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Interactions Between Sucrose, Pain and Isolation Distress

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BLASS, E , E FITZGERALD AND P KEHOE *Interactions between sucrose, pain and isolation distress* PHARMACOL BIOCHEM BEHAV 26(3) 483–489, 1987 —Two experiments were conducted that establish an opioid-based, functional-relationship between the taste of sucrose, pain threshold and distress vocalization in isolated 10-day-old albino rats In the first experiment intraoral infusion of sucrose virtually doubled heat-withdrawal latencies This elevation was naltrexone (0 5 mg/kg b wt) reversible In the second experiment sucrose infusions caused a rapid and sustained diminution of distress vocalizations in rats totally isolated from dam and siblings These are the first demonstrations of a causal relationship between a positive affective system and ones mediating pain and stress

Sucrose Pain Isolation distress

SINCE the discovery of endogenous central opioids and their receptors many studies have assessed the possible contribution of opioid systems to the control of various behaviors [28, 33, 36]. These efforts have been rewarded as opioid peptides and their antagonists have been shown to influence the expression of various behaviors of both positive (ingestion) and negative (pain) valence Thus, non-deprived rats injected with morphine [15,34] or other opiate agonists [26,34] eat somewhat more than vehicle-treated rats Naloxone or naltrexone, opioid receptor antagonists, reverse this effect [10,27] and also somewhat reduce the amount of food eaten spontaneously by food-deprived rats [5a,14] These blockers similarly affect water intake elicited by a number of stimuli associated with dehydration; cellular dehydration, for example [5,5a].

The relationship between the ingestion of palatable solutions, sugar or saccharin for example, and the opioids has also been explored [33]. Naloxone sharply reduces intake of saccharin and sucrose solutions [19] Naloxone also causes a loss of preference for sweet solutions over water [19,35], a most remarkable finding. Interestingly though, total fluid consumption is not reduced below water intake [19]

In the realm of negative affect, central or peripheral opiate administration causes analgesia even in rats as young as 10-days of age [16]. This, too, is naloxone-reversible. Interactions among stressors have also been evaluated. Thus, repeated exposure to shock lengthens escape latencies [20], ice baths [4] and tail pinch [1] have the same effect. Some of these so called stress-induced analgesias are also naloxone-reversible Like deprivation-induced feeding, however, baseline latencies are resistant to antagonist treatment [9].

In addition to palliating physical stress, opioids appear to ease social distress. Panksepp and his colleagues, for example, have demonstrated that separation-distress vocalizations in chicks [31], puppies and infant guinea pigs are reduced by exogenous opiates [30], a finding replicated in 10-day-old rats by Kehoe and Blass [17]. The latter investigators also demonstated that distress influenced pain thresholds. Isolated pups removed their paw from a 48°C surface with a greater latency than non-isolated siblings, an exaggeration which also was naloxone reversible. These findings of distress exaggerating paw lift latency exactly parallel those obtained by morphine administration

Interactions between negative and positive affective states that are opioid mediated have been explored, although the studies have almost excusively evaluated how stress affects ingestion. Tail pinch, which causes a naloxone-reversible increased pain threshold [1] also elicits naloxone-reversible feeding [26]. Interestingly, sweet foods are preferentially ingested under stress [2].

The other side of the interactions among positive and negative affective systems that are opioid-mediated remains unexplored except for two studies. In one, Lieblich, Cohen, Ganchrow, Blass and Bergmann [22] demonstrated that a "high-affect" strain of rats bred to drink more of sweet solutions [8] and to work more for stimulation of the medial forebrain bundle [21] showed elevated paw lift latencies after drinking a 3 mM saccharin solution as their sole fluid source for 28 days High-affect siblings maintained on water and "low-affect" rats that also drank the sweet solution did not present the elevated latency. Lieblich *et al* [22] also demonstrated naloxone reversibility.

Le Magnen *et al* [19] also suggest an interrelationship between positive and negative affective systems Naloxone elevated the acceptance threshold for quinine and caused a flattening of the glucose and saccharin preference functions. This was an important study conceptually but did not establish a functional link between appetitive and aversive opioid-mediated systems.

