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REVIEW ARTICLE

ANTINOCICEPTIVE EFFECT OF SUCROSE INGESTION IN THE HUMAN

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Abstract : Sucrose ingestion has been shown to alleviate pain and distress in rats, human infants as well as adults. Sucrose induced analgesia is related to the reward value associated with its sweet taste. The sweet taste of sucrose is a stimulus for the activation of endogenous opioid pool. The opioids in turn modulate pain perception. It has been demonstrated in a number of animal and human studies that sucrose ingestion increases the hypothalamic/CSF opioid levels. This gains support from the results obtained from naloxone challenge test, a neuro-endocrine method for assessment of endogenous opioid tone. Moreover, the analgesic effects of sucrose can be reversed by administration of opioid antagonists such as naloxone. On the other hand, long-term sucrose ingestion leads to hyperalgesia in rats and it has been hypothesized to result from a complex interaction of sucrose with the endogenous opioid system leading to a deficiency of opioids. In the present article mechanisms underlying sucrose induced analgesia including the interaction of the palatability and reward value of food with the neural substrates and its neuro-chemical basis have been reviewed in the light of both animal and human studies. In addition, clinical application of the knowledge about sucrose and its modulatory effect on the endogenous opioid system has been suggested.

Key words : sucrose induced analgesia palatability naloxone challenge test nociceptive flexion reflex

INTRODUCTION

Newborn infants are frequently exposed to a number of painful procedures during the course of routine investigations, which form an important part of modern medical practice as well as social custom. Painful experiences during early infancy may lead to late adverse consequences (1, 2). Moreover, any painful stimulus may pose an immediate risk due to hemodynamic instability, or increased intra-cranial pressure (3). In many cases, repeated requirement of these aversive techniques

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create a great burden of pain for newborns and contrary to the earlier belief that infants cannot feel pain, it is now widely accepted that they do feel pain since, all pathways for perception of pain are fully developed by 24 weeks of gestation. Hence, a safe yet effective and preferably natural substance would be the "analgesic" of choice in such cases. Sucrose is one such substance, which has been tried with promising results. Several reports have indicated that the analgesic effect of sucrose is not a myth. However, the possibility whether the conclusion of sucrose induced analgesia is a fact and related to its sweet taste vis-a-vis its palatability, or it is merely an observation due to inability of the infant to cry or distraction remains to be examined.

Palatability is the hedonic component of food reward and may be regarded as liking. Berridge (1996) has distinguished between "wanting" and "liking" related to food reward. "Wanting" is appetite or incentive motivation whereas liking is synonymous with pleasure or palatability (4). Further, palatability is associated with affective reactions, for example placing a sweet solution inside the mouth of an infant is associated with a series of expressions that are distinctively different from those produced by bitter, sour or very salty tastes. Mediation of liking related to food reward involves neurotransmitter systems such as opioids and gamma amino butyric acid (GABA)/benzodiazepine (4). The neural substrates involved are suggested to be ventral pallidum and brainstem primary gustatory relays (4).

It is now well-known that the endogenous opioids significantly contribute in the modulation of pain. In addition, they affect mood, motor control and autonomic functions (5, 6). Several opioid induced effects are mediated via a family of specific membrane bound receptors located in the nervous tissue. The stimulation of ε-opioid receptors in the brain facilitates the descending enkephalinergic pathway which originates in the brainstem and terminates in the spinal cord, where met-enkephalin is the principal mediator in anti-nociception (7). Moreover, pain modulation is a dynamic process and involves continuous interaction between complex ascending and descending pathways (8). The descending pathways converge at the dorsal horn, which is the main site for processing of nociceptive information. The descending pathways in turn can mediate both descending inhibition as well as facilitation. In the former case "OFF" cells at the level of rostroventral medulla are involved, while in the latter "ON" cells have been implicated. At the level of dorsal horn, the pathways mediating descending inhibition and descending facilitation exert opposite patterns of action (9).

