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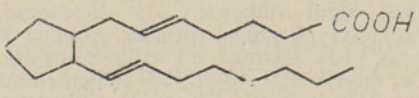
THE EFFECTS OF PROSTAGLANDINS E_2 AND $F_{2\alpha}$ ON THE CENTRAL AND PERIPHERAL LEVELS AND THE TURNOVER OF BIOGENIC AMINES

The prostaglandins (PGs) can be considered as derivatives of a hypothetical compound with the trivial name of prostanoic acid, the structure of which is as follows:



Different prostaglandins fall into several main classes — A, B, C, D, E, F, G, H, being distinguished by substituents of the cyclopentane ring. By number of double bands is side chains, these PGs are divided into series. PGs of the E and F are the most abundant (especially E_2 and $F_{2\alpha}$) and most intensively studied. Most *in vivo* cells seem capable of synthetizing PGs from the essential fatty acid precursors, and they are rapidly degraded and inactivated by tissue-bound enzymes. Some 80 to 90% or more of the PGs are destroyed during a single passage through the liver or the lungs. (PhI_2 is a very remarkable exception.) No other class of autacoids shows more numerous and diverse effects. Investigations in the area of PGs in the USSR were extended after improving their biosynthesis at the Institute of Chemistry of the Academy of Sciences of the Estonian SSR. PGE_2, the first home-produced preparation in the USSR, was made with the help of preparative biosynthesis. The $PGF_{2\alpha}$ was also biosynthesized there. Pharmacological investigation of these preparations was carried out at the Department of Pharmacology of Tartu State University (Хинрикус et al., 1979; Раявеэ et al., 1980).

In most species PGs are potent vasodilatators (Brus, Zabawska, 1976; Turier, 1980). There is an interrelationship between tromboxane biosynthesis, aggregation and 5-hydroxytryptamine secretion in human plateletes *in vitro*. PGEs and PGFs cause strong contraction of isolated rat uteri and bowels (Оттер et al., 1980). PGE_2 inhibits gastric secretion. On the other hand, there has been noted an increase in the volume, bicarbonate concentration, and enzyme content of pancreatic secretion. PGs often modify the function of sympathetic neuroeffector (Poddubiuk, 1976; Poddubiuk, Kleinrock, 1976; Boonyaviroj, Gutman, 1979). Many stimulating and depressant effects of PGs on the CNS have been reported. Among them there is sedation in small rodents (in which the blood—brain barrier is immature): stupor, catatonia, and other behavioural changes follow an injection of PGE_2 (but not $PGF_{2\alpha}$) into the cerebral ventricles (Poddubiuk, 1976; Hillier et al., 1980). PGE_2 significantly increases the body temperature of rats in a dose-dependent fashion (Гурин et al., 1981). All PGs have lengthened the latency of the response of rats on a «hot plate». Maximum protection is achieved at 30 and 45 min after administration.

The physiological role of PGs and their participation in the central regulatory mechanisms are still unclear. Systematically administered PGs act on many organs and tissues, making it difficult to identify specific central actions (Abdelhalin et al., 1979; Rosenkranz et al., 1980). In addition, systemically administered PGs do not completely penetrate into the central nervous system. The numerous effects of PGs point to their interaction or mediation by some universal mechanisms. One of such mechanisms is the activity of monoaminergic systems: N. Feuerstein et al. (1979) reported that endogenous prostaglandins modulate adrenal catecholamine secretion. The present report is an attempt to summarize the results of recent experiments carried out in our laboratory to demonstrate the effects of PGE_2 and $PGF_{2\alpha}$ on the central (brain) and peripheral (pancreas) levels and the turnover of catecholamine and indolamine in albino rats.

