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Endogenous opioids are necessary for benzodiazepine palatability enhancement: Naltrexone blocks diazepam-induced increase of sucrose-'liking'

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Abstract

Opioid agonists and benzodiazepine agonists each increase food intake. Both also increase hedonic 'liking' reactions to sweet tastes in rats. Do opioids and benzodiazepines share overlapping mechanisms of hedonic impact? Or are benzodiazepine and opioid effects on hedonic impact mediated by independent mechanisms? The present study examined whether blockade of opioid receptors prevents benzodiazepine-induced enhancement of taste palatability, as assessed by the affective taste reactivity test. Rats were implanted with oral cannulae, and prior to an oral infusion of bittersweet quinine–sucrose solution, all received i.p. injections of either vehicle, or diazepam alone (5 mg/kg diazepam+0 mg/kg naltrexone), naltrexone alone (1 mg/kg naltrexone+0 mg diazepam), or both diazepam plus naltrexone (5 mg/kg diazepam+1mg/kg naltrexone). Videotaped hedonic ('liking') and aversive ('disliking') orofacial reactions elicited by sucrose/quinine taste were compared across drug conditions. Diazepam administration alone more than doubled hedonic 'liking' reactions to the bittersweet taste, while reducing 'disliking' in half, compared to vehicle levels. Naltrexone by itself had little effect on taste-elicited affective reactions, and only marginally increased aversive gapes. However, naltrexone completely blocked diazepam's enhancement of positive hedonic 'liking' reactions, and naltrexone similarly disrupted diazepam-reduction of aversive 'disliking' taste reactions. These results indicate that endogenous opioid neurotransmission may be crucial to benzodiazepine enhancement of hedonic 'liking' for natural taste reward.

Keywords: Benzodiazepine; Opioid; GABA; Diazepam; Naltrexone; Naloxone; Taste; Food intake; Reward; Hedonic; Palatability; Parabrachial nucleus; Nucleus accumbens; Mesolimbic; Brainstem; Limbic system; Anxiolytic

1. Introduction

A thorough understanding of the behavioral and neurochemical determinants of appetite and ingestive behavior is essential to the study of food preferences and consumption. Two neurochemically defined systems identified in the brain which have been shown to have particular importance in the controls of eating behavior and food reward are the opioid and the $GABA_A$-benzodiazepine systems (Berridge and Peciña, 1995; Bodnar, 2004; Cooper, 2004). Stimulation of benzodiazepine receptors leads to increases in food consumption in rodent and primate species (Wise and Dawson, 1974; Cooper et al., 1985; Foltin et al., 1989; Clifton and Cooper, 1996), including humans (Haney et al., 1997; Evans et al., 1999). Similarly, activation of central opioid receptors increases food consumption (Gosnell and Levine, 1996; Kelley et al., 2002; Will et al., 2003), and opioid peptides may have an important role to play in the control of human ingestive behavior (Yeomans and Gray, 2002). Importantly, however, both of these central neurochemically defined systems appear to share a hedonic mechanism which underlies their effects on food consumption: in both cases considerable evidence indicates that they exert positive effects to enhance the hedonic impact of taste

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palatability and related rewards (Treit and Berridge, 1990; Parker et al., 1992; Doyle et al., 1993; Cooper and Higgs, 1994; Bodnar et al., 1995; Clarke and Parker, 1995; Drewnowski et al., 1995; Parker, 1995; Rideout and Parker, 1996; Levine and Billington, 1997; Yeomans and Gray, 1997; Higgs and Cooper, 1998; Berridge, 2000; Peciña and Berridge, 2000; Söderpalm and Berridge, 2000; Ferraro et al., 2002; Kelley et al., 2002; Berridge, 2003; Koob, 2004; Levine and Billington, 2004). In other words, stimulation of either opioid or benzodiazepine receptors are hypothesized to induce animals to 'like' the taste of food more, as part of an extended neuropsychological mechanism that makes them 'want' to eat more food. The question arises as to whether or not there is a common mechanism that mediates the effects of opioids and benzodiazepines on food ingestion and, specifically, on taste liking. Specifically, we ask whether opioid neurotransmission is needed for the mechanism by which benzodiazepines increase food palatability.

