serotonin-mediated. Recent studies from this laboratory indicate that PGD_2 augments serotonin concentrations of the whole brain and different areas of the brain in Wistar rats (13). It was noted that the maximal increase in serotonin concentrations were induced 15 min after PGD_2 administration. PGD_2 also enhanced the rate of accumulation of serotonin in the rat brain after tranylcypromine treatment (13), indicating that the PG increases the synthesis, and thereby turnover, of serotonin. PGE_1 has earlier been reported to augment the synthesis and turnover of serotonin (5).

A recent review (14) makes it evident that the role of monoamines in electroconvulsive seizures and in anticonvulsant drug action, is still equivocal. However, there are reports that indicate that serotonin enhances the threshold for electro-shock-induced tonic convulsions and may mediate anticonvulsant drug action (15–17, 20).

It may be argued that PGD_2-induced potentiation of anticonvulsant drug action is due to altered kinetics of PB or PTH brought about by the PG. There is no evidence that PGs alter the distribution, metabolism, excretion or CNS penetration of PB or PTH. Furthermore, all the pharmacologic agents used to study PGD_2-anticonvulsant drug interaction were administered centrally and have well documented effects on central serotonergic activity. It is, therefore, reasonable to assume that PGD_2-induced potentiation of the anticonvulsant actions of PB and PTH represents a pharmacodynamic potentiation caused by augmented central serotonergic activity.

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Central Serotonergic Modulation of Carrageenin-induced Pedal Inflammation in Rats

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Abstract: Putative central serotonergic modulation of acute peripheral inflammation was investigated in rats, using the carrageenin-induced pedal edema as the experimental model. Serotonin and the serotonin precursor 5-hydroxytryptophan (5HTP) produced a dose-related inhibition of the peripheral edema when given intracerebroventricularly (*icv*) and *ip*, together with the peripheral decarboxylase inhibitor benserazide. Quipazine, which inhibits neuronal release of serotonin, 5,6-dihydroxytryptamine (DHT), a specific serotonergic neurotoxin, and *p*-chlorphenylalanine, a selective serotonin synthesis inhibitor, augmented carrageenin inflammation upon *icv* administration. Metergoline, a serotonin receptor antagonist, inhibited the anti-inflammatory effect of centrally administered serotonin. However, another serotonin receptor antagonist, methysergide, produced a serotonin-like effect. The inflammation-inhibiting effect of centrally administered methysergide was antagonized after DHT-pretreatment. The findings indicate that in rats central serotonin has a modulatory inhibitory effect on acute peripheral inflammation. It was further shown that this inhibitory effect is not mediated either through activation of the peripheral sympathetic nervous system or the adrenal cortex.

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The mechanisms and the cascade of events underlying peripheral inflammation are now well elucidated (1). However, little is known about the role of the central nervous system (CNS) in putative modulation of peripheral inflammation (2). Schizophrenics are known to have an unusually low incidence of rheumatoid arthritis. In addition, these patients show reduced inflammatory response to injury or infection and exhibit minimal wheal-flare response to histamine (3). Acute inflammation is significantly reduced in anesthetised animals (4). Narcotic analgesics, spinal transection, acute and chronic denerva-

tion are all known to inhibit the early phase of formaline or carrageenin inflammation in rats (2). There are no reports available on the possible modulatory effect of central neurotransmitters on peripheral inflammation, apart from two recent communications from this laboratory indicating that central prostaglandins (5) and acetylcholine (6) exert a pro-inflammatory effect on carrageenin-induced pedal edema in rats. In this communication we report our findings on the role of central serotonin on acute peripheral inflammation induced by carrageenin.

