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Mesolimbic dopamine drives the diurnal variation in opiate-induced feeding

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Abstract

Brain opioid peptides modulate feeding behavior and opiate drugs have powerful orexigenic effects in mammals. Recent studies have shown that opiate-induced eating depends, though not exclusively, on mu-opioid receptors located in the ventral striatum. Here we report that morphine orexigenic effects vary with the time of day according to a biphasic pattern. The effects first increase and then decrease during the light phase, with the peak effect occurring in the middle of this phase. This diurnal profile is shifted toward the dark phase after dopamine deafferentation of the ventral striatum. Consequently, the peak effect of morphine is delayed and occurs just before the dark phase. This finding suggests that mesolimbic dopamine transmission contributes to the neural mechanisms that normally drive the circadian timing of opioid-dependent feeding.

Keywords: Ventral striatum; Circadian rhythms; Morphine; 6-Hydroxydopamine; Rat

1. Introduction

A critical challenge for neuroscience is to understand the regulation of feeding behavior in mammals (Hoebel, 1997; Kelley et al., 2002; Saper et al., 2002; Schwartz et al., 2000). Several brain neurotransmitter systems influence and are influenced by food intake. Among them, mu-opioid neurotransmission exerts a strong modulatory control over ingestive behavior. Opiate agonists increase and antagonists decrease food intake in food sated rats (Glass et al., 1999; Levine and Billington, 2004). The orexigenic effects of opiate agonists are mediated by mu-opioid receptors located in several brain regions, including the paraventricular nucleus of the hypothalamus, the nucleus of the solitary tract, the central nucleus of the amygdala and the ventral striatum (Bakshi and Kelley, 1993; Giraudo and Billington, 1998; Kotz and Billington, 1997; Stanley et al., 1988). Recent studies suggest that ventral striatum mu-opioid receptors, more than delta- or kappa-opioid receptors, influence feeding by increasing taste hedonics, presumably through the strong functional and anatomical links between the ventral striatum and lateral hypothalamus (Kelley et al., 2002).

As for spontaneous feeding, both unconditioned and conditioned orexigenic effects of morphine vary with the time of day (Bhakthavatsalam and Leibowitz, 1986; Kavaliers and Hirst, 1985; Kavaliers and Innes, 1987; Kelley et al., 2000; Sanger and McCarthy, 1981). These circadian phenomena are associated with daily fluctuations in the primary neuropharmacological substrate of mu-opioid agonists. Both brain opioid peptide levels and receptors have been shown to vary during the light–dark cycle (Naber et al., 1981; Wesche and Frederickson, 1979). For instance, forebrain naloxone binding sites start to increase just before the dark phase and decrease during the light phase of the daily cycle (Naber et al., 1981). However, the mechanism that drives circadian fluctuations in mu-opioid transmission is currently unknown. In the ventral striatum, dopamine

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could serve as one of the local mediator of the daily rhythm generated by the hypothalamic circadian pacemaker. In support of this possibility, ventral striatal dopamine has been shown to influence the behavioral effects of both opiates and opioid peptides (Stinus et al., 1992) and to exhibit up and down variations during the day, with peak dopamine levels occurring during the dark phase (Paulson and Robinson, 1994). However, these findings are only suggestive. They show that there are diurnal variations in dopamine levels and in opiate-induced feeding but they do not provide evidence supporting a link between these two phenomena. The present study was designed to test the hypothesis of a link between ventral striatum dopamine and diurnal variations in opiate-induced feeding in nondeprived animals.

2. Materials and methods

2.1. Subjects

A total of 53 male Sprague–Dawley rats (Iffa-Credo, France), weighing 199–220 g upon their arrival in the laboratory, were individually housed in a colony room maintained at a constant temperature of 23 °C and under a 14–10 h light–dark cycle (lights on from 6:00 to 20:00 h). Rats had ad libitum access to food and water. Rats were acclimated to these housing conditions for at least a week before the experiment began. All animal care was in strict accordance with institutional and international standards of care [UK Animals (Scientific Procedures) Act, 1986; and associated guidelines; the European Communities Council Directive (86/609/EEC, 24 November 1986) and the French Directives concerning the use of laboratory animals (décret 87-848, 19 October 1987)]. Rats were weighed throughout the experiment.

