The Antinociceptive Effect of Intracerebroventricularly Administered Prostaglandin E₁ in the Rat

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Abstract. It is generally accepted that prostaglandins (PGs) are nociceptive substances. However, earlier studies from this laboratory indicated that morphine analgesia, in the rat, was not only serotonin mediated, but involved PGs as well. Several PG synthesis inhibitors were shown to inhibit morphine analgesia and PGE₁ was shown to potentiate the antinociceptive effect of morphine. Intraperitoneal administration of PGE₁, but not PGE₂ and PGF₂α, elicited antinociceptive effect per se, by the radiant heat method. The present study was undertaken to confirm the antinociceptive action of PGE₁, after intracerebroventricular administration, against nociceptive impulses induced by radiant heat, pressure, and high frequency electric current. PGE₁ produced a dose-dependent antinociceptive effect by the radiant heat and pressure methods. It potentiated the antinociceptive action of morphine by the electrical stimulation method. The antinociceptive action of PGE₁ was not evident in 5,6-dihydroxytryptamine-pretreated rats, suggesting that this effect is serotonin mediated. The present study thus confirms the antinociceptive action of PGE₁ and suggests that, unlike its peripheral action, the central action of PGE₁ results in suppression of nociceptive responses which may be serotonin mediated.

Key words: Antinociception - PGE₁ - 5,6-Dihydroxytryptamine - Serotonin

It is generally accepted that prostaglandins (PGs) are nociceptive substances, mediating pain and inflammation (Collier et al., 1972; Ferreira, 1972; Vane, 1972; Ferreira and Vane, 1974; Gyires and Knoll, 1976). However, some recent studies from this laboratory have shown that, in rats, PGE₁ not only potentiates the antinociceptive action of morphine (Bhattacharya et al., 1975b), but also exhibits significant antinociceptive effect per se, (Sanyal et al., 1977). Furthermore, a number of PG synthesis inhibitors were shown to antagonize the antinociceptive action of morphine in this species (Srivastava et al., 1978). In addition, immobilization stress-induced antinociception was shown to be, at least in part, PG mediated (Bhattacharya et al., 1978). It was thought possible that the peripheral and the central actions of PGs are different. Unlike its action in the periphery, PGE₁ may have a significant antinociceptive effect in rats. Our earlier studies were conducted with i.p. administered PGE₁, in doses which might be regarded as unphysiologic, and using the radiant heat technique only. It was therefore thought essential that the antinociceptive action of PGE₁ should be confirmed by other experimental parameters, after central administration of the drug.

Materials and Methods

Norwegian strain of inbred rats (150–200 g) of both sexes were obtained from the Department of Animal Breeding, Veterinary College, Jabalpur.

Intracerebroventricular (i.c.v.) cannulation was carried out according to the method of Feldberg and Lotti (1967). Indwelling cannulas were inserted into the right lateral ventricle using an Inco stereotaxic apparatus. Artificial cerebrospinal fluid (CSF) was passed through the implanted cannula and nonregurgitation of the fluid gave an indication of the position of the cannula in the lateral ventricle. After completion of the experiments, dilute solution of methylene blue in artificial CSF was injected into the cannula. The brain was removed, sectioned, and examined to verify the site of the injection.

The antinociceptive activity was determined by the following methods, 10 min before and at 15-min intervals for 60 min after i.c.v. administration of graded doses of PGE₁ or artificial CSF, the volume of the injections being kept constant at 30 μl.

1. Radiant heat method — The rat tail-hot wire technique of Davies et al. (1946) was used. The increase in the latent period of tail flick response after PGE₁ administration was taken as the index of antinociception.
2. Tail pressure method - A modified method of Green and Young (1951) was used. Uniformly increasing pressure on the tip of the tail of the rat was applied with the help of a vertical syringe connected to another horizontal syringe and a mercury manometer. A pincher cut to size from an ampul cutter was fixed to the piston of the vertical syringe. The struggling response after increasing pressure on the tail was taken as the index of nociception. At a pressure of 45 mm Hg, all the animals struggled. Absence of a struggling response after PGE1 administration was taken as the antinociceptive effect, and results have been expressed as the percentage of animals showing no struggling response at a pressure of 50 mm Hg.