In addition, research studies over the past decade have shown an association between the endogenous opioids and food intake. It has been seen that administration of opioid agonists increases intake of mainly palatable foods while administration of opioid antagonists decreases intake of palatable food (10). A link between the hedonic properties of food and the opioids is provided by the studies, which illustrate a change in the analgesic property of morphine by the consumption of palatable foods (11). Therefore, palatable food intake may in some way modulate pain perception

by activation of endogenous opioid system. This system supports the contention that the preference to a sweet solution involves brain rewarding system, opiates and opiate receptors as revealed by the abolition of preference by naloxone. There is a cross-link vis-à-vis an overlap amongst brain reward, pain modulation and the opioid systems. Lately, a need to minimize pain in infants undergoing routine painful procedures was being felt, and therefore, on the basis of the available literature, sucrose is being used and advocated as an analgesic in young humans.

Sucrose as an analgesic in infants

Pain relieving procedures in infants: Empirically, there are a number of practices utilised for relieving pain in infants. Feeding, carrying, providing sweets and candy are some of the common interventions used by almost all the caregivers/parents for relieving distress in infants/children. However, for infants in a hospital undergoing routine investigative procedures, repeated administration of analgesics may be needed. This may have many side effects besides causing added pain. In such infants intervention with a non-pharmacological agent such as sucrose could be considered as an alternative analgesic. The analgesic efficacy of sucrose has been studied extensively in human neonates including pre-term and very low birth weight infants. In a systematic review and meta-analysis, which covered 13 studies it was reported that administration of sucrose with or without pacifiers was the most frequently studied non-pharmacologic intervention for relief of procedural pain in neonates (12).

Choice of parameters: The parameters most commonly used to assess pain response in infants following sucrose ingestion are crying time, oxygen saturation, respiratory rate and autonomic effects such as heart rate, in response to a painful procedure (heel lancing and venepuncture) (13, 14), while, others have attempted to correlate pain intensity especially in newborn babies with nociceptive behaviour such as facial expressions namely, brow bulge, eye squeeze, nasolabial furrow and open mouth. A score of 1 is given if any one of these is present and zero, if absent (15).

Efficacy of sucrose as an analgesic: Efficacy of sucrose solution as an analgesic for infants was tested during two common standard painful procedures namely, blood collection via heel lance and circumcision. Infants who drank 2 ml of a 12% sucrose solution prior to blood collection cried for 50% less duration, and only 31% of the time during circumcision (14). A multimodal approach to achieve analgesia during the process has been utilized and non-pharmacological interventions such as sucrose on pacifier and specially designed restraining chairs have been recommended (16). Circumcision is quite a common surgical procedure performed in the neonatal period. The use of sucrose during circumcision also suggests that sucrose induced analgesia may last for a variable period of time, which may extend up to about 30 minutes. Moreover, different strengths of sucrose solution such as 12% or 25% are also equally effective (13). A 24% sucrose solution was used to relieve pain associated with eye examinations for retinopathy of prematurity, a significant difference was found in the premature infant

pain profile score between the sucrose and water group during these examinations (17).

Sucrose as an analgesic versus other procedures : Sucrose has been compared with other interventions in a number of studies. Analgesic effect of sucrose was compared with simulated rocking in pre-term neonates undergoing painful procedures. The pain response, measured from facial expressions indicated lesser pain in the sucrose fed group as compared to the neonates subjected to rocking alone (18).

The efficacy of per oral sucrose administration and human milk has also been compared on the pain response during heel prick in the newborns. It was concluded that the orosensorial antinociceptive effects of human milk are not as effective as those of a concentrated sucrose solution (19). The effect of non-sucrose, sweet tasting solutions and different concentrations of sucrose solutions prior to heel prick have been also compared. Infants were given either a commercially available non-sucrose sweet-tasting solution or a 25% or 50% sucrose solution prior to a heel lance. There was a significant reduction in crying time in all the groups suggesting thereby, that even other sweet tasting solutions have similar analgesic potency as that of sucrose (15). The study highlights the importance of sweetness *per se* in alleviating pain.