The present studies seek to directly establish a causal link between positive and negative affective systems in 10-day-old albino rats by evaluating if and how intraoral infusions of

sucrose affect distress vocalizations in isolated (i.e., socially stressed) rats and their withdrawal latencies from the heat There was reason to believe that such interactions would be forthcoming. First, the Lieblich *et al.* [22] and Le Magnen [19] studies pointed in that direction Second, morphine influences the expression of both sweet ingestion and of withdrawal from pain. Third, stress elicits naloxone-reversible feeding behavior It was possible, therefore, that ingestion of sweet, through an opioid intermediary (among others), should ease stress. The present experiments provide data in support of these hypotheses

GENERAL METHOD

Subjects

Subjects were the progeny of Sprague-Dawley albino rats (Camm Laboratories, Wayne, NJ) mated and bred in our colony Pregnant females (nulliparous and multiparous) were housed 7–10 days prepartum in plastic cages (38×30×77 cm) covered with stainless steel wire lids The floor of each cage was covered with a bedding of wood shavings; Purina rat chow and water were available ad lib in the cage top Temperature was kept constant at 25°C, humidity uncontrolled. Lights were on in the colony room from 0700 to 2100 hours daily.

Pregnant females were checked late in the afternoon of each day for births Pups then discovered were considered born on that day and designated 0 days of age, on the day after birth they were designated as 1-day-of-age, etc On the day after birth, litters were culled to 10 pups In all experiments, 10-day-old pups weighing between 19–28 g were used and each pup was studied once only.

Surgical Procedures

Pups assigned to operated conditions received intraoral cannulae [12] 2–6 hr prior to the testing session The 10 cm cannulae were constructed from PE-10 Intramedic Polyethylene Tubing (Clay-Adams) by flanging one end with heat Implantation was accomplished by using a curved length of piano wire, one end attached to the cannula, the other inserted beneath the tongue of the animal and maneuvered out the ventral surface of the jaw The surgical procedure was completed in about 20 sec

Testing Environment

All testing was conducted in an environmentally controlled chamber (Forma Scientific, Inc.), that maintained a constant temperature of 32 5°C at approximately 90% humidity

Apparatus

A heat-stimulation procedure designed for testing 10-day-old rats [16] was employed. The apparatus consisted of a stainless steel hot plate (maintained at 48–49°C) connected in series with a variable DC power supply and a clock/counter (Lafayette Instrument Co), accurate to 0 001 sec The pup's right forelimb, two hindlimbs, and trunk were gently yet firmly supported in the experimenter's right hand allowing the animal's left forelimb to rest lightly on the surface of the hot plate

Substances

Four different substances were used in these experiments 3.5%, 7 5%, and 11 5% sucrose and distilled water Sucrose solutions were made using distilled water and crystal sucrose, C12-H22-011 (J T. Baker Chemical Co.), mixed by weight Solutions were warmed prior to infusion to 32–34°C

Substance Delivery

Pups were infused with their designated substances using a hypodermic syringe attached to a length of PE-50 Intramedic Polyethylene Tubing (Clay-Adams) which in turn was attached to the individual pup's cannula The fluid was delivered via an infusion pump (Sage Instruments) at the rate of 0.06 cc/min Delivery time for 0 2 cc of fluid, i e , approximately 1% of the animal's body weight, was 3 min, 20 sec

Statistical Evaluation

Statistical evaluation consisted of two-way analysis of variance, fixed effects design, one-way analysis of variance, non-repeated measures design, and *post hoc* analysis using Tukey's HSD, as designated in each experiment [13]

EXPERIMENT 1

In Experiment 1 we demonstrate an exaggeration in paw lift latency in non-stressed rats as a result of intraoral infusions of different sucrose concentrations The enhancement is fully naltrexone reversible

EXPERIMENT 1a

This experiment established analgesic consequences of sucrose infusion in 10-day-old rat pups Pups were infused with either 7 5% sucrose, distilled water, or no substance and then tested on a hot plate after specified time periods to determine paw lift latency The time lags evaluated if the analgesia persisted after the taste had presumably diminished in intensity through saliva-dilution, habituation, or both

Procedure

Eighty pups 10 days of age were studied Each was assigned to one of three substance conditions 7 5% sucrose (S), distilled water (W), and no substance (NS), and to one of four time conditions 0, 1, 3, or 5 minutes after delivery completion There were a total of ten groups in all, as follows S-0, S-1, S-3, S-5, W-0, W-1, W-3, W-5, NS(cannulated)-0, NS(non-cannulated)-0 No two pups in any given litter were ever assigned to the same condition

