CENTRAL ENHANCEMENT OF TASTE PLEASURE
BY INTRAVENTRICULAR MORPHINE

Peciña, S. and Berridge K. C.

Department of Psychology, University of Michigan,
525 E. University, Ann Arbor, MI 48109-1109, USA

Do centrally-administered opioid agonists stimulate feeding by enhancing the palatability of foods? This hypothesis has been supported by several lines of evidence, including previous ‘taste reactivity’ studies of the influence of systemic morphine on affective (hedonic and aversive) behavioral reactions to taste palatability. The present study examined whether opioid agonists enhance palatability by acting centrally on brain palatability systems. Here we report the effect of intraventricular microinjections of morphine (0, 12, 25, 50 nmols) on hedonic taste reactions to a 0.12 M sucrose solution. The effect on feeding was also assessed in order to determine whether feeding and palatability enhancement are linked, as would be required by the hypothesis that feeding is due to enhanced palatability. Both hedonic taste reactivity patterns and feeding were significantly increased together by morphine administration into the lateral ventricle. We conclude that opioid-induced enhancement of the hedonic palatability of food is a centrally mediated effect. Enhancement of food palatability may be an important psychological route by which intracranial administration of opioid agonists induce feeding.

Key Words: Feeding; Food Intake; Palatability; Taste reactivity; Lateral ventricle; Opioid; Morphine

INTRODUCTION

Opioid neural systems have long been implicated in the mediation of feeding behavior. For example, ingestion of palatable food naturally activates endogenous opioid brain systems [Blass et al., 1993; Blass & Hoffmeyer, 1991; Gosnell, 1987; Lieblich et al., 1983]. Further, both systemic and intracranial administration of opioid agonists stimulate feeding in animals [for reviews see Cooper et al., 1988; Gosnell, 1987; Levine et al., 1985; Morley et al., 1983; Reid, 1985]. Conversely, opioid antagonists suppress intake of palatable foods [Apfelbaum & Mandenoff, 1981; Calcagnotto et al., 1990; Cooper et al., 1988; Gosnell, 1987; Gosnell & Majchrzak, 1990; Levine et al., 1982; Morley, et al., 1983; Reid, 1985; Rockwood & Reid, 1982; Rowland et

Correspondence should be addressed to: Susana Peciña or Kent Berridge
University of Michigan,
Department of Psychology,
Ann Arbor, MI 48109-1109, USA
E-mail: pesu@umich.edu or berridge@umich.edu

1216 8063/95$ 5.00 © 1995 Akadémiai Kiadó, Budapest
al., 1980b; Stapleton et al., 1979]. Thus the degree of activation of brain opioid systems appears correlated with behavioral feeding under a variety of circumstances.

What is the psychological process by which opioid agonists stimulate feeding? Opioid agonists might increase food intake by increasing the perceived palatability of food [Cooper & Gilbert, 1984; Cooper & Kirkham, 1993; Cooper & Turkish, 1981; Evans & Vaccarino, 1990; Gosnell & Majchrzak, 1990; Oomura et al., 1986; Wise & Raptis, 1986], by inhibiting caloric satiety [Kirkham & Cooper, 1988], by reducing neophobia [Gosnell, 1987], or by acting on other processes involved in feeding. These hypotheses are not mutually exclusive, and it is likely that opioids enhance feeding by activating more than one psychological process.

