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Additive satiety-delaying effects of capsaicin-induced visceral deafferentation and NMDA receptor blockade suggest separate pathways

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Abstract

Both ablation of visceral afferents and blockade of NMDA receptor-mediated glutamatergic transmission by MK-801 result in overconsumption of sucrose solution and other food, apparently by interrupting visceral signals and thus delaying satiation. If these two manipulations act on the same pathway, namely, the propagation of vagal afferent signals to NTS neurons, their effects would be expected to be non-additive. To test this hypothesis, two groups of rats — one with prior systemic capsaicin ($n=11$) and one with vehicle treatment ($n=10$) — were trained to drink 15% sucrose solution after 15 h food deprivation every 3–4 days, and then injected with MK-801 (100 μg/kg, i.p.) or saline. Both capsaicin and MK-801 produced the expected significant ($p<.001$) increase in 30 and 60 min sucrose intake if compared to their respective controls. Administration of MK-801 to capsaicin-treated rats further increased 60 min sucrose intake significantly ($p<.001$) in a fully additive fashion. These results suggest that the two treatments do not impinge on the same neural pathway to delay satiation. MK-801 may interfere with signals from capsaicin-resistant vagal afferents, or alternatively may act on other areas in the brain or periphery. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Vagal afferents; Visceral satiety signals; Gastric distension; Primary afferents; Caudal brainstem; Hindbrain; NTS; Glutamate; *N*-methyl-D-aspartate receptor; Satiation; Meal termination

1. Introduction

Visceral afferents, particularly vagal afferent fibers innervating the gastrointestinal tract, play a significant role in the satiation process and meal termination. Both gastric tension receptors and duodenal nutrient sensors send information about the arrival of food in the gut to the nucleus tractus solitarius (NTS) in the caudal brainstem through vagal afferent fibers. Selective surgical transection of vagal afferents [27,33,36], as well as chemical ablation of a population of vagal and dorsal root afferents by systemic capsaicin treatment [15,23], leads to a transient increase in short-term, deprivation-induced food intake by delaying the onset of satiety. At the periphery, an important role for cholecystokinin (CCK) and its CCKA receptor in the transduction of chemical and mechanical stimuli into electrical activity of vagal afferent fibers [17] and its pro-satiating consequence has also been demonstrated [28,29,34,35].

It should also be possible to delay satiation by interfering with satiety signals as they reach the brainstem and higher brain areas. If gastrointestinal satiety signals were carried by vagal afferents that use a specific transmitter at their central terminals in the NTS and area postrema, it should be possible to delay satiety by blocking this transmitter from its action on receptors on second-order neurons. There is evidence that glutamate might be this transmitter, acting on NMDA receptors present in the NTS [2]. Systemic administration [6,12,13] and local infusion into the 4th ventricle [37,41] or directly into the NTS [37] of the selective NMDA receptor blocker, MK-801, resulted in delayed satiation and increased short-term drinking of sucrose solutions in food-deprived rats. In addition, there is considerable evidence that glutamate is involved at the equivalent first synapse involved in gustation [25] and cardiovascular regulation [1,32].

To further pursue this question, we argued that if MK-801 produces its satiety-delaying effect by blocking the very first transmission step from primary afferent to second-order

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neurons in the NTS, then prior ablation of vagal afferents should prevent it from doing so. In other words, the delay in satiation and thus increase in sucrose intake produced by both vagal afferent ablation and MK-801 administration would not be expected to be additive, if combined in the same rat. Additivity of the effects would suggest that the two manipulations impinge on separate pathways. We, therefore, tested the effectiveness of MK-801 to increase short-term sucrose intake in rats with capsaicin-induced ablation of visceral (including vagal) afferents and in control rats with vehicle treatment. Sucrose intake in food-deprived rats was chosen to guarantee rapid generation of satiety signals that could be interfered with by the blocker within a certain time window.

2. Materials and methods

2.1. Animals

Twenty-one male Sprague–Dawley rats (Harlan Industries, Indianapolis, IN) were used, weighing 200–240 g at the time of capsaicin or vehicle treatment. The animals were housed individually in hanging wire mesh cages under standard laboratory conditions (12:12 h lighting schedule, lights on at 0700 h, 22 ± 3°C). 5001 Purina lab chow and tap water were available ad libitum except as noted prior to tests. The rats were maintained on water bottles rather than the automatic watering system to ensure familiarity with spouts. All testings were conducted in the light phase between 0830 and 1300 h.

