Published in final edited form as:

Pharmacol Biochem Behav. 2014 February ; 117: 34–39. doi:10.1016/j.pbb.2013.12.002.

Antinociceptive actions of peripheral glucose administration

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Abstract

The effects of intraperitoneal (ip) D-glucose administration on antinociception were studied in male Long–Evans rats. Rats were assessed for antinociception using the hot-water tail-withdrawal procedure (54 ± 0.2 °C) to determine if peripheral administration of D-glucose (300, 560, or 720 mg/kg) would enhance morphine-mediated antinociception (MMA) (1.0, 3.0, 4.2, 5.6, and 10.0 mg/kg cumulative-dosing regime) and if D-glucose (560, 720, or 1000 mg/kg) alone could produce antinociceptive activity that was naloxone (0.32 mg/kg) reversible. Additionally, the actions of D-glucose on MMA were compared with a stereoisomer, L-glucose, which is not metabolized. The results of these studies demonstrate that peripheral administration of D-glucose significantly enhances MMA and that D-glucose alone produces antinociceptive actions that are potentially mediated by the endogenous opioid system. Furthermore, L-glucose failed to have an effect on MMA suggesting that the alterations in antinociception seen with D-glucose are not due to stressors such as osmolality or injection. The current studies provide evidence that D-glucose alteration of antinociception is not simply a response to taste or gustation.

Keywords

Morphine; Glucose; Antinociception; Rats

1. Introduction

Rats consuming sweet solutions are more sensitive to the analgesic effects of opioid agonists than are rats not given a sweet solution (Calcagnetti and Holtzman, 1992; D'Anci, 1999; D'Anci et al., 1997; Kanarek et al., 1991, 1997; Suri et al., 2010). For example, rats chronically consuming a 32% sucrose solution in addition to water demonstrate enhanced antinociceptive responses after both peripheral and central administration of the μ -opiate receptor agonist, morphine, or the κ -opiate receptor agonists, U50,488H and spiradoline, when compared to rats drinking water alone (D'Anci et al., 1996; D'Anci et al., 1997; Kanarek and Homoleski, 2000; Kanarek et al., 2000, 2001, 1997, 1991; Mandillo and Kanarek, 2001).

One way in which palatable foods and fluids might influence opiate-mediated events is by acting directly on the endogenous opioid system (EOS). In support of this possibility, intake of caloric sweet-tasting foods stimulates the release of β -endorphins in the hypothalamus (Dum et al., 1983), while intake of a sucrose solution increases opiate receptor binding in rats (Gagin et al., 1996; Kanarek et al., 1997; Marks-Kaufman et al., 1989) and increases the

potency of opioid antagonists to produce discriminative effects (Jewett et al., 2005). Further support for the hypothesis that sweet substances alter the EOS comes from work by Pomonis et al. (2000) who found that c-Fos immunoreactivity in response to naloxone was significantly enhanced in rats that had consumed sucrose relative to those not given the sugar. Moreover, mRNA activity in sucrose-dependent rats is similar to that in morphine-dependent rats, decreasing dopamine receptor D2 and opioid mRNA, while increasing dopamine receptor D3 mRNA in the striatal forebrain (Spangler et al., 2004).

One question raised by the preceding data is whether it is the hedonic qualities of palatable foods and fluids, and/or their nutritive value, which alters the activity of the EOS and opioid-mediated behaviors. Early research demonstrating that chronic intake of minimally caloric sweet-tasting solutions (e.g. saccharin solutions) did not enhance the pain relieving properties of opioid drugs (D'Anci et al., 1997; Kanarek et al., 1997) or increase opioid receptor binding (Holder and Bolger, 1988), indicates that sweet taste alone may be insufficient to activate the EOS, and alter opioid-induced antinociception. Although, one study (Yamamoto et al., 2000), found that cerebral spinal fluid levels of β -endorphin were elevated in water-deprived rats after they were allowed to drink 'taste' solutions, with sucrose and saccharin solutions having the most effect relative to water, or quinine hydrochloride and sodium chloride solutions. Sucrose became ineffective at elevating β -endorphin after a conditioned taste aversion was established. Yamamoto et al. (2000) concluded that the alteration in endogenous opioid levels in response to sucrose and saccharin ingestion was related to the palatability of these solutions.

Determining whether the enhancing effects of palatable sweet substances on opiate-mediated antinociception are related to their hedonic and/or nutritive content is an important aspect of this relationship that needs to be addressed in more depth. Thus, the current set of studies investigated the effects of bypassing gustatory responses to sugars on morphine-mediated antinociception by administering D-glucose into the intraperitoneal cavity. If intraperitoneal (ip) administration of D-glucose amplifies the antinociceptive actions of morphine, it would support the argument that the effects of D-glucose are not solely mediated by a gustatory mechanism. Demonstrating that D-glucose produces antinociception in the absence of morphine would indicate that D-glucose's actions augment morphine's actions. Additionally, if D-glucose alone produces antinociception, an opioid antagonist should block or reduce its effects. Finally, as environmental stressors have been shown to alter MMA (Akil et al., 1986; Vaccarino and Kastin, 2001), it is important to assess whether the actions of D-glucose are not better explained as resulting from physiological stress, for example through osmotic stress.