2.2. Dopamine depletion

Dopamine terminals in both the nucleus accumbens and the olfactory tubercles were destroyed as described elsewhere (Rassnick et al., 1993). Briefly, rats were anesthetized with chloral hydrate (6% w/v) and placed in a stereotaxic frame with incisor bar set at +5.0 above the interaural line. The stereotaxic coordinates were as follows (in mm from bregma): AP + 2.3; L ± 1.7; DV − 8.1 for nucleus accumbens and AP + 2.3; L ± 1.7; DV − 9 for olfactory tubercles (Pellegrino et al., 1979). 6-Hydroxydopamine (6-OHDA, HCl, SIGMA ref H-4381, dissolved in isotonic saline containing 0.01% ascorbic acid, final concentration: 4 μg/μl) or vehicle were administered bilaterally through 30-gauge stainless steel cannulae (2 μl into the nucleus accumbens and 1 μl into the olfactory tubercles). Thirty minutes prior to surgery all animals received pargyline (30 mg/kg, SIGMA ref P-5013) to increase the efficacy of the toxin.

2.3. Apomorphine challenge

To asses the efficacy of the lesion before behavioral testing, all rats were challenged with a subthreshold dose of apomorphine (100 μg/kg, s.c., Aguettant laboratory, France) 4 weeks post surgery and locomotor activity was measured, as described elsewhere (Ahmed et al., 1993). In brief, animals were first habituated to activity cages equipped with photoelectric infrared cells during 1 h after which they were challenged with apomorphine. Crossovers (i.e., locomotion through the length of the cage) were recorded for 1 h after drug injection. Only 6-OHDA lesioned rats should respond to a subthreshold dose of apomorphine by dramatically increasing their locomotion (Ungerstedt, 1971).

2.4. Spontaneous and morphine-induced feeding

All rats (sham, $n = 19$; 6-OHDA, $n = 34$) were tested for morphine-induced eating (0.5 mg/kg, s.c.) at different intervals during the light phase of the cycle: early (8:00–10:00), middle (13:00–15:00) and late (18:00–20:00) part of the light phase. Only one subgroup of sham ($n = 6 – 7$) or 6–OHDA ($n = 9 – 10$) animals was tested per interval. No testing took place during the dark phase of the cycle because of high levels of spontaneous eating. The dose of morphine tested was selected because it induced the maximal effect on feeding in a preliminary dose-effect study conducted in the middle of the light phase (0.32 ± 0.07 g/100 g body weight compared to 0.07 ± 0.05 and 0.15 ± 0.05 g/100 g body weight with 0.25 and 1 mg of morphine, respectively; Ahmed and Stinus, unpublished results). The amount of food eaten during each 2-h interval was measured twice, once after vehicle administration (day 1, spontaneous feeding) and once after morphine administration (day 2). Thus, there was a 24-h washout period between injections. For each subgroup, food intake was measured as follows: 1 h before each testing interval, corresponding subgroups were transported in their individual home cages to the experimental room where they were left undisturbed. After acclimatization, all food pellets were removed and replaced by 10 fresh, pre-weighed pellets (≅35 g). Immediately after food replacement, animals were injected with vehicle or morphine. At the end of the 2-h testing period, the total amount of food left (including food spillage) was subtracted to the initial, pre-weighed amount to obtain food intake, in grams. Water was available during the entire testing session but water intake was not recorded. Though 6-OHDA-lesioned rats weighted slightly less than sham-operated animals, they were able to maintain their body weight (427.5 ± 5.7 versus 456.6 ± 8.5), as it is well documented in the literature. Nevertheless, to ensure that this slight initial difference does not influence the results of the study, feeding data were expressed as the amount eaten per 100 g of rat body weight.