The experimental protocol was approved by the Institutional Review Committee for Use of Animal Subjects and is in accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals.

2.2. Capsaicin treatment and verification of effectiveness

Rats were treated consecutively with increasing doses of capsaicin. On each of 3 days, rats were injected under inhalation anesthesia (isoflurane) with either vehicle as a control, or a dose of capsaicin (12.5, 30, and 75 mg/kg, i.p., Sigma, 98% grade). Capsaicin was dissolved freshly in a mixture of Tween 80 (10%), ethanol (10%), and sterile saline (80%) at the specific concentration. Following the first injection, all rats exhibited respiratory arrest of between 1 and 5 min. Assistance by manually massaging the chest or artificial respiration induced the resumption of spontaneous breathing. During subsequent injections with the higher doses, artificial respiration was less often necessary. Capsaicin-treated rats weighed the same as vehicle-treated rats within 10 days following treatment (265 ± 3 g) and gained weight at a similar rate throughout the study.

Eight days following capsaicin treatment, one drop of 1% NH_4OH was applied to the left eye with a Pasteur pipette and the number of eye wipes in 30 s and the latency to the first wipe were recorded. All capsaicin-treated rats fulfilled the criterion of less than three wipes and a latency of >5 s to the first wipe. All vehicle control animals wiped vigorously, with a latency of <1 s and >15 wipes/30 s. In addition, we have previously shown that this capsaicin treatment regimen completely abolishes CCK-induced suppression of food intake [23].

2.3. Experimental protocol

Rats with successful capsaicin treatment ($n = 11$) and vehicle controls ($n = 10$) were put on a food deprivation schedule with normal lab chow ad libitum except for 15 h of overnight food deprivation every 3–4 days. On days after food deprivation, rats were trained to lick 15% sucrose from a drinking spout. Since the rats took part in a separate experiment, measuring intake of various concentrations of corn oil and sucrose, they were all highly trained, and their 60-min intake had stabilized. On the first test day, all rats received saline injections, and on 2 additional test days, half of the animals of each group was given injections of MK-801 (100 μg/kg, i.p.) and the other half saline in a counterbalanced order, 15 min before access to the drinking spout. Volume (ml) consumed was measured to the nearest 0.1 ml from inspection of the fluid level in the calibrated burette every 5 min for 60 min. The dose of MK-801 chosen was based on observations by Burns and Ritter [13], showing an optimal intake-enhancing effect with 100 μg/kg.

2.4. Statistical analysis

Individual intakes of 15% sucrose in milliliters were subjected to a three-way, doubly repeated measures ANOVA with time (5, 10, 15, 20, 30, 45, and 60 min) and trial (1, 2, and 3) as repeated factors, injection (MK-801 or saline) as an additional within-subject factor, and treatment (capsaicin or vehicle) as a between-subject factor. The covariance among the observations of an individual rat was modeled

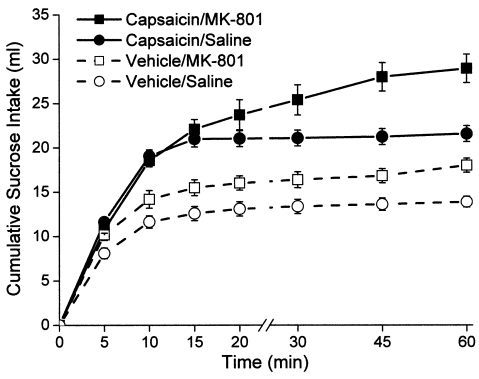

Fig. 1. Effect of MK-801 or saline administration (100 μg/kg, i.p.) in vehicle- or capsaicin-treated rats on intake of 15% sucrose solution in food-deprived rats. Means ± S.E.M. of 10–11 rats per group. For statistical analysis, see results and Fig. 2.

as unstructured for the trial effect and as compound-symmetric for the time effect in each trial.

3. Results

Rats of all groups and conditions started drinking vigorously immediately after access to the spout. Generally, drinking activity was high during the first 10 min, with very few pauses and rapidly decreased thereafter, with only sporadic drinking episodes (Fig. 1). Both main effects of capsaicin vs. vehicle treatment [$f(1,19)=58.3$, $P<.0001$] and MK-801 vs. saline injection [$f(1,394)=17.4$, $P<.0001$] were significant (Fig. 2). Although the effect of MK-801 in vehicle-treated rats was modest, it reached significance at 20 min [$t(394)=2.85$, adjusted $P<.05$] and was significant at 60 min [$t(394)=3.97$, $P<.001$]. The effect of capsaicin treatment in saline-injected rats was robust and already evident at 5 min [$t(394)=3.90$, adjusted $P<.001$].