Materials and Methods

The studies were conducted on inbred Wistar strain albino rats (120–180 g) of either sex, obtained from the Institute animal house. The rats were housed in colony cages at an ambient temperature of 25 ± 2°C and fed on standard Hind Lever chow. Experiments were conducted at this ambient temperature between 9.00 and 14.00 h. Pedal inflammation was induced by carrageenin (Sigma Type 1, 0.1 ml of 1% suspension in 0.9% saline) injected below the plantar aponeurosis of the hind paws (7). The paw volume, up to the ankle joint, was measured before and at hourly intervals for 4 h after carrageenin administration, by means of a mercury plethysmograph. The increase in paw volume was expressed in units, each unit representing one cm (volume = 0.075 ml) length of the displaced mercury column. Intracerebroventricular (*icv*) cannulation of the right lateral ventricle was performed in pentobarbitone sodium (40 mg/kg, *ip*) anesthetised rats, and an indwelling cannula was stereotaxically inserted (8). A sham operated control group (Control II), in which the surgical procedure except the actual cannulation was performed, was maintained. Bilateral adrenalectomy was performed under ether anesthesia. The rats were given saline (0.9%) instead of water during the post-operative period. The rats were used one week after cannulation or sham operation and 48 h after adrenalectomy.

The following drugs, with doses, pretreatment times and routes of administration given in parenthesis, were used: 5-hydroxytryptamine creatinine sulfate (serotonin, 10, 20 and 50 μg, 15 min, *icv*), 5-hydroxytryptophan (250 μg, 15 min, *icv*), 5-hydroxytryptophan (75 mg/kg, 30 min, *ip*) with benserazide hydrochloride (50 mg/kg, 30 min, *ip*), quipazine maleate (20 μg, 30 min, *icv*), 5,6-dihydroxytryptamine creatinine sulfate (75 μg, 72 h, *icv*), *p*-chlorophenylalanine methyl ester hydrochloride (100 μg, once daily for 3 days, *icv*), methysergide maleate (10 μg, 15 min, *icv*), metergoline (10 μg, 15 min, *icv*), and 6-hydroxydopamine hydrochloride (100 mg/kg, 72 h, *ip*). Drugs that were given *icv* were dissolved in 10 μl of artificial cerebrospinal fluid (8) and those given *ip* were dissolved in 0.5 ml normal saline. Control animals received equivalent volumes of artificial cerebrospinal fluid (Control I) or normal saline (Control II) through the appropriate routes. The doses mentioned refer to the respective salts. The doses and pretreatment times used in the study are based on earlier studies from this laboratory (9, 10).

In a separate paradigm, the drugs that were administered *icv* were given *ip* to groups of rats, following the same dose and pretreatment time schedule, dissolved in 0.5 ml of normal saline. A control group administered with the vehicle was maintained (Control III). Carrageenin-induced inflammation was induced and assessed as mentioned earlier.

Statistical analysis was done by the Student's *t*-test.

Results

The results are summarized in Tables I, II and III. The increase in pedal edema, induced by carrageenin, was statistically significant throughout the 4 h period of observation, peaking at 3 h. Though the inflammation induced by carrageenin in the artificial cerebrospinal fluid (*icv*) treated group (Control I) was qualitatively similar to that seen in the sham operated saline (*ip*) treated (Control II) and the unoperated saline (*ip*) treated (Control III) groups, the degree of edema was significantly less in Group I (Table II). There was no difference in the degree of edema induced by carrageenin in the Groups II and III (Table III). Serotonin (10, 20 and 50 μg) produced a dose-related decrease in carrageenin-induced inflammation on *icv* administration; however, only the latter two doses produced significant inhibition. Similarly, 5-hydroxytryptophan (5HTP), the serotonin precursor, significantly attenuated carrageenin edema when administered centrally as well as when given peripherally together with a peripheral decarboxylase inhibitor, benserazide, in sham operated rats (Table I and II). Quipazine, a serotonergic agonist, paradoxically enhanced carrageenin-induced inflammation (Table I). 5,6-Dihydroxytryptamine (DHT), a specific serotonergic neurotoxin, and *p*-chlorophenylalanine (PCPA), a serotonin synthesis inhibitor, both augmented the inflammatory response to carrageenin (Table I). Of the two serotonin receptor

Table I Effects of *icv* Administered Serotonin Agonists and Antagonists on Carrageenin-Induced Pedal Edema in Rats.

