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Possible Involvement of Prostaglandins in Cataleptic Behavior in Rats

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ONO, N., R. SAITO, T. ABIRU, H. KAMIYA AND T. FURUKAWA. *Possible involvement of prostaglandins in cataleptic behavior in rats*. PHARMACOL BIOCHEM BEHAV 25(2) 463–467, 1986.—Involvement of prostaglandin (PG) in cataleptic behavior was investigated by a high bar test method in rats. PG F_{2alpha} (F_{2a}) and E_2 administered intracerebroventricularly (ICV) elicited cataleptic behavior in a dose-dependent manner. The cataleptic behaviors produced by PGs were markedly inhibited by ICV pretreatment with propranolol. The cataleptic behaviors induced by haloperidol were also inhibited by propranolol. The PG F_{2a}- and haloperidol-induced cataleptic behaviors were almost abolished by the thermal coagulation of bilateral striatum where the dopaminergic and cholinergic link is found. The pilocarpine-induced cataleptic behavior was potentiated by ICV treatment with PG F_{2a}. On the other hand, the cataleptic behavior elicited by haloperidol was reduced after oral treatment with aspirin, a PG synthesis inhibitor. These results suggest that PGs seem to be participated in incidence of cataleptic behavior, which might involve alteration of brain beta-adrenoceptor activity.

Prostaglandin Cataleptic behavior Propranolol Haloperidol Aspirin

THE presence of prostaglandin (PG) F_{2a} and E_2 have been identified in the central nervous system of several mammalian species [1, 6, 13, 16, 24], and several considerable evidences show that PGs may play a role as a putative transmitter or a modulator in the central nervous system [11, 12, 20, 22, 23].

Intracerebroventricularly (ICV) administered the series of PG E were demonstrated to induce sedation, stupor, catatonia as well as cataleptic behavior [3]. On the other hand, the cataleptic responses to antipsychotic agents observed in rodents are accepted to be mediated through the central dopaminergic inhibition, accompanied with activation of cholinergic mechanism. Since further experiments in the rat reported that the ICV administration of PG E_1, E_2 and F_{2a} potentiated the neuroleptics-induced cataleptic behavior [10], it seems that the central dopaminergic mechanism is involved in the effects of PGs. The tardive dyskinesia induced by chronic treatment with neuroleptics was reported to be improved by clonidine, alpha-2 agonist, suggesting also a possible participation of the noradrenergic system in the extrapyramidal symptoms [14,15]. However, the central role of PGs in the neuroleptics-induced behaviors remains to be elucidated.

We have recently reported that the centrally mediated cardiovascular changes by ICV PG F_{2a} were reduced by ICV pretreatment with propranolol [17,18]. These findings imply that the central actions of PG involve beta-adrenergic mechanism. The present study was concerned with the contribution of PGs, and the participation of beta-adrenoceptor mechanisms to cataleptic behavior.

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METHOD

The animals used were male rats of the Wistar strain obtained from Kyudo Animal Ltd. (Saga, Japan). The body weights were 210–250 g at arrival and 300–360 g at the beginning of experiments. The animals were housed on a 12 hr light-dark cycle at an environmental temperature 24±1°C and moisture 50±10%, and were permitted food and water ad lib except during the measurement of cataleptic behavior. The food consisted of LABO MR STOCK (GE: 4.18 kcal/g), NIHON NOSAN Industries Ltd. (Kanagawa, Japan).

For ICV administration, rats were implanted stereotaxically with a 22 ga guide cannula into the right lateral ventricle under pentobarbital anesthesia (40 mg/kg, IP) 7 days before testing cataleptic behavior. After the implantation, the rats were treated with 50,000 units of penicillin IM daily for 5 days. The animals which indicated a favorable increase in body weight were used in the experiments. ICV administrations were made in volumes of 10 μl for 1 min by using a 27 ga injection pipe connected to a Hamilton microsyringe through the guide cannula pre-implanted. The cannula placement was identified by injection of malachite green dye after the experiment and thereby observing distribution of dye in the ventricle.