In particular, the hypothesis that opioid-induced feeding is mediated at least in part by enhanced taste pleasure is supported by findings in animal studies that opioid agonists selectively increase the intake of palatable food or saccharin over that of ordinary food or water [Evans & Vaccarino, 1990; Milano et al., 1989; Shor-Posner et al., 1986], and by findings that opioid antagonists attenuate the preference for palatable foods or fluids [Apfelbaum & Mandenoff, 1981; Calcagnetti et al., 1990; Gosnell & Majchrzak, 1990; Levine, et al., 1982; Rockwood & Reid, 1982; Rowland et al., 1980a; Stapleton, et al., 1979]. In this vein, studies of subjective reports of palatability in humans have produced suppression of subjective food pleasantness in some studies [Drewnowski et al., 1992; Fantino et al., 1986], but not in others [Hetherington et al., 1991]. Such discrepancies in findings from studies of human reports are difficult to interpret. They might result in part because human subjective reports of affect may sometimes be distorted by the cognitive processes of interpretation required for their generation [Nisbett & Wilson, 1978]. Under at least some conditions, subjective reports concerning taste pleasantness may fail to accurately reflect basic underlying affective events [Berridge, in press; Mook & Votaw, 1992; Wilson & Schooler, 1991]. For this reason, it is helpful to 'double-check' putative changes in taste palatability induced by opioid agents using a measure, such as affective reactions, that can be applied to animals.

Affective reactions elicited by taste palatability can be measured in animals using the taste-reactivity paradigm developed by Grill and Norgren [Grill & Norgren, 1978b]. The taste reactivity test measures species-typical hedonic and aversive reactions. Hedonic reactions, such as tongue protrusions, paw-licks, etc., are emitted by rats in response to preferred sweet tastes. Aversive reactions, such as gapes, head-shakes, etc., are emitted to bitter tastes. Many manipulations that alter feeding, such as caloric hunger or satiety, sodium hunger, benzodiazepine administration, conditioned taste aversions, brain lesion-induced aphagia, etc., change rat hedonic and aversive reaction patterns in the appropriate direction [Berridge, 1991; Berridge et al., 1984; Berridge & Peciña, 1995; Cabanac & Lafrance, 1990; Grill & Norgren, 1978a; Pelchat et al., 1983; Pfaffmann et
al., 1977]. These manipulations appear to control feeding in part by altering the affective perception of food palatability. A few manipulations change feeding without altering affective reaction patterns, such as electrical stimulation of the lateral hypothalamus and mesotelencephalic dopamine depletion [Berridge & Valenstein, 1991; Berridge et al., 1989]. These manipulations appear to control feeding by acting on a process that is separate from basic affective perceptions of palatability [Berridge, in press]. Thus, the taste reactivity paradigm can be used to discover whether a particular brain system mediates food pleasure and aversion, versus whether it controls feeding by some alternative psychological process [Berridge & Peciña, 1995; Berridge, in press; Grill & Berridge, 1985].

Using the taste reactivity measure of affective reactions, Parker and colleagues found that systemic morphine suppressed aversive reactions to a bitter quinine taste [Parker et al., 1992], and suggested that opioid activation reduced the aversiveness of the bitter taste. To further determine whether opioid activation actually enhances hedonic taste palatability, Doyle et al. examined the effect of systemic morphine (2 mg/kg), a dose that stimulates feeding, upon affective reactions to a sucrose-quinine solution directly infused into the mouth [Doyle et al., 1993]. Doyle et al. [1993] found that morphine selectively enhanced positive hedonic reactions to the bittersweet taste, without enhancing aversive reactions, at a time when the feeding increase would be maximal. The authors concluded from their results that opioid-induced feeding is at least partly mediated by an increase in the hedonic palatability of food.

Do opioid agonists enhance hedonic reactions by acting directly on brain systems that process food palatability? All taste-reactivity studies of opioid agents so far have used only systemic administration. By contrast, elicitation of feeding has been shown to result from central, as well as systemic, administration of opioid agonists. In order to determine whether palatability enhancement is produced by central administration, we investigated whether intraventricular opioid microinjections into the forebrain lateral ventricle, which have been shown to elicit feeding [Gosnell, 1987; Imura et al., 1986; Morley, et al., 1983; Robert et al., 1989], also are sufficient to enhance hedonic reactions to a sweet taste.

