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Ingestion analgesia occurs when a bad taste turns good

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Abstract

During ingestion of water, chocolate, sucrose, and saccharin, pain-related behaviors are suppressed. This ingestion analgesic effect was reversed when the hedonic valence of a food is switched from good to “bad” as occurs during conditioned taste aversion. Here, we tested the converse hedonic shift to determine if ingestion analgesia occurs when 0.3 M NaCl is made palatable by inducing a sodium appetite. In Experiment 1, sham- and sodium-depleted rats were tested for paw withdrawal and lick latencies to brief noxious heat during quiet wake and intraoral NaCl ingestion. Only sodium-depleted rats showed a suppression of heat-evoked reactions during NaCl ingestion. In Experiment 2, we tested whether this analgesic effect is mediated by the brainstem nucleus raphe magnus (NRM). Inactivation of NRM with muscimol blocked ingestion analgesia during NaCl ingestion by sodium-depleted rats. This attenuation was not due to a hyperalgesic effect of NRM inactivation. Muscimol microinjections into a nearby region, the nucleus raphe obscurus (NRO), were ineffective. The present findings demonstrate that the internal *milieu* of an animal can modify ingestion analgesia, and that the analgesia during NaCl ingestion by sodium hungry rats is mediated by NRM.

Keywords

ingestion; sodium depletion; rostral ventromedial medulla; nociception; muscimol

During ingestion, reactions to acute pain are suppressed, a phenomenon termed ingestion analgesia (Foo & Mason, 2005). This analgesic effect was initially shown in food deprived animals (Casey & Morrow, 1983; Wylie & Gentle, 1998) and subsequently in nondeprived ones (Foo, Crabtree, Thrasher, & Mason, 2009; Foo & Mason, 2005, 2009). *Ad lib* fed rats showed fewer and delayed reactions to acute noxious stimulation during chocolate chip or chow ingestion than during grooming or quiet waking (Foo & Mason, 2005, 2009).

Ingestion analgesia occurs when palatable fluids are infused directly into the mouth, indicating that neither food-seeking, or procurement, nor self-initiated feeding is necessary (Foo & Mason, 2009). Further, by infusing different substances into the mouth, the types of ingestates capable of eliciting analgesia were ascertained (Foo & Mason, 2009). The consumption of intraoral sucrose produced analgesia, an effect that is only superficially similar to sucrose-induced analgesia reported in neonates (Blass, Fitzgerald, & Kehoe, 1987;

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Blass & Hoffmeyer, 1991; Blass & Shide, 1994; Ren, Blass, Zhou, & Dubner, 1997). Unlike neonatal sucrose analgesia, ingestion analgesia is present in adults and does not persist after ingestion. Furthermore, ingestion of saccharin or water also produces analgesia, indicating that the ingestate can be devoid of sucrose, calories, or a sweet taste. The analgesic effect, however, is not a result of ingestion *per se* because ingestion of hypertonic NaCl does not produce analgesia.

We have proposed that the hedonic properties of an ingestate determine whether its ingestion elicits analgesia (Foo & Mason, 2009). In support of this view, intraoral sucrose which normally produces analgesia is no longer able to do so after being paired with LiCl-induced illness. Thus, when a good taste turns bad, ingestion analgesia fails to occur. The aim of Experiment 1 was to test the reverse proposition, that is, whether ingestion analgesia occurs when a bad taste turns good. We used the finding that sodium-depletion induces a physiological need for sodium which in turn leads to a positive shift in palatability and an increase in the consumption of hypertonic NaCl (Berridge, Flynn, Schulkin, & Grill, 1984; Breslin, Kaplan, Spector, Zambito, & Grill, 1993; Flynn & Grill, 1988). If food hedonics determines ingestion analgesia, an analgesic effect is predicted during the consumption of hypertonic 0.3 M NaCl by sodium-depleted rats.