Groups	n	Increase in paw volume in units (mean ± S.E.M.) 1 h	2 h	3 h	4 h
1. Control I (artificial CSF icv)	16	1.52 ± 0.13	2.4 ± 0.17	2.64 ± 0.14	2.51 ± 0.15
2. Serotonin (10 μg)	6	1.36 ± 0.11[a]	2.21 ± 0.09[a]	2.34 ± 0.16[a]	2.28 ± 0.19[a]
Serotonin (20 μg)	6	1.13 ± 0.11[b]	1.92 ± 0.08[b]	2.12 ± 0.11[b]	2.02 ± 0.09[b]
Serotonin (50 μg)	9	0.92 ± 0.07[d]	1.7 ± 0.08[d]	1.86 ± 0.1[d]	1.75 ± 0.07[d]
3. 5-HTP	5	0.94 ± 0.2[b]	1.4 ± 0.26[c]	1.6 ± 0.23[d]	1.56 ± 0.23[c]
4. Quipazine	6	2.08 ± 0.14[b]	2.98 ± 0.12[b]	3.29 ± 0.18[c]	3.06 ± 0.13[b]
5. DHT	5	2.1 ± 0.17[b]	3.0 ± 0.21[b]	3.3 ± 0.27[b]	3.2 ± 0.29[b]
6. PCPA	5	1.94 ± 0.21[a]	2.86 ± 0.26[a]	3.28 ± 0.18[c]	2.98 ± 0.09[d]
7. Methysergide	10	0.87 ± 0.16[b]	1.17 ± 0.13[d]	1.54 ± 0.14[d]	1.41 ± 0.18[d]
8. Metergoline	6	1.61 ± 0.17[a]	2.26 ± 0.15[a]	2.92 ± 0.14[a]	2.7 ± 0.16[a]
9. Methysergide + Serotonin (50 μg)	5	1.16 ± 0.06[x]	1.76 ± 0.09[x]	2.0 ± 0.18[x]	1.9 ± 0.11[x]
10. Metergoline + Serotonin (50 μg)	6	1.39 ± 0.12[x]	2.24 ± 0.11[y]	2.42 ± 0.12[y]	2.3 ± 0.1[y]
11. DHT + Methysergide	5	2.36 ± 0.16[z]	3.42 ± 0.18[z]	3.84 ± 0.24[z]	3.56 ± 0.22[z]

Statistical significance (P) in relation to:
Control Group I: a > 0.05; b < 0.05; c < 0.01; d < 0.001
Serotonin (50 μg) group: x > 0.05; y < 0.05
Methysergide group: z < 0.001

Table II. Effects of Peripherally Administered 6-Hydroxydopamine (HD) and Bilateral Adrenalectomy (AD) on the Anti-Inflammatory Effect of 5HTP in Carrageenin-Induced Pedal Edema in Rats

Groups	n	Route	Increase in paw volume in units (mean ± S.E.M.) 1 h	2 h	3 h	4 h
1. Control I (artificial CSF)	16	*icv*	1.52 ± 0.13	2.4 ± 0.17	2.64 ± 0.14	2.51 ± 0.15
2. Control II (sham operated-saline)	15	*ip*	2.15 ± 0.15[a]	3.04 ± 0.19[b]	3.13 ± 0.2[a]	3.04 ± 0.21[a]
3. 5HTP	5	*icv*	0.94 ± 0.2	1.4 ± 0.26	1.6 ± 0.23	1.56 ± 0.23
4. HD	7	*ip*	2.21 ± 0.27[x]	3.27 ± 0.21[x]	3.52 ± 0.2[x]	3.31 ± 0.18[x]
5. HD + 5HTP	5	*ip* *icv*	1.22 ± 0.26[d]	1.7 ± 0.2[d]	1.92 ± 0.16[d]	1.75 ± 0.05[d]
6. 5HTP + Benserazide	14	*ip*	1.71 ± 0.12[y]	2.15 ± 0.2[y]	2.19 ± 0.15[z]	2.01 ± 0.18[z]
7. AD	14	—	2.04 ± 0.14[x]	2.9 ± 0.13[x]	3.45 ± 0.14[x]	3.38 ± 0.14[x]
8. AD + 5HTP + Benserazide	6	*ip*	1.16 ± 0.12[c]	1.71 ± 0.13[c]	2.1 ± 0.13[c]	1.86 ± 0.12[c]

Statistical significance (P) in relation to:
Control Group I: $a < 0.05$; $b < 0.01$
Control Group II: $x > 0.05$; $y < 0.05$; $z < 0.001$
5HTP Group: $d > 0.05$
5HTP + Benserazide Group: $c > 0.05$

Table III. Effects of *ip* Administered Serotonin Agonists and Antagonists, in *icv* Administered Doses and Pretreatment Times, on Carrageenin-Induced Pedal Edema in Rats.