There is evidence that indicates benzodiazepines may indeed interact with endogenous opioid peptides in their effects on reward and motivation, including hyperphagia (Billingsley and Kubena, 1978; Stapleton et al., 1979; Cooper, 1980; Koob et al., 1980; Birk and Noble, 1981; Cooper, 1983; Naruse et al., 1988; Higgs and Cooper, 1997; Kelley et al., 2000; Navarro et al., 2004). Benzodiazepine-induced hyperphagia can be selectively blocked by opioid receptor antagonists such as naloxone and naltrexone (Stapleton et al., 1979; Birk and Noble, 1981; Cooper, 1983; Naruse et al., 1988; Higgs and Cooper, 1997; Kelley et al., 2000). At a behavioral level, these data on eating suggest that benzodiazepines may also magnify the hedonic impact of taste by activation of endogenous opioid peptides in the brain. For example, benzodiazepine modulation of BZD/GABA receptors on hedonic-related neurons might lead indirectly to activation of opioid neurons downstream, or benzodiazepine and opioid receptor effects might interact on particular neurons that are crucial to palatability enhancement. Whatever the anatomical or neuronal basis of interaction, benzodiazepine enhancement of taste hedonic impact may at least require permissive co-activation of endogenous opioid receptors somewhere in the brain. To date, this hypothesis has not been investigated directly.

The hypothesis predicts that administration of an opioid antagonist, like naltrexone, would block the increased hedonic palatability of taste stimuli that is normally caused by a benzodiazepine agonist such as diazepam. If this prediction were to be upheld, then it would indicate that benzodiazepine receptor-mediated increases in taste liking involves a critical endogenous opioid link in the brain systems that enhance hedonic impact. If it were disconfirmed, then it would indicate that benzodiazepine and opioid brain mechanisms for hedonic enhancement are independent. In that case, benzodiazepine-induced enhancement of taste palatability would proceed without further mediation by endogenous opioids, regardless of any interaction between the opioid and benzodiazepine systems controlling food intake.

Sweet and bitter tastes elicit valenced positive and negative patterns of taste reactivity in rats. These affective 'liking' and 'disliking' orofacial reactions are homologous to taste-elicited affective facial expressions of human infants, great apes and Old and New World monkeys (Grill and Norgren, 1978; Steiner, 1979; Berridge, 2000; Steiner et al., 2001; Berridge, 2003). Taste reactivity patterns therefore provide useful objective indicators of palatability or hedonic evaluations of taste stimuli, without requiring knowledge of unobservable subjective states. In the present experiment we have used the taste reactivity paradigm to investigate the question whether the enhancement of positive hedonic taste reactivity caused by diazepam is blocked by concurrent naltrexone-induced antagonism of opioid activity.

The results obtained in the study provide support for the view that benzodiazepine liking effects require activation of endogenous opioid brain systems as a necessary link in the neural pathways that amplify the positive hedonic impact of taste.

2. Method

2.1. Subjects

Eighteen male Sprague–Dawley rats (weighing 200–350 g at time of surgery) were group-housed on a 12;12 h light/dark cycle. Food pellets (Purina rat chow) and water were always available ad libitum. Procedures were approved by the University of Michigan Institutional Review Committee for the use of Animal Subjects, following guidelines of the current National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Surgery

Rats were pretreated with atropine sulfate (0.1 ml, i.p.) and penicillin (aquacillin; 45,000 U, i.m.), and anesthetized with a mixture of ketamine HCl (100 mg/kg, i.p.) and Rompun (80 mg/kg, i.p.). Each rat was bilaterally implanted with two chronic oral cannulae (heat-flared PE-50 tubing) for subsequent oral infusions and taste reactivity tests. Cannulae allowed for taste infusions into the mouth in subsequent taste reactivity testing. Oral cannulae 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. Cannulae were affixed firmly to the dorsal skull via cranial screws and acrylic cement. These cannulae allow the direct infusion of solutions into the mouth for taste reactivity tests, and do not interfere with normal eating behavior.

2.3. Drugs for behavioral testing

To allow within-subject comparison of effects, each rat was tested with all 4 drug/vehicle combinations (drug order

counterbalanced across rats) on 4 consecutive tests spaced 72 h apart. On each test day, a rat received one of 4 combinations of 2 i.p. injections in the half-hour immediately prior to taste reactivity testing: a) vehicle, vehicle; b) diazepam, vehicle; c) diazepam, naltrexone; d) vehicle, naltrexone. Naltrexone (1 mg/kg, i.p.) or its vehicle was administered 25 min prior to behavioral testing. Diazepam (5 mg/kg, i.p.) or its vehicle was injected 10 min prior to testing. Drugs and vehicles were: diazepam (Abbott Laboratories, North Chicago) dissolved in 40% propylene glycol, 5% sodium benzoate, 5% benzoic acid, 1.5% benzyl alcohol, and 48.5% deionized water. Naltrexone (Sigma Chemical Co., St. Louis) was dissolved in sterile isotonic saline. To acclimate rats to sedative effects of diazepam before the experiment began, animals also received diazepam injections (5 mg/kg, i.p.) once a day for 4 days prior to the first behavior test.