2.5. Post mortem neurochemical analysis

At the end of the experiment, lesioned and sham-operated rats were killed by decapitation. Brains were rapidly removed; the nucleus accumbens and the olfactory tubercles were dissected bilaterally at 4 °C and were immediately frozen on dry ice. Dissected structures were stored at −80 °C until biochemical assays. Tissue concentrations of DA, dihydroxyphenylacetic acid (DOPAC), 5-hydroxyindole acetic acid (5-HIAA) and serotonin [5-hydroxytryptamine (5-HT)] were determined by high-performance liquid chromatography (HPLC) coupled with electrochemical detection. Tissue preparation, chromatographical separation and electrochemical detection of biogenic amines were performed as previously described (Bjijou et al., 2002).

2.6. Data analysis

Multifactorial analysis of variance (MANOVA) followed by Newman–Keuls or Student's *t*-test were used for statistical evaluation of behavioral and neurochemical results (Statistica modules, StatSoft Inc., France).

3. Results

Twenty-eight out of thirty-four 6-OHDA-lesioned rats were hypersensitive to apomorphine (i.e., at least 2 standard deviations above the mean value of sham-operated rats [mean = 5.5; 1 SD = 10.5]) and had ventral striatum dopamine contents depleted by more than 90% of control values. Only these rats were considered in the subsequent analysis. The 6-OHDA lesion was specific to dopamine

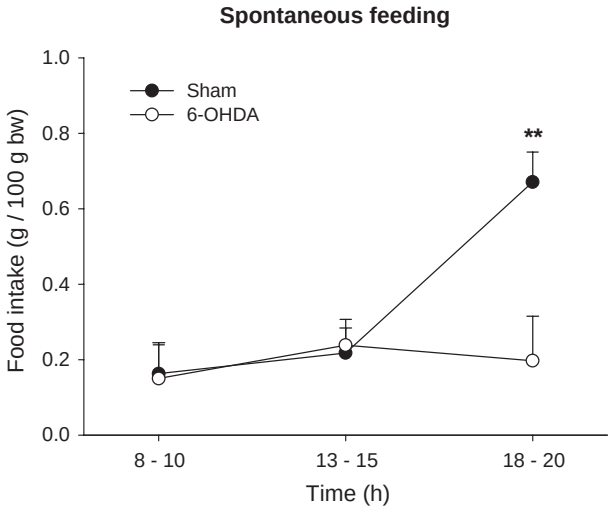

Fig. 1. Spontaneous diurnal variations in food intake. The results are expressed as the amount of food eaten per 100 g of rat body weight (bw). Each point represents the mean ± S.E.M. of 6–10 rats. Significantly different from early morning (**$p < 0.01$). Post-hoc comparisons were performed with the Newman–Keuls test.

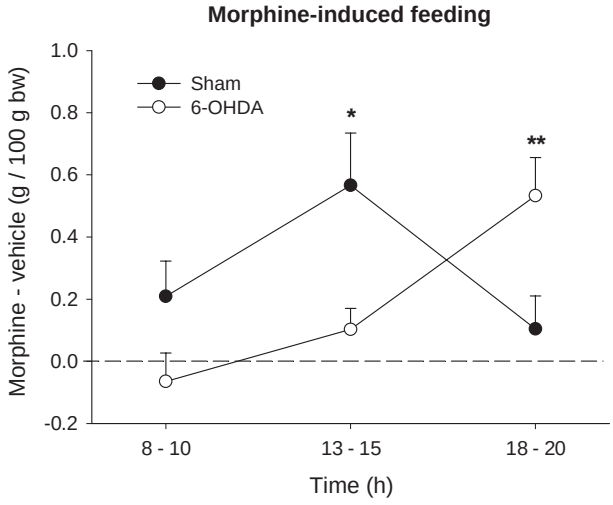

Fig. 2. Net effect of morphine on food intake. Each point represents the mean difference ± S.E.M. from spontaneous food intake, expressed in g per 100 g of rat body weight (bw). Significantly different from zero (*$p < 0.05$ and **$p < 0.01$, respectively, after a Student's *t*-test).

since it produced a large depletion in DOPAC [84%, $F(1,41) = 110.79$, $p < 0.001$] and dopamine contents [93%, $F(1,41) = 375.32$, $p < 0.001$] without significantly decreasing 5HIAA [10%, $F(1,41) = 2.74$, $p = 0.11$, n.s.] and serotonin contents [5%, $F(1,41) = 0.08$, n.s.].

