tive determination of tocainide in the presence of its metabolites.

Since antiarrhythmic drugs are frequently used in combination therapy, several common antiarrhythmic drugs and their metabolites were examined for possible interference (Table IV). All parent drugs were clearly separated, while two metabolites partially overlapped with tocainide.

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Prostaglandin D_2 Induced Potentiation of the Anticonvulsant Actions of Phenobarbitone and Phenytoin in Rats. Role of Serotonin

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Abstract: Prostaglandin D_2 (PGD_2) produced a dose-related potentiation of the anticonvulsant actions of sub-effective doses of phenobarbitone and phenytoin against maximal electroshock-induced seizures in rats. PGD_2-induced potentiation of phenobarbitone and phenytoin was significantly attenuated following pretreatment with centrally administered 5,6-dihydroxytryptamine, a selective neurotoxin for serotonergic neurones, *p*-chlorophenylalanine, a specific inhibitor of serotonin biosynthesis, and methysergide, a serotonin receptor antagonist, indicating that the potentiation was serotonin-mediated.

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Prostaglandins (PGs) are now known to exert a variety of physiological functions in the mammalian central nervous system (CNS), modulation of central neuronal activity being one of them (1, 2). Catecholamines and serotonin stimulate the biosynthesis and release of PGs (2, 3), and the latter are known to influence central catecholaminergic and serotonergic activities (4–6). Till recently PGs of the E and F series had attracted maximal scientific interest in relation to mammalian brain functions (1). However, it is now evident that there is considerable species variation in the distribution of central PGs and that PGD_2 is by far the most dominant PG in the rat and mouse brain, the levels of PGE_2 and $PGF_{2\alpha}$ being substantially lower (7). Recent studies indicate that PGD_2 shares some of the behavioral effects shown by PGs of the E series (8). PGD_2, like PGE_1, has a sedative effect in rodents and potentiates pentobarbital hypnosis (9–11). PGE_1 has been shown to potentiate the anticonvulsant action of phenobarbitone in rats by a serotonin-mediated mechanism (12). We have recently shown that, like PGE_1 (5), PGD_2 increases the serotonin concen-

tration of the rat brain and enhances the rate of synthesis of serotonin in tranylcypromine-treated rats (13). PGD_2-induced decrease in locomotor activity and potentiation of pentobarbital hypnosis have been reported to be serotonin-mediated actions (10). The role of brain monoamines in electroconvulsive threshold and in the mediation of anticonvulsant drug action is equivocal (14). However, some studies indicate a greater serotonergic involvement in maximal electroshock-induced tonic convulsions. Rats classified by maximal electroshock as flexors are converted to extensors by induced depletion of serotonin. Conversely, extensor rats are converted to flexors by treatments that increase central serotonergic activity (15, 16). The anticonvulsant action of phenobarbitone has been shown to be serotonin-mediated (17). In view of these reports, the present study was undertaken to investigate whether PGD_2, like PGE_1, potentiates the action of anticonvulsants and to assess the role of serotonin in this interaction.

Materials and Methods

Wistar strain albino rats (120–180 g) of both sexes were used. The rats were housed in colony cages at an ambient temperature of 25 ± 2°C and fed on standard pellet diet, with water given *ad libitum*. Experiments were conducted at this ambient temperature between 9.00 and 14.00 hours. Food was withdrawn 18 h prior to and water just before testing for anticonvulsant activity. Supramaximal electroshock (150 mA, 0.2 sec) was given through a pair of corneal electrodes using a convulsiometer. The hind limb extensor response was taken as the end point (18). The rats were pretested and only those showing extensor response were used 48 h later. Intracerebroventricular (*icv*) cannulation of the right lateral ventricle was performed in pentobarbitone (40 mg/kg, *i.p.*) anesthetized rats, and indwelling cannulae were inserted stereotaxically. The rats were used one week after cannulation. The drugs that were administered *icv*, were dissolved in 10 µl artificial cerebrospinal fluid (CSF).