2.4. Taste reactivity test

After injections, one of each rat's oral cannulae was connected to a fluid delivery line (PE-50 tubing attached to a PE-10 nozzle), and the rat was placed into a transparent test chamber. A mirror positioned beneath the transparent floor of the chamber reflected a view of the rat's face and mouth into the close-up lens of a video camera to permit videotaping of affective facial and body reactions. A 0.75 ml volume of a mixed solution of 7% sucrose and .01% quinine HCl was infused into the rat's mouth through the oral cannula by a syringe pump over a period of 45 s (at a rate of 1 ml/60 s). This bittersweet mixture typically elicits a moderate number of both hedonic and aversive reactions. These moderate levels of positive/negative affective reactions should be capable of being modulated either upwards or downwards by drug effects on palatability. In order to bracket the time course of drug effects over the hour after injections, each rat received two separate taste reactivity tests on each day: one at 25 min after its last injection, and another at 40 min. Affective reactions elicited by the taste solution were videotaped for subsequent analysis.

2.5. Slow-motion video scoring and analysis

Affective reaction patterns were scored in slow motion video analysis (1/30 s frame-by-frame to 1/10 actual speed). Positive hedonic reactions included rhythmic midline tongue protrusions, lateral tongue protrusions, and paw licking. Aversive reaction patterns included gapes, headshakes, forelimb flails, face washing, chin rubs, and paw treading. Neutral reactions (less strongly linked to hedonic/aversive evaluations) were rhythmic mouth movements and passive drip of the solution. In order to ensure that every component could make a roughly equal magnitude contribution to the final hedonic or aversive scores, several reactions that occur in continuous bouts were scored in time bins (Berridge, 2000). These components usually emitted in repetitive bouts were: rhythmic tongue protrusions, chin rubs, and paw treading were scored in 2 s bins (continuous repetitions within 2 s scored as 1 occurrence; repetition persisting 2–4 s was scored as a second occurrence, etc.). Components that typically have even longer bout durations, such as paw licking, rhythmic mouth movements, passive drip, and face washing were similarly scored in 5 s bins. Other reactions that can occur as single behaviors were scored as separate occurrences (lateral tongue protrusions, gapes, headshakes, forelimb flails). Finally, a positive hedonic 'liking' total was compiled by adding scores for rhythmic tongue protrusions, lateral tongue protrusions, and paw licks. A negative aversive 'disliking' total was compiled by adding scores for gapes, headshakes, forelimb flails, paw treading, and chin rubs. 'Liking' and 'disliking' total scores were compared across drug combination conditions, and analyzed by 2-way repeated measures ANOVA (drug × time) for hedonic, aversive, and neutral reactions separately. Where significant differences were found, further post hoc analyses were conducted by Bonferroni tests.

3. Results

3.1. Total hedonic reactions

Positive affective or 'liking' reactions elicited by oral sucrose–quinine infusions were altered by drug treatment (ANOVA (drug) $F(3,142)=6.466$, $p<.001$). Specifically, prior diazepam administration significantly increased positive hedonic reactions over >200% above vehicle levels (vehicle+diazepam vs. vehicle+vehicle: Bonferroni test $p<.05$; Fig. 1). This 'liking' enhancement was completely blocked, however, if diazepam was preceded by naltrexone administration: after combined naltrexone+diazepam, hedonic reactions to the bittersweet taste were no longer different from vehicle control levels (Bonferroni, n.s.), and were lower than after diazepam alone (Bonferroni $p<0.01$). Naltrexone administration by itself had no significant effect on hedonic reactions compared to vehicle (naltrexone+vehicle vs. vehicle+vehicle: Bonferroni, n.s.), even though naltrexone had blocked the diazepam-induced increase. All these effects were identical at both the 25 min post-injection and 40 min post-injection taste reactivity tests, and there were no differences across the two times of test (ANOVA (time) $F(1, 142)=0.181$; $p=$n.s.).

