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Effect of centrally administered prostaglandin D_2 and some prostaglandin synthesis inhibitors on carrageenan-induced paw oedema in rats

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Abstract—The putative modulatory role of central prostaglandins (PGs) on peripheral inflammation has been explored by investigating the effects of intracerebroventricularly (i.c.v.) administered PGD_2, the major rodent brain PG, hydrocortisone, a phospholipase A_2 inhibitor, and the cyclo-oxygenase inhibitors, paracetamol and mefenamic acid, on carrageenan-induced paw inflammation in rats. PGD_2 produced a dose-related inflammation-augmenting effect, whereas hydrocortisone and the PG synthesis inhibitors, paracetamol and mefenamic acid, induced attenuation of the peripheral oedema. These findings confirm an earlier report from this laboratory which had indicated that central PGs may modulate peripheral inflammation and that conventional anti-inflammatory agents exert at least part of their effect by inhibiting central PG synthesis.

The role of peripheral prostaglandins (PGs) in the mediation and modulation of the inflammatory response has been investigated extensively (Ferreira & Vane 1979). Like other models of experimental inflammation, the role of peripheral PGs including that of PGD_2 in carrageenan-induced acute paw oedema is well accepted (Vane 1987). An excellent correlation has been shown to exist between the anti-inflammatory effects of a large number of non-steroidal anti-inflammatory agents in this model of acute inflammation and their PG synthesis inhibiting potential (Lombardino et al 1975). The hyperthermic effect of phlogistic doses of carrageenan are known to be mediated through central PGs (Bhattacharya et al 1987) and the hyperalgesic effect through central and peripheral PGs (Ferreira et al 1978). The analgesic (Ferreira et al 1978) and antipyretic (Flower 1974) effects of aspirin-like drugs have been shown to be due to inhibition of PG synthesis. Rat brain PGE_2 and $PGF_{2\alpha}$ levels were found to be significantly elevated during carrageenan-induced paw inflammation in the rats (Bhattacharya & Das 1984a). Centrally administered PGE_2 was shown to augment carrageenan-induced oedema in rats, whereas $PGF_{2\alpha}$ and the cyclo-oxygenase inhibitors, sodium salicylate and diclofenac, administered i.c.v. attenuated the oedema (Bhattacharya & Das 1984b). It is now apparent that, contrary to the earlier belief, PGD_2 is the major rodent brain PG, the levels of PGE_2 and $PGF_{2\alpha}$ being significantly lower (Wolfe 1982). We have now extended our earlier studies to investigate the effect of centrally administered PGD_2 on carrageenan-induced inflammation in rats.

Materials and methods

The studies were conducted on inbred Wistar strain albino rats (150–200 g) of either sex. The rats were housed in colony cages at an ambient temperature of 25±2°C and 45–55% relative humidity, with a 12 h light/dark cycle. The rats were fed on standard pellet chow and given tap water through drinking bottles. Experiments were conducted at this ambient temperature between 0900 and 1400 h. Paw inflammation was induced by carrageenan (0·1 mL of 1% suspension in 0·9% saline) injected below the plantar aponeurosis of the hind paw (Winter et al 1962). The paw volume, up to the ankle joint, was measured before and at hourly intervals for 4 h after carrageenan administration, by means of a mercury plethysmograph. The increase in paw volume has been expressed in units, each unit representing 1 cm (volume = 0·075 mL) length of the displaced mercury column.

Intracerebroventricular (i.c.v.) cannulation of the right lateral ventricle was performed in pentobarbitone sodium (40 mg kg^{-1} i.p.) anaesthetized rats and an indwelling cannula was stereotaxically inserted (Feldberg & Lotti 1967). The rats were used a week after the cannulation. All the drugs, except PGD_2, were administered i.c.v. dissolved in 10 μL of artificial cerebrospinal fluid (CSF). PGD_2 was initially dissolved in 1% ethanol before dilution with artificial CSF and administered in a volume of 10 μL. Since the paw oedema induced by carrageenan in control rats receiving either 10 μL of artificial CSF or 10 μL of 1% ethanol in artificial CSF was not significantly different, the former vehicle administered group was maintained as the control group. The increase in paw volume (in units ± s.e.m.) after administration of 10 μL of 1% ethanol in artificial CSF at 1, 2, 3 and 4 h was 1·46±0·18, 2·37±0·21, 2·77±0·25 and 2·64±0·22, respectively (n = 10).

