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EFFECTS OF BIOGENIC AMINES AND PSYCHOTROPIC DRUGS ON ENDOGENOUS PROSTAGLANDIN BIOSYNTHESIS IN THE RAT BRAIN HOMOGENATES

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Abstract—Phenylalkylamine and indolalkylamine derivatives, as well as several drugs acting on the central nervous system, were tested for their effects on endogenous prostaglandin, (PG) biosynthesis in the rat brain homogenates. In the particulate suspension obtained by the removal of the soluble fraction from the rat brain homogenates PG-biosynthesis could be stimulated by noradrenaline, dopamine, adrenaline, serotonin, tryptamine and to a slight extent by tyramine. Isoprenaline, DOPA, α-methyl noradrenaline, α-methyl dopamine, α-methyl tryptamine and 5-hydroxy tryptophan were ineffective. PG-biosynthesis stimulated by catecholamines or indolalkylamines responsively could be inhibited by compounds with monoamine oxidase blocking properties. In the total rat brain homogenates another type of PG-biosynthesis could be demonstrated in the absence of catecholamine or indolalkylamine that could not, or but to a slight extent, be inhibited by monoamine oxidase blocking agents. Apomorphine, oxypertine, α-methyl noradrenaline, promethazine, DOPA, reserpine, chlorpromazine, desipramine, yohimbine and tetrabenazine inhibited this type of PG-biosynthesis, though they failed to influence PG-formation stimulated by catecholamine or indolalkylamine. A correlation could be established between the PG-formation inhibitory and lipid peroxidation antagonizing effects of these compounds. Non-steroidal anti-inflammatory agents, such as indomethacin, acetylsalicylic acid and dipyrone, inhibited both types of PG-biosynthesis. The results permit the conclusion that psychotropic drugs exert their effects on endogenous PG biosynthesis in the rat brain homogenates by inhibiting various activation processes.

Psychotropic compounds have proved to be effective inhibitors of prostaglandin (PG) biosynthesis in rat uterine strips [1] in subcellular preparations from guinea pig lungs [2] and bovine seminal vesicles [3, 4]. It has been concluded from the results that inhibition of PG synthetase is not a pharmacodynamic action peculiar to compounds belonging to the class of non-steroidal anti-inflammatory agents [3]. The possibility has been raised that the inhibition of PG-biosynthesis might play a role in the pharmacological effect of antidepressants [2, 3] and tranquilizers [4]. However, the possibility of influencing PG-biosynthesis in brain preparations by psychotropic drugs has not yet been elaborated upon.

Brain tissue is known to synthetize exceedingly low amount of PGs from exogenous arachidonic acid [5, 6]. However it is very active in forming PG-s from an endogenous pool of arachidonic acid [5–8]. PG synthetized during the incubation of various brain preparations is mainly of the F-type [5–8]. The formation of PG-s in the brain tissue cannot be influenced by glutathione and hydroquinone [5–8], the combined administration of which is the most extensive method to activate PG-biosynthesis in other organs [9]. On the other hand, PG-biosynthesis could be increased by a high amount of noradrenaline or dopamine either in slices and homogenates from the rat cerebral cortex [5–7]. Recently it has been demonstrated that the stimulatory effect of noradrenaline is also manifested in formation of thromboxanes [10].

The present investigations were designed to gain a deeper insight into the possibility of influencing endogenous PG-biosynthesis, characteristic of the brain tissue, by biogenic amines and psychotropic drugs. In order to accomplish this, we studied various phenylalkylamine and indolalkylamine derivatives and a high number of drugs acting on the central nervous system.

MATERIALS AND METHODS

CFE rats of both sexes weighing 150–250 g were used. The brains were quickly removed and homogenized in three volumes of 0.1 M Tris–HCl buffer pH 8.0 or pH 7.4 (as indicated in the text). The total homogenate and the particulate suspension prepared from it were used as the test preparation. To produce this later, the homogenates were diluted 2-fold with Tris buffer and centrifuged at 100,000 *g* for 1 hr. The pellet was suspended in Tris buffer by restoring the original volume. A fresh preparation was produced for each experiment. Of the above preparations, 1.4 ml was added to the 2 ml incubation system, containing the actual compound to be tested. Incubation was performed under constant shaking at 37° for 20 min and stopped by adding 6 ml ice-cold isopropanol (I. K. Szabó and G. Cseh, personal communication) to the system. The precipitate formed was removed by centrifugation and isopropanol from the supernatant was evaporated. The residue was diluted with 5 ml distilled water and acidified to pH 3.0 by formic acid. The lipid fraction was extracted by 3 × 25 ml ether. After ether evaporation the samples were dissolved in ethanol and stored at −16°. PG-s were separated by thin layer chromatography in the