Sucrose versus analgesics : Oral sucrose was also compared with a pharmacological agent namely, lidocaine-prilocaine cream (a local anaesthetic), for pain relief during venepuncture in neonates. The duration of cry was significantly decreased in the sucrose and sucrose plus lidocaine-prilocaine cream group. It was therefore concluded that oral sucrose solution compares favorably with the local anaesthetic cream as a safe and cheap analgesic to decrease pain responses to venepuncture in newborns (20).

The possible biological relevance of a system, which can induce calming effects in young humans in response to a sweet substance in the mouth, is lacking in the literature. The ontogeny of such a system is not known. Nonetheless, the hedonic effect of intra-oral sucrose undergoes changes during development. Children are known to prefer sweetened solutions than adults and since, the analgesic effect of sucrose is related to its hedonic qualities, its analgesic potency might also be diminishing with age (21). However, several studies have reported contrary to it.

Sucrose as an analgesic in children and adults

Miller et al (1994) studied the efficacy of per-oral sucrose as an analgesic during a cold pressor test (CPT, water at 10°C) in pre-pubertal school children (21). They noted pain threshold (which is the time when the arm begins to hurt) and pain tolerance (which is the time they remove their arms from cold water because they can no longer tolerate it). In addition the visual analogue scale was used for intensity rating. Holding sucrose in the mouth was associated with a significant prolongation (35%) in the threshold time; however there was no detectable effect on tolerance and intensity ratings using visual analogue scale (VAS). This was the first study to indicate analgesic properties of intra-oral sucrose in pre-pubertal children (21).

The effect of ingesting sweet substances such as carbonated soft drinks with glucose or fructose (22% w/v) on response to experimental pain in adults was studied in both male and female volunteers. Female volunteers showed increased pain tolerance while no such difference was appreciated in men. Based on these observations, only women were given palatable (chocolate Chip Cookies), unpalatable (black olives) or neutral (rice cakes) food to study analgesic effect. Volunteers receiving palatable food showed significant tolerance to experimental pressure pain. It was proposed that hedonic /reward value of the ingested substance may play a critical role in pain perception in females (22). From this study, however, it is difficult to comment conclusively on sweet food related analgesia. This is owing to the fact that the exact composition of carbonated soft drinks is unknown. Also palatability or unpalatability in terms of chocolate chips or black olives cannot be exactly quantified. A measured amount of sucrose solution as used by other authors is more appropriate in this regard. Therefore, further studies are needed to be conducted in adult humans to conclusively comment upon the effects of ingestion of sweet/ palatable substance on nociception.

A major bulk of the studies conducted in humans constitutes those carried out in infants. The assessment of pain is rather difficult in infants, however, non-verbal measures such as behavioural criteria (facial expression, crying) and physiological measures (heart rate, oxygen saturation etc.) have been used to assess the analgesic effect of sucrose. In a few studies conducted in children and adults VAS has been used to quantify pain following administration of sucrose or any palatable substance. Nevertheless, more convincing objective methods are required to substantiate the

