats for 1 h (i.e., from 16.00 to 17.00). Rats were then offered sweet condensed milk (Friesland Dairy Foods, Leeuwarden, The Netherlands) for 30 min (i.e., from 17.00 to 17.30). Finally, food was returned at 17.30. Rats were trained for 6 days on this paradigm. On the test day (day 7), rats were injected i3vt with either saline (4 μl) or the MCH1-R antagonist (A, 10 μg in 4 μl saline) between 16.30 and 17.00, i.e., 30 min before being given access to the sweet condensed milk. This timing was chosen since it was effective in Experiments 1–3. The sweet condensed milk intake was assessed and expressed as a percentage of the average intake calculated over the 3 last days of the training period.

2.4. Statistics

Results are presented as means ± SEM. All statistical analyzes were performed using SPSS 12.0.1 (Chicago, IL). A paired-samples *t* test was used to test the significance (*P* < 0.05) of the differences between the different injections (MCH vs. saline, MCH vs. MCH + A, and A vs. saline, respectively). An ANOVA with repeated mea-

sures was used to test the effect of the treatments (saline, MCH, MCH + A or A) on the 24-h cumulative food intake in Experiment 3.

3. Results

3.1. Experiment 1: effects of MCH and MCH1-R antagonist (A) on food intake

Intra-cerebroventricular (i3vt) injection of MCH significantly increased food intake in rats fed a lab chow diet (Fig. 1, results expressed in kcal). The orexigenic effect of MCH was the strongest during the first 3 h of the dark phase. When compared to the rats injected saline, the increase in food intake reached +94% (*P* < 0.01) at 2 h and +56% (*P* < 0.05) at 3 h.

The MCH1-R antagonist (A) significantly attenuated the orexigenic effect of MCH from 2 to 4 h after the start of the dark phase (−41%, −43% and −43% vs. MCH at 2, 3 and 4 h, respectively, *P* < 0.05). Even at time point 24 h, the cumulative food intake of the rats given MCH together with the MCH1-R antagonist was still significantly reduced compared to the rats given the MCH injection (−22% vs. MCH, *P* < 0.05). When given alone, the antagonist did not affect food intake nor body weight when compared to the control injection.

The same experiment was repeated in rats fed a medium high fat diet (MHF diet, 42% of energy as fat) (Fig. 2, results expressed in kcal). MCH injected centrally before lights off stimulated food intake during the first hour of the dark phase (+98% and +60% vs. saline at 2 and 3 h, respectively, *P* < 0.05). The antagonist significantly attenuated the MCH-induced food intake during the first 6 h of the dark phase (−62%, −61% and −51% vs. MCH at 3, 4 and 6 h, respectively, *P* < 0.01). Moreover, when injected alone, the antagonist significantly reduced food intake compared to the control condition (−39% at 4 h and −20% at 6 h vs. Saline, *P* < 0.05).
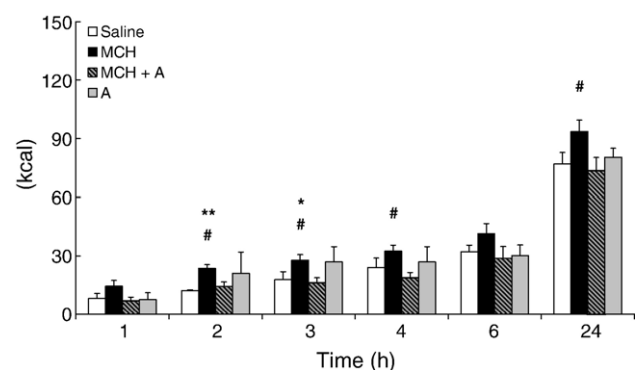

Fig. 1. Cumulative food intake (kcal) after an acute i3vt injection of saline (*n* = 7), MCH (5 μg, *n* = 7), MCH (5 μg) + A (10 μg) (*n* = 7) or A (10 μg, *n* = 3) in rats fed lab chow. Means ± SEM. *, **, ***P* < 0.05, 0.01 and 0.001, MCH vs. saline. #, ##, ###*P* < 0.05, 0.01 and 0.001, MCH vs. MCH + A. $, $$, $$$*P* < 0.05, 0.01 and 0.001, A vs. saline.