AI system as described by Green and Samuelsson [11]. The PGE and PGF zones located by means of PGE_2 and $PGF_{2\alpha}$ standards were scraped off, extracted by methanol and stored at $-16°$. PG-s were measured by bioassay on rat stomach strips [12] in an organ bath using Krebs' solution that contained the required antagonists [13] as well as idomethacin [14]. Prior to measurement ethanol or methanol was evaporated and the samples were dissolved in sodium carbonate solution pH 7.4 (about 10^{-3} M). The activity of the PGF and PGE zones obtained by thin layer chromatography was measured against $PGF_{2\alpha}$ and PGE_2 standard responsively. In the experiments where no thin layer chromatography was done, the changes in total PG-like activity were measured. Stomach strips were about three times more sensitive to PGE_2 than to $PGF_{2\alpha}$. Since 3–4 times more PGF than PGE was formed in the systems studied, the isolated organ used proved to be rather adventageous for the simultaneous measurement of the two different types of activity.

The efficiency of the extraction and separation methods applied was controlled in several experiments. In the course of these procedures no alterations could be demonstrated in the quantities of the PGE_2 and $PGF_{2\alpha}$ standards added to the samples before extraction or chromatography. However, only differences higher than 10 per cent can be reliably demonstrated by the method used for measurement of PG-s. Thus, the possibility of losses up to 10 per cent cannot be excluded. In the course of separation by thin-layer chromatography only the zones corresponding to the PGE_2 and $PGF_{2\alpha}$ standards showed biological activity on rat stomach strips and the sum of activities measured in the PG-zones always equalled the total PG-like activity measured in the unseparated extracts.

The following drugs were employed: PGE_2 and $PGF_{2\alpha}$: Upjohn, Kalamazoo; L-noradrenaline bitartrate, dopamine hydrochloride, L-adrenaline: Sigma, St. Louis; tyramine hydrochloride, tryptamine hydrochloride, serotonin creatininsulphate, DL-DOPA, DL-5-hydroxytryptophan: Fluka, Buchs; L-α-methyl noradrenaline hydrochloride: Hoechst, Frankfurt; DL-α-methyl dopamine hydrochloride: C. H. Boehringer Sohn, Ingelheim; DL-isoprenaline hydrochloride: E.GY.T., Budapest; DL-α-methyl tryptamine hydrochloride was synthetized in our laboratories; D-amphetamine sulphate, harmaline hydrochloride: Koch-Light, Colnbrook, Bucks; pargyline: Abbot, North Chicago; clorgylin: May and Baker, Dagenham; tranylcypromine sulphate: Smith Kline and French Philadelphia; dipyrone: Polfa, Poland; reserpine phosphate: Ciba-Geigy, Basel; oxypertine: Winthrop, Surbiton; tetrabenazine (Nitoman ampullas): Hoffman-La Roche, Basel; desipramine hydrochloride, Geigy, Basel; deprenil (E-250), indomethacin, yohimbine hydrochloride: Chinoin, Budapest; nialamide, promethazine hydrochloride, chlorpromazine hydrochloride: E.GY.T., Budapest, Acetylsalicylic acid, apomorphine hydrochloride: Ph. Hg. VI.; AB-15 (1-meta-aminophenyl-2-cyclo-propyl-amino-ethanol dihydrochloride): Research Institute for Pharmaceutical Chemistry, Budapest.