The drugs, used with doses and pretreatment times given in parentheses, were: PGD_2, Sigma Chemicals, USA (5, 10, 20 μg, 15 min), paracetamol, Sigma Chemicals, USA (20, 50 μg, 30 min), mefenamic acid, Sigma Chemicals, USA (10, 20 μg, 30 min) and hydrocortisone hemisuccinate, Lyka Pharmaceuticals (20, 50 μg, 30 min). The doses and pretreatment times are based on data available from earlier studies from this laboratory after i.c.v. administration of drugs (Bhattacharya & Mohan Rao 1987; Bhattacharya et al 1988).

Statistical analysis was by the two tailed unpaired Student's *t*-test. *P* values above 0·05 were taken as statistically insignificant.

Results

The results are summarised in Tables 1 and 2. PGD_2 (5, 10 and 20 μg, i.c.v.) produced a dose-related augmentation of the carrageenan-induced paw oedema, though the effect of the first dose (5 μg) was statistically insignificant. The cyclo-oxygenase inhibitors, paracetamol and mefenamic acid, and the phospholipase A_2 inhibitor, hydrocortisone, attenuated the inflammation induced by carrageenan, though the effect of the smaller doses of paracetamol and hydrocortisone were statistically not significant (Table 1). None of these pharmacological agents had any significant effect on carrageenan oedema when administered i.p. in doses used for i.c.v. administration (Table 2).

Discussion

Centrally administered PGE_2 has been reported to accentuate the phlogistic effect of carrageenan in rats (Bhattacharya & Das 1984a). It is now evident that PGD_2, the major rodent brain PG, exerts a similar pro-inflammatory effect. A remarkable similarity in the central actions of PGD_2 and PGEs is on record. Both these PGs potentiate hexobarbitone hypnosis (Bhattacharya et al 1976; Bhattacharya & Parmar 1985a) and the anticonvulsant

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Table 1. Effect of i.c.v. administered PGD_2, hydrocortisone, mefenamic acid or paracetamol on carrageenan-induced pedal oedema in rats.

	Increase in paw volume in units (mean ± s.e.m.)			
Groups	1 h	2 h	3 h	4 h
Control (artificial (CSF))	1·54 ± 0·11	2·32 ± 0·19	2·98 ± 0·12	2·24 ± 0·08
PGD_2 (5 μg)	1·86 ± 0·12	2·67 ± 0·16	3·20 ± 0·11	2·58 ± 0·12
PGD_2 (10 μg)	2·15 ± 0·16[a]	3·18 ± 0·12[b]	3·52 ± 0·10[a]	3·02 ± 0·12[a]
PGD_2 (20 μg)	2·68 ± 0·14[b]	3·79 ± 0·16[b]	4·12 ± 0·16[b]	3·52 ± 0·11[b]
Hydrocortisone (20 μg)	1·29 ± 0·14	2·08 ± 0·15	2·36 ± 0·18	2·02 ± 0·16
Hydrocortisone (50 μg)	0·78 ± 0·09[b]	1·27 ± 0·10[b]	1·76 ± 0·12[b]	1·52 ± 0·07[b]
Mefenamic acid (10 μg)	1·08 ± 0·06[a]	1·64 ± 0·11[a]	2·12 ± 0·09[b]	1·74 ± 0·12[a]
Mefenamic acid (20 μg)	0·86 ± 0·08[b]	1·48 ± 0·11[a]	1·94 ± 0·10[b]	1·62 ± 0·09[b]
Paracetamol (20 μg)	1·28 ± 0·14	2·06 ± 0·13	2·42 ± 0·12	2·02 ± 0·13
Paracetamol (50 μg)	0·98 ± 0·09[a]	1·62 ± 0·12[a]	2·04 ± 0·11[b]	1·71 ± 0·11[a]

n = 6 in each group except the control group where it is 8.
[a] and [b] indicate statistical significance in comparison to the control group as $P < 0·01$ and $< 0·001$, respectively. Values without superscripts indicate that they are statistically non-significant (P values more than 0·05) (Student's t-test).

Table 2. Effect of i.p. administered (in the same doses as used i.c.v.) PGD_2, hydrocortisone, mefenamic acid or paracetamol on carrageenan-induced pedal oedema in rats.