**METHODS**

**Subjects**

Seven Sprague-Dawley male rats (from the breeding colony in our laboratory) weighing 300 to 350 grams at the beginning of the experiment were housed in pairs on a 14-10 LD cycle and tested in individual cages. Rats had free access to food and water. All surgery and testing was performed during the light phase of the cycle. Experiments were conducted between 9:00 a.m. and 5:00 p.m.
Cannulae Implantation

Rats were pretreated with Atropine (1 mg/kg) and anesthetized with Ketamine (100 mg/kg) and Rompun (5 mg/kg). Each animal was surgically implanted with a unilateral intracranial cannula (22 gauge) aimed at either the right or the left lateral ventricle. With Bregma and Lambda in the same horizontal plane, skull holes were drilled and the dura was opened. A 22-gauge stainless steel guide cannula was placed using the stereotaxic coordinates from the atlas of Paxinos and Watson [Paxinos & Watson, 1982]. The coordinates used were A-P= -0.8 mm from bregma, L= ± 1.5 mm, and V=3.5 mm from skull surface. Following surgery, a dummy cannula was placed in the guide cannula to prevent occlusion. Rats were allowed to recover for at least one week before testing.

![Lateral ventricle targets. Adapted from Paxinos and Watson [Paxinos and Watson, 1982]](image)

Each rat was also implanted with two bilateral chronic oral cannulae. The cannulae (heat-flared PE 100 tubing) entered the mouth just lateral to the first maxillary molar, ascended lateral to the skull, and exited the head at the dorsal part of the skull, where they were attached to a 19 gauge steel tubing. These cannulae do not interfere with the normal eating behavior of the animal, and they allow the direct infusion of solutions into the mouth. All cannulae were anchored with skull screws and acrylic cement.

**Morphine doses and stimuli**

Morphine sulfate (Sigma) was dissolved in bacteriostatic physiological saline. The order of drug administration (0, 12, 25, 50 nmols) was randomized across animals except for the first and the last injections which were always vehicle alone (0 nmols morphine). Morphine doses were administered in a volume of 1.0 μl, and were chosen from the existing literature on morphine-induced stimulation of feeding and from pilot studies performed in our laboratory. The taste stimulus used for oral infusions was a 0.12 M sucrose solution, given in a 1 ml volume. The palatable food used for the feeding test was a cereal mash (1g commercial baby cereal/3 ml of water) given ad lib throughout the intake test.
Habituation

During the 10-day recovery period after surgery, rats were supplied with cereal mash in their home cages to reduce neophobia. In addition, during the last five days of this period, rats were mock-injected each day and exposed to the exact sequence of events that would later be exposed to during the real experiment. The purpose of this initial habituation phase was to familiarize animals with the experimental paradigm and ensure that stable baseline levels for both feeding and taste reactivity would be attained by the time microinjections began.

Feeding Tests

Testing began 10 days after surgery and continued every other day for 10 days. Rats were taken in individual cages to the testing room and food pellets were removed from the top of the cages. Rats were intracranially injected with either morphine sulfate or the saline vehicle, and left undisturbed for three hours. On each test day, a rat received either morphine or vehicle in a counterbalanced order. Since previous reports on opioid-induced feeding suggested that stimulation of feeding is greatest around two to three hours after the drug injection [Stanley, Lanthier, and Leibowitz, 1989; Woods and Leibowitz, 1985], both taste reactivity and feeding tests were administered in that order beginning three hours after the microinjection.

Taste reactivity test

Three hours after administration of the drug, one of the rat’s oral cannulae was connected to a stimulus delivery tube, consisting of PE 50 tubing attached to PE 10 fine tubing. The rat was then placed in a cylindrical test chamber. After ten minute habituation period, a 1 ml volume of the 0.12 M sucrose solution was infused into the mouth of the animal at a constant rate (1 ml/min) during one minute. The behavior of the rat was videotaped during testing via a mirror mounted beneath the transparent floor, which allowed the camera to zoom up so that the face and the mouth of the rat filled the entire screen. The entire taste reactivity procedure took approximately 12 minutes.