RESULTS

Stimulation of the PG-biosynthesis in the particulate fraction of rat brain homogenates by the presence of the soluble fraction or by catecholamines and indolalkylamines. None or hardly any, PG content could be

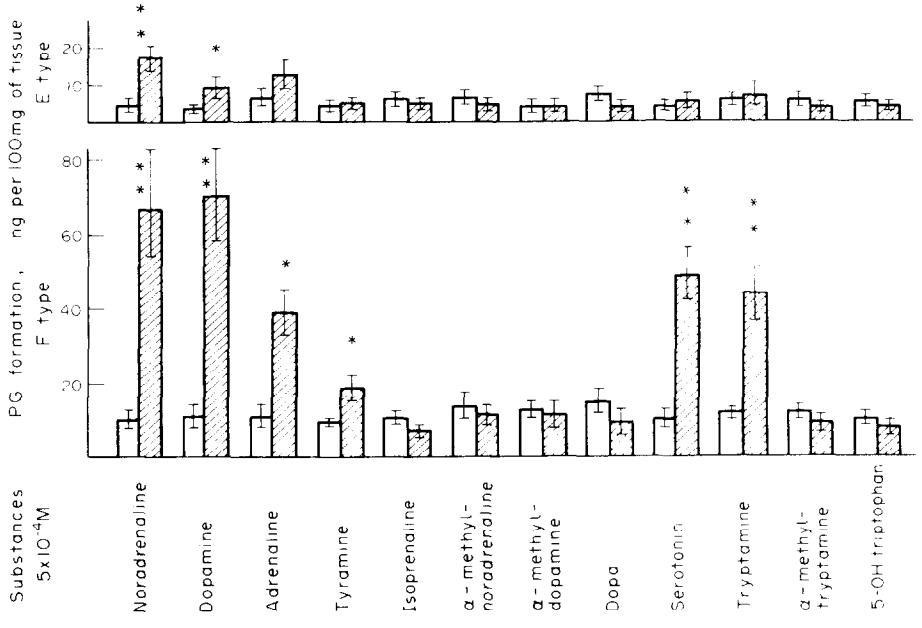

Fig. 1. Effect of phenylalkylamine and indoalkylamine derivatives on PG-biosynthesis in the particulate fraction of rat brain homogenates. Unhatched columns: PG-formation in the control samples; hatched columns: PG-formation in the presence of the compounds tested. PG-s were separated by thin layer chromatography and measured on rat stomach strips against $PGF_{2\alpha}$ and PGE_2 standards. The results are presented as means of at least five experiments in duplicate ± S.E. *: $P < 0.05$; **: $P < 0.01$ according to Student's *t*-test.

demonstrated from the rat brain homogenates kept cold. However, PG is synthetized and released into the medium during incubation. On the basis of five experiments PGF-like activity measured against $PGF_{2\alpha}$ proved to be 32.0 ± 11.7, while PGE-like activity in terms of PGE_2 was found to be 10.4 ± 3.2 ng/100 mg brain tissue (means ± S.E.). If the soluble fraction was removed from the total homogenates by centrifugation at 100,000 *g* and a particulate suspension was made, PGF-formation diminished to about one-third, PGE to about one-half, presumably due to the removal of endogenous cofactors contained in the soluble fraction. In the particulate fraction PG-biosynthesis could be stimulated by noradrenaline (NA). Activation began at the concentration of 5×10^{-5} M and maximal activation occurred at 5×10^{-4} M. Several phenylalkylamine and indoalkylamine derivatives were tested at a concentration of 5×10^{-4} M for their stimulatory effect on PG-biosynthesis in the particulate fraction of the rat brain homogenates (Fig. 1). Beside NA, dopamine (DA), adrenaline, tyramine, serotonin and tryptamine also increased PGF-formation. In the presence of NA and DA PGE formation was also increased, in accord with the results of Wolfe *et al.* [5–7]. Adrenaline was less effective than NA, while isoprenaline was ineffective. The stimulatory effect of DA was considerably reduced by the omission of one catechol OH (tyramine). The α-methyl analoguus of NA and DA as well as the α-carboxyl analogue of DA, DOPA failed to increase PG-biosynthesis. A similar structure-specifity could be observed for the indolalkylamines, too. The α-methyl analogue of tryptamine and the α-carboxyl analogue of serotonin, the 5-OH tryptophan were ineffective.