Specific taste reactivity components were reliably increased by diazepam administration: rhythmic tongue protrusions (ANOVA (drug) $F(3, 143)=2.941$, $p<.05$) and non-rhythmic lateral tongue protrusions (ANOVA $F(3, 143)=5.25$, $p<.01$). Both of these hedonic reaction components were enhanced over vehicle levels by diazepam alone (each Bonferroni $p<.05$; Fig. 2). Naltrexone pretreatment prevented the diazepam-induced enhancement of both of

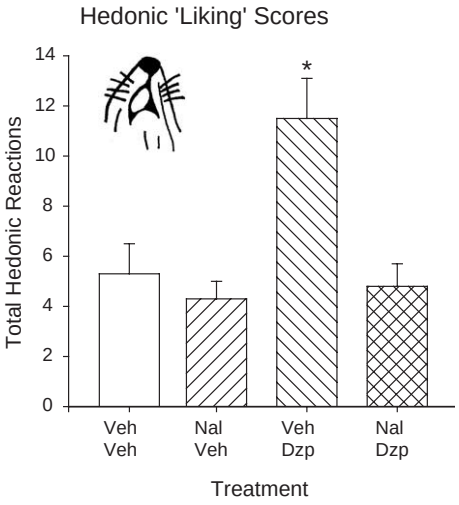

Fig. 1. Positive hedonic reactions. Total number of positive hedonic or 'liking' reactions elicited by taste of sucrose/quinine solution after drug combinations: Veh/Veh=vehicle+vehicle (control condition); Nal/Veh=naltrexone+vehicle (naltrexone alone condition); Veh/Dzp=vehicle+diazepam (diazepam alone condition); Nal/Dzp=naltrexone+diazepam (combination condition; mean+SEM in each case). Star denotes statistically significant difference from vehicle.

these components, and reduced their level to below the diazepam alone level (Bonferroni $p<.5$ each).

3.2. Total aversive reactions

Aversive 'disliking' reactions to the bitter component of sucrose–quinine infusions were conversely altered by prior drug administration, usually in the opposite direction from 'liking' reactions above (ANOVA $F(3, 142)=7.21$, $p<.001$; Fig. 3). Diazepam administration by itself decreased aversive reactions elicited by the bittersweet taste to a level that was only 25% of vehicle (Bonferroni $p<.01$). Pretreatment with naltrexone prior to diazepam cut the benzodiazepine suppression of aversion in half (Bonferroni, $p<0.05$), leaving the number of aversive reactions midway between the low level produced by diazepam alone and the higher level observed after vehicle l (Bonferroni, $p<0.05$). Naltrexone administration by itself did not cause the total number of aversive reactions to rise above vehicle level (Bonferroni, n.s.). Overall, slightly more aversive reactions were elicited during the taste reactivity test conducted 10 min post-injection than at the test conducted 25 min post-injection, ($F(1, 142)=5.64$, $p<.05$). However, that decline over time did not differ between vehicle and drug treatment groups, nor interact with the drug effects described above, which were as described at both times.

3.3. Aversive components

Specific aversive components suppressed by benzodiazepine treatments were gapes ($F(3, 142)=4.868$, $p<.01$) and forelimb flails ($F(3, 142)=2.92$, $p<0.05$). Diazepam administration reduced both gapes and forelimb flails below their vehicle levels (Bonferroni, $p<.05$ each; Fig. 4). Both components also remained reduced from vehicle after combined diazepam plus naltrexone ($p<0.05$). Finally, administration of naltrexone alone failed to produce a

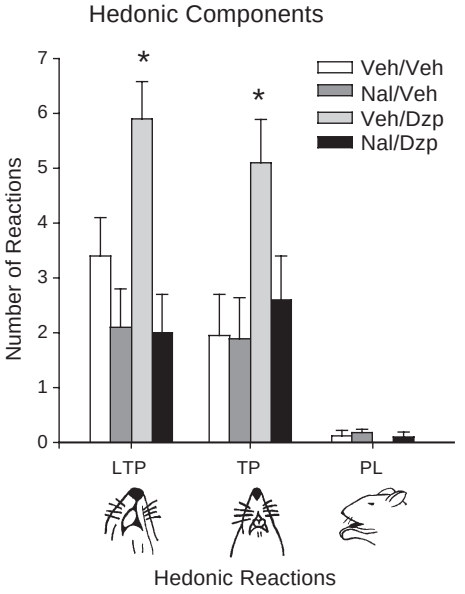

Fig. 2. Negative aversive reactions. Total number of negative aversive or 'disliking' reactions elicited by taste of sucrose/quinine solution after drug combinations: Veh/Veh=vehicle+vehicle (control condition); Nal/Veh=naltrexone+vehicle (naltrexone alone condition); Veh/Dzp=vehicle+diazepam (diazepam alone condition); Nal/Dzp=naltrexone+diazepam (combination condition; mean+SEM in each case). Stars denote statistically significant difference from vehicle.