The pups were cannulated 2 to 6 hr prior to the test session as described above and returned to the dam All pups in a particular session were then removed from the dam 15 minutes prior to the start of the session, group-housed in a Plexiglas bin containing soiled nest-chips, and allowed to acclimate to the testing environment

Each pup was infused with its designated substance and at the completion of the infusion, allowed to remain with the group for its specified time period The pup was then tested on a hot plate (48–49°C) for paw lift latency [16] Latency (in sec) was determined and the hot plate temperature verified (Tele-thermometer, Yellow Springs Instrument Co , Inc)

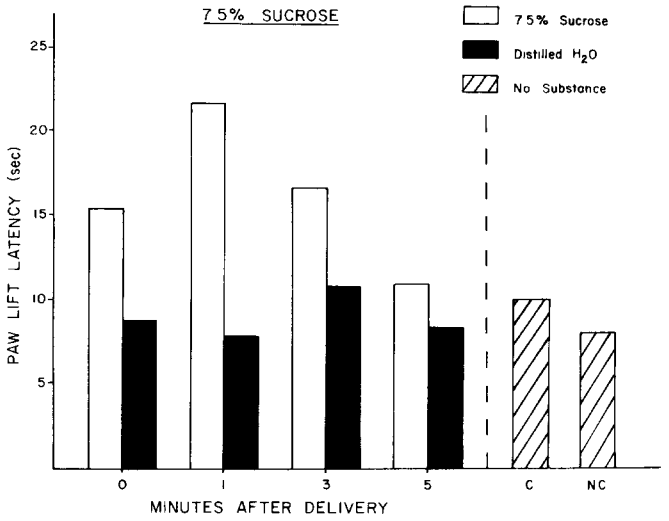

FIG 1 Mean paw lift latencies in 10-day-old rats following intraoral infusions of 7 5% sucrose solution or water at time delays of 0, 1, 3 and 5 min from the end of the infusion period c—Cannulated rats did not receive infusions, NC—non-cannulated control rats

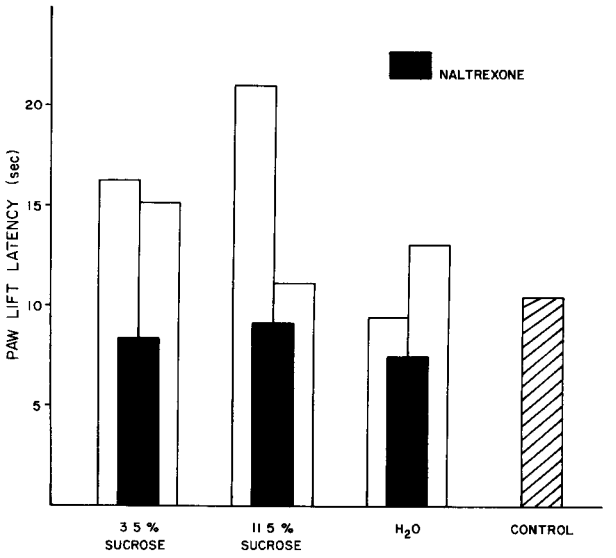

FIG 2 Paw lift latencies at 1 and 3 min past infusion following intraoral infusions of 3 5 or 11 5% sucrose solution or water in rats receiving intraperitoneal injections of naltrexone (filled histograms) or isotonic saline (open histograms)

The pup's snout and ventral temperatures were determined as well as its gender, and the pup returned to the group To control for possible experimenter bias, one experimenter controlled the infusion procedure, another the paw lift latency procedure

RESULTS

Sucrose (7 5%) infusions markedly elevated paw lift latencies relative to those of rats receiving either water infusions or no infusions at all (Fig 1). A two-way analysis of variance, fixed effects design (2×4 factorial, i e., substances × time delay) revealed significant differences between solutions, $F(1,56)=37\ 00$, $p<0.01$, but no significant differences across time-delay treatments. The interaction between the two variables was statistically significant, $F(3,56)=3\ 73$, $p<0\ 05$, as is obvious from Fig 1. Analysis of variance of conditions W-0, NS(cannulated)-0, NS(non-cannulated)-0 yielded significant main effects, $F(2,21)=4.576$, $p<0.05$, and Tukey's HSD was significant between operated and non-operated controls, $q(3,23)=6\ 4$, $p<0\ 05$

