Prostaglandin Synthesis Inhibitors Reduce *Cannabis* and Restraint Stress Induced Increase in Rat Brain Serotonin Concentrations

S. K. Bhattacharya and D. Bhattacharya

Department of Pharmacology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India

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Cannabis resin (CI) produced a dose-related increase in rat brain serotonin concentrations, whereas restraint stress produced maximal rise of the neurotransmitter concentrations at 1 h, followed by a tendency to normalise by 4 h. The prostaglandin (PG) synthesis inhibitors, diclofenac and paracetamol, antagonized CI and restraint stress induced rise in serotonin concentrations. The findings lend credence to earlier reports that PG synthesis inhibitors antagonize serotonin-mediated neuropharmacological actions of CI and restraint stress in rats.

In some recent reports from this laboratory, PG synthesis inhibitors were shown to antagonize several central actions of cannabis [1], which had earlier been reported to be serotonin-mediated actions, namely, cannabis antinociception and anticonvulsant action in rats and catalepsy in mice [2–4]. Similarly, PG synthesis inhibitors were reported to antagonize restraint stress-induced potentiation of the anticonvulsant actions of phenobarbitone and diphenylhydantoin [5], hexobarbitone hypnosis [6], cannabis antinociception [7] and the *per se* antinociception [8], in rats. All these stress-induced effects were shown to be serotonin mediated responses. Both cannabis and restraint stress have been reported to enhance rat brain serotonergic activity [9, 10]. It was therefore thought worthwhile to investigate the effect of PG synthesis inhibitors on cannabis and restraint stress induced change in rat brain serotonin levels.

Experimental

The study was conducted on male Wistar albino rats (150–200 g). All experiments were conducted at an ambient temperature of 25 ± 2 °C between 9 a.m. and 2 p.m. Food was withdrawn 18 h prior to and water just before experimentation.

Reprint requests to S. K. Bhattacharya.

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The rats were restrained in metallic adjustable immobilisation chambers, after tying the fore and hind limbs separately and then together.

Cannabis resin (CI) was extracted from the flowering tops of *Cannabis indica* with petroleum ether (60–80 °C) and was suspended in 1% Tween-80 for experimentation. The delta-9-tetrahydrocannabinol (THC) content of the resin was biologically assayed, using pure THC as standard and hypothermic activity in rats as the assay parameter. The THC content of the resin was 15%.

Graded doses of CI were administered i.p. and the pretreatment time was kept constant at 1 h. Restraint stress was given for 1, 2 and 4 h. Rats were killed by decapitation and whole brain serotonin was estimated fluorometrically [11].

Diclofenac sodium (15 mg/kg, i.p.) and paracetamol (100 mg/kg, i.p.) were administered 4 h and 30 min, respectively, before administration of CI or induction of restraint. Control animals re-

Table I. Effect of PG synthesis inhibitors on cannabis and restraint stress induced increase in rat brain serotonin levels.

Groups	*n*	Serotonin (μg/g wet tissue)	
		Mean ± S.E.M.	P
Tween-80 (Vehicle)	5	0.74 ± 0.05	–
CI (50 mg/kg)	5	0.78 ± 0.02	N.S. [a]
CI (100 mg/kg)	5	0.94 ± 0.03	< 0.01 [a]
CI (200 mg/kg)	5	1.09 ± 0.07	< 0.001 [a]
CI (500 mg/kg)	5	1.21 ± 0.08	< 0.001 [a]
Diclofenac	5	0.76 ± 0.09	N.S. [a]
Paracetamol	5	0.72 ± 0.06	N.S. [a]
Diclofenac + CI (50)	5	0.72 ± 0.04	N.S. [b]
Diclofenac + CI (100)	6	0.76 ± 0.05	< 0.05 [b]
Diclofenac + CI (200)	6	0.82 ± 0.06	< 0.05 [b]
Diclofenac + CI (500)	6	0.88 ± 0.05	< 0.01 [b]
Paracetamol + CI (50)	5	0.74 ± 0.06	N.S. [b]
Paracetamol + CI (100)	5	0.79 ± 0.03	< 0.01 [b]
Paracetamol + CI (200)	5	0.88 ± 0.04	< 0.05 [b]
Paracetamol + CI (500)	5	0.91 ± 0.05	< 0.05 [b]
Unstressed Control	10	0.82 ± 0.02	–
Restraint-1 h	6	2.24 ± 0.03	< 0.001 [a]
Restraint-2 h	6	1.87 ± 0.08	< 0.001 [a]
Restraint-4 h	6	1.75 ± 0.02	< 0.001 [a]
Diclofenac + Restraint (1 h)	5	1.56 ± 0.09	< 0.001 [b]
Diclofenac + Restraint (2 h)	5	1.08 ± 0.08	< 0.001 [b]
Diclofenac + Restraint (4 h)	5	0.98 ± 0.12	< 0.001 [b]
Paracetamol + Restraint (1 h)	5	1.75 ± 0.08	< 0.01 [b]
Paracetamol + Restraint (2 h)	5	1.22 ± 0.05	< 0.001 [b]
Paracetamol + Restraint (4 h)	5	1.04 ± 0.09	< 0.001 [b]

[a] and [b] indicate statistical significance in comparison to respective control and CI or restraint groups, respectively (*t* test). N.S. indicates statistical non-significance ($P > 0.05$).

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ceived equivalent volume of normal saline through the same route.

Results and Discussion

The results are summarized in Table I. As reported earlier [9, 10], CI produced a dose-related increase, whereas restraint stress induced maximal increase of rat brain serotonin levels at 1 h with gradually decreasing concentrations at 2 and 4 h stress. Both the PG synthesis inhibitors, diclofenac and paracetamol [12], antagonized CI and restraint stress effects on rat brain serotonin levels. There was no significant difference between the effects of the two drugs, though diclofenac appeared to have a somewhat more pronounced action.

The biochemical findings of the present study are in conformity with earlier reports that PG synthesis inhibitors antagonize several serotonin-mediated central pharmacological actions of CI and restraint stress [1–8]. They also support an earlier report from this laboratory indicating that PG synthesis inhibitors antagonize morphine-induced increase in rat brain serotonin levels and inhibit the serotonin-mediated antinociception of morphine in this species [12, 13].

Based on the observations that PGE_1 enhances [14] and $PGF_2\alpha$ decreases [15] rat brain serotonergic activity, together with the findings indicating that PG synthesis inhibitors are capable of antagonizing several serotonin-mediated drug responses [16], it has been postulated that PGs may have a modulating influence on central serotonergic neurotransmission [16]. The present findings lend credence to this postulate.

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Erratum

A. Andreoni, R. Cubeddu, S. De Silvestri, G. Jori, P. Laporta, and E. Reddi, Time-Resolved Fluorescence Studies of Hematoporphyrin in Different Solvent Systems, Z. Naturforsch. **38 c**, 83–89 (1983).

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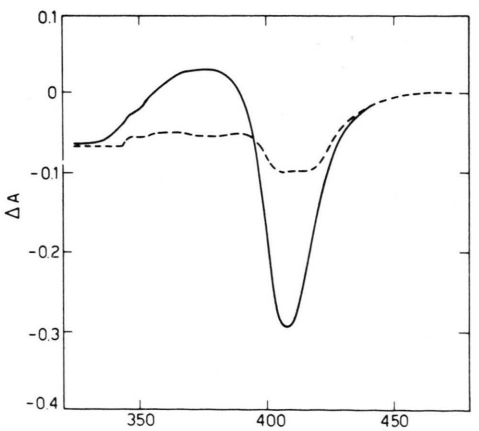
Fig. 2 is corrected in the following way:



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