It is well established that the brainstem nucleus raphe magnus (NRM) is critically involved in the endogenous control of pain (Gebhart, 2004). Previously, we have shown that NRM mediates the analgesic effects observed during self-initiated ingestion of chocolate or intraorally-induced ingestion of water (Foo & Mason, 2005, 2009). Experiment 2 aims to investigate the role of NRM in modulating reactions to brief noxious heat during 0.3 M NaCl ingestion.

Materials and Methods

Subjects

Subjects were 48 naive male, Sprague-Dawley rats (Charles River Laboratories, Portage, MI) weighing 268 – 552 g at the start of experiments. They were housed singly in plastic cages (26 × 46 × 20.5 cm: width × length × height) kept in a 12 hr light-dark cycle vivarium (23 – 25°C) and were given *ad lib* access to food and water. Rats were handled and habituated to the apparatus and procedure. They were exposed at least once to noxious heat stimulation to minimize any novelty-induced analgesia and to intraoral infusions of 0.3 M NaCl to minimize neophobia during testing. All testing was conducted during the light phase. The procedures used were approved by IACUC of the University of Chicago and in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Apparatus

The test chamber was an elevated home cage with a wire mesh floor. A custom-made Hargreaves apparatus (Hargreaves, Dubner, Brown, Flores, & Joris, 1988) located beneath the box was used to deliver radiant heat to the rat's hind paw. Heat intensity was set to elicit baseline withdrawal latencies of ~3 s and lasted for a maximum duration of 8 s. Three cameras recorded the rat's behaviors from the front, side and below. A fourth camera recorded a timer synchronized to data acquisition. All images were acquired simultaneously with an Everplex Quad Processor (Everfocus, Duarte, CA) and recorded onto videotapes. Intraoral infusions were made via PE tubing connected to a fluid swivel (Instech Laboratories, Inc., Plymouth Meeting, PA) and syringe. A syringe pump (Beehive, BAS, West Lafayette, IN) delivered 0.3 M NaCl at a rate of 0.35 ml/min.

Surgery

Rats were anesthetized with sodium pentobarbital (60 mg/kg, i.p.), placed on a heated blanket, and in a stereotaxic instrument. An intraoral cannula was implanted in all animals according to an established method (Foo & Mason, 2009; Grill & Norgren, 1978). For rats in Experiment 2, a 26 G stainless steel guide cannula (Plastics One, Roanoke, VA) was also implanted to target either the NRM or the nucleus raphe obscurus (NRO) (AP: -11.3, L: 0.0, V: -7.5 or -6.0 respectively, relative to bregma). The cannula was attached to the skull with dental acrylic and capped with an obturator to maintain patency. All rats were allowed 4–7 days to recover.

Sodium and sham depletion

Sodium depletion was achieved by combining two injections of the diuretic furosemide (5 mg, 0.5 ml per injection, s.c.), given 1-hr apart, with 24-hr exposure to a sodium-deficient diet (Taklad-Harlan 90228). Sham-depleted rats were injected with equivolumes of saline and remained on a global 18% protein rodent diet (Teklad-Harlan 9218). All rats were weighed before the first injection and 2 hrs after the second injection.

Microinjections

Drugs were microinjected intracerebrally via a 33 G microinjector which extended 3.0 mm beyond the tip of the guide cannula. The microinjector was connected to a swivel and a 1.0 μ l Hamilton microsyringe via PE20 tubing. Muscimol (50 ng in 250 nl) or saline (250 nl) was microinjected intracerebrally at a rate of 100 nl/min (Foo & Mason, 2009).