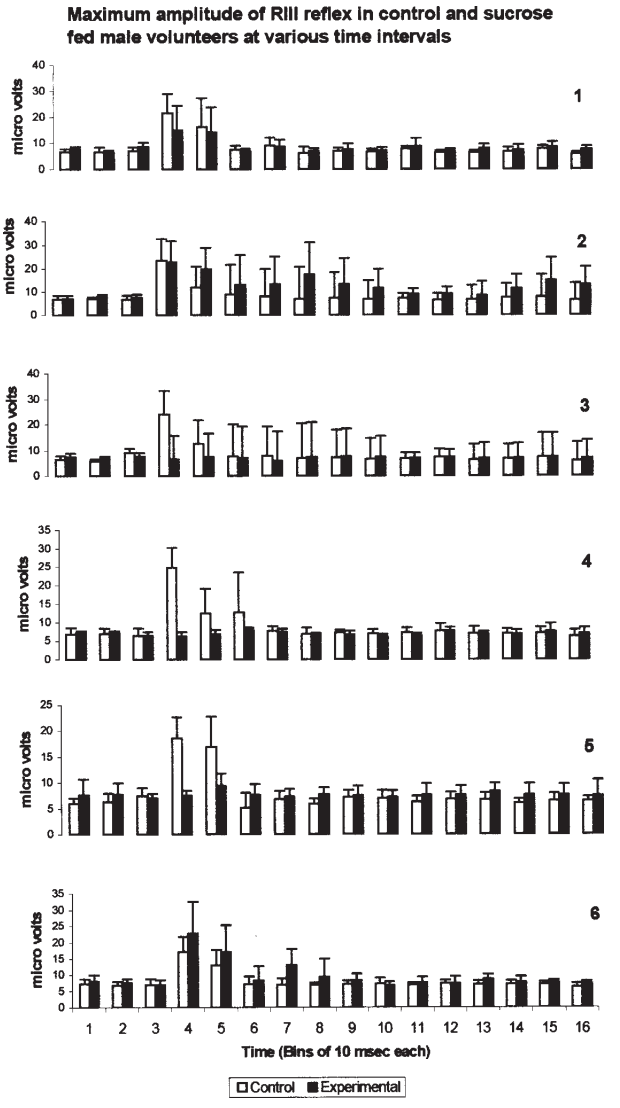

Fig. 1 : Comparison between the maximum amplitude (mean ± SD, µv) of RIII reflex in control and experimental group of male volunteers before and after intervention with water (clear bars) or sucrose (filled bars) respectively. Maximum amplitude (mean ± SD, µv) of RIII reflex 1 : before intervention 2, immediately after intervention, 3 through 6, 5, 10, 15 and 20 min after intervention, respectively.

analgesic efficacy of sucrose as an analgesic in adults. Our own studies have provided evidence by utilizing objective neurophysiologic techniques about the duration, intensity and gender variation in sucrose fed analgesia. Healthy adult volunteers were randomly divided into control and sucrose fed groups. Nociceptive flexion reflex (RIII) was recorded in all the volunteers before and after ingestion of either water or a 25% sucrose solution. This technique is a highly reliable, reproducible and objective tool for assessing the nociceptive status of an individual (23).

In our study on a total of 18 volunteers (12 male and 6 female) the pain was assessed before and after ingestion of 25% sucrose solution. The nociceptive flexion (RIII) reflex was recorded at 5 min interval until 20 min. Post sucrose ingestion, RIII reflex could not be elicited for 15 min in male subjects (Fig. 1) and for only 5 min in female subjects (Fig. 2) at a current strength, which could elicit the reflex prior to ingestion of sucrose. This study provides direct evidence of sucrose fed analgesia in human adults, besides a gender bias in the sucrose induced analgesia. A gender difference can be accounted for by the fact that sucrose consumption not only produces opioid mediated analgesia, it also has complex interactions with other factors affecting nociception such as hormonally induced differences in nociception. Frye et al (1992) assessed pain sensitivity during several phases of the estrous cycle (24). Tail flick latencies were measured in 10 cycling rats, during the luteal phase and in ovariectomized rats on oestradiol and progesterone. The tail flick latencies were longer during the luteal phase and shorter in ovariectomized rats. However, this pattern was lost when the ovariectomized rats with treatment were allowed to drink a 32% sucrose solution chronically.