2. General methods

2.1. Animals

Adult male Long-Evans rats (Charles River Breeding Laboratories, Portage, MI), weighing 250–300 g, at the beginning of the experiment were housed individually in standard stainless-steel cages in a temperature-controlled room (22 ± 1 °C) and maintained on a reverse 12–12 h light–dark cycle (lights on: 2000–0800 h). Rats had unrestricted access to Purina Rodent Pellets (#5001) and water. All rats were allowed to acclimate to the laboratory and handling procedures for at least one week prior to the initiation of all experiments. Rats were handled daily by the same experimenter to reduce the possibility of stress-related behaviors during antinociceptive testing. In all experiments, testing took place during the dark phase of the 24-hour cycle (beginning at approximately 0900 h for all experiments). Additionally, the order of testing of animals in each drug group for all experiments was counterbalanced to control for the effects of time of testing for nociceptive responses.

2.2. Drugs

Morphine sulfate (generously provided by the National Institute on Drug Abuse) was dissolved in 0.9% saline and administered subcutaneously using a cumulative dosing regime to achieve doses of 1.0, 3.0, 4.2, 5.6, and 10.0 mg/kg and delivered in a volume of 1.0 ml/kg body weight. Physiological saline was used as a control.

Naloxone (provided by the National Institute on Drug Abuse) was dissolved in physiological saline to a concentration of 0.32 mg/ml and was administered ip in a volume of 1.0 ml/kg.

D- and L-glucose (ICN Biomedicals, Inc.) were dissolved in sterile water and administered ip in a volume of 1.0 ml/kg body weight. Sterile water was used as a control.

2.3. Antinociceptive responses

The hot-water tail withdrawal procedure (D'Amour and Smith, 1941; Morgan and Picker, 1996) was used to measure antinociceptive responses. Rats were gently held in a clean towel and placed on a platform, even with the top of a hot-water bath. The rats' tails were gently lowered 4 cm into hot water maintained at 54 ± 0.2 °C. Criterion was removal of the tail from the hot water. To prevent tissue damage, if a rat failed to remove its tail after 15 s, the tail was gently removed from the water bath by the experimenter. Tail-withdrawal latency was measured to the nearest 0.01 s.

2.4. Blood glucose analysis

Blood glucose was assessed one week after antinociceptive testing to allow any drugs to clear from the rats' systems. A baseline blood glucose level was assessed. Each rat was then administered 3.2 mg/kg morphine (sc) along with the same dose of glucose (ip) they had received previously. Tail blood was collected using the tail-snip procedure and analyzed for blood glucose levels. Blood glucose levels were measured using the Prestige™ animal validated blood glucose monitor (Palm Lab, Inc., model #527600) with Prestige™ Smart System blood glucose test strips.

2.5. IACUC approval

The Tufts University Institutional Animal Care and Use Committee approved all of the experimental protocols used in these studies.

2.6. Statistical analysis

Antinociceptive responses are expressed as percent maximal possible effect (%MPE) using the formula (Dewey and Harris, 1975; Harrison et al., 1998):

$$\%MPE = \frac{\text{test latency} - \text{baseline latency}}{\text{maximum latency} - \text{baseline latency}} \times 100.$$

Where applicable IED₅₀s (the individually effective dose to produce 50% antinociceptive effect) were calculated and analyzed using oneway ANOVA followed with Bonferonni's post-hoc test to assess comparisons and differences between groups. Repeated-measures ANOVA was used to analyze the %MPEs across time with dose of D-glucose as a between-subjects factor and either dose of morphine or time after D-glucose administration as the within-subjects measure. A repeated-measures ANOVA was used to analyze the %MPEs across time with dose of D-glucose as a between-subjects factor and time after D-glucose administration and naloxone administration as within-subjects measures. Post-hoc comparisons were assessed with Bonferonni t-tests to assess group differences.

3. Experiment 1

3.1. D-glucose and morphine-mediated antinociception

Experiment 1 examined the effects of peripherally administered doses of D-glucose on antinociceptive responses to morphine. Forty male Long–Evans rats were tested for antinociceptive responses as described in the General methods section. Following the determination of baseline tail-withdrawal latencies, rats were injected (ip) with 300, 560, or 720 mg/kg D-glucose or the vehicle, sterile water, and the first dose (1.0 mg/kg) of morphine. Rats were tested for antinociceptive responses 30 min after morphine administration, and then were injected with the subsequent dose of morphine and retested on the tail withdrawal test after an additional 30 min. This procedure was repeated until the final cumulative dose of 10 mg/kg morphine was achieved.