Groups	n	Increase in paw volume in units (mean ± S.E.M.) 1 h	2 h	3 h	4 h
1. Control III (no surgery)	6	2.34 ± 0.21	3.28 ± 0.26	3.46 ± 0.19	3.19 ± 0.21
2. Control II (sham operated)	15	2.15 ± 0.15	3.04 ± 0.19	3.13 ± 0.2	3.04 ± 0.21
3. Serotonin (10 μg)	5	2.41 ± 0.26	3.22 ± 0.17	3.58 ± 0.22	3.21 ± 0.19
Serotonin (20 μg)	5	2.52 ± 0.19	3.42 ± 0.24	3.66 ± 0.24	3.28 ± 0.21
Serotonin (50 μg)	5	2.64 ± 0.26	3.72 ± 0.23	3.81 ± 0.26	3.4 ± 0.24
4. 5HTP	5	2.58 ± 0.19	3.64 ± 0.22	3.78 ± 0.21	3.32 ± 0.18
5. Quipazine	5	2.46 ± 0.2	3.12 ± 0.17	3.62 ± 0.16	3.32 ± 0.14
6. DHT	5	2.52 ± 0.19	3.54 ± 0.23	3.76 ± 0.22	3.33 ± 0.19
7. PCPA	5	2.44 ± 0.18	3.46 ± 0.19	3.62 ± 0.21	3.24 ± 0.16
8. Methysergide	5	2.21 ± 0.14	3.12 ± 0.16	3.22 ± 0.19	3.0 ± 0.16
9. Metergoline	5	2.26 ± 0.12	3.16 ± 0.18	3.34 ± 0.16	3.08 ± 0.14

None of the values in groups 2 to 9 were statistically significant ($P > 0.05$) when compared to Control group III.

antagonists used, methysergide not only failed to affect the inflammation-attenuating effect of serotonin but exerted a serotonin-like anti-inflammatory effect. However, the other antagonist, metergoline, antagonized the anti-inflammatory effect of centrally administered serotonin (Table I). The inflammation-attenuating effect of methysergide was not evident in DHT-treated rats (Table I).

6-Hydroxydopamine (HD), which induces peripheral chemical sympathectomy on *ip* administration, insignificantly accentuated carrageenin edema but failed to affect the anti-inflammatory effect of centrally administered 5HTP (Table II). Similarly, bilateral adrenalectomy performed in rats sham operated for *icv* cannulation failed to affect the inflammation-inhibiting effect of 5HTP administered peripherally in conjunction with benserazide, a peripheral decarboxylase inhibitor (Table II). Recourse had to be taken to this route of administration of 5HTP because of the high rate of mortality (50–60 %) of *icv* cannulated rats undergoing bilateral adrenalectomy.

Serotonin, 5HTP, quipazine, DHT, PCPA, methysergide and metergoline did not show any statistically significant effect on carrageenin-induced inflammation when administered *ip* in the doses and pretreatment times used for *icv* administration (Table III).

Discussion

The carrageenin-induced inflammation in rats was adopted as the experimental parameter because it has been extensively investigated and the mechanism underlying the inflammation is well elucidated (11). Furthermore, an excellent correlation has been shown to exist between the anti-phlogistic effect of a number of drugs against this model of experimental inflammation and their clinical anti-arthritic effects (12).

Carrageenin-induced edema was significantly less marked in *icv* cannulated rats that were administered artificial cerebrospinal fluid (Control I), as compared to the sham operated but uncannulated rats administered normal saline *ip*. Surgical procedures are known to induce transient suppression of inflammation in experimental animals, probably by inducing release of endogenous corticoids (13). However, in this study the surgical stress is unlikely to be the cause of the attenuated inflammatory response in *icv* cannulated rats because they were used one week after surgery. Furthermore, there was little difference between the inflammatory response of carrageenin in the sham operated (Control II) and the unoperated (Control III) groups. It is, however, possible that the physical presence of the cannula and the administration of artificial cerebrospinal fluid serve as stressors. The high mortality in this group following bilateral adrenalectomy, lends credence to this possibility.