Materials and methods

Male and female albino rats averaging 200—250 g in weight were used. PGE_2 and $PGF_{2\alpha}$ produced at the Institute of Chemistry of the Academy of Sciences of the Estonian SSR were dissolved and administered intraperitoneally (i.p.) and directly into a lateral brain ventricle (i.v.c.) of the rat for direct central action. Under light aether anaesthezia, holes were drilled in the skull for intraventricular administration of $PGF_{2\alpha}$. Intraventricular injections were made to freely moving rats with a Hamilton syringe. The control rats received the same volume of PG solvent liquid by the same routes. Both PGs studied were given i.v.c. in doses of 4.0, 10.0 μg per rat, in volumes of 4 and 10 μl respectively. Intraperitoneally PGs were administered in doses of 20, 1000, 2000 and 4000 μg/kg (0.02, 1.0, 2.0, 4.0 mg/kg).

The concentrations of noradrenaline (NA), dopamine (DA) and its chief metabolite, homovanillic acid (HVA), were determined spectrofluorometrically by the method described by M. K. Schellenberger and J. H. Gordon (1971) and modified by P. F. Spano and N. H. Neff (1971), with the use of a Hitachi spectrophotofluorometer. The serotonin (5-HT) and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) concentrations were determined spectrophotofluorometrically by the method of G. Curzon and A. Green (1970).

For biochemical studies rats (a group of 8) were decapitated 15 and 30 min after the administration of PGs, and their brains and pancreases (P) were immediately frozen in liquid nitrogen. Afterwards the brains were dissected and the forebrain FB (striatum, hyppocampus, amygdala and some cortex), mid-brain MB (hypothalamus, thalamus, preoptical area), and brainstem BS were removed. Student's t-test was used in the statistical analysis of the results.

Results and discussion

In our experiments at least four aspects in the way of the action of PGs were studied: their action on monoamine content and turnover of peripheral organs by systemic (intraperitoneal) administration, the action of systemic administration of high and low doses of PGs on the central (brain) monoamine content, and the action of the intracerebroventricular injection of $PGF_{2\alpha}$ on the concentration of brain monoamines and their metabolism.

As mentioned above, PGE_2 increases pancreatic secretion in the volume, bicarbonate concentration and enzyme content. This is followed

Table 1

The effects of intraperitoneally injected PGE_2 and $PGF_{2\alpha}$ on the concentration of NA, DA, HVA, 5-HT and 5-HIAA in the pancreas

Treatment	Dose, µg/kg	Effect noticed after treatment, min	Mean concentration in µg/g of wet tissue ± S.E.M.				
			NA	DA	HVA	5-HT	5-HIAA
Control			0.72±0.06	0.65±0.06	0.1±0.008	1.09±0.1	0.22±0.02
PGE_2	20	15	0.74±0.07	0.82±0.08	0.32±0.02**	0.60±0.05*	0.64±0.05**
		30	0.81±0.08	0.83±0.08	0.10±0.01	1.93±0.18*	0.28±0.01
		60	0.67±0.06	1.12±0.10**	0.10±0.01	1.17±0.02	—
$PGF_{2\alpha}$	20	15	0.77±0.07	2.64±0.3**	0.38±0.03**	0.61±0.06*	0.80±0.08**
		30	0.91±0.08*	1.16±0.11**	0.20±0.02*	0.79±0.07*	0.78±0.08*
$PGF_{2\alpha}$	1000	15	0.54±0.05	0.57±0.06	0.30±0.03**	0.34±0.03**	0.15±0.01
		30	0.88±0.08	0.64±0.06	0.51±0.05**	0.33±0.03**	0.24±0.02

* $P \leqslant 0.05$. ** $P \leqslant 0.01$. Each group consisted of 8 rats.