Fig. 2. Cumulative food intake (kcal) after an acute i3vt injection of saline ($n = 6$), MCH (5 μg, $n = 6$), MCH (5 μg) + A (10 μg) ($n = 7$) or A (10 μg, $n = 6$) in rats fed a 42% fat diet. Means ± SEM. *, **, ***$P < 0.05$, 0.01 and 0.001, MCH vs. saline. #, ##, ###$P < 0.05$, 0.01 and 0.001, MCH vs. MCH + A. $, $$, $$$$P < 0.05$, 0.01 and 0.001, A vs. saline.
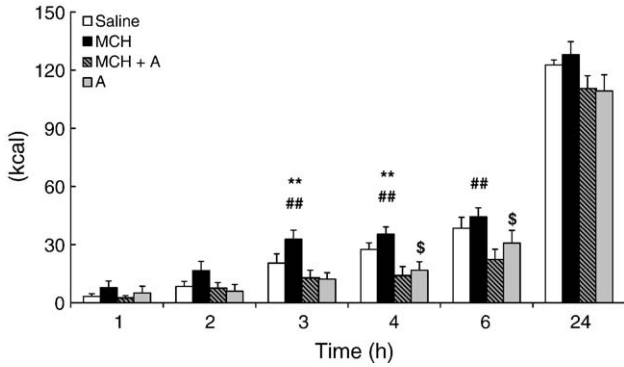
3.2. Experiment 2: effects of MCH and MCH1-R antagonist (A) on water intake

Fig. 3 presents the 6-h cumulative water intake of rats injected saline, MCH, MCH + A or A alone 30 min before the start of the dark phase. MCH injected centrally significantly stimulated water intake from the 1st hour to 6 h after light off (+109%, +131%, +93%, +68% and +49% vs. saline at 1 ($P < 0.01$), 2 ($P < 0.001$), 3 ($P < 0.01$), 4 ($P < 0.01$) and 6 ($P < 0.05$) h, respectively). The MCH1-R antagonist was able to block MCH-induced water intake (−44% vs. MCH at 2 and 3 h, $P < 0.05$). Water intake of the rats injected MCH + A was not different from that of the rats given saline injection. When injected alone, the MCH1-R antagonist had no effect on water intake.

3.3. Experiment 3: effects of MCH and MCH1-R antagonist (A) on meal pattern

Fig. 4 shows the 24-h cumulative chow intake (expressed in grams) of rats injected with saline, MCH, MCH + A or A alone 30 min before the start of the dark phase. There was a
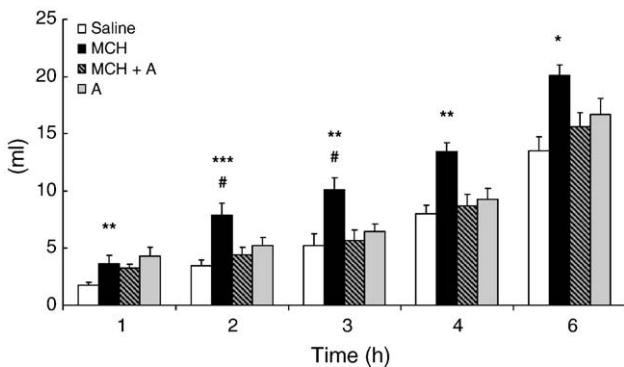

Fig. 3. Cumulative water intake (ml) after an acute i3vt injection of saline ($n = 12$), MCH (5 μg, $n = 12$), MCH (5 μg) + A (10 μg) ($n = 12$) or A (10 μg, $n = 12$) in rats. Means ± SEM. *, **, ***$P < 0.05$, 0.01 and 0.001, MCH vs. saline. #, ##, ###$P < 0.05$, 0.01 and 0.001, MCH vs. MCH + A. $, $$, $$$$P < 0.05$, 0.01 and 0.001, A vs. saline.

