Effect of morphine on caloric intake and macronutrient selection in male and female Lou/c/jall rats during ageing

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Abstract

Previous studies have showed a shift of preferences from carbohydrate to fat in the Lou/c/jall rat with advancing age when they are submitted to a self-selection procedure. Protein intake also decreased according to the age, earlier for males (after 16 months) than for females (29 months). The present study aimed at investigating the mechanism underlying these modifications. We analysed the effect of the reference μ agonist, morphine (5 mg/kg subcutaneous), on the caloric intake, body weight and macronutrient intake of 30 male and 30 female rats divided in four age groups: young adults (10), mature (17), old (24) and senescent rats (29 months). During the experiment, animals had the choice between separate sources of the three pure macronutrients. Morphine injection reduced total daily caloric intake and induced a decrease in body weight. The weight loss was age- and sex-related (males and old rats were more affected by the drugs). The injection of morphine evoked a triphasic influence on the chronology of the intake. A brief (1 h) hypophagia was followed by an hyperphagia (3 h) and a persistent hypophagia (8 h). No modification in the diet composition was observed. These results did not support a clear involvement of the opioid system concerning the modifications in macronutrient rates in diet previously observed across ageing. © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Morphine; Ageing; Macronutrient; Body weight; Lou/c/jall rat

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1. Introduction

Studies performed on rats showed modifications in caloric intake and dietary preferences as a function of age when animals were allowed to choose their diet from pure macronutrient sources (protein, fat, and carbohydrate). Carbohydrate intake has been found to decrease and fat intake to increase in growing rats (Kanarek, 1985), protein intake was unchanged (McArthur and Blundell, 1982) or increased from weaning to maturity (Leibowitz, 1988) but very few studies deal with modifications of dietary preferences during ageing. The results obtained in our group showed a shift of preferences from carbohydrate to fat diets and a decrease in protein intake in the Lou/c/jall rat with advancing age. The decrease in protein intake occurred earlier for males (after 16 months) than for females (29 months) (Veyrat-Durebex and Alliot, 1997; Veyrat-Durebex et al., 1998; Boghossian and Alliot, 2000). Moreover, females but not males are able to increase caloric intake and keep a constant body weight in advanced age. (Veyrat-Durebex and Alliot, 1997; Veyrat-Durebex et al., 1998).

The mechanisms underlying age- and sex-related modifications in food intake and macronutrient choices are now under investigation. Many studies provided extensive evidences for the role of brain monoamines and neuropeptides in the control of food intake, meal pattern and appetite for specific macronutrients (Leibowitz, 1988; Kalra et al., 1999). Among the specific neuropeptides that have an evident physiological role, endogenous opioids are thought to play a role in diet selection and to mediate, at least in part, the rewarding properties of palatable foods (Yim and Lowy, 1984; Reid, 1985). The effect of opiates ligands on feeding behaviour were studied using various approaches. Some studies aimed at investigating the role of the opioid system in central structures involved in the control of food intake (Ragnauth et al., 2000) while others evaluated the general effect (i.e. central and peripheral) of systemic doses of opioid drugs on feeding behaviour. In this later case, if we consider the short-term effects (2–6 h post-injection), agonists and antagonists may respectively increase and decrease food and water intake and modify macronutrients selection (Marks-Kaufman, 1982; Gosnell and Majchrzak, 1989; Welch et al., 1994). For example, morphine has been shown to increase fat consumption while either decreasing or having no effect on carbohydrate or protein intake (Marks-Kaufman, 1982). Besides, when long-term (24 h) effects were studied, the opiate agonist morphine evoked a polyphasic influence on food intake (Gosnell and Krahni, 1993; Leshem, 1988).

Furthermore, the opioid system seems to be affected by ageing. Various studies dealing with the density and the affinity of opioid receptors or with the concentration of their endogenous ligands showed modifications across ageing (Piva et al., 1987; Petkov et al., 1988; Dondi et al., 1992; Kowalski et al., 1992). These data suggest that changes in the opioid system’s activity could be involved in the age-related changes in macronutrient intake.

The aim of this study was to determine the effect of opioids on feeding behaviour across ageing. In order to make relevant comparisons, we have chosen a well-documented approach using acute and sub-chronic systemic administration of the
reference µ agonist, morphine. The effect of the drug was studied on daily caloric intake, body weight and macronutrient selection in young adults, mature, old and senescent male and female rats. Moreover, as the effect of morphine on food intake seems to be, at least, biphasic (Leshem, 1988; Gosnell and Krahn, 1993), behavioural parameters were monitored during the night before treatment and following the injection of the drug.

