Baldessarini, R. J., Kula, N. S., Walton, K. G. (1977) Psychopharmacology 53: 45–53

Costall, B., Naylor, R. J., Nohria, V. (1978) Eur. J. Pharmacol. 50: 39–50

Ezrin-Waters, C., Muller, P., Seeman, P. (1976) Can. J. Physiol. Pharmacol. 54: 516–519

Friedman, A., Everett, G. M. (1964) in: Garattini, S., Shore, P. A. (eds) Advances in Pharmacology. Vol. 3 Academic Press, New York, pp 83–127

Goldensohn, E. S., Hardie, J., Borea, E. (1962) J. Am. Med. Assoc. 180: 840–842

Marsden, C. D. (1975) in: Williams, D. (ed) Modern Trends in Neurology. Vol. 6 Butterworths, London, pp 141–166

Protais, P., Costentin, J., Schwartz, J. C. (1976) Psychopharmacology 50: 1–6

Vossen, R. (1958) Dt. Med. Wochenschr. 83: 1227–1230

Westerink, B. H. C., Lejeune, B., Korf, J., Van Praag, H. M. (1977) Eur. J. Pharmacol. 42: 179–190

Zimmerman, F. T., Burgemeister, B. B. (1958) Neurology (Minneap.) 8: 769–775

The role of monoamine oxidase in catecholamine-stimulated prostaglandin biosynthesis of rat brain homogenates

MÁRTA KOMLÓS, ANDRÁS SEREGI*, ANDRÁS SCHAEFER, *Institute of Experimental Medicine, Hungarian Academy of Sciences, H-1450 Budapest 9. P.O. Box 67, Hungary*

Brain tissue is known to synthesize only small amounts of prostaglandin (PG) from exogenous precursors while it forms a considerable amount of $PGF_{2\alpha}$ and PGE_2 from an endogenous pool of arachidonic acid (Coceani & Wolfe 1965; Wolfe et al 1976 a,b). Endogenous PG-biosynthesis taking place during the incubation of cortex slices, brain homogenates and synaptosomes could be enhanced by catecholamines, 5-HT and tryptamine (Hillier et al 1976; Leslie 1976; Schaefer et al 1978). Our earlier investigations have shown that the stimulating effect of catecholamines and indolalkylamines on PG-biosynthesis in rat brain homogenates can be blocked by inhibitors of monoamine oxidase (MAO) (Schaefer et al 1978). On the other hand, PG-biosynthesis could be activated only by those catecholamines and indolalkylamines that were substrates of MAO. Thus, α-methyl- and α-carboxyl-derivatives, as well as isoprenaline, proved to be ineffective. It was suggested that some relationship might exist between the stimulation of PG-biosynthesis by catecholamines or indolalkylamines and the function of MAO. We have examined the effect of in vivo pretreatment with MAO inhibitors on the catecholamine-induced stimulation of endogenous PG-biosynthesis in rat brain homogenates.

CFY rats of either sex, 150–250 g, were treated intraperitoneally with various MAO-blocking agents or with 0·9% NaCl (saline). At a definite time after treatment the brains were rapidly removed and homogenized in three volumes of 0·1 M Tris-HCl buffer, pH 7·4. The soluble fraction was removed by centrifugation at 100 000 g for 1 h. The pellet was resuspended in the original volume of Tris buffer. This total particulate suspension obtained from the brain homogenate was tested for noradrenaline (NA)-stimulated PG-biosynthesis and for oxidative deamination of NA.

To measure the PG-biosynthesis, 1·4 ml of the particulate suspension was incubated at 37 °C for 20 min under constant shaking with or without 5×10^{-4} M NA. The final volume of the incubation mixture was 2 ml. The reaction was stopped by the addition of 6 ml ice cold isopropanol. PG-s were extracted, separated and measured by bioassay on rat stomach strips as described by Schaefer et al (1978). In preparations obtained from control animals, PGF-like activity measured against $PGF_{2\alpha}$ varied between 50–90, while PGE-like activity in terms of PGE_2 varied between 8–15 ng/100 mg brain tissue after incubation in the presence of 5×10^{-4} M NA. We have recently confirmed this value for $PGF_{2\alpha}$ by radioimmunoassay measurements. The changes in the total PG-like activity were determined.

For the determination of MAO activity, 200 μl of the incubation mixture contained 140 μl of particular suspension, 5×10^{-4} M NA and 0·1 μCi ^{3}H-NA ($8{\cdot}5 \times 10^{-8}$ M). Incubation was at 37 °C for 20 min and was stopped by the addition of 200 μl 0·02 M HCl saturated with NaCl. The metabolites were extracted from the acidified reaction mixture with 2 × 1 ml ethyl acetate by the method of Leeper et al (1958) and the organic phase was measured by liquid scintillation. Specific activity for MAO was: 10·8–13·5 nmol amine deaminated/100 mg brain tissue per 20 min.

Table 1. Effect of in vivo pretreatment with MAO inhibitors on oxidative deamination of NA, and on NA-stimulated PG-formation in rat brain homogenates. MAO inhibitors were given i.p. 1 h before decapitation, Concentration of NA: 5×10^{-4} M in both mixtures. Inhibitory effect of the drugs was determined at five different concentrations. For each concentrations 9 animals were used, ID50 values were determined graphically,

	ID50 values (mg/kg^{-1})	
Compounds	MAO-activity	PG-formation
Tranylcypromine	0·55	0·74
Clorgyline	0·77	2·3
Pargyline	13·9	24·0
Deprenyl	19·3	36·1

* Correspondence.