Experiment 1: Ingestion analgesia in sodium-depleted rats

Rats were randomly allocated into 2 weight-matched groups, which differed in terms of whether they were sham- (Sham) or sodium-depleted (Dep) (Sham: $M = 411.9 \pm 8.2$ g; Dep: $M = 420.4 \pm 14.7$ g) [$F(1,12) < 1.0$]. On Day 1, rats were brought to the laboratory and given a 20 min two-bottle preference test to assess intakes of water and 0.3 M NaCl. The bottle positions were counter-balanced across subjects. On Day 2, rats were sham- or sodium-depleted. On day 3, rats were tested for paw withdrawal and lick latencies during quiet wake (QW) and intraoral 0.3 M NaCl infusions (Salt). A total of four heat trials were given in the following order: QW, Salt, QW, and Salt. Heat onset began at an average latency of 10.4 ± 1.7 s after the start of salt infusion, with an average of 0.17 ± 0.01 ml delivered per infusion on these trials. The inter-trial interval was > 10 min. In order to minimize any association between noxious paw heat and Salt, Salt-alone trials were interspersed with Salt-heat trials. At least 30 min after testing, preferences for water and 0.3 M NaCl were assessed as on Day 1.

Experiment 2: RVM-mediated ingestion analgesia

Rats were randomly allocated into 5 weight-matched groups (Sham:Sal, 435.2 ± 22.8 g; Sham:Mus, 391.7 ± 26.6 g; Dep:Sal, 399.3 ± 25.6 g; Dep:Mus, 384.9 ± 10.8 g; Dep:NRO-Mus, 392.2 ± 25.8 g) [$F(1,29) < 1.0$]. Four groups differed in terms of whether rats were sham- (Sham) or sodium-depleted (Dep) and whether they received intra-NRM administration of saline (Sal) or muscimol (Mus). These groups are referred to as Sham:Sal, Sham:Mus, Dep:Sal and Dep:Mus. The fifth group of rats, Dep:NRO-Mus, was sodium-depleted and received muscimol microinjections into a control site, the nucleus raphe obscurus (NRO), located dorsal to NRM. On Day 1, sodium preference was assessed. On the following day, rats in two groups were sham-depleted and those in the remaining three groups were sodium-depleted. On day 3, rats were acclimatized to the test chamber for at least 15 min before receiving microinjections. At least 10 min later, they were tested for reactions to noxious heat during QW and intraoral infusion of 0.3 M NaCl (Salt), with a

minimum inter-trial interval of 10 minutes. The testing order of QW and salt trials (QW, Salt, QW, and Salt) was the same across all animals. Heat onset began at an average latency of 21.5 ± 2.6 s after the start of salt infusion, with an average of 0.17 ± 0.02 ml delivered per infusion on these trials. As above, salt-alone trials were interspersed among Salt-heat trials to minimize any association of noxious heat with salt infusions. At the end of the experiment, rats were euthanized with sodium pentobarbital (120 mg/kg), and perfused transcardially with saline followed by 10% phosphate buffered formalin. Brains were stored in formalin, and then in 30% sucrose formalin. Frozen coronal sections 40 μ m thick were taken through the rostral-caudal extent of NRM, mounted onto slides, and stained with cresyl violet. A total of 34 rats had histologically verified injection sites within the target areas (Sham:Sal, n = 6; Sham:Mus, n = 6; Dep:Sal, n = 8; Dep:Mus, n = 8; Dep:NRO-Mus, n = 6). Microinjection sites for each of the groups were plotted on representative sections from a rat brain atlas (Paxinos & Watson, 1998) and are illustrated in Figure 2B.

Data analyses

The difference in the amount of weight loss between saline- and furosemide injected rats was tested for significance with an ANOVA. Preference for NaCl before and after sham- or sodium-depletion was calculated using the formula $\text{NaCl intake}/\text{total intake}$ and analyzed with repeated measures ANOVAs. Paw withdrawal and lick latencies were calculated as the interval between heat onset and paw withdrawal or paw lick from video recordings. To ensure that latency measurements were not influenced by experimenter bias, an independent observer, blind to the objectives of the study, determined withdrawal and lick latencies on all trials. On trials where no response was observed, a latency of 8 s was assigned. This time corresponded to the maximum duration of the heat stimulus. Mean withdrawal and lick latencies during QW and Salt were calculated for each animal in each of the groups. A repeated-measures ANOVA (SigmaStat, Systat Software) was used to determine statistical significance within-subjects (QW versus Salt) for each of the groups.