3. Electrical stimulation method - The method of Ferri et al. (1974) was used with slight modification. The base of the rat tail was electrically stimulated by way of a pair of electrodes connected to an Inco electronic stimulator (square waves, pulse width 2 ms, pulse rate 100/s). Voltage was increased by 0.5 V until the rat responded to the electrical stimulation by squeaking. This response was taken as indicating the pain threshold, which was expressed in volts.

In all these methods the effect of PGE1 was compared with control groups where only 30 μl of artificial CSF was administered i.c.v.

In another group of rats, 5,6-dihydroxytryptamine (DHT) (50 μg/rat) was administered i.c.v. in artificial CSF. The effect of DHT treatment on the antinociceptive effect of PGE1 was noted by the radiant heat method, 48 h after DHT administration.

In another two groups of rats, the effect of PGE1 on the antinociceptive action of morphine, as assessed by the electrical stimulation method, was noted by administering PGE1 i.c.v. 30 min after i.p. administration of morphine in doses of 2.5 mg/kg (sub-analgesic) or 10.0 mg/kg (analgesic).

Results
The vehicle, artificial CSF, had no effect per se in any of the three experimental parameters used (Tables 1, 2, and 3).

PGE1 produced a dose-dependent antinociceptive action by the radiant heat and pressure methods (Tables 1 and 2). The peak antinociceptive effect was observed 15 min after PGE1 administration. Higher doses produced a more prolonged effect. Doses higher than 20 μg/rat were not tried because PGE1 tended to produce marked sedation and catalepsy at these dose levels. By the electrical stimulation method, PGE1 did not show any antinociceptive effect up to a dose of 15 μg/rat. However, a higher dose (20 μg/rat) produced some slight, but statistically significant, antinociceptive activity only at 15 min after PGE1 administration (Table 3).

PGE1 (4.0 μg/rat) significantly potentiated the antinociceptive action of the subanalgesic and analgesic doses of morphine, as tested by the electrical stimulation method (Fig. 1).

Pretreatment with DHT significantly inhibited the antinociceptive action of PGE1 (10 μg/rat) on day 2, as tested by the radiant heat method and it lasted for 2 to 5 days (Fig. 2).

Discussion
The findings of the present study confirm our earlier observation that PGE1 has significant antinociceptive action in rats (Sanyal et al., 1977), at least in situations where thermal and pressure receptors are involved in the causation of pain. Though PGE1 did significantly enhance the pain threshold (voltage) induced by electrical stimulation, the antinociceptive action elicited by this method was less marked and more transient. It is difficult to offer an explanation for the difference in the antinociceptive action of PGE1 in this experimental model. It may be possible that the mechanisms and pathways concerned in pain production by the above three methods are different. It is equally possible that a higher dose of PGE1 could have elicited worthwhile suppression of electrical stimulation-induced nociception. However, the dose of PGE1 was not increased beyond 20 μg/rat because of the marked sedation and catalepsy induced by higher doses of PGE1. It may be mentioned here that we have previously shown that sedation induced by PGs is not related to their antinociceptive action. Not only are PGE2 and PGF2α devoid of any antinociceptive action in doses producing

<table>
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<tr>
<th>PGE1 (μg/rat)</th>
<th>Latent period of tail-flick response (s)</th>
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<tr>
<td></td>
<td>Before 15 min</td>
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<tr>
<td>Artificial CSF</td>
<td>6.3 ± 0.12</td>
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<tr>
<td>2.5</td>
<td>7.0 ± 0.19</td>
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<tr>
<td>5.0</td>
<td>7.3 ± 0.18</td>
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<tr>
<td>7.5</td>
<td>6.9 ± 0.17</td>
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<tr>
<td>10.0</td>
<td>6.8 ± 0.31</td>
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<tr>
<td>15.0</td>
<td>6.9 ± 0.20</td>
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<tr>
<td>20.0</td>
<td>7.3 ± 0.26</td>
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N = 6. Results expressed as mean ± SEM. Statistical significance at *P < 0.01 and **P < 0.001, respectively (paired t-test)