3.2. Results

Repeated measures ANOVA was significant across doses of morphine ($F_{4,140} = 114.96$, $p < 0.0001$). The main effect for glucose indicated that glucose enhanced morphine-mediated antinociception ($F_{3,35} = 4.02$, $p = 0.02$). Post-hoc Bonferroni t-test revealed that the antinociceptive response across increasing doses of morphine in rats receiving 720 mg/kg D-glucose was elevated relative to rats receiving sterile water ($t = 23.63$, $p = 0.009$). One-way ANOVAs at the individual doses of morphine confirmed that after receiving glucose and 3.0 mg/kg morphine rats that had glucose demonstrated elevated antinociceptive responding relative to those that received sterile water and morphine ($F_{3,35} = 4.23$, $p = 0.012$). The findings summarized in Fig. 1 demonstrate that 720 mg/kg D-glucose enhanced the antinociceptive actions of morphine as assessed using post-hoc Bonferroni t-tests ($t = 34.82$, $p = 0.008$). There were no interaction effects for dose of D-glucose across increasing doses of morphine.

When IED_{50} s were used as the measure of antinociceptive behavior, rats receiving 560 and 720 mg/kg D-glucose demonstrated significant decreases in the amount of morphine that it took to produce a relative 50% antinociceptive effect (Fig. 2) (mean $\pm$ SE sterile water 5.73 ± 0.53 , 300 mg/kg glucose 3.79 ± 0.46 , 560 mg/kg glucose 4.02 ± 0.53 , 720 mg/kg glucose 3.30 ± 0.74 ; $F_{3,32} = 3.53$, $p = 0.026$). Post hoc Dunnett's t with sterile water as the common control indicated that the 300 and 720 mg/kg doses of glucose differed from the control ($p = 0.04$ and 0.017 respectively).

Blood glucose levels were measured in response to glucose and morphine administration. Testing took place one week after the original experiment to allow the drugs to clear from the rats' systems. Neither baseline blood glucose levels nor glucose levels assessed after glucose and morphine administration differed as a function of experimental conditions.

4. Experiment 2

4.1. Antinociceptive responses to D-glucose

Experiment 2 examined the ability of peripheral D-glucose administration to produce antinociceptive behavior on its own. Additionally, to determine if the effect of glucose on pain sensitivity was mediated by the endogenous opioid system, effects of the opioid-antagonist naloxone were assessed on glucose-induced antinociception. Eighty drug-naïve male Long–Evans rats were used. For two days prior to the start of the experiment, rats were given ip injections of saline to habituate them to the testing procedures. Rats were tested for baseline tail-withdrawal latency followed by an ip injection of either 0.32 mg/kg naloxone or saline. Five minutes after the naloxone or saline injection, rats were injected with 0 (sterile water), 560, 720 or 1000 mg/kg D-glucose. Tail-withdrawal latencies were assessed

12, 24 and 36 min after D-glucose administration. After testing, rats were returned to their home cages. One week later, in order to fully assess within-subjects results, all rats were again assessed for antinociceptive responses. Rats not receiving naloxone on the first trial received naloxone on the second test while those rats injected with naloxone on the first trial were injected with saline. Rats received the same dose of glucose as on the first test day. Order of drug administration and testing was counterbalanced.

4.2. Results

As no differences in antinociceptive responses were found between the two experimental days, the data for the two days were combined and analyzed together. The results of Experiment 2, as depicted in Fig. 3, demonstrate that D-glucose has antinociceptive properties on its own.

Repeated-measures ANOVA demonstrated that administration of D-glucose, ip, led to significant increases in antinociceptive responses ($F_{3,75} = 11.66$, $p < 0.0001$). Overall, differences in %MPE were detected at all times in rats that had glucose relative to those injected with sterile water ($F_{2,150} = 81.73$, $p < 0.0001$). Multivariate ANOVA revealed that %MPEs across the three measurement times were significantly elevated for rats given 560, 720 or 1000 mg/kg D-glucose relative to rats injected with sterile water ($F_{2,150} = 41.24$, $p < 0.0001$)(Fig. 3). As can be seen in Fig. 3B, naloxone administration altered the antinociceptive effects of D-glucose at 12 min after glucose exposure ($F_{2,150} = 6.46$, $p = 0.002$) but not at any other time-point. Percent MPE significantly changed across time for rats when they received both glucose and naloxone ($F_{1.734,130.085} = 54.90$, $p < 0.0001$ *Greenhouse-Geisser*). There was an interaction between the overall effects of glucose and %MPE across time that corroborates the main effect for change in %MPE seen when rats were given naloxone in addition to glucose ($F_{6,150} = 2.33$, $p = 0.035$). However, there was no three-way interaction between %MPE, glucose, and naloxone.