The bilateral striatal lesions were performed by the method of thermal coagulation (Radio Frequency Lesion Generator RFG-4, Radionics Inc.) before the implantation of cannula ICV. The animals were anesthetized with pentobarbital and the electrode (the tip diameter, 0.7; the tip length, 1.5; shaft length, 100 mm) was inserted to the striatal

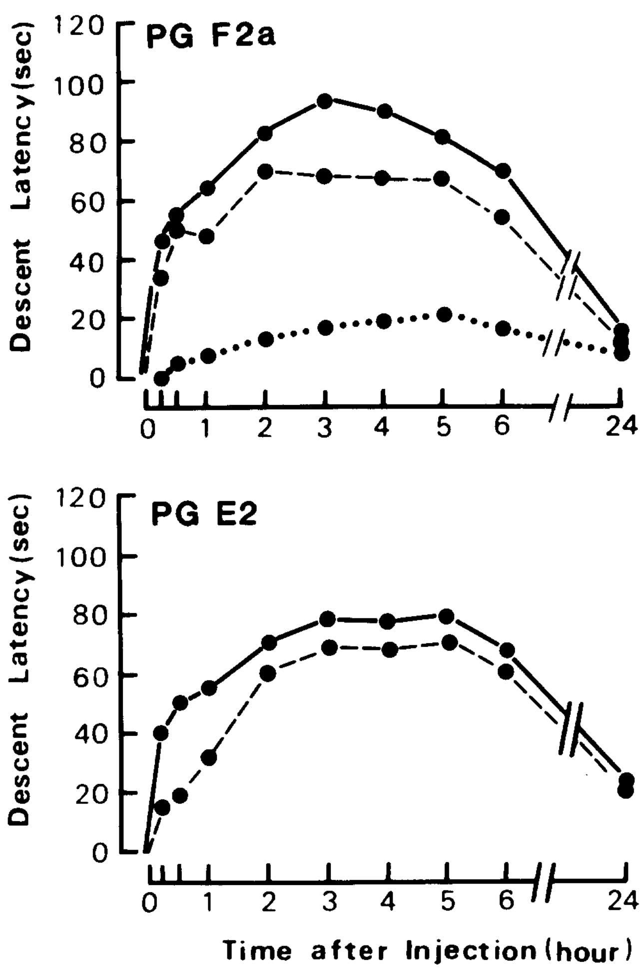

FIG. 1. Cataleptic behavior induced by PG F_{2a} and PG E_2 administered ICV in rats. Each point shows the mean value in each group. ●—● 100 nmol ICV (n=6, PG F_{2a}, and n=5, PG E_2), ●— —● 50 nmol (n=7, PG F_{2a}, and n=8, PG E_2), ●···● 30 nmol (n=4).