2. Materials and methods

2.1. Animals

Male and female Lou/c/jall rats were used. These animals, bred in our laboratory for more than 10 years, are derived from the Lou/c strain (University of Louvain, Belgium), which have been described as of Wistar origin (Bazin, 1990). Those rats exhibit a lighter body weight with no development of obesity with age and show an increased longevity compared to more usual strains of rats (Veyrat-Durebex et al., 1998).

Rats were housed in pairs in plastic cages and maintained at 22 ± 1 °C on a 12:12 h cycle (lights off at 20:00 h) with food and water available ad libitum. Before the present experiment, all rats had been allowed to adapt to the self-selection procedure from the age of 4 months according to the procedure routinely used in the laboratory (Veyrat-Durebex and Alliot, 1997).

2.2. Self-selection diet

The self-selection diet was separated sources of the three pure macronutrients. The protein component (metabolizable energy 3.12 kcal/g) was composed of 93% casein (Louis-François, France). The fat component (7.88 kcal/g) contained 91% lard, 2% sunflower oil, and the carbohydrate component (3.34 kcal/g) consisted in 85% corn starch (cerestar 12 018 Louis-François), 8% commercial grade sucrose. Each macronutrient diet was supplemented with 2% cellulose powder (UAR), 1% vitamins (UAR 200) and 4% salt mixture (UAR 205 b).

2.3. Experimental procedure

This study was carried out with 30 males and 30 females. They were divided into four groups of age: 10 months (eight males and eight females), 17 months (eight males and eight females), 24 months (seven males and eight females), and 29 months (seven males and six females).

The duration of the protocol was 30 days. Animals were submitted to the self-selection regimen for three weeks so that at the end of this period, their diet composition was stable. Furthermore, during the last 7 days of this period, animals were given subcutaneous (s.c.) saline administration in order to allow their adaptation to injections. The last 3 days of saline injections were considered as the basal period.
Then, animals have been submitted to morphine or saline administration for 9 days as following.

- On day 1, morphine (Sigma 5 mg/kg s.c.) was injected between 18:30 and 19:30 h. The dose of 5 mg/kg s.c. of morphine was chosen because it has been shown to induce an effect on daily caloric intake and macronutrient selection in the rat (Welch et al., 1994).
- On day 2, rats were injected with saline s.c. (a preliminary study had shown that, in young animals, caloric intake went back to control level after a single day interruption of morphine treatment).
- On days 3–5 morphine (5 mg/kg s.c.) was injected between 18:30 and 19:30 h. It has been shown that after 3 days of treatment with morphine, the maximum effect was reached (Gosnell and Krahn, 1993).
- On days 6–9, rats were injected with saline s.c.

Body weight and macronutrient intake of all rats were recorded twice a day, at 08:00 and 18:30 h while animals were injected.

In order to evaluate the potential influence of environmental modifications during the experiment, food intake and body weight of a control group of 37 rats (24 males and 13 females from 10 to 24 months) were also studied. These rats were submitted to the same protocol but they only received saline injections throughout the experiment. The number of 29-month-old rats did not allow to have a control group for this age.

2.4. Study of meal pattern and general activity during the night

In addition, the behavioural effect of morphine was analysed on 16 rats (four male rats per age group) using continuous video recordings between 20:00 and 08:00 h (dark period). Four parameters were used: time spent in access to fat, carbohydrate and protein sources, locomotion and grooming. In a previous study (Veyrat-Durebex, 1998), we have shown a direct correlation between time spent in macronutrient intake and the quantity of eaten food. Two recordings were realised on the same animal: before the injection of the drug (basal conditions) and after the last injection of morphine (day 5).

2.5. Statistical analysis

All data are given as means ± SE. Effect of treatment was evaluated using analysis of variance (ANOVA) with repeated measures performed on control and experimental groups (except 29-month-old one).

The effect of morphine as a function of sex and age was evaluated using only experimental groups. Each animal was its own control (saline conditions vs. morphine conditions). The ANOVA with repeated measures was followed by a Fisher PLSD test for an a-posteriori means comparison. Significance at $P < 0.05$. 
3. Results

When nutrient intake was analysed in basal conditions, already described changes in caloric intake and macronutrient choices were seen.