Post hoc Bonferroni t-tests showed that percent MPEs following administration of 560, 720 and 1000 mg/kg D-glucose were significantly higher than %MPEs following sterile water at all time-points after D-glucose injection ($t_{1,76} = 12.16$, $p = 0.002$, 14.21 , $p < 0.0001$, and 16.80 , $p < 0.0001$, corresponding to the 3 doses of glucose). When rats were given naloxone and D-glucose injections, only the %MPEs following 720 and 1000 mg/kg of D-glucose were significantly higher than those following sterile water injections ($t_{1,75} = 9.46$, $p < 0.016$ and 8.42 , $p = 0.046$, respectively). This final difference was only significant at 24 min after glucose administration.

5. Experiment 3

5.1. D- and L-glucose effects on morphine-mediated antinociception

Experiment 3 investigated whether the enhancement of morphine-mediated antinociception by ip D-glucose administration was the result of osmotic stress. Osmotic stress represents the response of an organism or cell to changes in the concentration of solutes outside the organism or cell (Stein et al., 2004). It is possible that an influx of D-glucose molecules into the peritoneum of the rat could produce an osmotic challenge to the animal, thereby, altering behavioral responses to noxious stimuli. Environmental stressors can alter morphine-mediated analgesia (Akil et al., 1986; Vaccarino and Kastin, 2001). For example, Calcagnetti and Holtzman (1992) reported that restraint stress enhanced morphine-mediated antinociception in rats and that a saccharin/glucose sweetened water solution significantly diminished that enhancement. In contrast, Hawranko and Smith (1999) found that the repeated stress of hot-plate exposure reduced the antinociceptive potency of morphine in rats. The differences in results could be attributed to the use of different types of stressors or

the use of a repetitive stressor versus an acute one. However, it can be argued that stress does alter morphine-mediated antinociceptive responses. It is possible that the ip injection of D-glucose produces acute osmotic stress. To address this issue, the following experiment examined the effects of D-glucose and its stereoisomer, L-glucose on morphine-mediated antinociception. As D- and L-glucose are molecularly mirror images of each other and have the same molecular structure (Wardlaw and Insel, 1993), they should lead to similar osmotic responses. If osmotic stress is responsible for the alterations in morphine-mediated antinociception observed in Experiment 1, then both D- and L-glucose should enhance that effect.

Fifty male Long-Evans rats were given injections of saline for two days prior to the initiation of nociceptive testing to habituate them to the testing procedures; reducing the possibility of injection-related stress as a potential confound. Baseline tail-withdrawal latencies were assessed and rats were injected with 3.2 mg/kg morphine. The dose of morphine was chosen based on the data collected in Experiment 1, which demonstrated that the greatest effect of glucose on morphine-mediated antinociception was found with a similar dose. Eighteen minutes later rats were injected with sterile water, 560 mg/kg or 720 mg/kg D-glucose, or 560 mg/kg or 720 mg/kg L-glucose. Nociceptive testing began 12 min after glucose administration and was reassessed at 24 and 36 min after injections.

5.2. Results

D-glucose enhanced morphine-mediated antinociception while its stereoisomer L-glucose did not (Fig. 4). While there was no main effect for glucose alone, there was a significant interaction for %MPEs and doses of D- and L-glucose across the three time-points ($F_{8,90} = 3.22$, $p = 0.003$) suggesting that D-glucose decreased the time it took for morphine to act. One-way ANOVAs at the three time-points revealed significant differences among the glucose groups at 12 min after glucose injection ($F_{4,45} = 3.208$, $p = 0.021$). A posteriori two-tailed Dunnett's t-tests with sterile water as the control indicated that at 12 min after glucose administration the 560 and 720 mg/kg doses of D-glucose enhanced morphine-mediated antinociception while L-glucose did not alter the pain relieving actions of morphine ($t_4 = 38.29$ mean difference, $p = 0.039$ for the 560 mg/kg glucose dose and $t_4 = 40.70$ mean difference, $p = 0.026$ for the 720 mg/kg dose). At 24 min after glucose administration, only rats receiving 560 mg/kg D-glucose still had significantly elevated tail-withdrawal latencies relative to sterile water ($t_4 = 31.20$ mean difference, $p < 0.05$).

Blood glucose levels were measured in response to glucose and morphine administration one week after testing for antinociception, as in Experiment 1. While blood glucose levels did not vary as a function of glucose or morphine injections, rats that received D-glucose demonstrated slight elevations in their blood glucose levels relative to rats receiving L-glucose or sterile water (Fig. 5).

6. Discussion

Intraperitoneal injections of glucose heightened the antinociceptive actions of morphine in the absence of taste hedonics or gustatory responses. Furthermore, administration of glucose, alone, had pain-relieving properties. As D-glucose, but not L-glucose, enhanced morphine's pain relieving actions, the antinociceptive actions of ip glucose injections do not appear to be the result of osmotic stress.