Serotonin, administered *icv*, produced a dose-related inhibition of the peripheral inflammation induced by carrageenin. A similar inhibition was induced by its precursor, 5HTP, both when given centrally as well as peripherally, with a peripheral decarboxylase inhibitor. Unlike serotonin and 5HTP, quipazine, a serotonin agonist, paradoxically augmented carrageenin-induced edema. Quipazine has been reported to decrease the neuronal release of serotonin by acting presynaptically on the serotonergic neurones resulting in inhibition of neuronal firing and accumulation of serotonin in the neurone (14, 15). DHT, which induces selective degeneration of central serotonergic neurones when administered *icv*, and PCPA

which inhibits serotonin biosynthesis by inhibiting tryptophan hydroxylase, both augmented carrageenin-induced edema. DHT and PCPA have been reported to significantly reduce rat brain serotonin levels on *icv* administration in earlier studies from this laboratory (16).

The two serotonergic receptor antagonists, methysergide and metergoline, showed qualitatively different effects in this study. Metergoline had little effect *per se* on carrageenin edema, but significantly antagonized the anti-inflammatory effect of centrally administered serotonin. In contrast, methysergide not only failed to block the inflammation-attenuating effect of serotonin but actually mimicked the effect of serotonin. This paradoxical effect of methysergide was not evident in DHT-treated rats suggesting that functional integrity of central serotonergic neurones is a prerequisite for the observed anti-inflammatory effect of methysergide. In a recent study (17), it was shown that, unlike metergoline which produced complete inhibition of (^{3}H)serotonin binding in rat spinal cord, methysergide produced an increase rather than the expected decrease in the binding of (^{3}H)serotonin. An examination of structurally similar ergolines showed that the enhancement of the binding was specific for methysergide. Our findings with metergoline and methysergide conform with these observations. Methysergide is known to potentiate certain electrophysiological actions of serotonin (18). The concept of presynaptic autoreceptors for serotonin neurones is a matter of controversy (19). However, it is possible that methysergide functions as a presynaptic receptor antagonist, leading to enhanced neuronal release of serotonin (20). Since the anti-inflammatory effect of centrally administered methysergide was antagonized by DHT, this may explain the paradoxical effect of methysergide. The pro-inflammatory effect of quipazine, a reported serotonin presynaptic receptor agonist (15), favors this point of view.

The findings of this study, thus, indicate that central serotonin exerts a modulatory inhibiting effect on peripheral inflammation in rats. Treatments that enhance central serotonergic activity induce an inflammation-attenuating effect, whereas treatments that decrease it induce an inflammation-augmenting effect. Since all the centrally administered pharmacological agents failed to affect carrageenin edema when administered peripherally in similar doses, it can be concluded that the observed effects are a function of their central action and not due to possible leakage into the periphery.

Attempts were made to elucidate the mechanism of the anti-inflammatory effect of central serotonin. Two possibilities were considered, one that the effect is due to activation of the hypothalamo-pituitary adrenal axis and secondly that the effect is due to augmented peripheral sympathetic activity. Bilateral adrenalectomy produced only partial and statistically insignificant antagonism of the inflammation attenuating effect of 5HTP administered peripherally with a peripheral decarboxylase inhibitor, indicating that activation of the hypothalamo-pituitary-adrenal axis and consequent release of endogenous corticoids is unlikely to be the involved mechanism of action of central serotonin. The literature on the effect of central serotonin and adrenal corticoid activation is equivocal, and there are reports to suggest that central serotonin increases, decreases or has no effect on ACTH secretion (21).

It has long been known that peripheral catecholamines attenuate inflammation (22). Activation of central serotonergic pathways has been shown to be reflected in augmented peripheral sympathetic activity (23). Peripherally administered 6-hydroxydopamine, which leads to near complete degeneration of peripheral sympathetic neurones (24), produced a statistically insignificant pro-inflammatory effect but failed to affect the anti-inflammatory activity of centrally administered 5HTP. This indicates that functional integrity of the peripheral sympathetic nervous system is not a prerequisite for the inflammation-attenuating effect of central serotonin. It is apparent that the mechanism of the central anti-inflammatory effect of serotonin is not dependent upon the adrenals or the sympathetic system and has to be sought for elsewhere. This study is now in progress.

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