BIOCHEMICAL JOURNAL LETTERS

Is there a brain tyrosine aminotransferase?

Tyrosine is the precursor amino acid of the catecholamines, and it has been speculated that increased transamination in the brain could shunt this precursor away from neurotransmitter synthesis (Gibb & Webb, 1969; Fuller, 1970; Zigmond & Wilson, 1973; Lees & Weiner, 1975; Cahill & Ehret, 1981). Several papers on 'brain tyrosine aminotransferase (EC 2.6.1.5)' have appeared recently (Cahill & Ehret, 1981; Elam & Barnett, 1981; Snape & Badawy, 1981) and, in this *Journal*, Snape & Badawy (1981) described an enhancement of this enzyme by cortisol. However, we felt that a few words of caution be necessary when weighing the significance of these papers.

In the liver, tyrosine aminotransferase (EC 2.6.1.5) is a cytoplasmic enzyme that has a very short half-life and is inducible by several agents (Ohisalo, 1977). The enzyme has multiple forms (Ohisalo & Pispá, 1976; Hargrove & Granner, 1981) that share the same K_m values (1 mM for tyrosine) and have isoelectric points between 4.8 and

5.9. In addition to this enzyme, the mitochondrial isoenzyme of aspartate aminotransferase (EC 2.6.1.1) can transaminate tyrosine due to its wide substrate spectrum (Ohisalo & Pispá, 1976; Rej, 1976). This enzyme is present in all tissues. Its K_m value for tyrosine is much higher than that of EC 2.6.1.5 (exact determination is hindered by the low solubility of tyrosine) and the total activity with tyrosine is insignificant compared with that of EC 2.6.1.5, even when measured at 6 mM-tyrosine (Ohisalo, 1977). The isoelectric point of this enzyme is above pH 9 (Ohisalo & Pispá, 1976, 1977; Andersson *et al.*, 1980).

In the brain, total 'tyrosine aminotransferase activity' is 1–10% of that in the liver (Miller & Litwack, 1969; Fuller, 1970; Vogel *et al.*, 1973; Snape & Badawy, 1981) and is located in the mitochondria (Miller & Litwack, 1969; Aunis *et al.*, 1971). The isoelectric focusing profile of the activity is shown in Fig. 1. It is evident that the tyrosine aminotransferase activity of the brain is solely due to mitochondrial aspartate aminotransferase (EC 2.6.1.1); no specific tyrosine aminotransferase (EC 2.6.1.5) could be demonstrated. This is in good agreement with the results of Noguchi *et al.* (1975)

Fig. 1. Isoelectric focusing of rat brain tyrosine aminotransferase activity

The brains of two female Wistar rats were homogenized in 2 vol. of 320 mM-glycerol/0.5% Triton X-100 by using a Potter-Elvehjem glass homogenizer. The homogenate was centrifuged at 100 000 *g* for 30 min and 5 ml of the supernatant was electrofocused and the fractions were analysed as described previously (Ohisalo & Pispá, 1976). The tyrosine aminotransferase activity of the supernatant was 1.5 nmol of *p*-hydroxyphenylpyruvate formed/min per mg of protein. ●, Tyrosine aminotransferase activity; ○, aspartate aminotransferase activity; ●●●●, pH.

obtained by using different techniques. The activity of the mitochondrial enzyme towards tyrosine is negligible when measured at physiological tyrosine concentrations (60 μ M) especially if aspartate, the physiological substrate, is present (Ohisalo & Pispä, 1976; Ohisalo, 1977). Therefore, the nonspecific mitochondrial aspartate aminotransferase is probably of no significance in normal tyrosine metabolism, although it has been suggested to cause the appearance of transaminated tyrosine metabolites in hereditary tyrosinaemia (Fellman *et al.*, 1969). Further, isotopic tracer studies have suggested that oxidation of tyrosine in extrahepatic tissues is quantitatively insignificant (Noda & Ichihara, 1976).

In conclusion, there is no specific tyrosine aminotransferase (EC 2.6.1.5) in rat brain; the low 'tyrosine aminotransferase activity' that can be demonstrated at unphysiological tyrosine concentrations is due to aspartate aminotransferase (EC 2.6.1.1) and is of no significance in normal tyrosine metabolism.

Jorma J. OHISALO, Birgitta M. ANDERSSON,
Alli A. VILJANEN and Sture M. ANDERSSON
*Department of Medical Chemistry, University of
Helsinki, Siltavuorenpenger 10A, SF-00170
Helsinki 17, Finland*

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Brain tyrosine aminotransferase: identity and possible role in the regulation of catecholamine synthesis

In the preceding letter, Ohisalo *et al.* (1982) suggested that brain tyrosine aminotransferase is identical to aspartate aminotransferase and that its activity is normally too small to exert a significant effect on tyrosine metabolism. We should like to make a brief comment on the identity of this enzyme and to present evidence suggesting that its activity can in fact influence the intracerebral availability of tyrosine for catecholamine synthesis.

We have never suggested that transamination of brain tyrosine is achieved by a specific aminotransferase, and the isoelectric-focusing data of Ohisalo *et al.* (1982) leave no doubt that transamination of aspartate and tyrosine is catalysed mainly by the same enzyme. Moreover, such a conclusion has already been reached more than 6 years ago from work on the transfer of the amino groups of kynurenine (Noguchi *et al.*, 1975a) and other aromatic amino acids (Noguchi *et al.*, 1975b). We, however, feel that further work on the cerebral-cytosolic form of this non-specific enzyme may be fruitful in relation to the possible influence of dietary, hormonal and other physiological conditions, because previous work with the two isoenzymes of hepatic aspartate aminotransferase has revealed that only the cytosolic, but not the mitochondrial, form is sensitive to factors such as low- and high-protein diets, cortisol, adrenalectomy and starvation (Nakata *et al.*, 1964). Also, if the reported (Laboritt & Thuret, 1977; Snape & Badawy, 1981) enhancement by cortisol of tyrosine transamination is confined to the cerebral-cytosolic form, which is less than 20% of the total-brain enzyme, then it could represent some 6–7-fold increase in this form and may therefore cause a dramatic effect on intracellular tyrosine compartmentation.