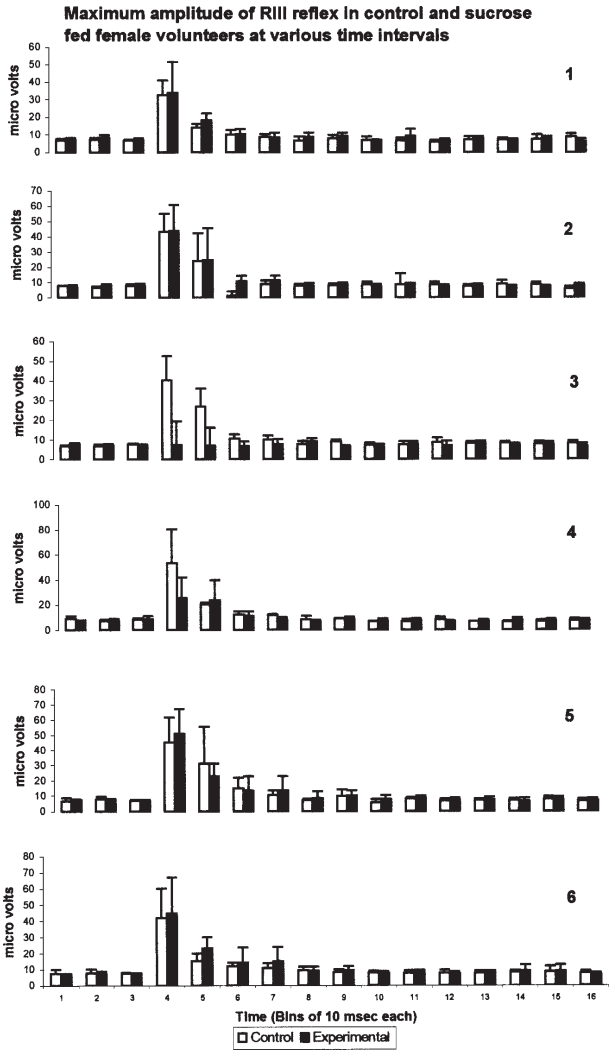

Fig. 2 : Comparison between the maximum amplitude (mean ± SD, μv) of RIII reflex in control and experimental group of male volunteers before and after intervention with water (clear bars) or sucrose (filled bars) respectively. Maximum amplitude (mean ± SD, μv) of RIII reflex 1 : before intervention 2, immediately after intervention, 3 through 6, 5, 10, 15 and 20 min after intervention, respectively.

The possible mechanism of action of sucrose induced analgesia is of significant interest to research workers. Most of the reports have emerged from studies on animal models while some are from human studies.

Mechanism of action

Based on available evidence from animal studies and human studies, we believe that sucrose induced initial analgesia as well as late hyperalgesia can be explained on the basis of sucrose-opioid interaction. Figure 3 gives a tentative summary of the sucrose opioid interaction. In the following section, we highlight the major evidence that supports the proposed mechanism of sucrose action on nociception.

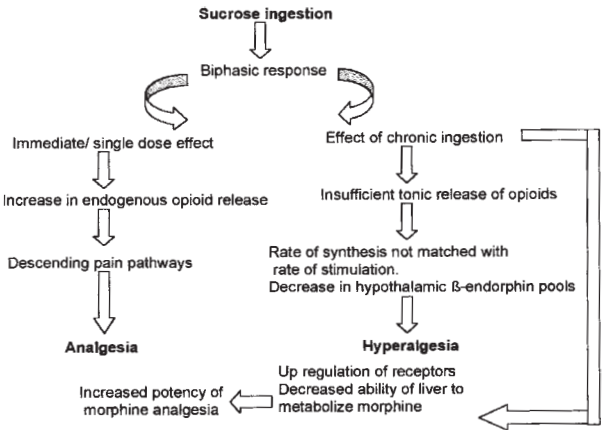

Fig. 3 : The figure shows biphasic response of sucrose ingestion and its interaction with endogenous opioid system.