Most importantly, MK-801 injection in capsaicin-treated rats further delayed satiation and increased sucrose intake if compared to vehicle-treated rats, such that treatment × injection interaction was not significant [$f(1,394)=0.22$, n.s.]. However, there was an interaction of this additive effect with time as indicated by the significant treatment × injection × time interaction [$t(1,394)=12.21$, $P<.0001$]. For the first 20 min, there was no further MK-801-induced increase in volume consumed in capsaicin-treated rats [at 20 min; $t(394)=2.2$, adjusted $P=0.18$] (Fig. 1). It was only after 20 min that capsaicin-treated rats given MK-801 ingested significantly more than saline-injected rats [30 min, $t(394)=3.63$, $P=0.0021$; 60 min, $t(394)=6.0$, $P<.0001$]. At the end of the 1-h test period, rats treated with the combination of capsaicin plus MK-801 drank 15.0 ml more than baseline (vehicle–saline) condition (Fig. 2). This difference is even larger than the sum (12.2 ml) of the net effects of capsaicin alone (7.5 ml) and MK-801 alone (4.7 ml), and thus fully additive.

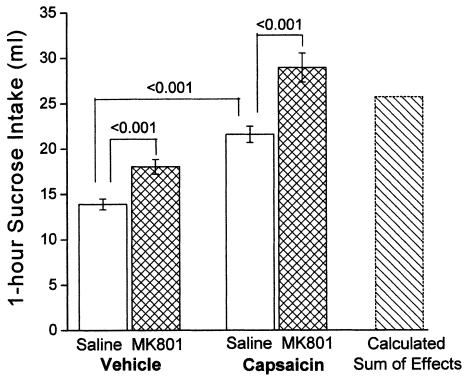

Fig. 2. Comparison of effects of MK-801, capsaicin, and the combined treatments on 60 min sucrose intake. The column on the right shows the calculated value for the sum of the effects of the two treatments, illustrating the more than additive effect. Means + SEM of 10–11 rats. All comparisons are significant based on ANOVA, followed by Bonferroni adjusted *t*-tests.

4. Discussion

Both capsaicin treatment and injection of the NMDA receptor antagonist, MK-801, independently increased short-term ingestion of sucrose solution, confirming several earlier observations [12,16,23,37,41]. When these two manipulations were combined by injecting MK-801 into capsaicin-treated rats, there was a significantly larger effect than with the individual treatments on intake during the later phases of the 1-h test, indicating an additive effect. This effect was not seen during the first 15 min. However, because initial rate of intake was very high ($\sim$2 ml/min) in the capsaicin-treated, saline-injected rats, a ceiling effect may have physically prevented the MK-801-injected rats from drinking even faster. When the rate of intake rapidly dropped after about 15 min in the capsaicin-treated saline controls, the additive effect became immediately apparent.

This additive effect suggests that the two manipulations do not impinge on the same neural pathway leading to ingestive behavior. Capsaicin treatment, as used in this study, has been shown to permanently destroy a class of thin, unmyelinated visceral afferents of both dorsal root [21] and vagal (nodose ganglion) origin [7,31]. Because of the dense innervation of the stomach by vagal afferents [8], we assume that the major reason for capsaicin's effectiveness in delaying satiety is its destruction of vagal afferents carrying gastric distension signals, although the involvement of dorsal root afferents cannot be ruled out [5]. As compared to vehicle treatment, capsaicin treatment increased short-term, food-deprivation-induced consumption of 10% sucrose solution [16,23], water consumption induced by hypertonic saline or polyethylene glycol injection, and NaCl consumption induced by DOCA injection [16]. This non-specific overingestion response is consistent with a lack of gastric distension signals as the primary defect. However, the effect can be masked if the sucrose concentration is increased or other high-calorie foods are used, and is not seen when familiar laboratory chow is the food source [15,23]. Because such high-energy foods were only over-consumed on the first 1-h test but not on subsequent tests, we argued that rats learn to use capsaicin-resistant redundant mechanisms to counteract the lacking gastric satiety signals and normalize meal size.