Fig. 4. Cumulative 24 h food intake (kcal) after an acute i3vt injection of saline ($n = 6$), MCH (5 μg, $n = 6$), MCH (5 μg) + A (10 μg) ($n = 7$) or A (10 μg, $n = 6$) in rats. Means ± SEM. MCH (−●−), Saline (−○−), MCH + A (−▼−) and A (−▽−). *, **, ***$P < 0.05$, 0.01 and 0.001, MCH vs. saline. #, ##, ###$P < 0.05$, 0.01 and 0.001, MCH vs. MCH + A. $, $$, $$$$P < 0.05$, 0.01 and 0.001, A vs. saline. **$P < 0.01$ A vs. saline.
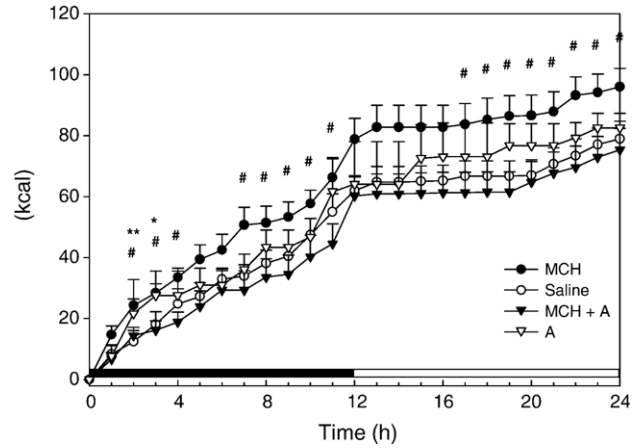
significant overall effect of the treatment (saline, MCH, MCH + A or A) on the 24-h cumulative food intake curves (ANOVA with repeated measures, $P = 0.005$).

Table 1 shows the results of the meal pattern analysis performed after i3vt injections of saline, MCH, MCH + A or A alone. The meal pattern analysis was performed over the first 2 h of the dark phase, and over the entire dark phase (0–12 h).

During the first 2 h of the dark phase, meals number ($P < 0.05$ vs. saline), meal duration ($P < 0.05$ vs. MCH + A), meal size and ingestion rate were increased in the MCH-treated rats, all contributing to a significantly higher 2 h cumulative food intake in those rats ($P < 0.05$) when compared to the rats injected saline or MCH + MCH1-R antagonist. The antagonist injected alone had no effect on the parameters measured.

Over the entire 12-h dark period, MCH injected i3vt led to a higher number of meals and a slightly increased meal duration (but these changes were not statistically significant) compared to what was observed in the 3 other groups. This resulted in an increased 12 h cumulative food intake. This difference, however, was significant only when compared to the MCH + A-treated rats ($P < 0.05$).

3.4. Experiment 4: sweet condensed milk intake after an i3vt injection of MCH1-R antagonist in satiated rats

Rats were very eager to drink the condensed sweet milk, and ingested in average (calculated on the 3 days prior to the experiment) 13.3 ± 0.6 g within 30 min. Fig. 5 shows the condensed sweet milk intake of the rats on the 3 training days before the experiment and the results of the acute i3vt injection of the MCH1-R antagonist. There was a significant reduction ($P = 0.004$) in the sweet condensed milk intake

Table 1
Meal pattern analysis, over the 1st hours of the dark phase and the entire 12 h dark phase