Evidence from animal studies : The analgesic action is possibly not secondary to distraction, but related to the hedonic qualities of sucrose (25). Sucrose ingestion results in relief of both tonic and phasic pain (26). Moreover, the duration of analgesia after a single dose of oral sucrose is up to 20–30 min as it is effective throughout minor surgical procedures such as circumcision. Therefore, the immediate effect of sucrose ingestion is analgesia, which is opioid mediated (27). However, uninterrupted availability and thereby ingestion of sucrose ad libitum (in addition to laboratory food) lowers pain threshold and enhances morphine analgesia (10). In a similar report Mukherjee et al (2001) studied the effect of ad libitum sucrose ingestion for 6, 12 and 48 hours on phasic and tonic pain in adult rats (28). Ingestion of sucrose for 48 hours reduced tail flick latency, threshold of simple vocalization and vocalization after discharge, but the threshold of tail flick was not affected. The results suggested hyperalgesic response to phasic stimuli and analgesic response to tonic stimuli. When sucrose was ingested similarly from weaning to adulthood a hyperalgesic response to both tonic and phasic pain including threshold of tail flick was observed (29). Similarly, in ventromedial hypothalamus lesion rats, ingestion of sucrose was ineffective and 2Deoxyglucose (glucose anti-metabolite) infusion (1 µl/h for 7 days) in ventromedial hypothalamus abolished the sucrose induced effects thereby suggesting the involvement of glucoreceptor neurons therein. Most of the neuronal signals that are generated by food intake originate in or pass through the ventromedial hypothalamus. Glucose sensitive neurons participate in autonomic and behavioural regulation of food intake by monitoring the metabolic status of the body (30). Roane and Martin (1990) have demonstrated a significant decrease in tail-flick latency in sucrose fed rats when compared to control rats (31). The differences in the two groups were abolished

following administration of naloxone. In addition there was an increased potency of morphine analgesia. The latter could be due to a decrease in the ability of liver to metabolize morphine opioids and probably initiation of mechanism that inhibit tonic release of endogenous opioids thereby resulting in up regulation of receptors (31, 32). Hence, both the immediate and late effects of sucrose ingestion on nociceptive response can be explained on the basis of endogenous opioid modulation. Rats fed sweet food shortly before sacrifice show both a decrease in hypothalamic B-endorphin level and opioid binding (33). Sucrose ingestion is also accompanied by an increase of pro-opiomelanocortin mRNA in the arcuate nucleus of the hyphothalamus (34). The literature therefore is indicative of a possible involvement of hypothalamus in sucrose induced analgesia. Of the different parts of the hypothalamus the ventro medial hypothalamus and lateral hypothalamic area have received the attention of scientists (35, 36, 37, 38). Electrolytic lesion of ventro medial hypothalamus leads to obesity due to increased consumption of palatable food (39). Also, ventro medial hypothalamus lesion abolishes both the analgesic and hyperalesic effects of sucrose feeding, thereby indicating a significant role of ventromedial hypothalamus in sucrose induced analgesia. (26, 40). In a recent report, Anseloni et al (2005) have demonstrated persistence of sucrose induced analgesia following mid-collicular transection in rats there by ruling out any role of the forebrain in sucrose induced analgesia. (41). However, they have reported sucrose induced cFos expression in the peri aqueductal grey (PAG) and nucleus raphe magnus (NRM), the two key brainstem sites involved in descending pain modulation The PAG has been extensively studied for its role in descending pain modulation. The PAG neurons respond to different types of peripheral noxious stimulation by increasing their firing rate while it respond to noxious stimulus of tooth pulp by predominantly decreasing its firing rate (42). Other studies have demonstrated an increased intake of sucrose following intra-peritoneal injection of midazolam, a benzodiazepine agonist when compared with saline injected control rats. The same effects were not seen for quinine ingestion (43). These results suggest that intrinsic opioids play an important role in the induction of palatability (44).

Evidence from human studies : It is evident from the aforesaid reports that sucrose or any other sweet solution has a rapid calming effect in newborns. The rapid onset of the effect suggests that afferent signals from the mouth, rather than gastric and metabolic changes, initiate these responses (21). This aspect of sucrose analgesia has also been investigated by administration of sucrose through a nasogastric tube to infants prior to heel lance to circumvent the activation of oral afferents. The baby's response was measured by behavioural response and crying time. The response to pain was reduced only in those infants who received oral sucrose whereas not in those who received it intragastrically. Therefore, the study clearly indicates that the engagement of the taste sense is essential to promote the "sucrose analgesia" (45).