Phenobarbitone (PB) and phenytoin (PTH), dissolved or suspended in 0.9 % saline, were administered in graded doses to groups of 10 rats *i.p.*, and the animals were subjected to anticonvulsant testing 30 min later. The dose of 2.5 mg/kg *i.p.* was found to be the sub-effective dose for both PB and PTH and has been used in this study. PGD_2, suspended in 1 % ethanol prior to dilution with 0.9 % saline, was administered in graded doses (0.5, 1.0 and 2.0 mg/kg *i.p.*) to groups of rats 15 min before administration of PB or PTH. Control rats received equivalent volume of 1 % ethanol in 0.9 % saline by the same route. The rats were tested for anticonvulsant activity 30 min after PB, PTH or saline administration. The drugs used to investigate PGD_2-anticonvulsant drug interaction, with dose given in parenthesis, were: 5,6-dihydroxytryptamine, creatinine sulphate (75 µg/rat), *p*-chlorophenylalanine methyl ester hydrochloride (100 µg/rat once daily for 3 days) and methysergide maleate (10 µg/rat). All the three drugs were administered *icv*. 5,6-Dihydroxytryptamine (DHT), *p*-chlorophenylalanine (PCPA) and methysergide were administered 72 h, 48 h and 15 min before the administration of PB or PTH, respectively. The doses and the pretreatment times of these drugs are based on data available in this laboratory (19). Statistical analysis was done by the chi square test.

Results and Discussions

The results are summarized in Table I. PGD_2 (0.5, 1.0 and 2.0 mg/kg *i.p.*) had no *per se* anticonvulsant effect but induced a dose-related potentiation of the anticonvulsant actions of a sub-effective (2.5 mg/kg, *i.p.*) dose of both PB and PTH. The potentiation was statistically significant with the higher two doses of PGD_2. Pretreatment with DHT, which is known to induce selective degeneration of central serotonergic neurones on *icv* administration, and PCPA, a specific serotonin synthesis inhibitor, significantly attenuated PGD_2 (2.0 mg/kg, *i.p.*)-induced potentiation of both PB and PTH anticonvulsant actions. DHT and PCPA, in the doses and pretreatment times used in this study, have been found to reduce rat brain serotonin concentration by 47 % and 54 %, respectively, in studies conducted in this laboratory (19). Methysergide, a well documented serotonin receptor antagonist, also antagonized PGD_2-induced potentiation of the anticonvulsant actions of PB and PTH.

The absence of any anticonvulsant effect of relatively high doses of PGD_2 conforms with reports that it does not antagonize electroshock or pentylenetetrazol seizures in rats (8). PGD_2-treated rats showed signs of sedation and reduced spontaneous motility but no motor incoordination. The ability of DHT, PCPA and methysergide to effectively attenuate PGD_2-induced potentiation of the anticonvulsant actions of PB and PTH indicate that the potentiation is dependent on the functional integrity of the central serotonergic system and that, like PGE_1 (12), the PGD_2 effect is

Table I. Effect of PGD_2 on the Anticonvulsant Actions of Sub-Effective Dose (2.5 mg/kg, *i.p.*) of Phenobarbitone and Phenytoin against Maximal Electroshock-Induced Seizures in Rats.

Groups	n	Anticonvulsant effect (%)	P
PGD_2 (0.5 mg/kg)	5	0	—
PGD_2 (1.0 mg/kg)	5	0	–
PGD_2 (2.0 mg/kg)	5	0	–
Phenobarbitone (PB)	10	0	–
Phenytoin (PTH)	10	0	–
PGD_2 (0.5 mg/kg) + PB	10	30	ns*
PGD_2 (1.0 mg/kg) + PB	10	60	< 0.01*
PGD_2 (2.0 mg/kg) + PB	10	100	< 0.001*
PGD_2 (0.5 mg/kg) + PTH	10	20	ns*
PGD_2 (1.0 mg/kg) + PTH	10	50	< 0.05*
PGD_2 (2.0 mg/kg) + PTH	10	90	< 0.001*
DHT + PGD_2 (2.0 mg/kg) + PB	10	0	< 0.001**
DHT + PGD_2 (2.0 mg/kg) + PTH	10	10	< 0.01**
PCPA + PGD_2 (2.0 mg/kg) + PB	10	30	< 0.02**
PCPA + PGD_2 (2.0 mg/kg) + PTH	10	40	< 0.05**
Methysergide + PGD_2 (2.0 mg/kg) + PB	10	50	< 0.05**
Methysergide + PGD_2 (2.0 mg/kg) + PTH	10	40	< 0.05**

* and ** denote statistical significance in comparison to PB or PTH group and PGD_2 (2.0 mg/kg)-treated PB or PTH group, respectively. ns indicates statistical non-significance at 5 % level (chi square test).

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-