Several lines of evidence suggested that the non-competitive NMDA receptor antagonist, MK-801, increases short-term food consumption by interfering with vagal satiety signal transmission at the level of the NTS. First, systemic administration of MK-801 facilitated ingestion of sucrose delivered via an intraoral fistula [6], and increased intake of 15% sucrose solution after food deprivation or palatable cookie intake [11,12]. Second, MK-801 injected into the 4th ventricle [37,41] and directly into the NTS [37] increased 1

h food-deprivation-induced intake of 15% sucrose. Third, the role of glutamate and its NMDA receptors in the transmission of primary visceral afferents involved in cardiovascular control [1,4,14,39] and gustation [9,25] is widely recognized.

Assuming that both capsaicin treatment and NMDA receptor blockade produce their intake-enhancing effect by interfering with the propagation of satiety signals from vagal afferents to NTS neurons, it could be expected that the blocker cannot further enhance intake in capsaicin-treated rats. Clearly, the effectiveness of MK-801 to enhance sucrose intake was not reduced in capsaicin-treated rats. This is in contrast to a recent report suggesting that capsaicin-treated rats are less sensitive to the satiety-delaying effect of MK-801 [13]. In that study, the effectiveness of a higher dose of MK-801 (100 μg/kg, as in the present study) was not significant, but that of a lower dose (50 μg/kg) was significantly attenuated in capsaicin-treated rats. The authors interpreted their findings as evidence for MK-801 to interfere with communication of nutrient-related afferent vagal signals. However, it is difficult to understand why the higher dose of the blocker would not have a similar effect, unless it acts, in addition, on some other neural substrate to delay meal termination. It is also important to note that capsaicin treatment in that study did not produce short-term overconsumption of 15% sucrose solution, as has been shown by others [16,23]. In our hands, overconsumption of low concentrations of sucrose solutions is one of the most reliable indicators of effective capsaicin treatment. More importantly, in the same experiment, subdiaphragmatic vagotomy completely abolished the effect of MK-801 [13] and suggests involvement of vagal *efferents* rather than *afferents* in the drug's effect on satiety. In fact, the same group of researchers has recently found that MK-801 increases short-term sucrose intake by accelerating gastric emptying [30]. Many neurons in the dorsal motor nucleus of the vagus contain NMDAR1 and NMDAR2 receptors (Refs. [10,26]; unpublished personal observations). Thus, vagal preganglionic efferents that control gastric emptying may be activated by an NMDA-receptor-mediated glutamatergic input during food ingestion, and blockade of these receptors may lead to increased emptying, which in turn could delay satiation.

Because it appears that capsaicin does not abolish all vagal afferent fibers innervating the stomach [7], it is also possible that MK-801 inhibited the effects of glutamate released from such capsaicin-resistant vagal afferents. Furthermore, because in the present study the blocker was administered systemically, it may also have blocked satiety signals that are not carried by vagal afferents. These could include satiety signals mediated by dorsal root afferents and/or by gastrointestinal hormones acting on the area postrema or elsewhere in the brain. Finally, because MK-801 injected into the lateral cerebral ventricle in pigeons [38] and AMPA/kainate receptor antagonists injected into the shell of the nucleus accumbens of rats [22] can elicit potent eating, the forebrain is another potential site of action.

Thus, the results obtained with the particular dose of MK-801 in the present study do not indicate an important role for NMDA receptors in the transmission of satiety signals originating from capsaicin-sensitive gastrointestinal vagal afferents. However, to completely rule out participation of this receptor, studies with additional doses of the blocker as well as different foods and experimental conditions will be necessary. Because of the strong evidence for glutamate as the vagal afferent transmitter, a role for non-NMDA receptors seems also indicated. Specific distribution patterns of the various AMPA receptor subunits have been found in the dorsal vagal complex by immunocytochemistry in the rat [24] and cat [2]. Evidence for non-NMDA receptors playing a role in afferent signal transmission for cardiovascular control is rapidly mounting [3,14,19,39]. Using Fos expression as indicator of gastric-distension-induced neuronal activation in the NTS, we have recently also found limited support for an important or unique role of the NMDA receptor at this first synapse in the dorsal medulla. Local 4th ventricular infusion of MK-801 was unable to block gastric-distension-induced net c-Fos expression in NTS neurons [41]. In preliminary experiments using selective AMPA/kainate receptor antagonist injections into the 4th ventricle, we found suppression, not augmentation, of sucrose drinking [40]. This may have resulted from interference with caudal brainstem mechanisms other than the processing of satiety signals. It can also not be excluded that metabotropic glutamate receptors [18,20] or non-glutamatergic transmitter systems, such as substance P, CCK, serotonin, or calcitonin gene-related peptide, play a role in satiety signal transmission between primary vagal afferents and NTS neurons.

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