Videoanalysis of taste reactivity records

The videotaped behavior of each rat was scored (frame-by-frame to 1/10 speed) for the occurrence of hedonic, aversive, and neutral reactivity components (see, [Berridge and Peciña, 1995; Grill and Berridge, 1985] for a discussion of taste reactivity analysis and taste reactivity components and classification). Hedonic actions were paw licking; lateral tongue protrusions; non-rhythmic protrusion past the lip followed by forward extension, lasting about 160 ms; and tongue protrusions, rhythmic tongue protrusion along the midline, with a cycle length of roughly 160 ms. Neutral components were rhythmic mouth movements at the same or lower frequency as rhythmic tongue protrusion; and passive dripping, the passive leaking of fluid from the mouth. Aversive actions were gaps, large openings of the mandible and retraction of the lower lips lasting about 125 ms; chin rubbing, bringing the mouth in direct contact with the floor and projecting the body forward; face washing, either a single wipe over the face with the paws or a bout of several wipes: forelimb flails, shaking of the forelimb with a frequency of greater than 60 HZ; head shaking, at greater than 60 HZ; and paw treading, planting of the limbs on the floor and alternating forceful strikes forward and back; and rapid locomotion around the chamber.
Videotapes were scored by an observer who was blind to microinjection condition in a slow motion analysis at 1/30 to 1/10 normal speed. For the purpose of quantifying the number of responses emitted, discrete actions such as lateral tongue protrusions, gapes, chin rubs, forelimb flails and head shaking, and bouts of face washing, paw treading, and locomotion were counted each time they occurred. Continuous actions that typically persist for relatively long periods were counted as follows: paw licks, mouth movements, passive dripping, face washing and locomotion were counted in 5 sec. bins (any occurrence of these behaviors up to 5 sec. in duration was counted as a single occurrence). Rhythmic tongue protrusions were scored in the same way in 2 sec. bins.

Verification of the cannulae placement

At the completion of the experiment, rats were deeply anesthetized with sodium pentobarbital (5 mg/kg). India ink was microinjected into the lateral ventricle, using the same procedure as for morphine. The rats were perfused intracardially ten minutes later. The brains were removed and cut midsagitally. The presence of ink in the lateral ventricle verified the correct location of the ventricular cannulae.

Statistical Analysis

The results were evaluated for statistical significance by a one-way ANOVA for repeated measures with dose of morphine sulfate as the main factor, and by post hoc Newman-Keuls tests for paired comparisons.

RESULTS

Feeding

Microinjections of morphine sulfate administration into the lateral ventricle significantly stimulate feeding, F(3, 24)= 3.02, p<0.05 (Fig.2). Individual post-hoc comparisons of the average amount of baby cereal ingested showed that morphine sulfate significantly stimulated feeding at all the doses tested: 12 nmols (p<0.05 Newman-Keuls), 25 nmols (p<0.01) and 50 nmols (p<0.05). The intermediate dose used, 25 nmols, proved to be the most effective one for increasing intake. Under the effects of this dose, animals ingested nearly twice as much cereal mash as they did after the vehicle alone.

Taste Reactivity

Microinjections of morphine into the lateral ventricle significantly enhanced the number of hedonic responses elicited by the 0.12 M sucrose solution, F(3,18)=3.24, p<0.05; (Fig.3). Although morphine appeared to increase the number of hedonic reactions at all the doses tested, a Newman-Keuls comparison indicated that only the intermediate dose, 25 nmols, significantly increased the number of hedonic reactions over baseline levels.
Central opioid enhancement of palatability

Fig. 2: Lateral ventricle microinjections of morphine enhance feeding. Consumption in a 1-h voluntary intake test of cereal mash after intraventricular morphine (ANOVA, p < 0.05)

Fig. 3: Lateral ventricle microinjections of morphine enhance hedonic taste reactions. Hedonic taste reactions elicited by a 0.12 M sucrose solution after intraventricular morphine (ANOVA, p < 0.05)
DISCUSSION

Microinjections of morphine into the lateral ventricle stimulated intake of a cereal mash and simultaneously enhanced hedonic affective reactions emitted in response to a 0.12 M sucrose solution. These results support the hypothesis that opioid agonists stimulate feeding behavior by enhancing the hedonic perception of food palatability. These results provide the first direct evidence that opioid enhancement of hedonic taste reactivity is a central effect of the drug on brain systems. Morphine appears to activate brain systems that process hedonic taste palatability. The relative contribution of particular opioid receptor subtypes to palatability enhancement remains to be determined.