The ability of glucose to enhance morphine-mediated antinociception is consistent with research indicating that rats consuming sucrose solutions are more sensitive to the pain relieving actions of morphine than rats not given the sugar (Bergmann et al., 1985; Blass and Shide, 1994; D'Anci et al., 1997; Holder and Bolger, 1988; Kanarek et al., 1997, 2001;

Nikfar et al., 1997; Roane and Martin, 1990). Additionally, acute ingestion of a concentrated sucrose solution has been shown to produce antinociceptive responses in male Wistar rats (de Freitas et al., 2012). The present results suggest that the effects of sugar intake on morphine-induced antinociception are not solely due to the hedonic properties of the sugar solution, but, also due to the physiological consequences of ingestion. In support of this suggestion, previous studies have shown that intake of sweet-tasting nutritive solutions (e.g. sucrose), but not intake of sweet-tasting non-nutritive solutions (e.g. saccharin) increases the pain relieving actions of opioid analgesics (D'Anci et al., 1997; Marks-Kaufman et al., 1988).

As rats in the present studies did not consume a sugar solution, it could be assumed that they did not experience any hedonic response to glucose. However, previous research by Bradley and Mistretta (1971) found that rats exposed to cobalt-60 irradiation after intravenous (iv) administration of sodium saccharin produced an aversion to the oral consumption of the saccharin solution, 24 h later. The authors suggested that the conditioned aversion was an indication that the rats perceived a taste from the iv saccharin injection and subsequently associated that taste with the negative experience of gamma radiation. It is important to note that the authors also indicated that an aversion is not produced when the saccharin is administered by ip injection, likely because this route of administration does not result in a high enough blood concentration of the sweetener. Rats in the current experiments received the glucose injections intraperitoneally.

Glucose injections not only enhanced morphine-mediated antinociception, but also had pain-relieving properties on their own. Rats that were tested for antinociception in response to glucose alone had higher %MPEs than rats injected with sterile water. It is interesting that the opiate-receptor antagonist, naloxone, altered the response pattern of rats to D-glucose, specifically decreasing the antinociception at 12 min after glucose administration. This result is consistent with Rebouças et al. (2005) who found that μ_1 -opioid receptor antagonists decreased chronic sucrose-induced antinociceptive behaviors and imply that, to some degree, glucose could be producing its antinociceptive actions through an opioid-mediated mechanism. However, these results are not definitive and further testing using a wider range of doses of naloxone and other opioid antagonists is needed; particularly because the dose of naloxone used was rather small and because naloxone is a general opiate receptor antagonist (Bianchi and Panerai, 1993; Pasternak, 1993). The use of a selective μ -opiate receptor antagonist, such as β -funaltrexamine could help clarify this relationship. To this end, an experiment was run in which β -funaltrexamine was administered 36 h prior to the assessment of antinociception in response to ip glucose administration. The results of this experiment demonstrated again, that glucose alone produced antinociception but, importantly, that β -funaltrexamine significantly diminished the glucose-mediated antinociception (Yamamoto and Kanarek, 2005).

It was important to ascertain whether the glucose solution was producing its antinociceptive actions as a result of osmotic stress. The 560 and 720 mg/kg doses of glucose have molarities of 3.1 and 4.0 respectively and could potentially be altering antinociceptive behaviors through stress mechanisms (Calcagnetti and Holtzman, 1992). To test this possibility, the actions of D-glucose were compared to those of its stereoisomer, L-glucose, which has the same molarity, on morphine-mediated antinociception. D-Glucose significantly enhanced morphine-mediated-antinociception while L-glucose and sterile water did not, demonstrating that the effects of D-glucose were not due to osmotic stress. Furthermore, this experiment helps to resolve the issue of whether the rats possibly tasted the injected glucose as L-glucose has been found to produce a sweet taste similar to that of D-glucose when sampled orally (Shallenberger, 1997). Additionally, recent studies demonstrating that administration of glucose directly into the periaqueductal gray also augments the pain

relieving properties of morphine (Yamamoto and Kanarek, 2005) indicates that osmotic stress is not a major factor in determining the effect of glucose on pain-related behaviors. Rather, it is hypothesized that glucose-induced alterations in central pain mechanisms are mediating the sugar's actions on pain-response behavior.

The present results indicate that gustatory responses to a sugar are not necessary to alter pain sensitivity. However, these results do not imply that the hedonic features of orally consumed sweet-tasting solutions do not contribute to the effects of these substances on pain-related behaviors. Indeed, research has shown that administration of a very small quantity of a sugar solution into the oral cavity of infant rats and human infants leads to analgesia (Axelin et al., 2009; Blass et al., 1987; Smith et al., 1990; Stevens et al., 2013). Pain relief begins within 30 s of exposure to the sweet solution. The small quantity of sugar needed and the time course of analgesia suggest that the palatability of the solution is key to its pain relieving actions. Additional evidence of the importance of palatability, in this situation, comes from work demonstrating that non-nutritive, as well as nutritive solutions induce analgesia (Barr et al., 1999; Rani and Gupta, 2012), while administration of the solution directly into the stomach fails to produce analgesia (Ramenghi et al., 1999). Studies demonstrating that pre-treatment with an opioid antagonist blocks the pain relieving effects of sweet-tasting solutions in young organisms indicate that the endogenous opioid system plays a role in determining these effects (Rebouças et al., 2005).