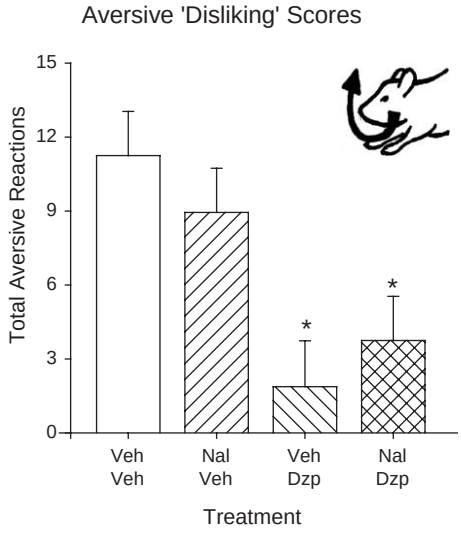

Fig. 3. Specific hedonic reaction components. Mean (+SEM) hedonic reaction components elicited by sucrose/quinine solution: PL=paw lick, LTP=lateral tongue protrusion; TP=rhythmic midline tongue protrusion. Veh/Veh=vehicle+vehicle (control condition); Nal/Veh=naltrexone+vehicle (naltrexone alone condition); Veh/Dzp=vehicle+diazepam (diazepam alone condition); Nal/Dzp=naltrexone+diazepam (combination condition). Stars denote statistically significant difference from vehicle.

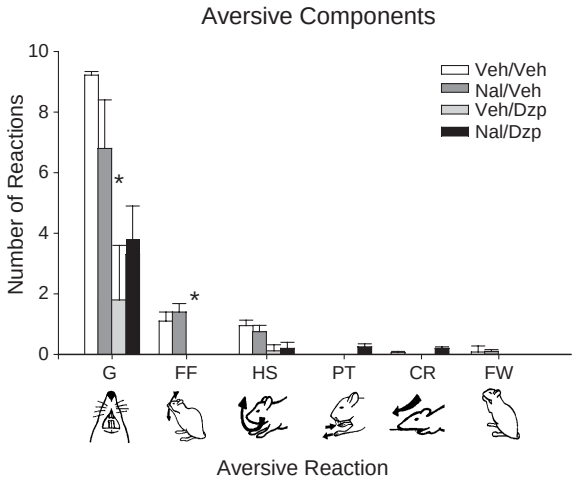

Fig. 4. Specific aversive reaction components. Mean (+SEM) aversive reaction components elicited by sucrose/quinine solution: G=gape, FF=forelimb flail, HS=headshake, PT=paw tread, CR=chin rub; FW=face wash. Veh/Veh=vehicle+vehicle (control condition); Nal/Veh=naltrexone+vehicle (naltrexone alone condition); Veh/Dzp=vehicle+diazepam (diazepam alone condition); Nal/Dzp=naltrexone+diazepam (combination condition). Stars denote statistically significant difference from vehicle.

significant change in any aversive components. Lack of a naltrexone effect on aversive reactions in the first minute of a taste may not be surprising, given that previous studies have reported failure of naltrexone at comparable doses to increase aversive reactions to a similar 1-min taste infusion (Parker et al., 1992; Ferraro et al., 2002), even though naltrexone has been reported to increase aversive reactions later during a longer 10-min taste infusion (Parker et al., 1992).

4. Discussion

The present results confirm previous findings that diazepam and other benzodiazepines enhance hedonic taste palatability as measured by rodent taste reactivity (Treit et al., 1987; Berridge, 1988; Treit and Berridge, 1990; Gray and Cooper, 1995; Parker, 1995; Clifton and Cooper, 1996; Peciña and Berridge, 1996; Söderpalm and Hansen, 1998; Manabe et al., 2001). Significantly, they indicate for the first time that benzodiazepine-induced hedonic enhancement of 'liking' reactions to sucrose requires the concomitant activation of endogenous opioid transmission. Diazepam increased hedonic 'liking' reactions to sucrose–quinine by more than 200% above vehicle levels (e.g. rhythmic tongue protrusions), and conversely decreased aversive 'disliking' reactions to about 25% of vehicle levels (e.g. gapes). Prior treatment with the opioid receptor antagonist, naltrexone, completely blocked diazepam's positive enhancement of 'liking' reactions to sweet taste, and markedly reduced diazepam's suppression of aversive 'disliking' reactions to bitter. This occurred at a dose level of naltrexone which, when given alone, had little or no effect on either 'liking' or 'disliking' reactions to a bittersweet taste infusion that lasted 1 min.