There was a significant group (sham versus 6-OHDA lesioned rats) × daytime (3 time points) × treatment (saline versus morphine) interaction [$F(2,41) = 8.47$, $p < 0.01$] indicating that the diurnal variation in either spontaneous or morphine-induced feeding was modified following ventral striatum dopamine depletion. Further analysis of spontaneous feeding data indicates that in sham-operated rats, food intake increased with the time of day [$F(2,16) = 8.98$, $p < 0.01$], with almost no eating during the early and middle parts of the light phase, and an increase in food intake during the late part of the light phase, just before the beginning of the dark phase (Fig. 1). This time-dependent pattern in spontaneous feeding was abolished in 6-OHDA-lesioned rats. DA-depleted, saline treated animals ate almost no food during the whole day [$F(2,25) = 0.30$, n.s.].

Similarly, the diurnal variation in morphine-induced feeding was significantly altered by ventral striatum dopamine depletion. In sham-operated rats, morphine significantly increased eating above vehicle levels during the middle part but not during the early and late parts of the light phase [$F(2,16) = 4.77$, $p < 0.05$, at 13–15 h]. In contrast, in dopamine-depleted rats, morphine significantly increased eating above vehicle levels only during the late portion of the light phase [$F(2,25) = 10.00$, $p < 0.01$] (data not shown). To better assess the effects of ventral striatum dopamine depletion on the orexigenic effects of morphine, feeding data were expressed as the difference from vehicle levels (Fig. 2). In sham-operated rats, the net effects of morphine were biphasic, with the peak effect occurring during the middle part of the light phase. This temporal

profile was shifted toward the dark phase of the cycle in DA depleted rats. As a result, the maximum recorded effect of morphine appeared at the end of the light phase, just before the beginning of the dark phase.

4. Discussion

The present study shows that morphine-induced eating varies with the time of day, with the maximum effect occurring during the middle part of the light phase. This diurnal profile in the orexigenic effects of morphine is dramatically altered by mesolimbic dopamine depletion. These data suggest that mesolimbic dopamine transmission contributes to the neural processes that normally drive the circadian rhythm of opioid-dependent behavior.

As expected, normal food intake in sham-operated rats is low throughout the day and begins to increase, rather abruptly, in the latter end of the light phase. This increase in feeding before the onset of the dark period probably reflects behavioral anticipation. Dopamine depletion (93%) of the ventral striatum appears to abolish this phenomenon. As a result, dopamine depleted animals virtually eat no food during the light phase. Nevertheless, these rats are able to maintain their body weight close to normal, suggesting that they probably compensate the missed meal late in the day by eating during the dark portion of the light–dark cycle. This interpretation is supported by earlier findings upon the effects of nucleus accumbens dopamine depletions on 24-h feeding. Generally, it has been reported that 24-h food intake is normal and that nucleus accumbens dopamine depleted animals maintain their body weight. More importantly, Koob et al. (1978) also found that nucleus accumbens dopamine depletions does not suppress, and in fact tend to enhance, mash intake in time-restricted sessions, a finding that was later reproduced by others (Evenden and Carli, 1985). Taken together, these findings suggest that accumbens dopamine depletions alter the temporal distribution of feeding during the light–dark cycle, with less eating during the light phase and with more eating during the dark phase.

This conclusion needs, however, to be received with some cautions. First, it is possible that the decrease in diurnal feeding observed after ventral striatum dopamine depletions results from a decrease in general activity (Koob et al., 1981). This nonspecific behavioral mechanism is unlikely, however. Previous studies have demonstrated that nucleus accumbens dopamine depleted rats can eat more, not less, despite being less active than sham rats (e.g., Koob et al., 1978; Evenden and Carli, 1985). Second, Salamone and colleagues have demonstrated that nucleus accumbens dopamine depletions have no effect or modest effects on operant responding for food under different reinforcement schedules (e.g., Cousins et al., 1993; McCullough et al., 1993). Since these studies were conducted in rats during the light part of the light–dark cycle (Salamone, personal communication), they indicate that the effects of nucleus accumbens dopamine depletions on feeding may depend on the specific experimental procedure used to measure food intake and motivation.