Understanding the interaction between glucose, opiate drugs, and the opioid system has implications for a number of clinically pertinent problems including pain management and drug addiction. For example, opiate drugs are among the most potent pain relievers, yet they are frequently under-prescribed by physicians concerned with the potential for development of tolerance and addiction (NIDA, 2011). Knowledge of the effects of dietary sugars on the analgesic actions of opiate drugs could facilitate more effective use of drug therapies for pain management.

Acknowledgments

This work was supported by an Individual National Research Service Award (grant 5F31 DA15258) from the National Institutes on Drug Abuse at the National Institutes of Health, to R. T. Yamamoto, a predoctoral trainee, under the sponsorship of R. B. Kanarek; grant DA02132, National Institutes on Drug Abuse.

Abbreviations

MMA	morphine mediated antinociception
EOS	endogenous opioid system

References

- Akil H, Young E, Walker JM, Watson SJ. The many possible roles of opioids and related peptides in stress-induced analgesia. *Ann N Y Acad Sci.* 1986; 467:140–53. [PubMed: 2942087]
- Axelin A, Salantera S, Kirjavainen J, Lehtonen L. Oral glucose and parental holding preferable to opioid in pain management in preterm infants. *Clin J Pain.* 2009; 25:138–45. [PubMed: 19333160]
- Barr RG, Pantel MS, Young SN, Wright JH, Hendricks LA, Gravel R. The response of crying newborns to sucrose: is it a “sweetness” effect? *Physiol Behav.* 1999; 66:409–17. [PubMed: 10357429]
- Bergmann F, Leiblich I, Cohen E, Ganchrow JR. Influence of intake of sweet solutions on the analgesic effect of a low dose of morphine in randomly bred rats. *Behav Neural Biol.* 1985; 44:347–53. [PubMed: 4084181]

- Bianchi M, Panerai AE. Naloxone-induced analgesia: involvement of κ -opiate receptors. *Pharmacol Biochem Behav.* 1993; 46:145–8. [PubMed: 8255904]
- Blass EM, Shide DJ. Some comparisons among the calming and pain-relieving effects of sucrose, glucose, fructose and lactose in infant rats. *Chem Senses.* 1994; 19:239–49. [PubMed: 7914461]
- Blass E, Fitzgerald E, Kehoe P. Interactions between sucrose, pain and isolation distress. *Pharmacol Biochem Behav.* 1987; 26:483–9. [PubMed: 3575365]
- Bradley RM, Mistretta CM. Intravascular taste in rats as demonstrated by conditioned aversion to sodium saccharin. *J Comp Physiol Psychol.* 1971; 75:186–9. [PubMed: 5087375]
- Calcagnetti DJ, Holtzman SG. Intake of sweet water attenuates restraint-stress-induced potentiation of morphine analgesia in rats. *Brain Res Bull.* 1992; 296:859–64. [PubMed: 1473017]
- D'Amour FE, Smith DL. A method for determining loss of pain sensation. *J Pharmacol Exp Ther.* 1941; 72:74–9.
- D'Anci KE. Tolerance to morphine-induced antinociception is decreased by chronic sucrose or polycose intake. *Pharmacol Biochem Behav.* 1999; 63:1–11. [PubMed: 10340517]
- D'Anci KE, Kanarek RB, Marks-Kaufman R. Duration of sucrose availability differentially alters morphine-induced analgesia in rats. *Pharmacol Biochem Behav.* 1996; 54:693–7. [PubMed: 8853191]
- D'Anci KE, Kanarek RB, Marks-Kaufman R. Beyond sweet taste: saccharin, sucrose and polycose differ in their effects upon morphine-induced analgesia. *Pharmacol Biochem Behav.* 1997; 56:341–5. [PubMed: 9077567]
- de Freitas RL, Kübler JML, Elias-Filho DH, Coimbra NC. Antinociception induced by acute oral administration of sweet substance in young and adult rodents: the role of endogenous opioid peptides chemical mediators and μ_1 -opioid receptors. *Pharmacol Biochem Behav.* 2012; 101:265–70. [PubMed: 22197708]
- Dewey, WL.; Harris, LS. The tail flick test.. In: Ehrenpreis, S.; Neidle, A., editors. *Methods in narcotics research.* Marcel Dekker; New York: 1975. p. 101-9.
- Dum J, Gramsch DH, Herz A. Activation of β -endorphin pools by reward induced by highly palatable food. *Pharmacol Biochem Behav.* 1983; 18:443–7. [PubMed: 6132412]
- Gagin R, Cohen E, Shavit Y. Prenatal exposure to morphine alters analgesic responses and preferences for sweet solutions in adult rats. *Pharmacol Biochem Behav.* 1996; 55:629–34. [PubMed: 8981594]
- Harrison LM, Kastin AJ, Zadina JE. Opiate tolerance and dependence: receptors g-proteins and antiopeptides. *Peptides.* 1998; 19:1603–30. [PubMed: 9864069]
- Hawranko AA, Smith DJ. Stress reduces morphine's antinociceptive potency: dependence upon spinal cholecystokinin processes. *Brain Res.* 1999; 824:251–7. [PubMed: 10196456]
- Holder MD, Bolger GT. Chronic sweet intake lowers pain thresholds without changing brain μ - and δ -opiate receptors. *Behav Neural Biol.* 1988; 50:335–43. [PubMed: 2849410]
- Jewett DC, Grace MK, Levine AS. Chronic sucrose ingestion enhances μ -opioid discriminative stimulus effects. *Brain Res.* 2005; 1050:48–52. [PubMed: 15967419]
- Kanarek RB, Homoleski BA. Gender and the modulation of morphine-induced analgesia by the chronic intake of palatable solutions. *Pharmacol Biochem Behav.* 2000; 66:653–9. [PubMed: 10899384]
- Kanarek RB, White ES, Biegen MT, Marks-Kaufman R. Dietary influences on morphine-induced analgesia in rats. *Pharmacol Biochem Behav.* 1991; 38:681–4. [PubMed: 2068206]
- Kanarek RB, Przypek J, D'Anci KE, Marks-Kaufman R. Dietary modulation of μ and κ opioid receptor-mediated analgesia. *Pharmacol Biochem Behav.* 1997; 58:43–9. [PubMed: 9264068]
- Kanarek RB, Homoleski BA, Wiater C. Intake of a palatable sucrose solution modifies the actions of spiradoline, a κ opioid receptor agonist, on analgesia and feeding behavior in male and female rats. *Pharmacol Biochem Behav.* 2000; 65:97–104. [PubMed: 10638642]
- Kanarek RB, Mandillo S, Wiater C. Chronic sucrose intake augments antinociception induced by injections of μ but not κ opioid receptor agonists into the periaqueductal gray matter in male and female rats. *Brain Res.* 2001; 920:97–105. [PubMed: 11716815]