Effect of psychotropic drugs on endogenous PG biosynthesis in the rat brain homogenates. Many drugs acting on the central nervous system were tested for their effect on PG-biosynthesis in the particulate fraction of the rat brain homogenates stimulated by 5×10^{-4} M of NA (concentration required to achieve the maximum activation) or by the presence of the soluble fraction (total homogenates). For the sake of comparison the effects of three non-steroidal anti-inflammatory agents known to inhibit PG biosynthesis as indomethacin, acetylsalicylic acid [15], and dipyrone [16] (the latter proved to be rather selective in the inhibition of brain PG biosynthesis) were also investigated. The compounds were tested in a concentration of 2×10^{-4} M and the changes in total PG-like activity measured on the rat stomach strips were calculated. The drugs exerting more than 50 per cent inhibition at the concentration of 2×10^{-4} M were also characterized by the determination of the ID_{50} value. For easier dissolution of the compounds, as against pH 8.0 applied in earlier experiments, the present ones and all the following experiments were performed at pH 7.4, that did not essentially interfere with the PG formation in the systems studied. These tests are summarized in Table 1.

The non-steroidal anti-inflammatory drugs inhibited the PG-biosynthesis both in total homogenates and in the particulate fraction in the presence of NA. Indomethacin was the most effective (ID_{50} at

Table 1. Effects of psychotropic drugs and non-steroidal anti-inflammatory agents on endogenous PG-biosynthesis in rat brain homogenates

Compounds	Total homogenates		Particulate fraction + 5×10^{-4} M NA	
	% inhibition* (2×10^{-4} M)	ID_{50}† (M)	% inhibition (2×10^{-4} M)	ID_{50} (M)
Indomethacin	80.3 ± 2.3	5.4×10^{-6}	75.5 ± 5.5	4.7×10^{-6}
Dipyrone	59.2 ± 4.7	8.7×10^{-5}	48.3 ± 8.5	—
Acetylsalicylic acid	32.0 ± 2.1	—	33.7 ± 4.9	—
Tranylcypromine	19.2 ± 6.5	—	78.2 ± 5.6	8.5×10^{-6}
Harmaline	26.7 ± 6.3	—	69.0 ± 8.2	1.3×10^{-5}
Clorgyline	55.0 ± 5.3	1.8×10^{-4}	79.0 ± 2.3	1.6×10^{-5}
Deprenil	22.0 ± 8.9	—	70.0 ± 5.0	2.3×10^{-5}
Amphetamine	<10	—	64.3 ± 11.2	3.5×10^{-5}
Pargyline	<10	—	70.7 ± 2.7	5.0×10^{-5}
AB-15‡	<10	—	58.0 ± 1.2	1.3×10^{-4}
Nialamide	<10	—	47.0 ± 12.2	—
Apomorphine	73.1 ± 2.5	8.0×10^{-6}	<10	—
Oxypertine	68.9 ± 3.1	3.4×10^{-5}	<10	—
α-Methyl NA	65.5 ± 3.2	4.7×10^{-5}	<10	—
Promethazine	67.7 ± 5.3	5.6×10^{-5}	<10	—
DOPA	60.6 ± 4.0	6.8×10^{-5}	<10	—
Reserpine	64.0 ± 4.1	7.5×10^{-5}	<10	—
Chlorpromazine	46.0 ± 11.0	—	<10	—
Desipramine	35.4 ± 5.2	—	<10	—
Yohimbine	34.0 ± 6.8	—	<10	—
Tetrabenazine	25.1 ± 4.0	—	<10	—

In 2×10^{-4} M proved to be ineffective in both systems: meprobamate, chlordiazepoxide, haloperidol, nortriptyline, phenobarbital, phenoxybenzamine, propranolol, mescaline, morphine, pentylenetetrazole, oxotremorein.

* Per cent inhibition of the total PG-like activity measured on rat stomach strips. Results are the means of at least three experiments in duplicate ± S.E.

† ID_{50} (inhibition concentration resulting in 50 per cent inhibition) values were determined graphically.

‡ For MAO inhibiting properties see Huszti *et al.* [19].

Table 2. Effect of drugs on the formation of F and E type prostaglandins in rat brain homogenates

Compound*	% inhibition of PG formation†			
	Total homogenates		Particulate fraction + 5×10^{-4} M NA	
	F type	E type	F type	E type
Dipyrone	56.3 ± 7.4	57.0 ± 7.6	41.0 ± 7.5	51.7 ± 4.6
Oxypertine	62.3 ± 0.7	59.6 ± 7.1	—	—
Promethazine	60.0 ± 6.7	61.0 ± 5.0	—	—
Deprenil	—	—	69.7 ± 6.3	65.7 ± 1.3
Clorgyline	—	—	79.3 ± 1.3	73.5 ± 6.5

* Concentration of the drugs: dipyron, oxypertine promethazine: 2×10^{-4} M; deprenyl, clorgyline: 10^{-4} M.

