tiates the contracting effect of histamine on guinea-pig isolated trachea by stimulating α_1-adrenoceptors. The guinea-pig trachea therefore radically differs from the dog trachea which contracts when its α_2-adrenoceptors are stimulated by clonidine or noradrenaline (Barnes et al 1983).

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Prostaglandin D_2-induced potentiation of hexobarbitone hypnosis in rats: role of 5-hydroxytryptamine

S. K. BHATTACHARYA*,. S. S. PARMAR†, *Department of Pharmacology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India, †Department of Physiology, School of Medicine, University of North Dakota, Grand Forks, ND 58202, USA*

Prostaglandin D_2 (PGD_2) produced a dose-related increase in the duration and incidence of induction of sleep induced by hexobarbitone, in rats. Pretreatment with pharmacological agents known to reduce selectively brain 5-hydroxytryptaminergic activity, significantly inhibited PGD_2-induced potentiation of hexobarbitone, indicating that this potentiation is mediated by 5-hydroxytryptamine.

Considerable evidence now exists which makes it possible to assign a physiological role for prostaglandins (PGs) in the central nervous system (Wolfe & Coceani 1979). Wolfe (1976) suggested that PGs exert a modulatory influence on central neuronal activity. PG biosynthesis and release is known to be stimulated by catecholamines and 5-hydroxytryptamine (5-HT) (Wolfe 1976; Schaefer et al 1978). Likewise, PGs are reported to influence central catecholaminergic (Bergstrom et al 1973) and tryptaminergic (Debnath et al 1978; Bhattacharya 1982) activity. Until recently, only PGs of the E and F series were investigated in mammalian brain functions. However, it is now evident that there is considerable species variation in the distribution of central PGs and PGD_2 is by far the most dominant PG in rat and mouse brains, the levels of PGE_2 and $PGF_{2\alpha}$ being considerably lower (Abdel-Halim et al 1977). Recent studies indicate that, like PGE_1 (Bhattacharya et al 1976), PGD_2 has a sedative action in rodents and potentiates pentobarbitone sleeping time (Laychock et al 1980; Hollingsworth & Patrick 1984). PGE_1-induced potentiation of hexobarbitone hypnosis has been shown to be a 5-HT-mediated response (Bhattacharya et al 1976). The present study was designed to investigate the role of 5-HT in PGD_2-barbiturate interaction.

* Correspondence.

Materials and methods

Male Wistar strain albino rats (120–180 g) were housed in colony cages at an ambient temperature of 25 ± 2 °C and fed on standard pellet chow with free access to water. Experiments were conducted at this ambient temperature between 0900 h and 1400 h. Food was withdrawn 18 h before and water just before the experiment.

Intracerebroventricular (i.c.v.) cannulation of the right lateral ventricle was performed in pentobarbitone sodium (40 mg kg^{-1} i.p.) anaesthetized rats (Feldberg & Lotti 1967). Experiments were conducted a week after the insertion of indwelling cannulae. All the drugs, except PGD_2 and hexobarbitone, were administered i.c.v. dissolved in 10 µl of artifical cerebrospinal fluid (csf). Control animals received an equivalent volume of artificial csf via the same route.

Two doses of hexobarbitone were used, one (100 mg kg^{-1} i.p.) which induced sleep in all rats, and the other (50 mg kg^{-1} i.p.) which had no detectable hypnotic effect. These two doses have been designated as the hypnotic and the sub-hypnotic dose of hexobarbitone, respectively. The sleeping time was measured as the interval between the loss and regaining of the righting reflex, with sufficient mobility to move beyond the border of a 12 in circle. In the groups in which the sub-hypnotic dose of hexobarbitone was used, percentage induction of sleep was the experimental criterion. No effort was made to assess the latency of the onset of hypnosis in either group. PGD_2, suspended in 1% ethanol was administered, after dilution with 0·9% NaCl (saline), in graded doses (0·2, 0·5 and 1 mg kg^{-1} i.p.) to groups of rats 15 min before hexobarbitone. Control animals received the equivalent volume of 1%