The daily caloric intake depends on age (main effect of age: \( F(3,91) = 4.3; P = 0.0067 \)) and sex (main effect of sex: \( F(1,91) = 49.9; P < 0.0001 \)). Females’ intake was lower than males’ one except in the oldest groups (interaction sex \( \times \) age: \( F(3,91) = 5.5; P = 0.0015 \)).

Protein intake decreased with age (\( F(3,91) = 12.8; P < 0.0001 \)) whereas fat intake increased (\( F(3,91) = 8.0; P < 0.0001 \)). Carbohydrate intake was decreased without reaching a significant level (\( P = 0.08 \)).

3.1. Effect of morphine on daily caloric intake

A main effect of treatment appeared (\( F(9,252) = 15; P < 0.0001 \)) on caloric intake. No changes were seen in control group throughout the experiment whereas a decrease appeared in experimental groups (Table 1).

The decrease in experimental groups was significant (\( F(1,25) = 36.6; P = 0.0001 \)) after a single injection (36.5 ± 1.6–25.6 ± 1.9 kcal before vs. after injection). No effect of age appeared (\( F(3,25) = 2.2 \) ns). The decrease tended to be less important in females (interaction sex \( \times \) injection \( F(1,25) = 3.2; P = 0.086 \)). Caloric intake went back to basal level after a single day interruption of morphine treatment.

Sub-chronic injections of morphine induced a decrease in caloric intake (\( F(3,75) = 24.5; P < 0.0001 \)). The effect was maximum from the first injection and similar to the one observed after a single administration.

After the end of morphine injections, food intake increased (\( F(3,69) = 13.0; P < 0.001 \)). The slope of the increase was more steep in young animal (10, 16 months) than in old ones but the effect of age did not reach the significant level (\( F(9,69) = 1.8; P = 0.08 \) ns) because of wide individual variations.

3.2. Effect of morphine on body weight

A main effect of treatment appeared (\( F(4,288) = 22; P < 0.0001 \)). No difference was observed throughout the experiment for the saline treated group, whereas a body weight loss was observed in morphine treated males and females. In this last groups, the effect of morphine was significant after acute (\( F(2,186) = 29.8; P < 0.0001 \)) and after sub-chronic administration (\( F(4,372) = 44; P < 0.0001 \)). Moreover, ANOVA showed an effect of sex (\( F(4,208) = 11.2; P < 0.0001 \)) and age (\( F(12,208) = 2.2; P < 0.01 \)). The treatment induced a progressive and more marked decrease in males (max: − 14 g) than in females (max: − 6 g). The effect of the drug was more important when rats were older except for the 29-months-old males. This last observation could be attributed to the fact that the oldest males were survivors (Fig. 1).

Termination of morphine administration induced significant increase in body weight (\( F(3,279) = 3.8; P < 0.01 \)). This body weight recovery depended on age...
Table 1
Effect of morphine on daily caloric intake (kcal) of 10, 17, 24 and 29-months-old male and female rats

<table>
<thead>
<tr>
<th></th>
<th>Basal (saline; reference 1)</th>
<th>Day 1 (morphine; acute injection)</th>
<th>Day 2 (saline; reference 2)</th>
<th>Day 5 (morphine; sub-chronic)</th>
<th>Day 9 (saline; end of recovery)</th>
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<tr>
<td><strong>Males</strong></td>
<td></td>
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<tr>
<td>10 months</td>
<td>44.9 ± 0.9</td>
<td>36.7 ± 3.3</td>
<td>40.1 ± 2.3</td>
<td>34.7 ± 2.9</td>
<td>52.7 ± 1.7a,b</td>
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<tr>
<td>17 months</td>
<td>42.7 ± 0.2</td>
<td>31.4 ± 3.5^a</td>
<td>42.9 ± 5.1</td>
<td>29.9 ± 4.4</td>
<td>53.9 ± 4.2</td>
</tr>
<tr>
<td>24 months</td>
<td>39.7 ± 0.6</td>
<td>23.8 ± 3.2^a</td>
<td>35.4 ± 2.0</td>
<td>19.3 ± 5.3^b</td>
<td>31.9 ± 3.9</td>
</tr>
<tr>
<td>29 months</td>
<td>43.3 ± 2.1</td>
<td>23.8 ± 5.2^a</td>
<td>35.0 ± 2.4^a</td>
<td>22.9 ± 3.5^b</td>
<td>49.7 ± 5.4</td>
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<td><strong>Females</strong></td>
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<tr>
<td>10 months</td>
<td>29.2 ± 1.7</td>
<td>21.4 ± 1.0^a</td>
<td>27.5 ± 1.3</td>
<td>26.0 ± 1.5</td>
<td>36.1 ± 4.5</td>
</tr>
<tr>
<td>17 months</td>
<td>25.7 ± 0.8</td>
<td>20.2 ± 1.2</td>
<td>30.7 ± 1.4^a</td>
<td>23.3 ± 0.5^b</td>
<td>40.6 ± 2.0^a,b</td>
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<tr>
<td>24 months</td>
<td>26.8 ± 1.5</td>
<td>16.3 ± 1.5^a</td>
<td>29.0 ± 1.2^a</td>
<td>23.5 ± 2.6^b</td>
<td>34.9 ± 1.3^a,b</td>
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<td>29 months</td>
<td>37.6 ± 7.9</td>
<td>31.8 ± 11.0</td>
<td>41.2 ± 10.9</td>
<td>31.5 ± 5.0</td>
<td>46.2 ± 4.6</td>
</tr>
</tbody>
</table>