Hence, the blockade of endogenous opioid systems by naltrexone prevented the increase in taste positive hedonic impact caused by diazepam and reduced the simultaneous diazepam-induced decrease in aversion. Our findings suggest therefore that the neural mechanisms by which benzodiazepines increase taste palatability depend at least in part on the activation of endogenous opioid brain circuits, consistent with the known interaction of benzodiazepines with opioids in modulating food intake and other motivational effects (Billingsley and Kubena, 1978; Stapleton et al., 1979; Koob et al., 1980; Birk and Noble, 1981; Cooper, 1983; Jackson and Sewell, 1985; Naruse et al., 1988; Higgs and Cooper, 1997).

The specific features regarding the relevant receptor subtypes and the neuroanatomical localization of the interactions between diazepam and naltrexone in modulating hedonic impact remain to be determined. Opioid modulation of benzodiazepine anxiolytic effects has been suggested to involve primarily μ and κ opioid receptors (Billingsley and Kubena, 1978; Koob et al., 1980; Agmo and Belzung, 1998). The use of selective opioid receptor antagonists would be appropriate in future taste reactivity studies to establish receptor subtype selectivity for liking effects. Several studies have indicated that one neuroanatomical location where benzodiazepines increase 'liking' reactions to sucrose and enhance food intake is in the lower brainstem, especially in or around the pontine parabrachial nucleus (Berridge, 1988; Higgs and Cooper, 1996a,b; Peciña and Berridge, 1996; Yamamoto et al., 1998; Söderpalm and Berridge, 2000). In addition, opioid neurotransmission in the parabrachial nucleus has been shown to modulate food intake (Moufid-Bellancourt and Velley, 1994; Wolinsky et al., 1996; Nicklous and Simansky, 2003; Wilson et al., 2003). Future taste reactivity studies could be directed to investigating if opioid neurotransmission in the parabrachial nucleus also modulates liking reactions to sucrose.

A number of investigators have reported opioid effects on food intake for a number of other brain structures, including the nucleus accumbens, ventral striatum, amygdala, ventral pallidum, hypothalamus, ventral tegmental area and nucleus of the solitary tract (Bakshi and Kelley, 1993; Giraudo et al., 1998; Glass et al., 2000; Zhang and Kelley, 2000; Koob et al., 2003; Smith and Berridge, 2003; Cooper, 2004; Hanlon et al., 2004; Kelley, 2004; Levine and Billington, 2004).

So far, identification of the location of opioid receptors that control taste 'liking' reactions in taste reactivity studies have focused on forebrain structures, including the nucleus accumbens shell and ventral pallidum (Peciña and Berridge, 2000; Smith and Berridge, 2003). It is unknown at present whether the interaction between opioid and benzodiazepine hedonic effects indicated here involves simultaneous actions on neurons in the same brain structure, or instead whether

activation of benzodiazepine receptors on neurons in one structure (e.g. parabrachial nucleus) triggers a chain of neural events that requires opioid receptor activation of neurons downstream in a different structure (e.g., nucleus accumbens) to magnify the hedonic impact of a taste reward. Future studies that combine location-specific microinjections with taste reactivity measures will be needed to determine the specific neuroanatomical bases for the opioid/benzodiazepine interaction in the controls of taste liking reactions which we have demonstrated here.

In conclusion, endogenous opioid neurotransmission may be crucial to the benzodiazepine-induced enhancement of hedonic impact for natural taste reward. Our results indicate that the activation of endogenous opioid systems may be a necessary component of the neural mechanisms through which benzodiazepines enhance taste palatability, as assessed by enhanced 'liking' reactions to sweet taste. Moreover, there would appear to be an integrated neural system, possibly acting across several levels of the neuroaxis, which can be modulated by benzodiazepine and opioid receptor activation to enhance the hedonic impact of tastes. Such a system may feature importantly in the central controls of food intake.

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