ethanol in saline. The drugs used to investigate PGD_2-hexobarbitone interaction, with doses and pretreatment times given in parentheses were: 5,6-dihydroxytryptamine creatinine sulphate (DHT, 75 μg/rat, 72 h), *p*-chlorophenylalanine methyl ester hydrochloride (PCPA, 100 μg/rat, once daily for 3 days) and methysergide maleate (10 μg/rat, 15 min). The doses and pretreatment times of these drugs are based on data from this laboratory (Amar et al 1982).

Statistical analysis of the data was by the unpaired *t* or the χ^2 test, depending upon the nature of the experiments.

Results and discussion

PGD_2 (0·2, 0·5 and 1 mg kg^{-1} i.p.) did not produce loss of righting reflex itself but induced a dose-related potentiation of hexobarbitone (100 mg kg^{-1} i.p.) sleeping time and a dose-related induction of sleep in hexobarbitone (50 mg kg^{-1} i.p.)-treated rats. However, the data were statistically significant with the higher two doses of PGD_2. Pretreatment with DHT, which is known to induce selective degeneration of central 5-HT neurons, PCPA, a specific 5-HT synthesis inhibitor, and methysergide, a 5-HT receptor antagonist, significantly attenuated PGD_2-(1 mg kg^{-1} i.p.) induced potentiation of hexobarbitone sleeping time and the induction of sleep induced by PGD_2 in rats treated with a sub-hypnotic dose of hexobarbitone (Table 1).

Table 1. Effect of PGD_2 on hexobarbitone hypnosis in rats

Groups	n	Hexobarbitone (100 mg kg^{-1}) Sleeping time (min) ± s.e.		Hexobarbitone (50 mg kg^{-1}) Percent sleep	
Hexobarbitone (H)	15	31·2 ± 3·2	—	0	—
PGD_2 (0·2) + H	10	37·6 ± 2·8	0·05*	20	0·05*
PGD_2 (0·5) + H	10	46·2 ± 2·7	0·01*	50	0·05*
PGD_2 (1·0) + H	10	58·4 ± 4·8	0·001*	90	0·001*
DHT + PGD_2 (1·0) + H	8	22·1 ± 3·6	0·001**	0	0·001**
PCPA + PGD_2 (1·0) + H	10	31·6 ± 2·9	0·001**	20	0·01**
Methysergide + PGD_2 (1·0) + H	10	39·8 ± 4·3	0·01**	40	0·05**

PGD_2 (0·2, 0·5 and 1·0 mg kg^{-1}) had no effect itself on the righting reflex. * and ** indicate statistical significance (*P*) in comparison to hexobarbitone and PGD_2 (1·0)-treated hexobarbitone groups, respectively.

The potentiation of hexobarbitone sleep, induced by PGD_2, is in conformity with earlier reports (Laychock et al 1980; Hollingsworth & Patrick 1984). The sedative action of PGD_2 is evident by its ability to induce sleep in rats administered a sub-hypnotic dose of the barbiturate. The ability of DHT, PCPA and methysergide to inhibit PGD_2-induced potentiation of hexobarbitone, indicates that the potentiation is 5-HT-mediated. PGE_1-induced potentiation of hexobarbitone hypnosis has earlier been shown to be 5-HT-mediated (Bhattacharya et al 1976). Recent studies (Bhattacharya et al 1985) indicate that PGD_2, in the doses used in this study, enhances 5-HT concentrations of different rat brain areas, peaking at 15 min after its administration. Furthermore, it was shown that PGD_2 enhances the rate of accumulation of rat brain 5-HT. Considerable evidence links brain 5-HT with sleep mechanisms (Jouvet 1972). Thus, it appears that PGD_2 potentiates hexobarbitone hypnosis by enhancing rat brain 5-HT turnover, an event antagonized by drugs which interfere with 5-HT activity.

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