^a Different from basal values.
^b Different from day 2 values (PLSD Fischer test).
Fig. 1. (Continued)
(F(9,156) = 4; P < 0.001). Females showed a better recovery than males (interaction sex × age F(9,156) = 2.5; P < 0.01).

3.3. Effect of morphine on macronutrient selection

There was a main effect of treatment on protein (F(9,252) = 6.1; P < 0.0001), carbohydrate (F(9,252) = 4.9; P < 0.0001) and fat intake (F(9,252) = 8.5; P < 0.0001). No difference was observed throughout the experiment for the saline treated group whereas the three macronutrients decreased (F(9,207) > 7.5; P < 0.0001) in morphine treated groups (Fig. 2).

The effect of morphine was neither age- nor sex-related. The decrease in protein intake (F(9,207) = 15.8; P < 0.0001) seemed to be stronger in males than in females (F(9,207) = 2.6; P < 0.008).

If we consider the percentage concentration scores of each macronutrient in the daily caloric intake (regimen composition), no significant effect of the drug was observed.

3.4. Study of meal pattern and general activity during the night

The time spent (min) on macronutrient intake and activity was recorded for each 1 h period. In each age group, we have used four male rats under basal conditions (day 1) and after morphine injection (day 5). The feeding patterns of young control rats showed three main meals: at the beginning (between 20:00 and 22:00 h), in the middle (around 01:00 h) and at the end (around 06:00 h) of the night. This pattern was modified across ageing. Senescent rats showed a disorganisation of their meal pattern with a wider distribution of the intake particularly during the second part of the night. Under morphine, a significant decrease (F(1,3) = 127.4; P < 0.002) in the total time spent on feeding was seen during the night (6.2 ± 0.8 against 4.4 ± 0.5 min/h for control and treated rats, respectively). A triphasic effect of morphine on feeding behaviour was evidenced (effect of time (F(11,33) = 6.5; P < 0.0001). A brief (1 h) hypophagia was followed by an obvious hyperphagia (between 21:00 and 00:00 h) and a persistent hypophagia (from 00:00 h to the end of the night) leading to a suppression of the third meal except for the oldest group. The first hypophagia was more marked in the oldest rats, but this age-related decrease in time spent on feeding did not reach the statistical significance (Fig. 3).

Fig. 1. Effect of morphine (5 mg/kg sc) on body weight. The data are expressed as difference with the basal period (mean of the 3 days of the control period). (A) Effect of morphine as a function of sex. No difference was observed throughout the experiment for the saline treated group whereas a body weight loss was observed in morphine treated males and females (F(4,288) = 22; P < 0.0001). Effect of morphine as a function of age in the female (B) and male (C) groups. The effect of the drug was greater when rats were older after acute (F(2,186) = 29.8; P < 0.0001) and sub-chronic administration (F(4,372) = 44; P < 0.0001) except for the 29-months-old males. This last observation had to be attributed to the fact the oldest males were survivors. An effect of sex (F(4,208) = 11.2; P < 0.0001) was also observed. The recovery depended on age (F(9,156) = 4; P < 0.001).
Fig. 2. Effect of morphine (5 mg/kg sc) on daily caloric intake and diet composition (expressed in kcal). Before injection, females’ caloric intake was lower than the males’ one except for the oldest groups. Morphine injection induced a dramatic decrease in caloric intake after acute or chronic treatment. No effect of the drug on regimen composition was observed.
Fig. 3. (Continued)
In basal conditions, a clear correlation between the time spent on feeding and time spent on activity was observed ($r^2 = 0.524; P < 0.0001$). Bursts of activity corresponded to the meals. Morphine induced both an increase in time spent on total activity during the night (11.5 ± 0.9 and 16.9 ± 2.3 min/h for control and treated rats, respectively) ($F(1,3) = 43.5; P < 0.008$) and a dissociation between activity and food intake. Indeed, an effect of time was observed ($F(11,33) = 28.8; P < 0.0001$): an obvious hyperactivity was seen during the first 2 h ($F(1,24) = 105.8; P < 0.0001$) while a reduction of locomotion occurred during the second part of the night ($F(1,24) = 40.8; P < 0.0001$).