† PG-formation in control samples: total homogenates: F type: 24.9 ± 4.3, E type: 7.7 ± 1.9; particulate fraction in the presence of NA: F type: 55.4 ± 9.9, E type: 14.2 ± 3.4 ng PG/100 mg brain tissue measured against $PGF_{2\alpha}$ and PGE_2 standards, respectively. Results are means of three experiments in duplicate ± S.E.

5×10^{-6} M in both systems), while acetylsalicylic acid proved to be a rather weak antagonist.

Surprisingly, the effects of the effective psychotropic compounds are different in the two systems. Na-stimulated PG-biosynthesis was inhibited only by drugs having monoamineoxidase (MAO) inhibitory activity. All the MAO-blocking agents investigated proved to be effective inhibitors of the NA-stimulated PG-biosynthesis. Tranylcypromine was the strongest inhibitor ($ID_{50} = 8.5 \times 10^{-6}$ M), the weakest nialamide (ID_{50} about 2×10^{-4} M). Clorgyline excepted, these same drugs did not inhibit, or inhibited very slightly PG-biosynthesis in the presence of endogenous cofactors in the total homogenates. However, clorgyline was a much more effective antagonist of PG formation in the NA stimulated system ($ID_{50} = 1.6 \times 10^{-5}$ M) than in the total homogenates ($ID_{50} = 1.8 \times 10^{-4}$ M). Prostaglandin biosynthesis proceeding in the total homogenates could be inhibited by apomorphine, oxypertine, α-methyl NA, promethazine, DOPA, reserpine, chlorpromazine, desipramine, yohimbine and tetrabenazine. Apomorphine was the most effective compound ($ID_{50} = 8 \times 10^{-6}$ M), while desipramine, yohimbine and tetrabenazine inhibited PG-biosynthesis to less than 50 per cent at the concentration of 2×10^{-4} M. These same compounds did not influence PG production in the NA-stimulated system. Apomorphine in the NA-stimulated system was tested in the presence of 10^{-4} M of ascorbic acid since apomorphine oxidation might result in the inhibition of enzyme activities in *in vitro* systems [17]. In the total homogenates ascorbic acid present in the soluble fraction [18] prevents the oxidation of apomorphine.

When adding the drugs found effective to the system by the end of incubation, immediately before stopping the PG-syntethase reaction with isopropanol, no change could be observed in the measurable PG-like activity. This excludes the possibility that the compounds would interfere with the extraction or with the bioassay.

The effect of some active drugs was studied also for PG-biosynthesis stimulated by 5×10^{-4} M serotonin. PG-formation could be inhibited by pargyline, deprenyl, harmaline amphetamine and dipyron, while promethazine oxypertine and desipramine were ineffective. This suggests that the activation mechanism of indolalkylamines is similar to that of catecholamines.

The F and E type PG-s were separated by thin layer chromatography in the NA-stimulated system in the case of dipyrone, clorgyline and deprenil as well as in the system with total homogenates in the case of dipyrone, oxypertine and promethazine. As found, the drugs inhibited the formation of both PG types (Table 2).

In the experiment shown in Fig. 2, the effects of reserpine and pargyline on PG-biosynthesis in total homogenates in the presence of 2×10^{-4} M of NA were studied. Inhibitory effect of reserpine on PG biosynthesis in the total homogenates is abolished by the presence of NA. At the same time, pargyline is capable of inhibiting PG-biosynthesis in total homogenates when NA is present. This suggests that in the combined presence of the soluble fraction and NA it is the catecholamine dependent activation mechanism, sensitive to MAO inhibitors that asserts itself.

