CENTRAL MODULATION OF BREWER'S YEAST-INDUCED PERIPHERAL INFLAMMATION BY NEUROPEPTIDES BRADYKININ AND SUBSTANCE P

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Abstract: Possible modulation of the Brewer's yeast-induced peripheral inflammation by two central neuropeptides, bradykinin and substance P (SP), was investigated in rats. Centrally administered bradykinin significantly increased pedal oedema and pain threshold whereas, SP produced significant augmentation of oedema volume and nociception. The results of the present study indicate that central bradykinin exerts pro-inflammatory and analgesic effects whereas, central SP exerts pro-inflammatory and pro-nociceptive effects on Brewer's yeast-induced peripheral inflammation.

Key words: bradykinin, oedema, substance P, Brewer's yeast, nociception

INTRODUCTION

Bradykinin (BK), a nonapeptide is associated with a variety of pathophysiological conditions (1). Several studies have demonstrated that BK has an important effect on CNS and has been implicated as a central neuromodulator (2). It has been demonstrated that BK exhibits behavioural activity characterised by initial transient stimulation followed by signs of depression (3, 4). However, other workers have observed only signs of depression following its central administration (5). Antinociceptive response in rats and mice is on record following central administration of BK (6, 7). Substance P (SP), an undecapeptide is thought to participate in pain mediation at spinal cord (8). In a recent study, SP has been found to be involved in early stages of carrageenin-induced paw oedema (9). There are conflicting reports about the effect of SP on pain. One group of workers have reported that icv or ip administration of the compound caused analgesic effect (10-12) while others have reported hyperalgesic effect (13, 14). These conflicting reports, as well as limited information on central modulatory role of BK and SP on peripheral inflammation, have prompted us to undertake the present study.

METHODS

Studies were conducted on adult male Sprague Dawley rats (150-200 g) obtained from National Laboratory Animal Centre, Central Drug Research Institute, Lucknow. The animals were caged individually with free-access to clean drinking water and balanced feed. Experiments were conducted at an ambient temperature of 25 ± 2°C. The animals were anaesthetized with pentobarbitone sodium (40 mg/kg, ip) and icv cannulation was performed stereotaxically and a polyethylene cannula was implanted into the right lateral ventricle (15). The cannulated rats were allowed to recover for 7 days and were divided into three groups.

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Bradykinin (Sigma) and substance P (Sigma) were dissolved in artificial cerebrospinal fluid (sodium chloride, 138.5 mM; potassium chloride, 3.35 mM; calcium chloride, 1.26 mM magnesium chloride, 1.16 mM; sodium bicarbonate, 21.0 mM; sodium dihydrogen orthophosphate, 0.5 mM; urea, 2.2 mM and glucose, 3.4 mM, dissolved in triple glass distilled water, pH 7.3, temperature 37°C). Bradykinin (5 μg) and SP (5 μg) were administered icv 15 min before the injection of phlogistic agent. A constant volume of 10 μl of drug solution was administered by a single icv injection. Control animals received an equivalent amount of artificial cerebrospinal fluid (CSF) through the same route.

Acute inflammation was induced in rats by injection of Brewer's yeast (0.1 ml of 20% suspension in 0.9% saline) below the planter aponeurosis of the hind paw (16). The paw volume of rats upto the ankle joints was recorded by a standard volumetric technique, using calibrated plethysmometer (Ugo Basile, Varese, Italy), immediately prior to Brewer's yeast injection (0 min, basal volume), then at 15, 30 min, 1 h and thereafter, every 1 h upto 5 h. The increase in paw volume after the injection of phlogistic agent was taken as an index of inflammation (expressed in ml). The change in paw volume in test group was compared with that of untreated control group.

After the termination of experiments, all the rats were administered 10 μl of 1% Evlan's blue dye solution icv and the brain was removed, sectioned and examined in order to ascertain the correct position of the cannulae in the ventricle.

Statistical analysis of data was performed by applying Student's 't' test to study the difference amongst the means (18).

RESULTS

The results of icv administered neuropeptides, bradykinin and substance P on Brewer's yeast-induced paw oedema are summarised in Table I. Bradykinin and substance P significantly increased the pedal oedema at 15 min.

Table II summarises the effect of icv administered neuropeptides on Brewer's yeast-induced pain. Bradykinin significantly (P <0.05) increased the withdrawal pain threshold.