Results

Experiment 1: Ingestion analgesia in sodium-depleted rats

Weight loss and sodium preference—Sodium-depleted rats (Dep) lost significantly more weight than sham-depleted rats (Sham) [$F(1,13) = 24.44$, $p < 0.001$]. Sham rats showed the same preference for NaCl before and after sham depletion ($M_{\text{pre-NaCl pref}} = 0.1 \pm 0.1$ vs $M_{\text{post-NaCl pref}} = 0.0$). In contrast, Dep rats showed a significant increase in preference for NaCl after sodium depletion ($M_{\text{pre-NaCl pref}} = 0.0$ vs $M_{\text{post-NaCl pref}} = 0.8 \pm 0.1$) [$F(1,6) = 208.4$, $p < 0.001$].

Reactions to noxious heat stimulation—The mean paw withdrawal and lick latencies during QW and Salt for Sham (n = 7) and Dep (n = 7) groups are shown in Figures 1A–B, respectively. Although baseline (QW) latencies of Sham rats appear longer than those of Dep rats, these differences were not significant and are within the range obtained previously (Foo & Mason, 2009). Sham rats displayed the same withdrawal latencies during QW as during Salt. They also displayed the same paw lick latencies during QW and Salt. In contrast, Dep rats showed significantly longer withdrawal latencies during Salt than during QW [$F(1,13) = 7.7$, $p = 0.03$]. Sodium-depleted rats also showed significantly longer paw lick latencies during Salt than during QW [$F(1,13) = 6.3$, $p = 0.04$].

Experiment 2: RVM-mediated ingestion analgesia in sodium-depleted rats

Weight loss and sodium preference—Sodium-depleted rats (Dep:Sal, Dep:Mus, and Dep:NRO-Mus) lost significantly more weight than sham-depleted rats (Sham:Sal and Sham:Mus) [$F(1,32) = 675.7$, $p < 0.001$]. Sham rats showed no significant change in

preference for NaCl ($M_{\text{pre-NaCl pref}} = 0.0$ vs $M_{\text{post-NaCl pref}} = 0.0$), whereas Dep rats showed a significant increase in preference for NaCl after sodium depletion ($M_{\text{pre-NaCl pref}} = 0.0$ vs $M_{\text{post-NaCl pref}} = 0.9 \pm 0.02$) [$F(1,21) = 1642.2$, $p < 0.001$].

Reactions to noxious heat stimulation—The mean paw withdrawal latencies for each of the five groups during QW and Salt are shown in Figure 2A. Sham-depleted rats given intra-NRM saline (Sham:Sal) showed the same latencies during QW and Salt. Similarly, sham-depleted rats given intra-NRM muscimol (Sham:Mus) also showed the same latencies during QW and Salt. Sodium-depleted rats given intra-NRM saline (Dep:Sal) showed significantly longer paw withdrawal latencies during Salt than QW [$F(1,7) = 13.0$, $p = 0.01$]. In contrast, no reliable differences in paw withdrawal latencies across the two conditions were displayed by sodium-depleted rats given intra-NRM muscimol (Dep:Mus), indicating an effective blockade of analgesia by NRM inactivation. Depleted rats treated with intra-NRO muscimol (Dep:NRO-Mus) displayed significantly longer latencies during Salt than during QW [$F(1,5) = 7.6$, $p = 0.04$], demonstrating that inactivation of a region dorsal to NRM was ineffective in blocking ingestion analgesia. None of the groups displayed significant differences in paw lick latencies during Salt compared with those displayed during QW (data not shown).