4. Discussion

Present study shows an effect of morphine on food intake and body weight. Caloric intake was decreased whereas regimen was not mainly modified. The effect on body weight was more marked in males than in females and in older groups than in younger ones.

The results concerning food intake are in accordance with data found in the literature. Regarding a 24-h period, it has been demonstrated that morphine decreased food intake (Kumar et al., 1971; Thornhill et al., 1979; Kunihara et al., 1983; Romsos et al., 1987). Furthermore, repeated injections (Marks-Kaufman and Kanarek, 1990) or infusion with micro-pumps (Gosnell and Krahn, 1993) of morphine induced a body weight loss while Ottaviani and Riley (1984) reported that the drug did not change body weight gain. We can think that differences in the age of the rats and in procedures used may account for this discrepancy with present results. Moreover, some authors suggested a substantial strain dependence in feeding behaviour and energy balance caused by the different genotypes (Van Den Brandt et al., 2000).

The changes in body weight but not in caloric intake were age-related, suggesting that the body weight loss was due to more than a reduction in food intake. This could be explained by the fact that morphine also reduces food utilisation which is the ratio of weight gain to energy consumed (Levine et al., 1988).

According to the results obtained in mice (Kavaliers and Hirst, 1985), present study shows that, rats under basal conditions, feeding pattern is altered in older animals. Moreover, it shows a complex influence of morphine on meal pattern. We

Fig. 3. Effect of morphine (5 mg/kg sc) on feeding behaviour and activity. The recording time (20:00–08:00) correspond to the dark phase. The results are expressed as the time spent (min) in protein, carbohydrate, fat intake and motor activity (locomotion, grooming). The first recording was made during the last night of the basal period and the second during the last night of treatment (day 5). The feeding patterns of young control rats showed three main meals. This pattern was modified across ageing, senescent rats showed a disorganisation of their meal pattern with a wider distribution of the intake. Injection of morphine induced a decrease in the time spent in feeding during the night and changed the meal patterns. Under saline conditions the bursts of activity corresponded to the meals. Morphine induced an increase in time spend in activity during the night.
found that acute injections of this opiate agonist evoked a triphasic influence on feeding. A brief (1 h) hypophagia followed by hyperphagia (3 h) and a persistent (4–24 h) hypophagia. This result is in accordance with another study (Leshem, 1988). But in the most part of the studies that used opiate ligands, the feeding behaviour was recorded during 2–6 h after the injection (Marks-Kaufman, 1982; Lowy and Yim, 1983; Morley et al., 1985; Welch et al., 1994). During this period, it has been demonstrated that opiate agonists and antagonists may, respectively, increase and decrease food intake. Besides, the time of injection can be a critical factor in the effect of morphine on food intake. Kunihara et al. (1983) have demonstrated that morphine increased food intake in rats 2 h after the administration during the light period (10:45 h) but decreased total daily intake. On the contrary, food intake was decreased during the dark period if the injection was performed at 18:45 h. As on one hand, acute morphine injection increases the release of corticosterone (Milanes et al., 1993) and as, on the other hand, high level of corticosterone is able to depress food intake (Deroche et al., 1993), it can be hypothesised that the effect of morphine can interact with circadian rhythm of corticosterone, inducing high level of this hormone when morphine is administered at the time of the pre-feeding peak of secretion.

The short-term effect of morphine was not age-dependent. This result differs from that of Kavaliers and Hirst (1985) who found that the opiates-related effect was reduced in old mice when compared to young ones. Furthermore, Gosnell et al. (1983) demonstrated that old Fisher-344 rats were less responsive to opiate agonists than young ones.