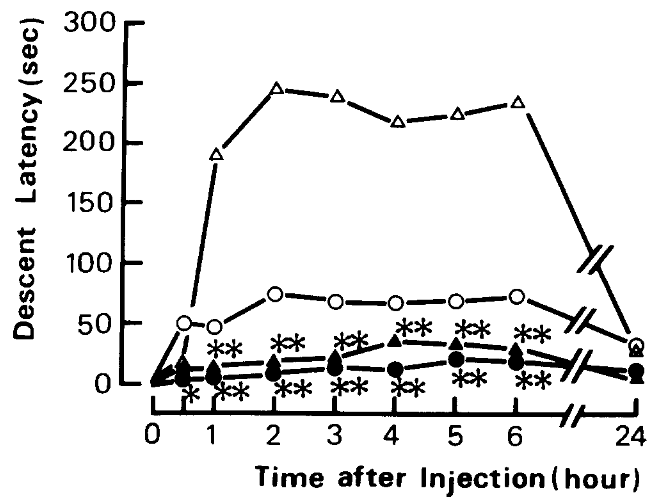

FIG. 2. Effects of bilateral lesions of the striatum on PG F_{2a}- and haloperidol-induced cataleptic behavior. (△) haloperidol 1.3 μmol/kg after sham operation (n=8), (▲) haloperidol 1.3 μmol/kg after lesion (n=5), (○) PG F_{2a} 50 nmol after sham operation (n=7), (●) PG F_{2a} 50 nmol after lesion (n=6). Haloperidol and PG F_{2a} were administered intraperitoneally and ICV, respectively. * and ** show significant change from sham operation rats ($p<0.05$ and $p<0.01$, respectively).

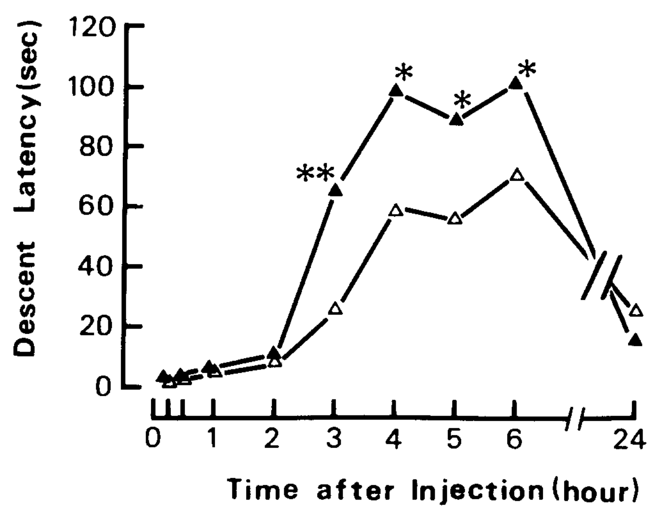

FIG. 3. Effects of ICV treatment with PG F_{2a} on the pilocarpine-induced cataleptic behavior. (△) pilocarpine 20.4 μmol/kg IP in combination with saline (n=7), (▲) pilocarpine 20.4 μmol/kg in combination with PG F_{2a} 50 nmol (n=7). Pilocarpine and PG F_{2a} were administered at the same time. The probability is shown in Fig. 2.

coordinate according to the brain atlas [19]. The temperature of the electrode tip was raised to 60°C within 30 seconds and maintained for 30 seconds. The lesion size was identified in histological examinations at the end of experiment by using the method of natural red stain.

Behavioral Measurement

A cataleptic behavior was measured with a high bar test method. Both of the animal's forelimbs were placed on a horizontal bar positioned 16 cm above the floor. The animal tested was considered to show a positive response when the forelimbs persisted in hanging onto the horizontal bar, and the intensity of the behavior was estimated by the amount of time in seconds that the rats kept such positive responses.

Statistical analysis was performed using the Mann-Whitney U-test.

Drugs

Drugs used were prostaglandin F_{2a} tromethamine (Upjohn Co. Ltd.), prostaglandin E_2, propranolol hydrochloride (Sigma Chemical Co.), haloperidol (Serenace Injection, Searle Co.), pilocarpine hydrochloride (Torii Co. Ltd.) and aspirin (Yoshitomi Pharmaceut. Co. Ltd.). Other substances utilized were obtained from normal commercial sources. PG E_2 was dissolved in ethanol and sodium carbonate (1 mg PG E_2 in 0.1 ml 95% ethanol and 0.9 ml of 0.22% w/v Na_2CO_3) solution and was prepared freshly for each experiment. Aspirin was suspended with 0.25% carboxymethylcellulose sodium solution. Other drugs were dissolved in saline.