	Eating parameter	Saline	MCH	MCH + A	A
0–2 h	Meal number	2.1 ± 0.6[a]	2.9 ± 0.4[a]	2.1 ± 0.4	2.0 ± 0.3
	Meal duration (s)	361 ± 69	422 ± 87[a]	248 ± 49[a]	287 ± 56
	Meal size (g)	1.9 ± 0.3	2.2 ± 0.2	1.8 ± 0.3	2.3 ± 0.4
	Ingestion rate (g/min)	0.33 ± 0.03	0.53 ± 0.21	0.70 ± 0.22	0.64 ± 0.13
	Cumulative FI (g)	5.0 ± 1.4[a]	9.6 ± 1.2[a,b]	5.8 ± 0.9[b]	7.3 ± 0.8
0–12 h	Meal number	8.3 ± 1.1	9.3 ± 1.0	7.7 ± 1.1	5.7 ± 0.4
	Meal duration (s)	431 ± 59	483 ± 58	363 ± 42	329 ± 41
	Meal size (g)	2.1 ± 0.2	2.4 ± 0.2	2.1 ± 0.1	2.9 ± 0.5
	Ingestion rate (g/min)	0.35 ± 0.03	0.45 ± 0.13	0.57 ± 0.11	0.68 ± 0.17
	Cumulative FI (g)	16.5 ± 1.4	21.2 ± 2.0[a]	15.6 ± 1.5[a]	16.2 ± 2.9

Means ± SEM. Within a row, values with the same superscript letter are significantly different, $P < 0.05$.

after the antagonist injection when compared to the i3vt saline injection.

4. Discussion

The experiments described in this paper were designed to investigate the effects of MCH and a MCH1-R antagonist on normal and palatable food intake, on meal patterns and on drinking behavior. The most important finding is that administration of the MCH1-R antagonist successfully reduced the intake of a palatable medium high fat diet and of a highly palatable sweet condensed milk but failed to inhibit the intake of regular chow. In addition, the MCH1-R antagonist prevented the MCH-induced increase in food intake, and this effect was more pronounced when animals were fed a medium high fat diet. These results support a role for endogenous MCH in the intake of, particularly, palatable food. Our results do also confirm that exogenous MCH also stimulates water intake, independently of food intake and that this effect can be blocked by a MCH1-R antagonist. Finally, the meal pattern analysis performed show that both an increased meal number and meal duration in the MCH

administered rats participated in the increased food intake observed.

The results of Experiment 1 show that exogenous MCH administered in the 3rd ventricle is able to stimulate food intake in rats on normal lab chow or a medium high fat diet. Two hours after lights off, food intake in the rats injected with MCH was doubled when compared to controls, and it was still increased by 56–60% at 3 h. This effect could be blocked by concomitant injection of the MCH1-R antagonist. Our results confirm those of, e.g., Rossi et al. [20] or Della-Zuana et al. [11], and further support the role of MCH as an orexigenic peptide involved in the central control of food intake, as well as a role for the MCH1-R in mediating the effects of MCH on food intake.

When injected alone, the MCH1-R antagonist did not affect food intake in the rats fed lab chow (Experiment 1a). In contrast, it induced a significant reduction in food intake at 4 (−39%) and 6 (−20%) h in the rats given the MHF diet (Experiment 1b). The antagonist was also more effective in blocking the MCH-induced increase in food intake in rats on the MHF diet (−50 to 60% compared to saline-injected rats) than in those on lab chow (−40%). The antagonist was also able to reduce the intake of a highly palatable food (sweet
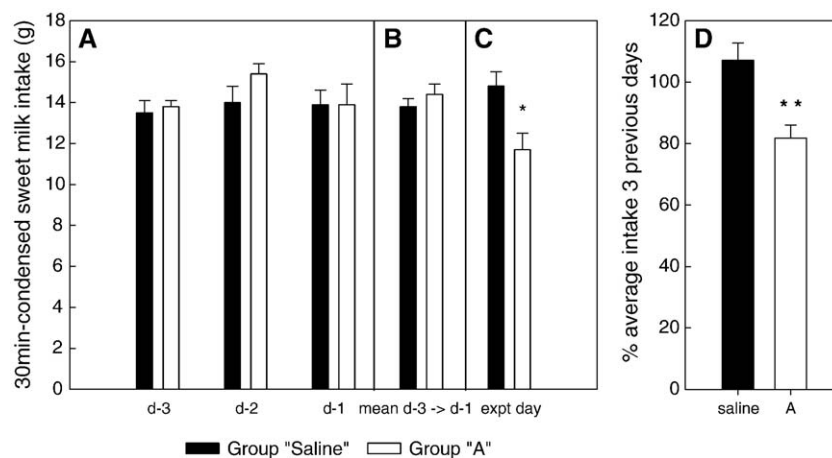