- Mandillo S, Kanarek RB. Chronic sucrose intake enhances nicotine-induced antinociception in female but not male long–evans rats. *Pharmacol Biochem Behav.* 2001; 68:211–9. [PubMed: 11267625]
- Marks-Kaufman R, Kanarek RB, Delanty SN. Sweet-tasting solutions modify the analgesic properties of morphine in rats. *FASEB J.* 1988; 2:a1567.
- Marks-Kaufman R, Hamm MW, Barbato GF. Effects of dietary sucrose on opiate receptor binding in genetically obese (ob/ob) and lean mice. *J Am Coll Nutr.* 1989; 8:9–14. [PubMed: 2538498]
- Morgan D, Picker MJ. Contribution of individual differences to discriminative stimulus, antinociceptive and rate-decreasing effects of opioids: importance of the drug's relative intrinsic efficacy at the mu receptor. *Behav Pharmacol.* 1996; 7:261–84. [PubMed: 11224419]
- NIDA. Prescription drugs: abuse and addiction. National Institute on Drug Abuse. 2011. 2013. <http://www.drugabuse.gov/publications/research-reports/prescription-drugs>
- Nikfar S, Abdollahi M, Etemad F, Sharifzadeh M. Effects of sweetening agents on morphine-induced analgesia in mice by formalin test. *Gen Pharmacol.* 1997; 29:583–6. [PubMed: 9352306]
- Pasternak GW. Pharmacological mechanisms of opioid analgesics. *Clin Neuropharmacol.* 1993; 16:1–18. [PubMed: 8093680]
- Pomonis JD, Jewett DC, Kotz CM, Briggs JE, Billington CJ, Levine AS. Sucrose consumption increases naloxone-induced c-fos immunoreactivity in limbic forebrain. *Am J Physiol Regul Integr Comp Physiol.* 2000; 278:R712–9. [PubMed: 10712293]
- Ramenghi LA, Evans DJ, Levene MI. “Sucrose analgesia”: absorptive mechanism or taste perception? *Arch Dis Child Fetal Neonatal Ed.* 1999; 80:F146–7. [PubMed: 10325795]
- Rani S, Gupta MC. Evaluation and comparison of antinociceptive activity of aspartame with sucrose. *Pharmacol Rep.* 2012; 64:293–8. [PubMed: 22661178]
- Rebouças EC, Segato EN, Kishi R, Freitas RL, Savoldi M, Morato S, et al. Effect of the blockade of mu1-opioid and 5ht2a-serotonergic/alpha1-noradrenergic receptors on sweet-substance-induced analgesia. *Psychopharmacology (Berl).* 2005; 179:349–55. [PubMed: 15821952]
- Roane DS, Martin RJ. Continuous sucrose feeding decreases pain threshold and increases morphine potency. *Pharmacol Biochem Behav.* 1990; 35:225–9. [PubMed: 2179969]
- Shallenberger RS. Taste recognition chemistry. *Pure Appl Chem.* 1997; 69:659–66.
- Smith BA, Fillion TJ, Blass EM. Orally mediated sources of calming in 1- to 3-day-old human infants. *Dev Psychol.* 1990; 26:731–7.
- Spangler R, Wittkowski KM, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF. Opiate-like effects of sugar on gene expression in reward areas of the rat brain. *Brain Res Mol Brain Res.* 2004; 124:134–42. [PubMed: 15135221]
- Stein L, McCouch S, Cartinhour S, Ware D, Jaiswal P. Summary for go term: response to osmotic stress. *Gramene.* 2004
- Stevens B, Yamada J, Lee GY, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev.* 2013; 1:CD001069. [PubMed: 23440783]
- Suri M, Jain S, Mathur R. Pattern of biphasic response to various noxious stimuli in rats ingesting sucrose ad libitum. *Physiol Behav.* 2010; 101:224–31. [PubMed: 20580642]
- Vaccarino AL, Kastin AJ. Endogenous opiates: 2000. *Peptides.* 2001; 22:2257–328. [PubMed: 11786209]
- Wardlaw, GM.; Insel, PM. Perspectives in nutrition. 2nd ed.. Mosby-Year Book, Inc.; United States: 1993.
- Yamamoto, RT.; Kanarek, RB. Tufts University; 2005. Unpublished observations
- Yamamoto T, Sako N, Maeda S. Effects of taste stimulation on beta-endorphin levels in rat cerebrospinal fluid and plasma. *Physiol Behav.* 2000; 69:345–50. [PubMed: 10869601]