DISCUSSION

Pain threshold was significantly elevated by intraoral infusion of a 7 5% sucrose solution in day 10 rats as compared to water-infused controls Additionally, the significant interaction between substance and time indicates that animals infused with 7 5% sucrose returned to group-housing, and allowed to wait for one or three minutes before testing, demonstrated a more marked difference in paw lift latency from water-infused rats It would appear that under the parameters of the current experiments peak analgesia occurred a few minutes after infusion, and was not sustained This suggests that central changes have to be maintained by peripheral sweet stimulation and are rather tightly linked peripherally. The rats may have habituated to the lingering sweet taste or had it diluted by saliva

Latencies of operated control pups was significantly elevated compared to those in the non-operated condition. This indicates analgesia induced by surgical stress and by bearing the cannula It would appear that such effects are reversed by the infusion of fluids, as seen in the latencies of the water animals However, animals receiving the 7 5% sucrose solution infusion had significantly higher latencies than those of the water-infused pups and of operated pups. Perhaps a dual phenomenon is in effect in which the stress (cannulation) induced analgesia is reversed by the infusion of fluids over the tender area, possibly reducing pain, 7.5% sucrose again induces analgesia, but by virtue of its sweetness

EXPERIMENT 1b

Experiment 1b assesses the reliability of sucrose-induced analgesia by testing day 10 rats for paw lift latencies after 3 5% or 11 5% sucrose solution infusions In this experiment we also determine whether the analgesia was opioid mediated This was achieved by treating certain sucrose-infused rats with the opioid antagonist naltrexone. Specifically, animals were infused with either 3 5% sucrose, 11 5% sucrose, distilled water, or no substance Paw lift latency was assessed at 1 or 3 min after completion of substance delivery Additionally, certain animals were injected with naltrexone 30 min prior to infusion and tested 1 min after delivery completion for each of the three substances

Procedure

Eighty-three pups, 10 days of age, were studied Each rat

was assigned to one of four substance conditions. 3.5% sucrose (3 5), 11 5% sucrose (11 5), distilled water (W), and no substance (NS), to one of two time conditions 1 and 3 min after delivery completion, and to one of two injection conditions· naltrexone (N) and no injection (C). There were a total of ten groups in all 3 5-1-C, 3 5-1-N, 3 5-3-C, 11 5-1-C, 11.5-1-N, 11 5-3-C; W-1-C, W-1-N, W-3-C; NS-C No two pups in any one litter were assigned to the same condition

The pups were tested as described above with the exception that pups in the injection condition (N) received an intraperitoneal injection 0 5 mg naltrexone/kg body weight prior to removal from the dam, and tested 15 min after the injection, (i e , 1 min after infusion termination).

RESULTS

Relative to non-infused control pups and those receiving water, 3 5% sucrose infusions enhanced paw lift latencies at 1 and 3 min after infusion and 11 5% sucrose was very effective at 1 min but not at 3 min (Fig 2) Moreover, naltrexone reduced paw lift latencies for the three test conditions to about 8 sec, i.e , the value of unoperated control rats in Experiment 1a, a value that we have consistently obtained with very little variability in control 10-day-old rats during the past three years of study [16,17]. These findings were confirmed by analysis of variance which yielded a significant main effect for naltrexone injections, $F(1,42)=17\ 0$, $p<0.01$, and for substance infused, $F(2,42)=4.92$, $p<0\ 05$·

DISCUSSION

Experiments 1a and 1b have demonstrated that sucrose (3 5, 7.5 and 11 5%) infusions reliably caused a substantial increase in paw lift latency in rats group-housed with their siblings until the time of testing The increased latency is not due to infusion per se, as siblings that received water infusions presented shorter latencies at virtually all points tested Moreover, the elevation was naltrexone-reversible, thereby suggesting that sucrose infusions caused a release of endogenous opioids that became available to central mechanisms subserving pain

EXPERIMENT 2

Exogenous opiates also determine how animals respond to stress This is especially clear in developing chicks [32], rats, guinea pigs, and puppies [30] in which distress vocalizations (or other measures such as tail wagging in dogs) caused by separation are reduced by opiate adminstration Moreover, adminstration of opioid antagonists increases rates of distress vocalization implicating an endogenous opiate system in modulating the frequency of ultrasonic calling. Thus, rate of distress vocalization may serve as a behavioral bioassay for opioid mediation in isolated pups Accordingly, Experiment 2 seeks to establish whether intraoral sucrose infusions, like exogenous opiate injections, will diminish distress vocalizations in isolated 10-day-old rats The logic of Experiment 1 was followed by establishing the phenomenon in Experiment 2a and then evaluating some of its properties in Experiment 2b