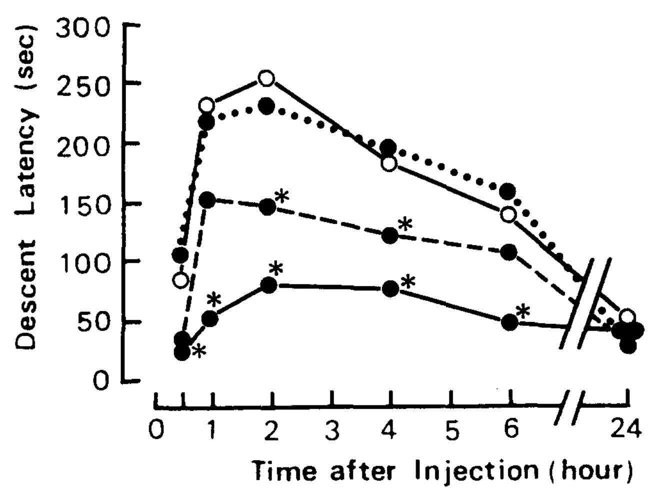

FIG. 4. Effects of aspirin on haloperidol-induced cataleptic behavior. ○—○ haloperidol 1.3 μmol/kg after vehicle (n=10), ●···● haloperidol after aspirin 1.7 mmol/kg (n=10), ●— —● haloperidol after aspirin 3.9 mmol/kg (n=10), ●—● haloperidol after aspirin 5.6 mmol/kg (n=10). Aspirin was administered orally 30 min before intraperitoneal injection of haloperidol. * shows significant change from vehicle group ($p<0.05$).

RESULTS

PG F_{2a} and PG E_2

As shown in Fig. 1, PG F_{2a} administered ICV at doses of 30, 50 and 100 nmol produced a dose-related cataleptic state. PG E_2 administered ICV at doses of 50 and 100 nmol also induced a similar cataleptic behavior. These behaviors were also similar in the intensity and duration between PG F_{2a} and PG E_2 at doses of 50 and 100 nmol. In the home cage, the behavioral pattern of animals was not altered after ICV administration of PG F_{2a} and E_2 at doses of 30 and 50 nmol, but a mild sedation appeared at a dose of 100 nmol.

Bilateral Lesions of the Striatum

After bilateral lesions of the striatum, the PG F_{2a} (50 nmol, ICV)-induced cataleptic behavior was almost abolished. In a similar manner, the haloperidol (1.3 μmol, IP)-induced cataleptic behavior was strongly inhibited by the lesions (Fig. 2).

Effect of PG F_{2a} on Pilocarpine-Induced Behavior

Pilocarpine alone (20.4 μmol/kg, IP) initiated hypersalivation, hypotonia of forelimbs, and decreased locomotor activity which lasted for about 2 hours. The drug subsequently induced cataleptic behavior. This pilocarpine-induced cataleptic behavior was potentiated by combined ICV administration of PG F_{2a} at a dose of 50 nmol, potentiation in the effect being significant 3–6 hours after drugs ($p<0.05$) (Fig. 3).

Effect of Aspirin on the Haloperidol-Induced Behavior

Aspirin alone (3.9 mmol/kg, PO) administered did not elicit any behavioral changes, including cataleptic behavior. When aspirin at doses of 1.7–3.9 mmol/kg was administered 30 min before haloperidol IP, 1.3 μmol/kg, the cataleptic state produced by haloperidol was inhibited in a dose-dependent fashion (Fig. 4).