General Discussion

The present results show that intraorally-induced ingestion of hypertonic NaCl was accompanied by analgesia in sodium-depleted rats but not in sham-depleted ones. In order to experimentally induce a rapid sodium loss, we used a combination of furosemide administrations with 24 hr *ad lib* access to sodium-free diet. This technique is widely used to induce sodium depletion and causes rapid excretion of urinary sodium (Jalowiec, 1974; Lundy, Blair, Horvath, & Norgren, 2003; Roitman, Na, Anderson, Jones, & Bernstein, 2002; Wolf, Schulkin, & Simson, 1984). While we did not evaluate urinary sodium loss, two measures suggest sodium-depletion did occur. First, the acute diuretic effects of furosemide were revealed by the considerable weight loss (> 16 g) that occurred shortly after drug treatment. Secondly, rats exposed to the sodium-depletion protocol showed marked increase in preference for NaCl after treatment.

The analgesic effects observed during hypertonic NaCl ingestion by sodium-depleted rats are likely due to the positive shift in the hedonic value of hypertonic NaCl resulting from sodium-depletion (Berridge *et al.*, 1984). According to this idea, ingestion of NaCl, palatable within the context of sodium depletion, elicits analgesia. This account complements our data that ingestion analgesia is eliminated when the hedonic value of sucrose is shifted from positive to negative (Foo & Mason, 2009). It is worth noting that sodium-depleted rats were not fully satiated by NaCl infusions administered during testing because they drank copious amount of NaCl post-test. Thus, it is possible that the remaining sodium hunger present in sodium-depleted rats either contributed directly to or modulated the analgesia observed.

We have shown previously that ingestion of chocolate in *ad lib* fed rats produced an analgesia of equal magnitude to that produced by consumption of less palatable substances, namely, sucrose, saccharin, and water (Foo & Mason, 2009). Thus, ingestion analgesia does not appear to be graded by palatability. In the present investigation, subjects were not tested for analgesia during chocolate consumption. Thus, it is unknown whether chocolate ingestion elicits analgesia in sodium-depleted rats, and if so, whether the analgesia would be equivalent in magnitude to that produced by NaCl ingestion.

Paw lick latencies yielded evidence for ingestion analgesia in sodium-depleted rats in Experiment 1 (Group Dep, Figure 1B) but not in Experiment 2 (Group Dep:Sal, data not shown). In the first experiment, noxious heat evoked paw licks on almost all QW trials (13 of 14) and on most Salt trials (11 of 14) in sodium-depleted rats. In Experiment 2, however, noxious heat evoked fewer paw licks in Group Dep:Sal on both QW (6 of 16) and Salt (4 of 16) trials. Thus, it is likely that the failure to detect ingestion analgesia on the paw lick response in Group Dep:Sal in Experiment 2 was due to insufficient occurrences of paw licks during baseline (QW trials). Our previous work has shown that paw licks occur on > 60% of QW trials and are a reliable measure of ingestion analgesia during intraoral ingestion (Foo & Mason, 2009). It is unclear why the frequency of paw licks during QW trials (37.5%) was so low in Dep:Sal rats in the current study.

The analgesic effects evident during self-initiated chocolate or intraorally-induced water ingestion (Foo & Mason, 2005, 2009) are mediated by NRM. In line with this work, the present data shows that analgesia during hypertonic NaCl ingestion shown by sodium-depleted rats also requires the functional integrity of NRM. Unlike NRM, inactivation of NRO did not block ingestion analgesia. The NRO was selected as an anatomical control site because of its close proximity to NRM and its capacity to modulate ingestion-related activities, such as hypoglossal motor output, gastric motility and pressure, anorectal motility, and plasma insulin and glucagon levels (Holmes et al., 1997; Krowicki, Arimura, & Hornby, 1996; Krowicki & Hornby, 1993, 1995; McCann, Hermann, & Rogers, 1989; Peever, Necakov, & Duffin, 2001). While the NRO may not be involved, the present results do not exclude the involvement of other areas neighboring NRM, such as the ventral reticular nuclei. We reported previously that several animals ($n = 4$) with misplaced cannulae directed at the reticular nuclei displayed longer median withdrawal latencies during water ingestion than during quiet wake after saline microinjections but not after muscimol microinjections (Foo & Mason, 2009). Areas adjacent to NRM have similar anatomical and physiological properties and it is certainly possible that they have a role in ingestion analgesia.