The further mechanism was elaborated by our study utilising naloxone challenge test. This test is based on the fact that the opioids exert a tonic inhibition on the Gn-

RH neurons in the hypothalamus (46, 47). This tonic inhibition may be reversed by naloxone, an opioid antagonist, which is accompanied by a discharge of LH-RH leading to a release of LH into the circulation (48). Serial estimation of LH in serum indicates the status of the endogenous opioid system (EOS) as well as its functional ability to some extent. This naloxone challenge test has been used to assess the EOS status in healthy individuals (Fig. 4) (47). Fedele (1998) and Facchinetti (1988) have utilized it with promising results in understanding pain perception in patients with syndrome X and in evaluation of central opiate activity in primary headache disorders (49, 50). The endogenous opioid status in patients with chronic tension type headache has been studied utilising this test. The LH response is blunted and is improved by yogic life style and botulinum injection in cervical muscles (51). The naloxone challenge test has also been used by Rengarajan et al (2005) to examine the endogenous opioid status in patients of trigeminal neuralgia (52). The LH levels therefore, indirectly reflect the endogenous opioid levels. The results of our study showed a higher concentration of LH in the sucrose fed group, which is indicative of sucrose mediated opioid release.

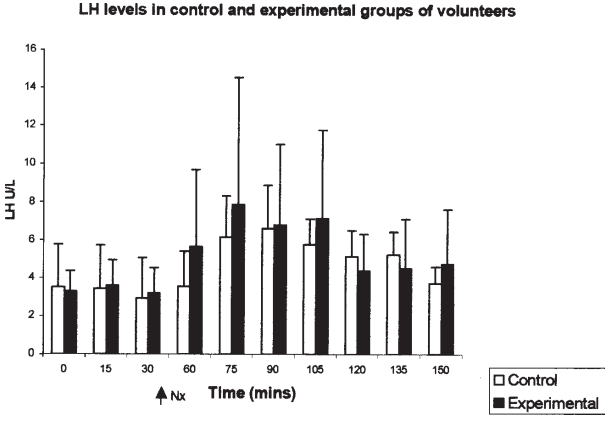

Fig. 4 : Levels of luteinizing hormone (mean ± SD) in control and experimental group of male volunteers. Nx, naloxone injection.

Potential application

The sensation of taste has both cognitive and hedonic components. The former allows discrimination amongst various tastes and is detected by definite neural pathways. The latter is concerned with development of preference or aversion to taste. Sweet foods have a higher reward value and therefore are more palatable and preferred. Ingestion of sucrose or any palatable substance hence leads to a feeling of pleasure, which in turn activates the endogenous opioid pool leading to alleviation of stress and pain. On the other hand, stress by itself produces analgesia. This effect too can be modified by sucrose ingestion. Mukherjee et al (2001) have reported an attenuation of the analgesic effects of chronic intermittent stress following *ad libitum* ingestion of palatable sucrose solution in rats (53).

Sucrose ingestion has a robust effect on the endogenous opioid peptides, which *per se* has wider applications. Derangement of the endogenous opioid system has been implicated in certain chronic painful disorders. The naloxone challenge test can be utilized to assess the status of endogenous opioids in these patients, and appropriate treatment modalities can be suggested in a variety of chronic pain such as headache, backache etc. On the other hand a potential role of the opioids in the genesis of obesity and eating disorders such as anorexia nervosa, bulimia and binge eating has been suggested (54). It is evident

from the findings of the naloxone challenge test that the endogenous opioid levels can be changed with very minor stimuli as for example sucrose ingestion. A better knowledge of the biological effects of sucrose ingestion can enable us to further understand certain aspects of the diseases in which the opioid levels are aberrant. In such cases, the endogenous opioid system may be non-pharmacologically manipulated with small amounts of sucrose, at the same time the possible adverse effects of deranged opioid levels may be avoided.

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