Table 2

The effects of intraperitoneally injected small dose of PGs (20 µg/kg) on the concentration of NA, DA, HVA, 5-HT, and 5-HIAA in FB and MB

Treatment	Effect noticed after treatment, min	Mean concentration in µg/g of wet tissue ± S.E.M.				
		NA	DA	HVA	5-HT	5-HIAA
Control						
FB		0.36±0.03	1.20±0.12	0.14±0.02	0.75±0.07	0.27±0.02
MB		0.68±0.05	0.56±0.06	0.39±0.03	1.27±0.09	0.69±0.07
PGE_2						
FB	15	0.36±0.01	2.58±0.24**	0.24±0.01*	0.39±0.03*	0.45±0.04*
MB		0.75±0.07	0.50±0.05	0.30±0.02	0.89±0.08*	0.56±0.05
FB	30	0.34±0.03	2.50±0.15*	0.14±0.01	0.35±0.03*	0.41±0.04*
MB		0.73±0.07	0.49±0.04	0.27±0.02	2.14±0.2**	0.33±0.03*
FB	60	0.36±0.03	1.16±0.15	0.16±0.01	0.67±0.06	0.21±0.02
$PGF_{2\alpha}$						
MB	15	0.66±0.05	0.16±0.11**	0.20±0.02*	0.79±0.07	0.78±0.07
MB	30	0.70±0.07	0.99±0.1*	0.25±0.02*	0.81±0.08*	0.59±0.06

by changes in the monoamines content of pancreatic tissue and in the speed of its metabolism. PGE_2 and $PGF_{2\alpha}$ increase the metabolism of dopamine and serotonine; the effect of low doses is more considerable (Table 1).

Results of experiments (Table 2) show that there is a similarity in the effects of small doses of PGE_2 and $PGF_{2\alpha}$. Both PGs enhance the turnover of the investigated monoamines in brain structures. They increase the content of metabolites, both of DA and 5-HT. At that, the content of DA increases, but the content of 5-HT decreases. On the basis of these changes there must be some united metabolic processes. The behavioural effects lasted for 5—10 min, but the biochemical changes were noticeable even after 30—60 min. It may be possible that PGs switch on some trigger mechanism, in which the effect of the action of PGs lasts longer and is connected with changes in the monoaminergic systems activity. One of these mechanisms may be the regulation of cyclic AMP formation in the brain tissue by α-adrenergic receptors, mediated by PGs of the E series (Partington et al., 1980).

There are some differences in the effects of PGE_2 and $PGF_{2\alpha}$. The effects of PGE_2 last for a shorter time, the effects of low and high doses being different. One can notice differences in the effects of intraventricularly and systemically administered $PGF_{2\alpha}$ (Tables 2—4). The low doses of $PGF_{2\alpha}$ increase the content of 5-HT within 15 and 30 min after administration, but with the use of high doses the content of 5-HT decreases in the FB as well as in the MB of the rat. These changes are accompanied by corresponding increase and decrease in the content of 5-HIAA. NA concentrations in the brain are decreased by PGE_2 and increased by $PGF_{2\alpha}$. PGE_2 and $PGF_{2\alpha}$ both enhance the turnover of NA, DA and 5-HT, as shown by the increase of the content of HVA and 5-HIAA.

In conclusion we may say that there is a similarity in the action of PGE_2 and $PGF_{2\alpha}$ (increasing the turnover of monoamines), but the effects of $PGF_{2\alpha}$ are more noticeable in the changes of 5-HT and NA contents, while the effect of PGE_2 is more reflected in the content of DA. The possible involvement of prostaglandins in the CNS activity is suggested by the presence of these substances in the brain. Prostaglandins A_1, E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$, given i.v.c., have a central depressant effect in the rat (Poddubiuk, Kleinrock, 1976).

Our data show that prostaglandins may act indirectly by changing the concentrations of the different neurotransmitters both in the peripheral and in the brain tissues. The changes observed after an injection of increasing doses of PGs may result from the fall of the NA concentration in the brain and decrease of the amount available at the receptor site (Hiller et al., 1980). Z. S. Herman (1976) suggests that the depression of the locomotor activity depends on lowered NA concentration in the brain. PGE_2 decreases the NA concentration and increases the DA concentration, while $PGF_{2\alpha}$ increases both the NA and DA concentration.