EXPERIMENT 2a

In Experiment 2a, pups were infused with either 7 5% sucrose, distilled water or no substance and their distress vocalizations, as captured by an ultraonic detection device, were recorded over a 6 min time period

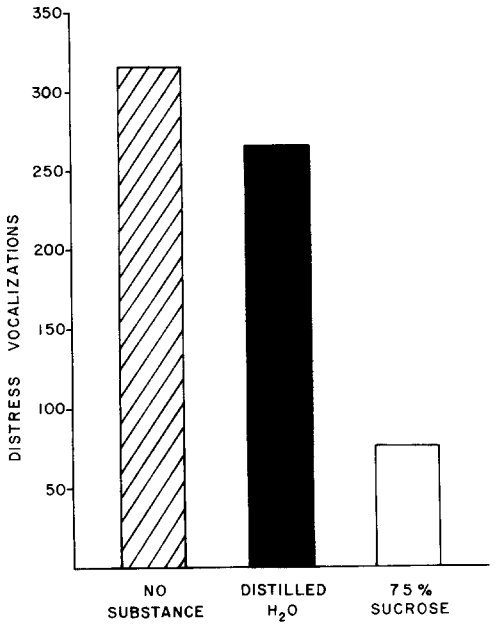

FIG 3 Total number of distress vocalizations in sucrose-infused rats and then control siblings Test duration was six min

Experimental Design

Twenty-four pups, 10 days of age, were tested in this experiment Each was assigned to one of three substance conditions 7 5% sucrose (S), distilled water (W), or no substance (NS) Each litter contributed a maximum of 3 pups/group Pups received intraoral cannulae 2 to 6 hr prior to the testing session, as described above, and were returned to the dam, where they remained until each individual testing session A pup was removed from the mother, nest, and siblings immediately before its testing session, placed in a styrofoam cup ($3^3/4''$ diam × $2^1/4''$) with clean wood shavings in the environmentally controlled chamber, and attached to the infusion apparatus, infusions started immediately

Pup distress vocalizations, as detected by an ultrasonic bat-detector (QMC Instruments) set at 45 kHz frequency, were determined from the start of the infusion on a minute-by-minute basis by hand counter Each pup received a 0 2 cc infusion of its designated substance in approximately 200 sec and the session was terminated after six minutes

RESULTS

Intraoral infusions of 7 5% sucrose markedly attenuated 6 min distress vocalizations in day 10 rats (Fig. 3) The differences between DVs of sucrose-infused rats and their controls were statistically significant, $F(2,21)=62\ 66$, $p<0\ 01$ The diminution was seen immediately (Fig 4) Rats receiving sucrose infusions emitted about 60% the number of DVs

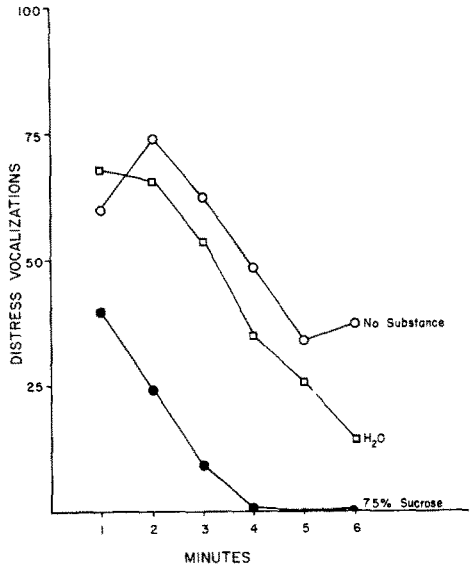

FIG 4 Time course of distress vocalizations in sucrose-infused and control rats isolated from their dam and siblings