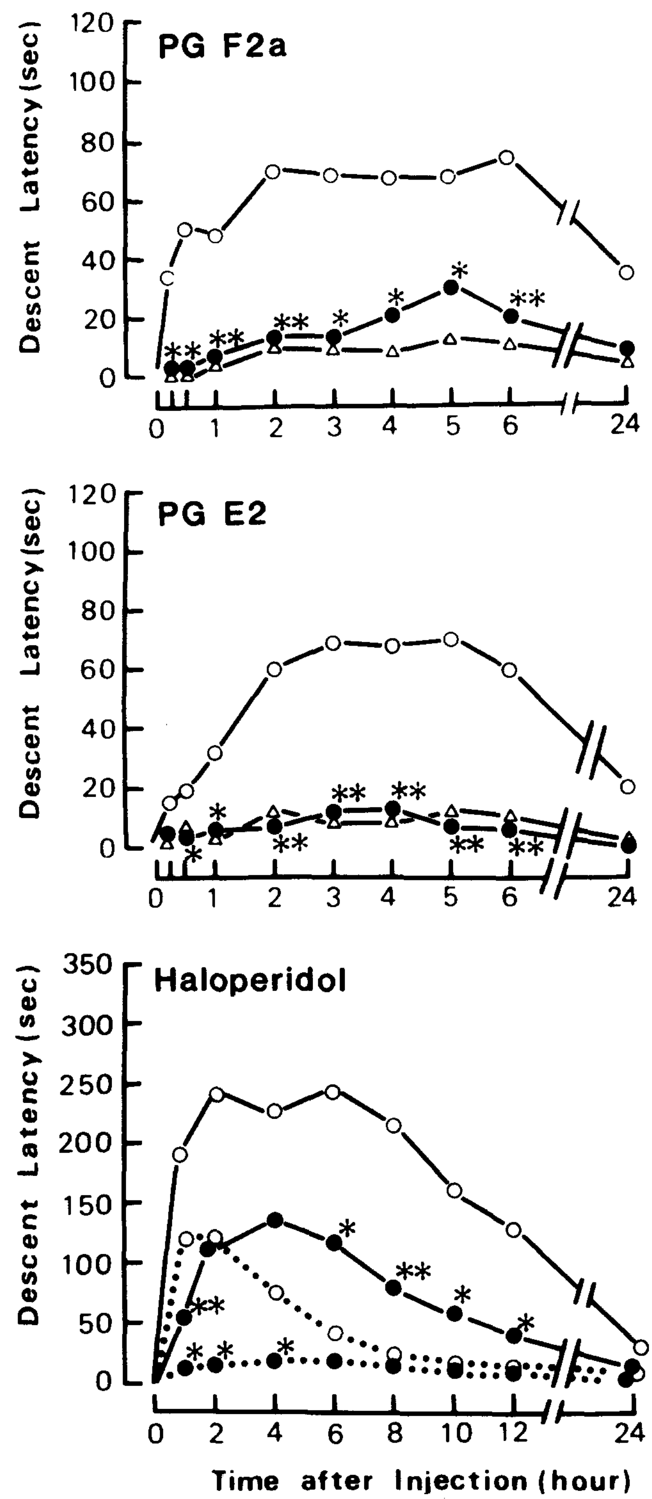

FIG. 5. Effects of pretreatment with propranolol on the PG F_{2a}-, PG E_2- or haloperidol-induced cataleptic behavior. In PGs-induced cataleptic behavior, △—△ saline (for PG F_{2a}) or vehicle (for PG E_2) after propranolol 1.58 μmol (n=4, each), ○—○ PG 50 nmol (n=7, PG F_{2a}, and n=8, PG E_2), ●—● PG 50 nmol after propranolol 1.58 μmol (n=6, PG F_{2a} and PG E_2). In haloperidol-induced one, ○···○ haloperidol 0.27 μmol/kg after saline (n=4), ○—○ haloperidol 1.3 μmol/kg after saline (n=8), ●···● haloperidol 0.27 μmol/kg after propranolol 1.58 μmol (n=5), ●—● haloperidol 1.3 μmol/kg after propranolol 1.58 μmol (n=6). Propranolol was administered ICV 15 min prior PGs or haloperidol. The probability is shown in Fig. 2.

Effects of Propranolol on the PG- or Haloperidol-Induced Behavior

Propranolol administered ICV at a dose of 1.58 μmol did not affect the behavioral state. When propranolol was administered 15 min before PG, the cataleptic behavior produced by PG F_{2a} or PG E_2 administered ICV at a dose of 50 nmol was inhibited by propranolol. The same pretreatment with propranolol also dose-dependently inhibited the cataleptic behavior produced by haloperidol (0.27 and 1.3 μmol/kg, IP) (Fig. 5).