Effect of lipid peroxidation inhibitory substances on endogenous prostaglandin biosynthesis in the rat brain homogenates. Since the psychotropic compounds found to be active in the total brain homogenates were exactly those that proved to be the antagonists

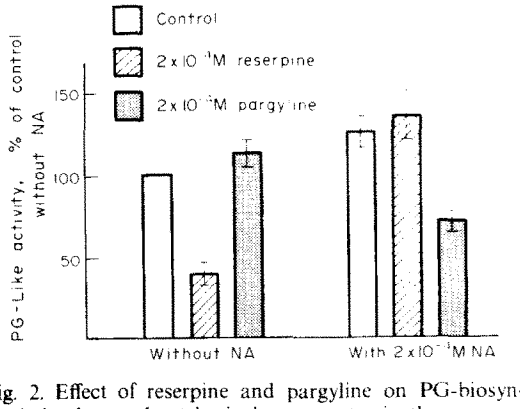

Fig. 2. Effect of reserpine and pargyline on PG-biosynthesis in the total rat brain homogenates in the presence and absence of noradrenaline. The changes in the total PG-like activity measured on rat stomach strips were calculated. Results are presented as means of three experiments in duplicate ± S.E.

Table 3. Effect of lipid peroxydation inhibitory substances on PG-biosynthesis in rat brain homogenates

Substances*	PG-formation (% of control)† Total homogenates	Particulate fraction $+5 \times 10^{-4}$ M NA
EDTA	49.0 ± 1.3	99.2 ± 0.8
o-Phenanthroline	21.8 ± 12.4	78.1 ± 4.7
p-Phenylenediamine	37.7 ± 4.8	100.3 ± 2.8
Co^{2+}(chloride)	31.2 ± 8.9	—
Mn^{2+}(sulphate)	29.1 ± 4.1	—

* Concentrations: *p*-phenylenediamine: 2×10^{-4} M, other substances: 10^{-4} M.

† Per cent of the total PG like activity in control samples measured on rat stomach strips. Results are means of three experiments in duplicate ± S.E.

of lipid peroxidation induced by ascorbic acid in the rat brain microsomes [20], we studied some well-known antagonists of lipid peroxidation in both systems: EDTA, *o*-phenanthroline, *p*-phenylenediamine, Co^{2+} and Mn^{2+} [20–23]. All these substances inhibited PG-biosynthesis in the total homogenates (Table 3). In the presence of *o*-phenanthroline a slight inhibition could also be observed in case of NA-stimulated PG-biosynthesis. The hydrophyl chelating agent EDTA and the antioxidant *p*-phenylenediamine, proved to be ineffective in the NA-stimulated system. Although in the latter system PG-biosynthesis did not change in the presence of 10^{-4} M Mn^{2+} and Co^{2+} either, these results cannot be taken into account, since in the presence of 5×10^{-4} M NA these metal ions might be bound in the form of chelate complexes.

DISCUSSION

On the basis of drug effect, two mechanisms of endogenous PG-biosynthesis can be distinguished in the rat brain homogenates. One type of PG-formation proceeds in the presence of catecholamines or indolalkylamines, the other in the presence of the brain soluble fraction containing endogenous cofactors. Catecholamines do not act to stimulate PG biosynthesis induced by endogenous substances in the total homogenate [5–7], but start some other type of PG-formation as demonstrated in Fig. 2.

The effect of catecholamines on the endogenous PG-biosynthesis in the brain tissue is so interpreted that it is presumably realized via the non-enzymatic reduction of endoperoxides [6–7]. Our results show that the effect of catecholamines and indolalkylamines is a function of definite chemical structures and cannot be correlated exclusively with their reductive or antioxidant properties. This suggests that specific interactions with definite membrane structures are also involved in the stimulatory effect of catecholamines and indolalkylamines on endogenous PG-biosynthesis in brain homogenates.

Raffel *et al.* [8], could not stimulate PG release in the synaptosome preparation obtained from rat brain either by catecholamines or serotonin. This failure might be ascribed not only to the different preparation but also to the low concentration of 3×10^{-5} M. The stimulatory effect of NA could first be observed at the concentration of 5×10^{-5} M, the semimaximum effect showed at 10^{-4} M, the maximum effect at about 5×10^{-4} M of NA in our experiments. Wolfe *et al.* [6, 7, 10] tested NA and DA at a concentration of 10^{-3} M.