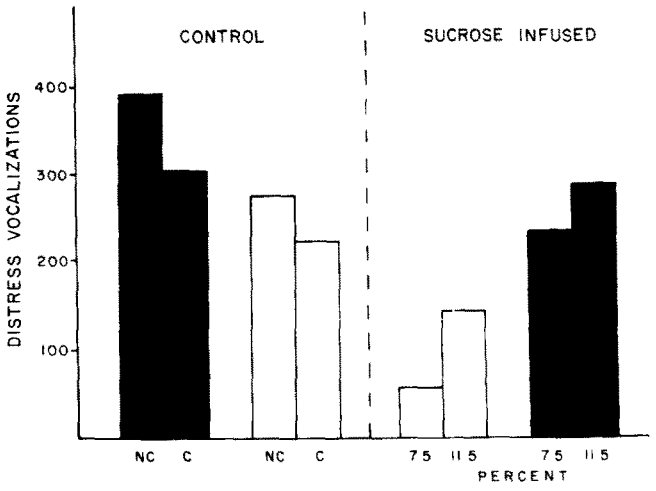

FIG 5 Total number of distress vocalizations emitted by 10-day-old isolated rats that received intraoral sucrose infusions or control treatments following IP injections of naltrexone (0 5 mg/kg b wt) or isotonic saline

as littermate controls The reduction was sustained as sucrose-infused animals were silent during the last 3 min of the 6 min test period This demonstrates, incidentally, that reduced vocalizing could not be attributed to interference by the infusion as infusions were terminated at 2 min 30 sec We find it of interest that the same pattern of a very low initial rate of calling with a rapid fall-off was also seen in isolated rats that received morphine injections [16]

EXPERIMENT 2b

Experiment 2b tested· (a) whether the distress vocalization reduction brought about by sucrose is dose related, and (b) whether naltrexone affects the sucrose-induced reduction of distress vocalizations in 10-day-old rats To achieve this, animals were infused with either 7.5% or 11.5% sucrose or no substance, and their distress vocalization profile was assessed over an 8-min time period The 8 min period replaced that of 6 min due to the possible comparisons to be drawn between this experiment and Experiment 1 (i.e., circa 3 min infusion and up to 5 min of waiting). In addition, all animals were injected with either saline or naltrexone 15 min prior to their individual testing sessions to control for injection effects

Experimental Design

Sixty-four pups, 10 days of age, were tested in this experiment Each was assigned to one of three substance conditions 7.5% sucrose (7 5); 11 5% sucrose (11.5), and no substance (NS), and to one of two injection conditions naltrexone (NX) and saline (S). There were a total of 8 groups in all as follows 7 5-NX, 7 5-S; 11.5-NX, 11 5-S, NS(cannulated)-NX, NS(cannulated)-S, NS(non-cannulated)-NX; NS(non-cannulated)-S No two pups from any one litter ever received the same treatment

The pups were tested in the same manner as in Experiment 2a with the following exceptions all pups were injected with either saline or naltrexone (0.5 mg/kg) 15 min prior to their individual testing session and the isolation time period was increased to 8 min

RESULTS

As in Experiment 2a, intraoral infusions of sucrose reduced the number of distress vocalizations emitted by isolated 10-day-old rat pups. This is appreciated by comparing in Fig 5 the open columns between control and sucrose-infused pups The reduction was marked sucrose-infused pups emitted about 50% the number of ultrasonic vocalizations as their control littermates. Moreover, the reduction was naltrexone-reversible (filled histograms, Fig. 5) as naltrexone markedly increased the level of ultrasonic vocalizations in all groups of rats, especially those receiving sucrose infusions

The time course of these effects may be appreciated from Fig. 6 which presents the cumulative number of distress vocalizations during the 8 min period, $F(1,56)=11.32$, $p<0$ 01. Animals that received naltrexone vocalized relatively constantly on a minute by minute basis throughout the session. Sugar unantagonized by naltrexone blunted vocalization rather soon after the start of the infusion. As indicated earlier, sucrose diminishes initial vocalization rate and precipitates its normal decline Naltrexone blocked both of these processes

GENERAL DISCUSSION

The present experiments have demonstrated that the taste of sucrose markedly affects pain threshold and the ultrasonic