### TABLE I: Effect of icv administered neuropeptides on Brewer's yeast-induced paw oedema in rats.

<table>
<thead>
<tr>
<th>Odema volume in ml (mean ± S.E.)</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 min</td>
</tr>
<tr>
<td>Control</td>
<td>0.46 ± 0.02</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>0.75 ± 0.05***</td>
</tr>
<tr>
<td>Substance P</td>
<td>0.73 ± 0.09*</td>
</tr>
</tbody>
</table>

*n = six animal in each group excepting control (12).

*P <0.05; ***P <0.001

basal volume ± S.E. Pain threshold was recorded by Randal Selitto assay (17), immediately prior to and at 1, 3 and 5 h after inducing inflammation by applying pressure to the inflamed paw at steadily increasing rate by means of pedal switch of analgesiometer (Ugo Basile, Varese, Italy). The pressure (g) necessary to cause the animal to struggle was recorded as the end-point or withdrawal 'pain threshold'. The change in pain threshold in test group was compared with that of untreated control group.
### TABLE II: Effect of icv administered neuropeptides on Brewer's yeast-induced nociception in rats.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>No of animals</th>
<th>Pain threshold in g (mean ± S.E.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 h</td>
</tr>
<tr>
<td>Control</td>
<td>12</td>
<td>97.50 ± 10.68</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>9</td>
<td>104.44 ± 10.05</td>
</tr>
<tr>
<td>Substance P</td>
<td>6</td>
<td>91.67 ± 12.16</td>
</tr>
</tbody>
</table>

Oh: Before injection of yeast  
*P < 0.05

increased pain threshold at 1 hr in comparison to the control value of 57.92 ± 4.74 g. Substance P significantly (P < 0.05) augmented nociception (40.00 ± 5.32 g) at 1 hr of observation. At 3 and 5 h, there was no significant effect of icv administration of bradykinin and substance P.

**DISCUSSION**

The Brewer's yeast model of acute inflammation in rats was selected because of its rapid production of large oedematous response and concomitant development of hyperalgesia (19). Bradykinin is known to be associated with a variety of pathophysiological conditions including peripheral inflammation (1). It is now evident that kinin exerts discernible effects on mammalian CNS leading to a postulate that it functions as central neuromodulator (2). In the present study, bradykinin significantly enhanced paw oedema volume. A similar augmentation of paw oedema by bradykinin has been reported in the carrageenin model of pedal inflammation (20). This peripheral action of kinin is speculated to be mediated by prostaglandins (21) as, centrally administered bradykinin has been reported to selectively increase the rat brain PGE2 level (22). An antinociceptive effect of bradykinin was observed on Brewer's yeast-induced inflammation. Similar effect of bradykinin has been noted on carrageenin model of pain (23). Bradykinin was found to promote central serotonin activity on icv administration (22) and central serotonin has been shown to inhibit formalin-induced pedal hyperalgesia in rats (24). Further, serotonin is reported to function as a neurotransmitter of neural tracts that inhibits pain signal (25). So, it can be suggested that antinociceptive effect observed with bradykinin, may be serotonin-mediated.

Substance P has been shown to mediate neurogenic plasma extravasation (26) and has been proposed as a mediator of nociception in the dorsal horn of the spinal cord (27). In the present study, icv administered SP significantly enhanced Brewer's yeast-induced paw oedema and nociception. The electrical stimulation of sensory nerves produced plasma extravasation in rats which was accompanied by the release of immunoreactive substance P into the blister fluid (28) suggesting the role of SP in oedema formation. In another study, SP was found to play an important role in early stage of carrageenin-induced paw oedema and reduction in the biosynthesis of SP lessened the severity of inflammatory response (1). Opiate analgesics have been shown to inhibit the evoked release of SP from the spinal cord (29). Moreover, the neurogenic inflammation and hyperalgesia have been shown to be reduced by depletion of SP from nerve endings by pretreatment with its antagonists (30). The hyperalgesic action is most probably mediated by intracellular
messengers, nitric oxide, arachidonic acid and protein kinase C as reported earlier in formalin pain model (31).

In conclusion, the present study demonstrates that central bradykinin exerts pro-inflammatory and analgesic effects whereas, SP exerts pro-inflammatory and pro-nociceptive effects on Brewer's yeast-induced acute pedal inflammation in rats.

REFERENCES