Fig. 5. (A) 30 min sweet condensed milk intake (g) during the last 3 days of the training period, (B) average 30 min sweet condensed milk intake (g) calculated over the last 3 days of the training period, (C) 30 min sweet condensed milk intake (g) on the experimental day after an acute i3vt injection of saline ($n = 7$) or A (10 μg, $n = 7$) and (D) 30 min sweet condensed milk intake (g) on the experimental day after an acute i3vt injection of saline or A (expressed as a percentage of the average intake calculated over the 3 previous training days) in rats. Means ± SEM. *$P < 0.05$ and **$P < 0.01$ A vs. saline.

milk test, Experiment 4), confirming the data of Borowsky et al. [4] (who used a different antagonist).

Taken together, our results are in agreement with the idea developed by Elliot et al. [12] that MCH might be involved in enhancing appetite for palatable food, which would be consistent with an involvement of MCH in the hedonic reward circuit. Recently, Georgescu et al. [14] showed that MCH acts in the Nucleus Accumbens (NAc) to modulate feeding behavior confirming earlier ideas by DiLeone et al. [11]. The NAc is a major reward region in the brain and shows enhanced expression of the MCH1-R mRNA [21]. It has been suggested that the MCH trafficking between the lateral hypothalamus (LH) and the NAc may play a role in communicating hedonic and/or rewarding aspects of food [22]. Several lines of evidence point to an involvement of the mesolimbic dopamine system in the effects of MCH on palatable food intake. First, the NAc is part of the mesolimbic dopamine system, and Smith et al. [26] showed an increased sensitivity of the mesolimbic dopamine system in MCH1-R KO mice, which may be indicative of altered reward mechanism. And second, Georgescu et al. [14] suggested that MCH could stimulate feeding via an increased drive to feed, through its interaction with the NAc dopamine system. And finally, Clegg et al. (personal communication) were able to block the MCH-induced hyperphagia with a dopamine antagonist. Taken together, this suggests that interactions between MCH and the monoamine systems might participate in the reward-related effects of MCH.

The results of Experiment 2 show that centrally administered MCH stimulates water intake independently of food intake, and that this effect can be blocked by the MCH1-R antagonist. In our experiment, water intake was also increased disproportionately to food intake. Three hours after the start of the dark phase, water intake was increased by 93% in the rats MCH-administered when compared to the control condition, when food intake was increased by only 57% and 60% (Experiments 1a and 1b, respectively). Taken together, those data are in line with a specific role for MCH in the control of water intake. Our results are in agreement with those of Clegg et al. [9], but not with those of Shearman et al. [23] who failed to find any effect of their MCH1-R agonist and antagonist on water intake. The different experimental set-ups might explain the disaccording results. In the present experiment and in the set-up used by Clegg et al. [9], food was removed during the experiment so that rats would have access to water only. This effect of MCH on fluid intake might also explain, in part, the effect of the MCH1-R antagonist on the intake of the condensed sweet milk in Experiment 4, since the appetitive diet was given to the rats in a liquid form. However, we believe that this effect is less important, based on the observation that the antagonist does not affect water intake by itself.

Lastly, our meal pattern analysis (Experiment 3) showed that animals administered MCH i3vt showed increased meal number ($P < 0.05$ vs. saline), increased meal duration ($P <$

0.05 vs. MCH + A) and a trend towards increased meal size. These data demonstrate that multiple parameters related to ingestive behavior contribute to MCH-induced increase in food intake, and are in contrast with those of Kowalski et al. [16] who showed that the MCH1-R antagonist T-226296 reduces food intake when given to DIO rats via a reduction in meal size but not meal frequency, supporting then a role for MCH in meal size regulation.

In conclusion, our results obtained with the MCH1-R antagonist further support an involvement of endogenous MCH in the enhanced intake of palatable food. Moreover, we confirm that MCH stimulates not only food intake but also water intake, and this, independently, of food intake.

Acknowledgments

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