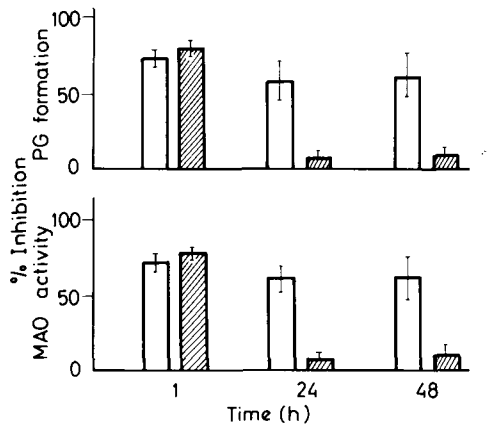

FIG. 1. Effect of in vivo pretreatment with clorgyline and with harmaline on MAO activity and NA-stimulated PG-formation in rat brain homogenates. The enzyme activities were measured in the presence of 5×10^{-4} M noradrenaline. Open columns: 5 mg kg^{-1} clorgyline; hatched columns: 5 mg kg^{-1} harmaline. Ordinate: percentage values of inhibition; vertical bars: standard errors. The number of animals in each group was nine. The animals were killed 1, 24, and 48 h after the treatment.

In accordance with previous in vitro studies (Schaefer et al 1978) we found that intraperitoneal pretreatment of the animals with various MAO inhibitors results in inhibition of the NA-stimulated PG-formation in rat brain homogenates. In Table 1 we have compared the ID50 values of tranylcypromine, clorgyline, pargyline and deprenyl, determined 1 h after pretreatment of the animals, for NA-stimulated PG-formation and MAO activity using NA as substrate. The drugs can be seen to have the same ranking of activity on the two enzymatic processes.

In the experiments in Fig. 1, animals were treated with 5 mg kg^{-1} clorgyline and harmaline, respectively MAO activity and NA-stimulated PG-biosynthesis in the brains were studied 1, 24 and 48 h after treatment. In animals treated with clorgyline, an irreversible MAO inhibitor, MAO activity as well as PG-biosynthesis was inhibited for more than 48 h. When harmaline, a reversible MAO inhibitor was given, only a transient decrease in the activity of both enzymatic processes could be measured. This indicates that pretreatment with irreversible and reversible MAO inhibitors has the same effect on MAO activity and PG-biosynthesis.

MAO blocking agents are known to inhibit the PG-biosynthesis in preparations obtained from various peripheral organs (Tothill et al 1971; Lee 1974; Bekemeier et al 1977). However, our previous investigations have shown that, with endogenous PG-formation in rat brain homogenates, MAO-blocking agents inhibited only the catecholamine or indolalkylamine stimulated PG-formation effectively, while PG-formation taking place in the presence of endogenous activators was unaffected or only slightly reduced by MAO inhibitors (Schaefer et al 1978).

The results of the present study show that activity of MAO and activation of endogenous PG-biosynthesis in rat brain homogenates by NA follow a parallel change after in vivo administration of MAO-blocking agents. This points to a relationship between NA-stimulated endogenous PG-biosynthesis and MAO activity. Accordingly, activation of PG-biosynthesis may be due to some oxidative metabolite derived from NA or to some by-product formed during the functioning of MAO; hydrogen peroxide has been shown to stimulate the PG-biosynthesis (Panganamala et al 1974; Morse et al 1977). The difference in potency between clorgyline and deprenyl seems to suggest that type-A MAO (Neff & Yang 1974) might have a preferable role in catecholamine-stimulated PG-biosynthesis.

A preliminary report of the results was presented at the 7th International Congress of Pharmacology, Paris, 1978.

February 8, 1980

REFERENCES

Bekemeier, H., Giessler, A. J., Vogel, E. (1977) Pharm. Res. Commun. 9: 587–598

Coceani, F., Wolfe, L. S. (1965) Can. J. Physiol. Pharmacol. 43: 445–450

Hillier, K., Roberts, P. J., Woollard, P. M. (1976) Br. J. Pharmacol. 58: 426–427

Lee, R. E. (1974) Prostaglandins 5: 63–68

Leeper, L. C., Weissbach, H., Udenfriend, S. (1958) Arch. Biochem. Biophys. 77: 417–427

Leslie, C. A. (1976) Res. Commun. Chem. Pathol. Pharmacol. 14: 455–469

Morse, D. E., Duncan, H., Hooker, N., Morse, A. (1977) Science 196: 298–300

Neff, N. H., Yang, H.-Y. T. (1974) Life Sci. 14: 2061–2074

Panganamala, R. V., Sharma, H. M., Sprecher, H., Geer, J. C., Cornwell, D. G. (1974) Prostaglandins 8: 3–11

Schaefer, A., Komlós, M., Seregi, A. (1978) Biochem. Pharmacol. 27: 213–218

Tothill, A., Bamford, D., Draper, J. (1971) Lancet 2: 381

Wolfe, L. S., Pappius, H. M., I. Marion, J. (1976a) in: Samuelsson, B., Paoletti, R. (eds) Advances in Prostaglandin and Thromboxane Research vol. 1. Raven Press, New York, pp 345–355

Wolfe, L. S., Rostorowski, K., Pappius, H. M. (1976b) Can. J. Biochem. 54: 629–640