Some authors (Hedquist, 1973; Feuerstein et al., 1979) suggest that locally formed prostaglandins of E series modulate transmitter release from sympathetic nerve terminals, presumably by restricting the influx of Ca^{2+} into the interior of the neuron. The present investigation confirms the data of the other authors (Abdelhalin et al., 1979; Boonyaviroj, Gutman, 1979) stating that PGE_2 and $PGF_{2\alpha}$ can markedly influence adrenergic neurotransmission both in the brain as well as in the pancreas.

$PGF_{2\alpha}$ increases both the 5-HT and 5-HIAA concentration, especially in the forebrain. It is interesting to note the hypothesis of I. R. Smythies (1979) that the complexes formed between prostaglandins and RNA enter the molecular composition of the different receptor sites of the CNS. According to this hypothesis, the prostaglandin of the F series — the

Tabel 3

The effects of intraperitoneally injected high doses of PGs on the concentration of NA, DA, HVA, 5-HT and 5-HIAA in FB and MB

Treatment	Dose, µg/kg	Effect noticed after treatment, min	Mean concentration in µg/g of wet tissue ± S.E.M.				
			NA	DA	HVA	5-HT	5-HIAA
Control							
FB			0.29±0.02	1.04±0.10	0.25±0.02	0.52±0.05	0.20±0.07
MB			0.71±0.07	0.60±0.05	0.12±0.01	1.18±0.10	0.61±0.05
PGE_2	2000						
FB		15	0.39±0.03	1.77±0.16*	0.11±0.008**	0.49±0.05	0.37±0.02*
MB			0.68±0.05	0.44±0.04	0.18±0.10*	1.15±0.10	0.66±0.06
FB		30	0.37±0.03	1.66±0.16*	0.92±0.08**	0.53±0.05	0.32±0.03*
MB			0.64±0.05	0.46±0.04	0.81±0.07**	1.01±0.10	0.70±0.07
Control							
FB			0.50±0.05	1.41±0.14	0.20±0.01	0.42±0.04	0.31±0.03
MB			1.00±0.10	0.54±0.03	0.20±0.02	1.00±0.10	0.70±0.06
$PGF_{2\alpha}$	4000						
FB		15	0.50±0.05	1.45±0.14	0.35±0.02*	0.51±0.05	0.39±0.04
MB			1.06±0.11	0.58±0.05	0.32±0.02*	1.19±0.11	0.56±0.07
FB		30	0.33±0.05*	1.58±0.15	0.33±0.03*	0.55±0.07	0.27±0.03
MB			0.77±0.06	0.55±0.05	0.35±0.03**	1.32±0.13	0.60±0.06

Table 4

The effects of intracerebroventricularly injected $PGF_{2\alpha}$ on the concentration of NA, DA, HVA, 5-HT and 5-HIAA in FB, MB and BS

Treatment	Dose of PGs, µg/rat	Effect noticed after treatment, min	Mean concentration in µg/g of wet tissue ± S.E.M.				
			NA	DA	HVA	5-HT	5-HIAA
Control							
FB			0.27±0.01	0.86±0.09	0.11±0.001	0.63±0.06	0.51±0.05
MB			0.49±0.02	1.18±0.10	0.12±0.001	1.37±0.14	0.91±0.10
BS							
$PGF_{2\alpha}$	4						
FB		15	0.32±0.02	0.98±0.009	0.19±0.02*	0.56±0.06	0.50±0.04
MB			0.64±0.03	1.37±0.13	0.20±0.02*	1.42±0.14	1.11±0.10
BS							
$PGF_{2\alpha}$	10						
FB		15	0.40±0.02*	1.61±0.14*	0.12±0.01	0.73±0.06	0.43±0.04
MB			0.66±0.04	1.41±0.14	0.20±0.02*	1.44±0.13	1.03±0.10
BS							

RNA complex — takes part in the molecular configuration of the 5-HT receptor site. Based on that suggestion, one can attempt to ascertain that an increased concentration of indolamines may be due to a direct action of $PGF_{2\alpha}$ on the 5-HT receptor site. As one can see from the results of our biochemical investigations into the concentrations of NA, DA and 5-HT, PGs may affect the turnover of these monoamines. The mechanism of an increased turnover may be connected with a modulatory role of PGs in the release of biogenic amines (Feuerstein et al., 1979; Boonyaviroj, Gutman, 1979; Hillier et al., 1980).

