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GENDER SPECIFICITY OF SUCROSE INDUCED ANALGESIA IN HUMAN ADULTS

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Abstract : Sweet, palatable substances such as sucrose are reported to calm infants undergoing routine investigative procedures. The analgesic effect persists in pre pubertal children and adults with a hint of gender dependent variation in the analgesic response. The present study was therefore designed to explore gender specificity of sucrose induced analgesia in adult volunteers utilizing the nociceptive flexion reflex, an objective tool for pain assessment.

Nociceptive flexion reflex was recorded, both before and after (up to 15 min) ingestion of 100 ml of 25% sucrose solution in 6 male and 6 female volunteers.

In the male volunteers the maximum amplitude of the response was 20.8 ± 7.7 µV before sucrose ingestion and 22.6 ± 9.1 µV, 6.6 ± 0.7 µV, 6.2 ± 1.1 µV, 7.5 ± 0.9 µV at 0, 5, 10 and 15 minutes post sucrose ingestion respectively. In female volunteers, the maximum amplitude of the response was 33.7 ± 17.7 µV before sucrose ingestion and 43.6 ± 17.2 µV, 7.1 ± 1.2 µV, 25.9 ± 16.1 µV, 50.6 ± 16.3 µV at the same time intervals post sucrose ingestion. The maximum amplitude values were significantly lower in the males at 10 and 15 minutes after sucrose ingestion ($P<0.05$).

This is the first objective report of gender specificity in sucrose induced analgesia in adult humans. The gender dependent variation in sucrose induced analgesia is prolonged in male (15 min) and short lived in female (5 min) volunteers. This knowledge may have important implications in pain management.

Key words : gender specificity sucrose induced analgesia nociceptive flexion reflex

INTRODUCTION

The analgesic efficacy of sucrose has been studied extensively in human infants. A systematic review and meta-analysis, of 13 studies revealed that administration of

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sucrose with or without pacifiers was the most frequently studied non-pharmacologic intervention for relief of procedural pain in neonates (1). The effect persists in pre-pubertal children (2, 3) and to some extent in adults (4). Mercer and Holder (4) reported analgesia in response to experimental pain following ingestion of palatable soft drinks in female volunteers only. This has been attributed to a reduced preference for sweet in men (5) possibly because of a smaller proportion of sweet sensitive cells in the parabrachial nucleus of the pons as demonstrated in male rats (6). In addition, there is a gender bias in experimental pain *per se* (7–10). Women report more severe pain and experience pain more frequently as compared to men (11). Therefore, both pain sensitivity and sweet preference exhibit a gender difference.

SIA is opioid mediated as it is abolished after naloxone (antiopioid) pretreatment (12, 13). Moreover, analgesic effects of opioids exhibit a gender difference (14, 15). Hence, the possibility of gender bias in SIA cannot be ruled out.

There is a dearth of literature regarding gender difference in SIA in adults. Moreover, most researchers have utilized only subjective measures such as visual analogue scale (VAS) for assessment of analgesia post sucrose ingestion. Recently, the nociceptive flexion reflex (NFR) mediated by type III fibers is being increasingly used as an objective measure of pain. It is a highly reliable and reproducible techniques (16). In the present study a gender bias in the analgesic efficacy of sucrose was studied in healthy adult volunteers using both objective (NFR) and subjective methods (VAS).

MATERIALS AND METHODS

The study was approved by the Institutional ethics committee of All India Institute of Medical Sciences. Healthy adult (6 male and 6 female, aged 18–40 years) volunteers from the institute campus were enrolled in the study. Persons suffering from chronic pain, peripheral neuropathy, diabetes, hypertension and history of morphinomimetic drug administration were excluded.

Recording of nociceptive flexion reflex

The NFR is elicited by stimulating the sural nerve and the response is recorded from the biceps femoris muscle (17). In all the volunteers, NFR was recorded at least 2 h after the last meal between 11:00–13:00 h at room temperature. Recording conditions for all subjects were comparable. NFR was recorded on Biopac (Biopac System Inc. CA 93117) recording system while the nerve was stimulated with an electronic stimulator (Ninon Kohden).

The subject was seated in a comfortable position with the knee flexed at 130° and the ankle at 90° to obtain complete muscular relaxation (18). The skin over the lateral retromalleolar path of the sural nerve was abraded using a mild scrubber and cleaned with spirit. Silver-silver chloride cup electrodes filled with electrode jelly were fixed over the cleaned area with the help of adhesive plaster. These were used for stimulation of the sural nerve. The posterior aspect of the thigh was cleaned similarly and disposable silver-silver chloride disc electrodes (Nessler Medizintechnik, Germany) were placed. The reflex response

from the biceps femoris muscle was recorded by placing cathode 2 cm proximal to the head of fibula just medial to the tendon of the long head of biceps (with the knee flexed), the anode over the tendon and the ground electrode over the head of fibula. The electrode lead was connected to MP 30 hardware of the Biopac recording system.

The subjects were first acquainted with an electrical stimulus and were asked to rate their sensation on a 10-point visual analogue scale (VAS) (Ref 4). The stimulus consisted of a train of 5–10, 1 msec pulses with interpulse duration of 1 msec. The current strength was gradually increased in steps of 1 mA. When the subjective pain rating was 8-9, NFR was recorded. The volunteers were then asked to drink 100 ml of 25% sucrose solution within 3–4 min. NFR responses were recorded at 0 through 15 min at intervals of 5 min.