Fig. 1.

Experiment 1: Intraperitoneal (ip) α -glucose injections increased the percent maximal possible effect (%MPE) to a cumulative dose of morphine in rats, relative to control rats injected with sterile water ($F_{3,35} = 4.02$, $p = 0.02$), with the strongest effect following the 3.0 mg/kg dose of morphine ($F_{3,35} = 4.23$, $p = 0.01$). The 720 mg/kg dose of α -glucose was significantly elevated across doses of morphine, relative to sterile water ($t_{\text{Bonferroni}} = 23.63$, $p = 0.009$). ** $p < 0.01$.

Fig. 2.

Experiment 1: IED₅₀s were lower in rats receiving 300 and 500 mg/kg glucose relative to sterile water ($F_{3,32} = 3.53$, $p = 0.026$). * $p < 0.05$.

Fig. 3.

A. Experiment 2: %MPEs of rats injected with glucose, ip, were significantly greater than of rats injected sterile water across all time points ($F_{3,75} = 11.66$, $p < 0.0001$) and at each dose of D -glucose (560 $t_{1,76} = 12.16$, $p = 0.002$, 720 $t_{1,76} = 14.21$, $p < 0.0001$, and 1000 mg/kg glucose $t_{1,76} = 16.80$, $p < 0.0001$). ** $p < 0.01$. B. Experiment 2: Glucose-mediated antinociception was altered after naloxone administration as measured by %MPEs. At 12 min after glucose and naloxone injections, %MPEs of glucose were lower than when rats received glucose and saline ($F_{2,150} = 6.46$, $p = 0.002$). With naloxone, only the %MPEs at 24 min post injection for 720 and 1000 mg/kg glucose remained elevated relative to sterile water ($t_{1,75} = 9.46$, $p = 0.016$ and 8.42 , $p = 0.046$, respectively) * $p < 0.05$ and ** $p < 0.01$.

Fig. 4.

Experiment 3: Intraperitoneal injection of D-glucose, but not L-glucose, altered tail-withdrawal latencies of rats in response to a low, 3.2 mg/kg, dose of morphine, relative to sterile water injection as demonstrated by %MPE. Morphine-mediated antinociception was elevated more rapidly following D-glucose and began to decrease sooner than L-glucose and sterile water ($F_{8,90} = 3.22$, $p = 0.003$). At 12 min after glucose and morphine injections, the %MPEs of both doses of D-glucose, but not L-glucose were significantly elevated relative to sterile water ($F_{4,45} = 3.208$, $p = 0.021$). * $p < 0.05$.

Fig. 5. Example of blood glucose levels from Experiment 3: Blood glucose levels were not different after any combination of ip injections of D -glucose, L -glucose or sterile water with saline or 3.2 mg/kg morphine.