	Increase in paw volume in units (mean ± s.e.m.)			
Groups	1 h	2 h	3 h	4 h
Control (saline)	1·78 ± 0·14	2·86 ± 0·19	3·54 ± 0·19	3·14 ± 0·18
PGD_2 (20 μg)	1·86 ± 0·09	3·04 ± 0·21	3·76 ± 0·22	3·06 ± 0·16
Hydrocortisone (50 μg)	1·52 ± 0·18	2·59 ± 0·17	3·22 ± 0·19	2·98 ± 0·11
Mefenamic acid (20 μg)	1·56 ± 0·12	2·54 ± 0·14	3·19 ± 0·21	2·86 ± 0·16
Paracetamol (50 μg)	1·72 ± 0·09	2·69 ± 0·12	3·26 ± 0·14	3·02 ± 0·08

n = 5 in each group except the control group where it is 10.
None of the values are statistically significant in comparison to the control group (P values more than 0·05) (Student's t-test).

action of phenobarbitone (Bhattacharya & Sanyal 1978a; Bhattacharya & Parmar 1985b), they attenuate pentetrazol-induced convulsions (Bhattacharya & Sanyal 1978b; Bhattacharya & Parmar 1987), and induce antinociception (Sanyal et al 1979; Bhattacharya 1986) and catalepsy (Bhattacharya et al 1984; Bhattacharya & Mohan Rao 1987). The mechanism of PGD_2-induced potentiation of an acute peripheral inflammation after central administration of the eicosanoid, is not apparent. However, in a recent review on central modulation of peripheral inflammation (Bhattacharya & Das Gupta 1988), it has been postulated that the pro-inflammatory effect of the centrally administered PGEs may be secondary to their facilitatory effect on central cholinergic and inhibition of central catecholaminergic neurotransmission (Wolfe 1982). The pro-inflammatory effect of the central cholinergic system (Das & Bhattacharya 1985) and the inflammation-attenuating role of the central noradrenergic system (Bhattacharya & Das 1986) has been extensively investigated in rats, using the carrageenan model of paw oedema. Like the PGEs, PGD_2 is also known to augment central cholinergic activity (Mohan Rao & Bhattacharya 1988) and attenuate central catecholaminergic neurotransmission (Hemker & Aiken 1980). It is, therefore, likely that the proposed mechanism for the inflammation promoting effect for PGEs may hold true for PGD_2 as well.

The phospholipase A_2 inhibitor, hydrocortisone (Gryglenwski 1979), and the cyclo-oxygenase inhibitors, paracetamol and mefenamic acid, administered centrally, attenuated carrageenan-induced paw oedema, indicating that inhibition at different levels of the PG synthesis cascade in the central nervous system can induce a significant anti-inflammatory effect. It may be argued that the inflammation-inhibiting effect of i.c.v. hydrocortisone may well be due to inhibition of leukotriene synthesis, since they are now known to be potent mediators of inflammation (Ford-Hutchison 1985). However, it is still doubtful if lipo-oxygenase metabolites are at all present in the mammalian brain (Wolfe 1982). The anti-inflammatory effect of cyclo-oxygenase inhibitors is now well accepted and sodium salicylate and diclofenac have been reported to attenuate inflammation on central administration as well (Bhattacharya & Das 1984a). It had been earlier stressed that paracetamol was devoid of significant anti-inflammatory effect, while retaining antipyretic and analgesic actions, because it selectively inhibited the central PGs (Flower 1974). However, it is now apparent that paracetamol does have considerable anti-inflammatory activity and can reduce pain and swelling in inflammatory conditions other than athritis, sometimes more effectively than aspirin (Cooper 1981). These observations support the concept of a central locus for anti-inflammatory activity of PG synthesis inhibitors, apart from their well documented peripheral PG synthesis inhibiting activity. Since none of the drugs used in the study had any discernible effect on the oedema induced by carrageenan, after peripheral administration in the doses used by the i.c.v. route, it can be asserted that the observed effects were central and not manifested after seepage into the peripheral circulation.

It has been suggested (Ferreira et al 1978) that carrageenan hyperalgesia, induced by subplantar administration of the phlogistic agent, has a central as well as peripheral component and that PG synthesis inhibitors exert an anti-algesic effect by preventing the hyperalgesia induced by central and peripheral

release of PGs. It is likely that a similar situation exists for the anti-inflammatory effect of these drugs, involving the central PGs in addition to peripheral PGs. At least one study (Bhattacharya & Das 1984b) indicates that rat brain PG levels are significantly increased during the course of carrageenan-induced paw oedema.

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