Sodium is detected by amiloride-sensitive chemoreceptors located on the tongue (Brand, Teeter, & Silver, 1985; DeSimone & Ferrell, 1985; Heck, Mierson, & DeSimone, 1984). In rodents, sensory information from taste receptors in the oral cavity is conveyed via the facial, glossopharyngeal, and vagus nerves to the nucleus of solitary tract, the first central synapse in the gustatory pathway (Pfaffmann, 1959; Torvik, 1956). Taste information is then conveyed to the pontine parabrachial nucleus (Norgren & Leonard, 1971). Information from PBN is then transmitted to forebrain areas such as the thalamic ventroposteromedial nucleus, the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and hypothalamus (Block & Schwartzbaum, 1983; Voshart & van der Kooy, 1981; Yasui et al., 1983).

The ability to sense and react to salt is largely preserved in rats with brains transected at the supracollicular level (Grill, Schulkin, & Flynn, 1986). Supracollicular decerebrate rats, however, do not show the normally observed increases in salt palatability and intake when sodium-depleted (Flynn & Grill, 1988). Thus, while the isolated hindbrain is sufficient for innate taste reactivity to salt, the forebrain is required to engage behavioral compensatory responses to satiate sodium hunger. If hedonic re-coding of salt following sodium-depletion occurs, then it is likely to take place in the nucleus accumbens. Accumbal neurons are sensitive to the rewarding properties of sucrose, the aversive properties of quinine, and to cues that predict these stimuli (Roitman, Wheeler, & Carelli, 2005). Moreover, morphological changes in nucleus accumbens neurons after sodium-depletion parallel those seen following sensitization to amphetamine (Robinson & Kolb, 1997; Roitman et al., 2002). Information about the hedonic value of a taste processed in the nucleus accumbens could be conveyed to NRM, via the hypothalamus and/or the periaqueductal gray (Hermann,

Luppi, Peyron, Hinckel, & Jouvet, 1997; Holstege, 1987; Hosoya & Matsushita, 1981; Murphy, Rizvi, Ennis, & Shipley, 1999; Sim & Joseph, 1991; Vertes & Crane, 1996).

In conclusion, our results demonstrate that the internal *milieu* of an animal modifies taste palatability and ingestion analgesia. Like the analgesic effects shown by non-depleted rats during chocolate or water ingestion (Foo & Mason, 2005, 2009), the analgesia displayed by sodium-depleted rats during salt ingestion is also mediated by NRM. Thus, ingestion of a substance required for homeostasis activates common descending pain inhibitory pathways as those activated during ingestion of foods that are normally tasty.

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Figure 1. Mean latencies to paw (A) withdrawal and (B) lick of sham- (Sham) and sodium-depleted (Dep) rats during quiet wake (QW) and intraoral ingestion of 0.3 M NaCl (Salt). Sodium-depleted rats showed significantly longer paw withdrawal and paw lick latencies during Salt than during QW. * Denotes statistical significance ($p < 0.05$).

Figure 2.

(A) Mean latencies to paw withdrawal of sham- (Sham) and sodium-depleted (Dep) rats microinjected with saline (Sal) or muscimol (Mus) into nucleus raphe magnus or muscimol into nucleus raphe obscurus (NRO-Mus). Rats were tested for reactions to noxious paw heat during quiet wake (QW) and intraoral ingestion of 0.3 M salt (Salt). Sodium-depleted rats given intra-NRM saline (Dep:Sal) showed significantly longer latencies during Salt than during QW. Muscimol administration into NRM in sodium-depleted rats (Dep:Mus) blocked the long latencies during Salt whereas intra-NRO muscimol (Dep:NRO-Mus) did not. * Denotes statistical significance ($p < 0.05$). (B) Locations of microinjection sites (●) for rats in each of the five groups are plotted.