DISCUSSION

Since it has been proposed that systemically administered PGs do not readily penetrate into the central nervous system [9] and are very quickly metabolized [12], PGs were injected directly into a lateral brain ventricle of the rat to conserve direct central action in this study. PG F_{2a} and E_2 administered ICV elicited cataleptic behavior in a dose-dependent manner, without eliciting a marked change of behavioral pattern in home cage. The cataleptic behavior produced by PG seems to be weaker than that by haloperidol at a dose of 0.27 μmol/kg. These observations are in accordance with previous reports [10,21].

Both types of PG F and E series intensify the cataleptic behavior induced by neuroleptics, dopamine antagonists. Since these phenomena were inhibited by apomorphine [10,21], the cataleptogenic effect of PGs seems to involve central dopaminergic mechanisms. Recent studies showed that PG E_2 and F_{2a} increased the dopamine and norepinephrine concentration in rat whole brain, respectively, though PG A_1 was unaffected [21].

On the other hand, the cataleptic behavior produced by pilocarpine was here potentiated by PG F_{2a}, ICV. It has been well documented that the central-acting cholinomimetic agents as well as dopamine antagonists produce the cataleptic behavior [2, 4, 25]. These facts demonstrate that the balance between dopamine and acetylcholine in the brain has an important function in the regulation of cataleptic behavior. In the peripheral nervous system, PG F_{2a} seems to increase the libration of acetylcholine from cholinergic nerve terminal [8]. Accordingly, it is also possible that central effect of PG F_{2a} in producing cataleptic behavior might be mediated via activation of cholinergic neuronal mechanisms. In this study, there was a delay of about 2 hours by appearance of cataleptic behavior after administration of pilocarpine, though it was reported that pilocarpine-induced cataleptic behavior reached to the maximum response at 1 to 2 hours after pilocarpine in rats pretreated with methylatropine [2]. We did not treat with a peripheral anticholinergic agent before pilocarpine. Therefore, the different phenomenon might be due to use of a different method.

As for possible participation of endogenous PG, aspirin has been proposed to inhibit irreversibly the covalent acetylation of fatty acid cyclooxygenase, the metabolizing enzyme from arachidonic acid to PGs [7]. Since haloperidol-induced cataleptic behavior was here inhibited in a dose-dependent manner by pretreatment with aspirin, the central effects of PG seem to involve dopaminergic and cholinergic neuronal mechanisms in the brain, at least in part.

Costall and Naylor [5] have reported that neuroleptic-induced catalepsy involves both a nigro-striatal and a mesolimbic site of action. In the present studies, the cataleptic behaviors evoked by haloperidol as well as by PG F_{2a} were almost eliminated by bilateral lesion of striatum. Consequently, the main site of action of PG F_{2a} in inducing cataleptic behavior, like neuroleptics, seems to be the striatum.

In our previous reports [17,18], the central effect of PG F_{2a} on the cardiovascular system was markedly inhibited by ICV treatment with propranolol. In this study, both PG E_2- and F_{2a}-induced cataleptic behaviors were also reduced by propranolol, ICV. In addition, haloperidol-induced behavior was markedly inhibited by propranolol, ICV. However, propranolol has not only the beta-adrenoceptor blocking effect but also the membrane stabilizing actions as pharmacological character. The central cardiovascular effects induced by PG F_{2a} ICV, which was abolished completely by propranolol, were not affected by ICV pretreatment with cocaine or procaine, potent membrane stabilizers [18], suggesting possible uninvolvement of local anesthetic as well as membrane stabilizing actions in this central effects of propranolol. Thus, although further experiments with other beta-adrenoceptor antagonist which do not possess membrane stabilizing action would be expected, it is presumable that cataleptic behavior involves beta-adrenoceptor in the brain. The present results imply that PGs seem to be involved in cataleptic behavior.

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