Thus, the central behavioural and some physiological effects of PGE_2 and $PGF_{2\alpha}$ may be explained by their indirect action upon the concentration and turnover of various neurotransmitters in the peripheral system, and it may likewise be related to their direct action on appropriate structures in the CNS. It seems that both indirect and direct mechanisms may play a role in the action of PGs, and they may exist simultaneously as well as independently from each other.

REFERENCES

Abdelhalin, M. S., Sjoquist, B., Anggard, E. Prostaglandin synthesis inhibition and monoamine metabolites in the rat brain. — Prostaglandins, 1979, **18**, 837—841.

Boonyaviroj, P., Gutman, Y. α- and β-adrenoreceptors and PGE_2 in the modulation of catecholamine secretion from bovine adrenal medulla *in vitro*. — Pol. J. Pharm. Pharmacol., 1979, **31**, 716—721.

Brus, R., Zabawska, J. Central action of prostaglandin $F_{2\alpha}$ and circulatory system in rats. — Pol. J. Pharm. Pharmacol., 1976, **28**, 455—462.

Curzon, G., Green, A. Rapid method for the determination of 5-hydroxytryptamine and 5-hydroxyindoleacetic acid in small regions of rat brain. — Brit. J. Pharmacol., 1970, **39**, 653—655.

Feuerstein, N., Feuerstein, G., Gutman, Y. Endogenous prostaglandins modulate adrenal catecholamine secretion. — Eur. J. Pharmacol., 1979, **58**, 489—492.

Hedquist, P. Prostaglandin as a tool for local control of transmitter release from sympathetic nerves. — Brain. Res., 1973, **62**, 483—488.

Herman, Z. S. The effects of noradrenaline on rat's behaviour. — Psychopharmacol. (Berl.), 1976, **16**, 369—374.

Hillier, K., Roberts, P. J., Tempelton, W. W. PGE_2 mediated negative feedback of noradrenaline overflow in the central nervous system. — Brit. J. Pharmacol., 1980, **68**, 134.

Partington, C. R., Edwards, M. W., Daly, J. M. Regulation of cyclic AMP formation in brain tissue by alpha-adrenergic receptors: requisite intermediacy of prostaglandins of the E series. — Proc. Nat. Acad. Sci. USA, 1980, **77**, 302—328.

Poddubiuk, Z. M. A comparison of the central actions of prostaglandins A_1, E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$ in the rat. I. — Psychopharmacol., 1976, **50**, 89—94.

Poddubiuk, Z. M., Kleinrock, Z. A comparison of the central actions of prostaglandins A_1, E_1, E_2, $F_{1\alpha}$ and $F_{2\alpha}$ in the rat. II. — Psychopharmacol., 1976, **50**, 95—102.

Rosenkranz, R. P., Thayer, R., Killam, K. F. Effects of prostaglandin E_2 on brain levels of GABA in mice. — Proc. W. Pharmacol. Soc., 1980, **23**, 147.

Shellenberger, M. K., Gordon, J. H. A rapid, simplified procedure for simultaneous assay of norepinephrine, dopamine and 5-hydroxytryptamine from discrete areas of brain. — Anal. Biochem., 1971, **39**, 356—372.

Smythies, J. R. A prostaglandin-RNA complex as a potential receptor site. — Neurosciences Res. Progr. Bull., 1979, **8**, 123—130.