The effects of mesolimbic dopamine depletions on spontaneous diurnal variations in food intake reported in the present study are in general agreement with several other previous studies. First, circadian cycles of physiological variables, such as temperature, heart rate and locomotor activity, are profoundly modified in animal models of Parkinson's disease (Ben and Bruguerolle, 2000; Hinneno et al., 1992). Second, under some circumstances, DA indirect agonists, such as stimulant drugs, can durably alter the circadian pattern of feeding behavior in rats (e.g., Giorgetti and Zhdanova, 2000). Together with the present study, this observation suggests that both up- or down-regulation of brain dopamine transmission can alter the circadian pattern of feeding behavior. Finally, brain clock genes, such as *per1* and *per2*, have recently been shown to affect DA-dependent processes, such as cocaine sensitization and reward in mice (Abarca et al., 2002) and flies (Andretic et al., 1999).

Mesolimbic dopamine depletion also disturbs the diurnal variation of morphine-induced eating. In control rats, the orexigenic effects of morphine are biphasic, with the peak effect occurring during the middle part of the light phase. This diurnal pattern is shifted toward the late part of the light phase in dopamine-depleted rats. As a result, the peak effect of morphine is delayed and occurs just before the start of the dark phase of the cycle. This novel observation suggests that ventral striatal dopamine may be part of the neural mechanisms that normally drive the daily cycle of opiate-induced feeding. How mesolimbic dopamine drives diurnal variations in opioid-dependent feeding is unkown at present. Nevertheless, it is possible that dopamine may modulate the synaptic effects of mu-opioid receptor stimulation. In support of this hypothesis, it was recently shown that the control of striatal cholinergic interneurons by opioid receptors (Rada et al., 1996) varies with the time of day and that this diurnal profile depends on basal dopamine levels (Jabourian et al., 2004). Future studies are needed to better delineate the mechanisms by which mesolimbic dopamine influences circadian fluctuations in opioid-mediated behavior.

In a preliminary study, we have shown that the dose-effect function for morphine-induced feeding in sated rats is U-inverted (Ahmed and Stinus, unpublished results): with increasing doses of morphine, the orexigenic effects of the drug first increase and then decrease toward zero. Similar u-inverted curves were previously reported with various opioid agonists and antagonists (Higgs and Cooper, 1998; Morley et al., 1985). Due to the complexity of the factorial design of the present study ($2 \times 2 \times 3$), we chose to test only one dose of morphine (0.5 mg/kg). The selected dose corresponds to the peak of the bell-shaped dose-effect function for morphine-induced eating, as measured in rats during the middle of the light period. This dose should allow

one–at least in theory–to detect any change in the pharmacological effects of morphine across different day times, whether they result from horizontal or vertical changes in the dose-effect function for morphine-induced feeding. However, future studies will be needed to better characterize the effects of the time of day on the whole dose-effect function for the orexigenic effects of morphine and how these circadian effects are regulated by ventral striatal dopamine. In this context, the present study may provide a good preliminary basis in this endeavor.

From a methodological standpoint, the present study suggests that the same behavioral phenomenon can be controlled by different neural mechanisms depending on the time of day. Indeed, as shown here, morphine-induced eating appears entirely dopamine-dependent during the early and middle parts of the light phase but becomes dopamine-independent later on. The time-dependent switch from a dopamine-dependent to a dopamine-independent modulation of opiate hyperphagia suggests that one testing time during the day may not be enough to establish the involvement of a given neurotransmitter system in feeding. In addition, this time-dependent switch in the neural substrates of opiate-induced feeding could represent a significant source of variations between studies that do not test animals during the same period of the day (see also, Kavaliers and Innes, 1987). Future studies will determine whether the time-dependent switch in the neural substrates of morphine-induced feeding can be extrapolated to other opioid-dependent behaviors, such as for instance opiate-induced analgesia and reward.

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