In addition, morphine administration led to a disorganisation of behavioural patterns. When analysing the activity of rats during the night in basal conditions, we noted a correlation between meals and activity. The temporal relationships between meals and high activity levels during the 24-h-cycle in the rat are well known (Mistlberger, 1994). Morphine induced an increase in motor activity mainly during the 3 h following the injection. This observation was classically reported with such low doses of morphine (Sills and Vaccarino, 1998). Then, with this dose, the decrease in food intake could not be explained by sedation. Several explanations can be suggested, which need to be further investigated. First, morphine influence on feeding pattern could be related to the effect on motor activity either as a consequence or as a cause. Second, a same physiological mechanism could be involved. Some studies showed that the effects of morphine on food intake and locomotor activity were at least in part mediated by its action in the mesolimbic dopaminergic system (Sills and Vaccarino, 1998). The two effects could also be induced by the activation of corticosterone secretion (Alliot and Alexinsky, 1991). At least, it is possible that two independent physiological mechanisms were implicated.

Regarding diet composition, the already described modifications in feeding patterns with advancing age is confirmed (Veyrat-Durebex and Alliot, 1997; Veyrat-Durebex et al., 1998). When they become older, rats select more fat and less carbohydrate and a gender difference appears in protein intake. In the literature, the effect of morphine on macronutrient choice was generally studied using only
two regimens, high-fat and high-carbohydrate (Welch et al., 1994). Only few studies used a self-selection protocol with the separated three macronutrients. We found a decrease of all the macronutrients intakes with no modification of the regimen composition. On the contrary, Marks-Kaufman and Kanarek (1990) found no effect on protein, an increase in fat intake and a decrease in carbohydrate intake. This discrepancy could be explained by differences in procedure. In Marks-Kaufman and Kanarek study, rats were restricted to a feeding period of 6 h following the injection whereas in the present study, animals had a permanent access to the three macronutrients. In addition, the dose of morphine was twice lower in present study.

There is some evidence that opioids could be involved in protein appetite. However, the very interesting review of Thibault and Booth (1999) pointed out that the influence of morphine was depending on the route of administration and the fat preparation offered with protein. Moreover, as in present study, only casein had been used. So, as concluded by the authors cited above, some question remains about the conclusion that systemic morphine facilitates protein appetite. The next step in our studies should be the use of other sources of macronutrients (e.g. lactoserum instead casein).

The age-related effect of morphine on body weight could be interpreted on a pharmacological point of view.

First, it could be suggested that morphine pharmacokinetic is altered in old rats. Physiological changes associated with ageing such as the decrease in the ratio of lean body vs. fat or the decrease in liver or renal function, could induce an increase in plasma concentration of morphine in older rats and also explain an increased effect of the drug. Nevertheless, a study of Van Crugten et al. (1997) demonstrated that plasma and brain concentration–time curves of morphine and its main metabolite morphine-6β-glucuronide were not different between young adult (3–6 months) and aged Wistar rats (24 months). Then, pharmacokinetic modifications could probably not be accounted to explain the present results.

Second, present data could result from functional changes in the brain opioid system inducing a higher sensitivity to the various physiological effects of morphine. The evolution of the number and affinity of μ-receptors and of the concentration of their endogenous opiate ligands (β-endorphin or enkephalin) was studied in the brain of various strains but not in the Lou/c rat. Tissular β-endorphin clearly decreased across ageing in the hypothalamus whereas the evolution of met-enkephalin was unclear (Kowalski et al., 1992; Wang et al., 1993). A decrease in the number of μ-receptors was observed across ageing (Piva et al., 1987; Petkov et al., 1988). Taken together, these data suggest that present results could be interpreted as a change in the physiological response to an exogenous ligand due to the fall in the activity of an endogenous regulatory system. However, the influence of these neurochemical modifications on feeding behaviour was not observed. An effect on peripheral mechanisms such as gut function could be suspected.

In conclusion, morphine injection caused modifications in feeding patterns, a reduction in total daily caloric intake, a decrease in body weight but no modification in the diet composition. The differences observed across ageing could probably
be interpreted as a pharmacodynamic effect, but further studies are needed to understand the involved mechanisms. The lack of effect of morphine on regimen composition does not allow us to conclude to a direct involvement of opiate system in the differences observed in macronutrient choice across ageing.

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