Data analysis

The maximum amplitude of NFR was analyzed independently for both the groups (male and female volunteers). For comparing data between the groups, Mann-Whitney U test was applied.

RESULTS

Effect of sucrose ingestion in male versus female volunteers :

The maximum amplitude of the response was greater in case of female volunteers (33.7 ± 17.7 µV) as compared to males (20.8 ± 7.7 µV) under basal conditions although it did not attain statistical significance. The maximum amplitude values in both males (22.6 ± 9.1 µV) and females (43.6 ± 17.2 µV) showed a similar trend, immediately after sucrose ingestion. At 5 minutes post sucrose ingestion the reflex was greatly attenuated, the maximum amplitude values being 7 ± 1.4 µV and 6.6 ± 0.7 µV in females and males respectively.

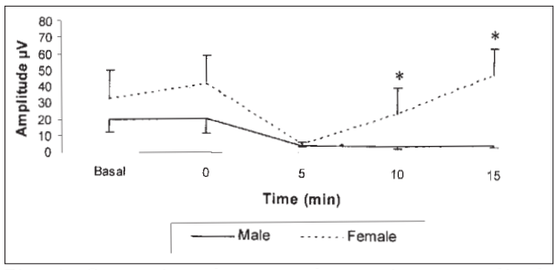

Fig. 1 : Comparison between the maximum amplitude (mean±SD, µV) of NFR in female and male volunteers pre and post sucrose ingestion up to a period of 5 minutes. (*P<0.05)

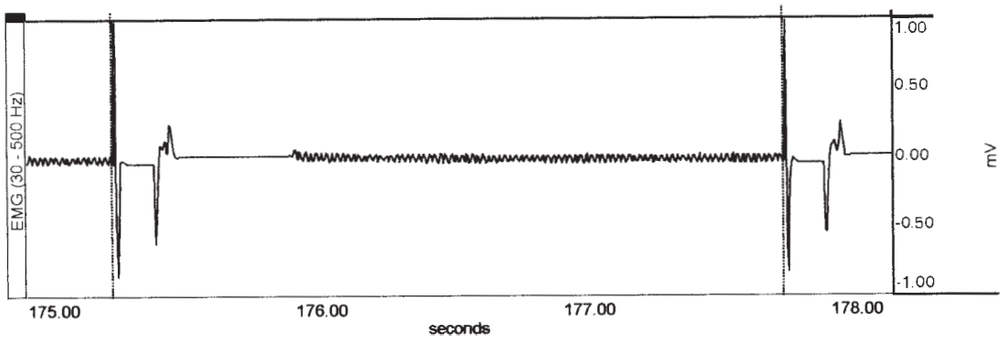

Fig. 2 : The figure depicts the record of nociceptive flexion reflex. Two such responses can be seen at 175 s and 178 s of the record. The interrupted lines indicate the points of stimulation.

The response remained suppressed for a period of 15 minutes in case of male volunteers. The reflex recovered at 10 min in case of female volunteers. The maximum amplitudes at 10 min (35.8 ± 16.1 μV) and 15 min (50.6 ± 16.3 μV) were comparable to the pre sucrose values (Fig. 1). In males, recovery of the response was observed at 20 minutes (22.7 ± 9.9 μV) although at a higher current strength.

DISCUSSION

In our study immediate analgesia (0 min post sucrose ingestion) was absent in either sex. Mercer and Holder (4) have reported an "immediate" analgesia in their volunteers. However, they have not specified the time lag between the palatable drink and pain evaluation, while we have systematically monitored the time. At 5 minutes the NFR was attenuated in both males and females. In the earlier report by Mercer and Holder (4) only female volunteers showed an analgesic response to a palatable drink while the males did not. In addition, our male volunteers showed a prolonged analgesic response (upto 15 min). Therefore, it appears that sucrose induced analgesia in adults appears in two phases namely; an early and a late phase. The former is noted up to 5 minutes while the latter extends up to 15 minutes post sucrose ingestion. The gender difference in sucrose induced analgesia is revealed in these temporal details.

The short term analgesia in females can be explained on the basis of reports which suggest females to be more sensitive to pain *per se* (11) or to studies reporting lower electrocutaneous pain thresholds in women (19). Incidentally, this was the mode of stimulation in the present study.

Alternatively, a change in the NFR threshold across the menstrual cycle has been reported in healthy women, with higher threshold during the luteal phase (20). The menstrual cycle status was not taken into account in the present study. However, this seems to be an insignificant factor in our study, because the pattern of response, post sucrose ingestion (attenuation of NFR at 5 min) is uniform across all the female volunteers. Such uniformity in response is possible either when all our volunteers are in the same phase of cycle, or it bears no influence on SIA. It appears that the latter may hold partially true in our study.

We feel that, emotions may play an important role in gender related differences in SIA through valence by arousal interaction (21). In our study group; the volunteers received a palatable sucrose solution which has a strong hedonic value. The hedonic value or valence of sucrose is different in males and females thereby dictating the results. The differential primary handling of sensory stimuli modulates the events following sucrose ingestion.

Conclusion

Our results suggest gender specificity in sucrose induced analgesia in human adults. The females exhibit a short lived analgesia while the males show a prolonged analgesic response. However, further studies are required on a larger sample size to conclusively comment on a gender dependent variation in sucrose induced analgesia. This study provides insight to a possible differential handling of analgesic agents

across the gender, thereby helping in individualization of pain management.

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