Spano, P. F., Neff, N. H. Procedure for the simultaneous determination of dopamine, 3-methoxy-4-hydroxyphenylacetic acid and 3,4-dihydroxyphenylacetic acid in brain. — Anal. Biochem., 1971, **42**, 113—118.

Turier, R. B. Prostaglandins: their potential in clinical medicine. — Postgrad. Med., 1980, **68**, 70—76.

Гурин В. Н., Висмонт Ф. И., Уарюк В. В. Влияние синаптически активных веществ на гипертермический эффект простагландина E_2 у крыс. — Бюл. экс. биол. мед., 1981, 3, 304—305.

Оттер М. Я., Нурманд Л. Б., Хиндикус Т. Х. Хронофармакологические аспекты действия простагландинов E_2 и $F_{2\alpha}$. — В кн.: Синтез и изучение физиологически активных веществ. Вильнюс, 1980, 81—83.

Раявеэ О. П., Хинрикус Т. Х., Оттер М. Я., Крузе И. Э. Фармакологические и технологические аспекты изучения простагландина E_2. — В кн.: Тез. докл. Всес. съезда фармацевтов. Кишинев, 14—17 октября 1980. 1980, 177.
Хинрикус Т. Х., Оттер М. Я., Раявеэ О. П. Влияние простагландинов E_2 и $Ф_{2\alpha}$ на содержание серотонина и катехоламинов в поджелудочной железе крыс. — В кн.: Механизмы регуляции деятельности и функциональная диагностика болезни поджелудочной железы. Тарту, 1979, 159—163.

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PROSTAGLANDIINIDE E_2 JA $F_{2\alpha}$ TOIME KESKNÄRVISÜSTEEMISSE JA PERIFEERSESSE BIOGEENSETE MONOAMIINIDE SISALDUSSE NING NENDE AINEVAHETUSSE

On kirjeldatud väga paljusid prostaglandiinide E_2 ja $F_{2\alpha}$ füsioloogilisi ja farmakoloogilisi efekte. Võib oletada, et nende ainete toimet loomorganismi vahendavad mingites universaalse tähtsusega biokeemilistes protsessides, näiteks monoamiinergilistes protsessides toimuvad muutused. Käesolevas uurimuses selguski, et prostaglandiinid muudavad monoamiinergiliste protsesside aktiivsust nii perifeersetes (pankrease) kui ka ajukudedes. Muutub nii noradrenaliini, dofamiini ja serotoniini sisaldus kui ka nende metabolismi kiirus. Paistab, et prostaglandiin $F_{2\alpha}$ toimel prevaleerivad muutused serotoniin- ja noradrenaliinergilise, E_2 toimel dofamiinergilise mediatsioonisüsteemi aktiivsuses.

Маргареете ОТТЕР, Тойво ХИНРИКУС

ДЕЙСТВИЕ ПРОСТАГЛАНДИНОВ E_2 И $F_{2\alpha}$ НА ЦЕНТРАЛЬНЫЙ И ПЕРИФЕРИЧЕСКИЙ УРОВЕНЬ БИОГЕННЫХ МОНОАМИНОВ И ИХ ОБМЕН

У простагландинов E_2 и $F_{2\alpha}$ описаны разные фармакологические эффекты. Можно полагать, что их действие на организм животного опосредовано изменениями в каких-либо универсальных биохимических процессах. В настоящем исследовании установлено, что как интрацеребровентрикулярное, так и внутрибрюшинное введение простагландинов E_2 и $F_{2\alpha}$ изменяют содержание биогенных моноаминов (норадреналина, дофамина и серотонина) и скорость их метаболизма в отдельных частях мозга и в тканях поджелудочной железы белых крыс. Простагландин $F_{2\alpha}$ изменяет преимущественно активность серотонин- и норадреналинергических медиаторных систем, а простагландин E_2 — дофаминергических систем.