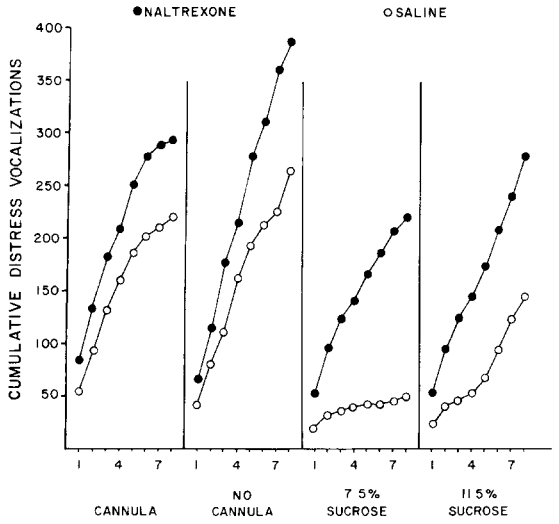

FIG 6 Cumulative distress vocalizations in sucrose-infused rats and their sibling controls following IP injections of naltrexone (0 5 mg/kg b wt) or isotonic saline

vocalization response to isolation in 10-day-old albino rats Both phenomena are robust and both are fully reversible by opioid antagonist (naltrexone) preadministration To our knowledge, this represents the first report that changes in a positive affective system markedly influence the operating characteristics of negative affective systems These findings may be understood within the contexts of (1) the consequences of ingesting sweet solutions, (2) adjustments to duress, and (3) the putative contributions of endogenous opioids to each of the processes

There is considerable evidence for a role of the opioids in the mediation of sweet taste [7, 19, 33] This is most clearly seen in the reductions of saccharin or sugar intakes following naltrexone administration. The remarkable findings by Le Magnen *et al.* [19] and Siviy, Calcagnetti and Reid [35] that preference for sweets is markedly diminished by antagonist administration suggests that the affective and perceptual properties as well as regulatory characteristics of palatability, sugar intake in particular, are opioid mediated These studies point to opioid involvement but do not discern whether the opioid systems are acting permissively or whether they are activated by the taste of sugar Our findings suggest that tasting sugar causes opioid release Moreover, it is this release that might sustain ingestive behavior and lead to sweet preference in the Le Magnen *et al* [19] and Siviy *et al* [35] studies. It follows that the more concentrated the sucrose solution, the more endogenous opioids are released or become available to the affective systems This is based in rats on the continuously increased rate and volume of sham drinking with increased sucrose concentration [23,35] the increased work output on fixed interval schedules with increased sucrose concentration [11] and by the preference for the sweeter of two tastes [38,39]

The perspective on pain and distress mechanisms must also be borne in mind in order to understand the implications of the present findings There is now an extensive literature demonstrating that many forms of stressful experience cause an increase in pain threshold (e.g , [6]) and in coping with social distress [31] Much of this is cross-tolerant with opiate administration This suggests that certain classes of intense, stressful events cause opioid release that, in turn, enhances the animal's [6] or the person's ability to better withstand and cope with pain and stress [18]

The present findings, which demonstrate "cross-talk" between certain positive and negative affective systems, suggest that opioids putatively released by sweet tastes become available to those systems involved in coping with pain and distress Whether other systems are involved in this cross-talk remains an open question The availability of the opioids is necessary for the cross-talk to occur because naltrexone blocks alteration in pain and distress responses The acts of tasting and swallowing the sugar in the presence of an opioid antagonist are not sufficient to cause analgesia in 10-day-old rat pups

Previous studies have demonstrated interactions between negative and positive affective states Specifically, tail pinch induces analgesia and also increases food intake, especially sweets A major cause of human overeating is considered to be stress related Thus, the cross-talk between these selective systems is, in fact, bidirectional

Together, these findings pose an important evolutionary problem why should engaging in one class of behavior influence an animal's reactions to an entirely different class of stimuli that demand completely different behavioral and physiological strategies That is, infants isolated from their mother and emitting distress vocalizations remain just as isolated even though they have tasted something sweet or ingested something palatable Moreover, to the extent that the paw lift response prevents tissue damage, then enhanced latencies following sucrose ingestion seems inappropriate In a similar vein, stressed humans or animals that engage in feeding behavior by virtue of opioid release have not in any way removed the source of their stress If anything, they avoid dealing with it

A phylogenetic perspective might be useful It is clear how a stress-sensitive pain coping system would confer phylogenetic advantage to animals that could better deal with pain and continue to perform during periods of stress It is also clear how a system that encourages ingestion of more foods that are energy-rich would also be selected The unusual aspect of these two systems is the shared functional neurochemical substrate as suggested here and by stress-induced feeding studies The extent of this mutuality must now be established for other systems

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