Of the doses tested (12, 25 and 50 nmols), the most effective dose for feeding enhancement was 25 nmols. Rats ingested almost twice the amount of cereal mash after this dose as they did after vehicle control microinjections. The same 25 nmol dose also produced the strongest enhancement of taste pleasure, as assessed by hedonic reaction patterns. Hedonic reactions to 0.12 M sucrose were nearly doubled by this dose compared to vehicle control levels. The similar magnitude of the effects on intake and on hedonic taste reactivity potentiation suggests that palatability enhancement may mediate the stimulation of feeding.

The anatomical site responsible for opioid-induced enhancement of taste pleasure is an important question that remains to be answered by future studies. Many different brain sites have been shown to be able to support opioid-induced feeding. For example, food intake is increased by opioid microinjections into the ventral tegmentum, the paraventricular and ventromedial nuclei of the hypothalamus, the nucleus accumbens, and the amygdala [Badan et al., 1995; Bakshi & Kelley, 1993a; Bakshi & Kelley, 1993b; Evans & Vaccarino, 1990; Gosnell, 1988; Hamilton & Bozart, 1988; Jenck et al., 1986; Leibowitz & Hor, 1982; Majeed et al., 1986; McLean & Hoebel, 1983; Mucha & Iversen, 1986; Nencini & Stewart, 1990; Noel & Wise, 1993; Stanley et al., 1989]. Whether all of these structures are responsible for palatability enhancement, or only some of them, remains to be seen. Although it is possible that all sites which support feeding would also enhance hedonic palatability, it is equally possible that some sites stimulate feeding via other functions. For example, opioid agents have been reported to modulate hypothalamic neuronal responsiveness to glucose [Aou et al., 1984; Karadi et al., 1992; Nishino et al., 1987; Ono et al., 1982; Ono et al., 1985; Oomura et al., 1974]. Such an effect might or might not alter hedonic reactions to taste, since at least some brain manipulations that stimulate feeding increase intake without enhancing palatability [Berridge, in press; Berridge & Valenstein, 1991].

Although anatomical sites that support opioid-induced feeding provide the most likely candidates for the opioid substrates of palatability, it is also possible that opioid modulation of palatability might occur earlier in the processing of the taste signal itself. Opioid systems do exist in the primary gustatory pathway: for example, in the nucleus of the solitary tract (first relay nucleus) and in the pontine parabrachial nucleus (second relay nucleus) [Carr et al., 1991; Herman & Novin, 1980; Mansour et al., 1987]. Benzodiazepine-induced hedonic
Central opioid enhancement of palatability

Enhancement, which acts via GABA_A neurotransmitter systems, has already been shown to act via brainstem systems [Berridge, 1988; Peciña & Berridge, 1992; Peciña & Berridge, submitted]. Although this may not be directly relevant to opioid-induced hedonic enhancement, it at least lends plausibility to the hypothesis that brainstem substrates are capable of mediating changes in palatability induced by pharmacological agents.

Future studies, which combine cannulae mapping with taste reactivity tests, will be needed in order to discover which among these various candidate brain structures contains the site(s) responsible for the central enhancement of hedonic taste palatability by opioid agonists. In any case, we can conclude from the present results that opioid agonists may stimulate feeding by enhancing the perceived palatability of food, and that palatability enhancement results directly from the action of opioid agonists on central brain systems.

Acknowledgment

This research was supported by a Rackham faculty grant from the University of Michigan and by NSF (IBN B19933) and NIDA (DA 08461) grants awarded to K.B.

REFERENCES


