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Substrate and strain-dependent differences in the development of monoamine oxidase in the rat brain

D. BLATCHFORD, M. HOLZBAUER* & M.B.H. YOUDIM

A.R.C. Institute of Animal Physiology, Babraham, Cambridge and M.R.C. Unit, Department of Clinical Pharmacology, Radcliffe Infirmary, Oxford

Physicochemical studies and *in vitro* experiments using different enzyme inhibitors have overwhelmingly pointed to the existence of different forms of the enzyme monoamine oxidase (MAO) (for review, see Sandler & Youdim, 1972). Their presence and independent function *in vivo* is more difficult to ascertain. It has been indicated in experiments on rats treated with progesterone in which the increase in adrenal MAO caused by this steroid was significantly different when different

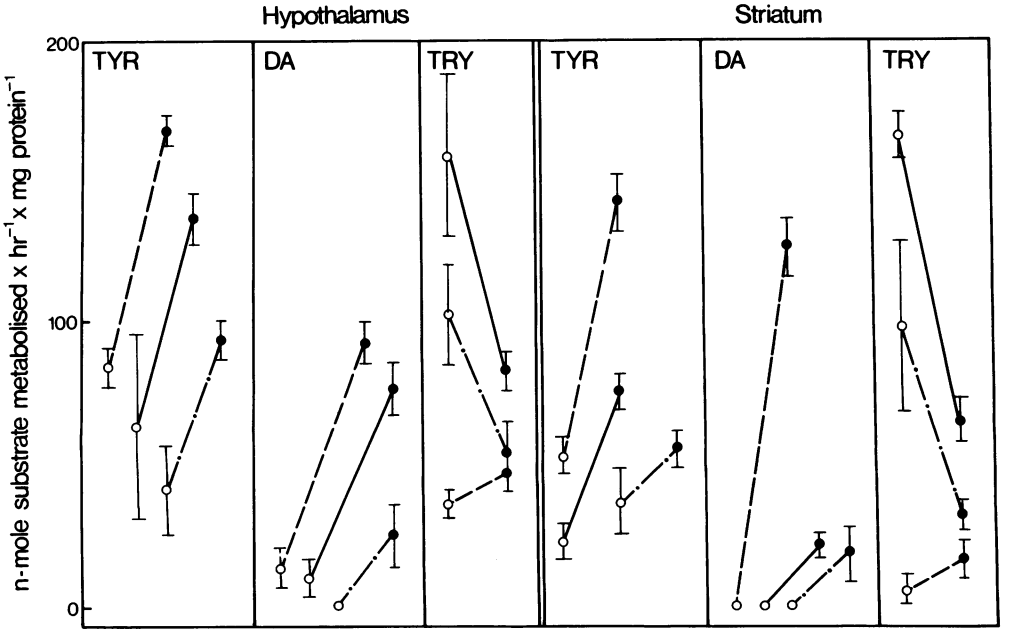

Figure 1 MAO activity in the hypothalamus and striatum of five day old (○) and 20 day old (●) rats. – – –: Porton rats. ——: Wistar rats, bred at Tuck's. · · · · ·: Wistar rats, bred from Tuck stock at Babraham. TYR = tyramine; DA = dopamine; TRY = tryptamine. Mean value ± s.e. of the mean (n = 5).

substrates were used (Youdim, Holzbauer & Woods, 1974). To further elucidate the problem experiments are in progress to examine whether the rate of the age dependent changes in brain MAO activity (Karki, Kuntzman & Brodie, 1962) varies when different substrates (kynuramine, K; tyramine, TYR; dopamine, DA; tryptamine, TRY; and 5-hydroxytryptamine, 5-HT) are used. The brain regions studied were the hypothalamus, striatum, septum and cerebellum. Litter mate rats (5, 10, 20, 40 and 80 days old) of different strains were used. Figure 1 shows examples of MAO-activity in the hypothalamus and striatum of 5 (○) and 20 (●) day old rats of three different colonies. With TYR and DA as substrate MAO activity was higher in both brain regions of the older rats of all three colonies. This was also the case with tryptamine in rats from the Porton strain, although to a lesser degree. In contrast, both brain regions of the five day old rats of the two Wistar colonies showed a considerably higher activity towards tryptamine than those of the 20 day old rats. In a group of five day old 'hooded rats' hypothalamic MAO activity towards tryptamine was only about one half that found in 30 day old rats of the same colony. However, the caudate nucleus of the five day old hooded rats exhibited five times more MAO activity towards tryptamine than that of the 30 day old rats. MAO activity towards DA was absent in the striatum of all five day old rats so far tested. The results obtained with other brain regions and peripheral tissues (adrenal glands, heart and liver) also showed differences in the rates of development of MAO activity depending on the substrate used.

Thus it appears possible that the postulated multiple forms of MAO do not develop at the same rate in the growing rat. This differential development may reflect the maturation of different mitochondria concerned with the metabolism of biogenic amines (Youdim, 1974).

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The specificity of the binding of ^{3}H-5-hydroxytryptamine (^{3}H-5-HT) to butanol extracts of rat brain

S. GODWIN* & J.M. SNEDDON

Department of Pharmacology, University of Bristol, Bristol BS8 1TD

In a previous communication to the Society (Godwin & Sneddon, 1974) we described the binding peak of ^{3}H-5-HT (5×10^{-7} M) eluted from an LH20 Sephadex column by a discontinuous chloroform-methanol (CM) gradient. This peak was found to be highly sensitive to the degree of hydration of the extract and was reduced by lysergic acid diethylamide (LSD) (3.2×10^{-7} M-2.5×10^{-6} M) in a concentration-dependent manner.

The following experiments examine the selectivity of this technique and measure the specificity of the 5-HT binding.

Atropine and amphetamine (both at 5×10^{-7} M) had no effect on the peak of eluted ^{3}H-5-HT when preincubated with the extract whereas 5×10^{-5} M amphetamine and tryptamine, and reserpine (4×10^{-6} M) and pargilline (5×10^{-7} M) all significantly reduced the proportion of the label eluted in the 5-HT binding peak.

Following double labelling of the extract with ^{14}C-Ach (10^{-6} M) and ^{3}H-5-HT (5×10^{-7} M), the elution profile of the 5-HT was unaltered (see figure). The ^{14}C-label was distributed between two peaks, one eluting in the C/CM 15 : 1 interface (peak *A*) and the other at the beginning of elution with CM 4 : 1 (peak *B*).

Preincubation with tubocurarine (5×10^{-7} M) had no effect on the ^{3}H-5-HT elution but greatly reduced the ^{14}C-label in peak *B*, proportionately increasing the level in peak *A*.

We have also studied extracts of that part of the rat diaphragm rich in motor nerve endplates (Hebb, Krnjević & Silver, 1964) and found that after double labelling and subsequent chromatography, there is a considerable increase in the proportion of ^{14}C-label in peak *B* (the overall