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Evaluation and comparison of antinociceptive activity of aspartame with sucrose

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Abstract:
Background: Artificial sweeteners are low-calorie substances used to sweeten a wide variety of foods. At present they are used increasingly not only by diabetics, but also by the general public as a mean of controlling the weight. This study was carried out to evaluate and compare antinociceptive activity of the artificial sweeteners, aspartame and sucrose and to study the mechanisms involved in this analgesic activity.
Methods: Forty eight white albino Wistar rats were divided into two groups of 24 rats each. Group 1 received sucrose and group 2 received aspartame solution *ad libitum* for 14 days as their only source of liquid. On 14th day, both groups of rats were divided into 3 subgroups having 8 rats each. Group Ia and IIa served as control. Group Ib and IIb were given naloxone and Ic and IIc received ketanserin, the opioid and serotonergic receptor antagonists, respectively.
Results: Tail withdrawal latencies (tail flick analgesiometer) and paw licking/jumping latencies (Eddy's hot plate method) were increased significantly in both aspartame and sucrose group. The analgesia produced by aspartame was comparable with sucrose. The opioid receptor antagonist naloxone and the 5-$HT_{2A/2C}$ serotonergic receptor antagonist ketanserin partly reversed the antinociceptive effect of these sweeteners.
Conclusions: Thus, the artificial sweetening agent aspartame showed antinociceptive activity like sucrose in rats. Reduction in antinociceptive activity of aspartame and sucrose by opioid and serotoninergic antagonists demonstrate the involvement of both opioid and serotonergic system.

Key words:
aspartame, ketanserin, naloxone, sucrose, sweet-substance-induced antinociception

Introduction

Artificial sweeteners are low-calorie substances which have been used to sweeten a wide variety of foods with the intent of reducing intake of calories. These substances are very popular and are being increasingly used not only by diabetics, but also by the general public as a mean of controlling the weight. Aspartame, one such noncaloric sweetener, has been in wide use with many foods and beverages. Since these sweeteners are being so commonly used by the general population, it may be essential to evaluate their other pharmacological properties. One such pharmacological effect which has been recently studied is their antinociceptive activity [10, 16, 20, 21]. So it may be hypothesized that in addition to their role in weight control, these may be of help in attenuation of pain, especially associated with diabetic neuropathy, where these sweeteners are frequently used to reduce the intake of sugar. Whether all the sweeteners used commonly may have an antinociceptive activity or not is not known. The mechanisms underlying this

antinociception action are also not very clear. Saccharin, one such sweetener, taken by rats for relatively long periods of time show an increase in the latency of paw withdrawal in the hot-plate test [4]. It was also demonstrated that consumption of concentrated sucrose solution seems to reduce crying and other pain related behavior in healthy normal babies [8]. It has also been shown that sweet substances may potentiate the analgesia of opiates [19].

Sweet palatable substances such as sucrose and polycose potentiate the morphine-induced analgesia, suggesting that interaction of these substances with opioid system modifies the sensitivity to pain stimuli [7]. There is evidence that endogenous opioid receptors may be involved in antinociception induced by the sweeteners [18]. It was also reported the involvement of serotonergic mechanism in sweet substance-induced antinociception as methylsergide and ketanserin antagonises the sweet-substance-induced analgesia. [18].

Since some neural pathways and some neurotransmitters play an important role in the complex modulation of pain transmission, the investigation of these modulatory mechanisms may have important implications for pain treatment. The use of different models for measuring pain is important because analgesic effect may be due to one or more mechanisms. For this reason, tail-flick is used for spinal reflex [25] and Eddy's hot plate test is used for measuring supraspinal pain-related mechanisms [14]. Therefore, this study was carried out to evaluate the antinociceptive activity of artificial sweeteners, aspartame and sucrose and also to explore the role of opioid and serotoninergic systems in such antinociceptive activity.

Materials and Methods

Animals

Wistar albino rats weighing 200–250 g with access to food and water *ad libtum* were used. These animals were housed eight per cage. The study was conducted in Department of Pharmacology, Pt. B.D. Sharma PGIMS, Rohtak. The protocol was approved by Institutional Animal Committee (IAEC) and all experiments were performed in accordance with the recommendations of guidelines for care and use of laboratory animals.

Drugs

The drugs used were aspartame in a dose of 1.6 g/l [17] and sucrose in a dose of 250 g/l, [20]; naloxone, 1 mg/kg [20] and ketanserin, 1 mg/kg [1] were used as antagonists. Aspartame and sucrose were dissolved in tap water just prior to administration. These were given orally for 14 days. Naloxone and ketanserin were given intraperitoneally on 14th day.

Experimental methods

Analgesia was evaluated using tail flick test (tail withdrawl from radiant heat) by Techno-analgesiometer and hot plate (paw licking or jumping from the hot plate at 55°C) method by using Eddy's hot plate analgesiometer.

Tail-flick test

The tail-flick test was used in rats to elicit a spinal tail flick response to noxious thermal stimuli. The test was performed with the tail-flick model using analgesiometer. Each rat was gently held with one hand and the distal half of its tail was positioned on the source of radiant heat. The tail-flick response was elicited by applying radiant heat to the ventral surface of the tail. The time elapsed till the animal flicked its tail was determined (usual response 3–4 s**).** A 10 s cut off latency was kept to prevent damage to tail.

Hot-plate test

The hot-plate test was performed using an electronically controlled hot plate heated to 55 ± 0.1°C. Each rat was placed unrestrained on the hot plate until either paw licking or jumping occurred. A cut of time was kept at 15 s.

Forty eight male Wistar albino rats were divided into two groups of twenty four rats each and were kept in six cages. Group I received sucrose solution 250 g/l and group II received 1.6 g/l aspartame solution orally *ad libitum*, respectively, for 14 days as their only source of liquid. Both the solutions were prepared in tap water. In both groups, pain threshold baseline (tail-flick latencies and paw licking or jumping responses) were recorded on day 1 and again on day 14. On 14th day each group of rats was divided into 3 subgroups having 8 rats each. Group Ia and IIa served as control. Group Ib and IIb were given na-