PG-biosynthesis stimulated by catecholamine or indolalkylamine could rather specifically be inhibited by drugs with MAO blocking properties. It is of interest that of the catecholamine and indolalkylamine analogues, those proved to be active are MAO substrates. The α-methyl and α-carboxyl analogues of catecholamines and indolalkylamines were ineffective. This raises the idea that some relationship might exist between the stimulation of PG-biosynthesis by catecholamines or indolalkylamines and the functioning of MAO, e.g. some product of MAO should be held responsible for the activation of PG-biosynthesis. This, however, is contradicted by the fact that in the lung homogenates PG-biosynthesis from tracer amounts of arachidonic acid could be inhibited by MAO blocking agents also in the absence of catecholamine or indolalkylamine [2]. However, the possibility cannot be excluded that the endogenous cofactor present in the soluble fraction of the lung homogenate is some MAO substrate. A NA-induced PG-biosynthesis could be inhibited by tranylcypromine and phenelzine in experiments performed on rat uterine strips [1]. On the other hand, the concentrations of the MAO blocking agents required for the inhibition of PG-biosynthesis appear to be rather high. Quite recently, however, we have succeeded in demonstrating that the stimulation of PG-biosynthesis by NA in particulate fraction of rat brain homogenates can be completely eliminated by intraperitoneal pretreatment of the animals with, e.g., 1 mg/kg tranylcypromine, 3 mg/kg clorgyline or 30 mg/kg pargyline (manuscript in preparation). Still, the problem requires further careful analysis since the possibility of an analogy between the two phenomena cannot be excluded either.

As shown by our experiments, another type of PG-biosynthesis proceeds in the presence of the rat brain soluble fraction, that is insensitive to MAO-inhibitors. Several such psychotropic compounds have blocked this type of PG-formation which, as shown by experiments on various peripheral organs, proved to be the inhibitors of PG-biosynthesis, such as chlorpromazine, prometazine, desipramine, reserpine [1–4]. At the same time apomorphine that proved to be an effective inhibitor in our experiments intensively stimulated PG-biosynthesis from exogenous arachidonic acid, in the presence of EDTA, in bull seminal

vesicle homogenate [24, 25], as well as in homogenate obtained from rabbit brain [26]. Morphine, ineffective in our experiments, acted similarly [24, 26].

PG-biosynthesis in total homogenates was inhibited by those drugs which proved to be the antagonists of ascorbic acid induced lipid peroxidation in microsomes isolated from the rat brain [20]. Although higher concentrations of these compounds are required for inhibiting PG-biosynthesis in the total homogenates than the concentrations for inhibition of lipid-peroxidation in microsomes, the efficiency sequence of the drugs is in accord. In addition to these psychotropic drugs, microsomal lipid peroxidation could be inhibited by catecholamines, too [20]. As established on the basis of the experiment documented in Fig. 2, NA also inhibits PG-biosynthesis proceeding in the presence of the soluble fraction, since PG-biosynthesis sensitive to MAO inhibitor is taking place in its presence. The α-methyl and α-carboxyl analogues of catecholamines proved to be the antagonists of PG formation in the total homogenates (Table 1). DOPA inhibited lipid peroxidation similarly to NA and DA (20). α-Methyl NA was active in a phenomenon [27] which was proved to be correlated with the inhibition of lipid peroxidation [20].

PG-biosynthesis proceeding in the total homogenates of the rat brain could be inhibited by other well known antagonists of lipid peroxidation as EDTA, *o*-phenanthroline, *p*-phenylenediamine, Co^{2+} and Mn^{2+} [20–23]. The aromatic cheleating agent *o*-phenanthroline had a slight inhibitory effect on NA-stimulated PG-formation, too (Table 3). *o*-Phenanthroline is known to act on PG-biosynthesis also, via some mechanism other than the chelatory effect [28].

Accordingly, it might be assumed that PG-formation taking place in total homogenates of the rat brain is related to certain lipid peroxidation processes. The psychotropic drugs found to be effective would exert their effect by inhibiting these processes. It is worth mentioning that in acetone powder preparations of the sheep vasicular gland one type of the fatty acid dioxigenase activity has proved to be sensitive to glutathion peroxidase [29], known to decompose lipid hydroperoxides [30, 31] or to inhibit their formation [32].

The non-steroidal anti-inflammatory agents inhibited PG-biosynthesis in both systems studied. This can be explained by their direct effect on PG-synthetase [33]. On the other hand our results show that psychotropic compounds found to be effective exert their effect on endogenous PG-biosynthesis in the rat brain homogenates depending on the different activation mechanisms, probably by inhibiting these activation processes.

The elaboration of the exact mechanisms of the different types of PG-formation in rat brain homogenates, as well as the elucidation of their importance in *in vivo* physiological or pathological processes requires further research.

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