

BIOCHEMICAL JOURNAL LETTERS

High-fat diets increase tryptophan availability to the brain: importance of choice of the control diet

Because long-chain NEFA are known to displace serum-protein-bound tryptophan [both *in vitro* (Curzon *et al.*, 1973) and after administration (Badawy & Evans, 1975)] and, thereby, increase brain tryptophan concentration and, hence, 5-hydroxytryptamine synthesis (Curzon & Knott, 1974), we were surprised by the findings that feeding rats chronically on diets rich in fat, which increases serum NEFA concentration, fails to alter tryptophan binding to serum proteins (Lawson *et al.*, 1981) or to influence brain tryptophan and 5-hydroxyindole concentrations (Cousins *et al.*, 1982). These latter two unexpected findings may be explained either by the high-fat diets exerting effects on tryptophan metabolism and disposition resulting in prevention of the expected NEFA-mediated increase in availability of circulating free tryptophan to the brain, or by the possibility that Lawson *et al.* (1981) and Cousins *et al.* (1982) have reached the above conclusions only because they compared data obtained in high-fat-fed rats with those from animals treated with high-carbohydrate diets, but not from those given the standard 41B diet. In the present work, we present evidence supporting this latter possibility by demonstrating that parameters of tryptophan metabolism and disposition were similar in rats chronically fed with corn oil, tallow, starch or sucrose, but that all such parameters differed significantly from those observed in animals maintained on the standard 41B diet.

Locally bred male Wistar rats ($150\text{g} \pm 7\%$ at the start of experiments) were maintained from weaning on cube diet 41B (Oxoid, Basingstoke, Hants., U.K.) and water. The 41B diet was then replaced by a pelleted diet rich in corn oil, tallow, starch or sucrose (Special Diets Services Ltd., Stepfield, Witham, Essex CM8 3AB, U.K.) for 3 weeks. Contents and other details of these diets have previously been described (Lawson *et al.*, 1981). Both test animals and controls (those kept on the 41B diet) were killed by decapitation between 12:30 and 14:30h. Standard procedures were used for the determination of liver tryptophan pyrrolase

(EC 1.13.11.11) activity and concentrations of the following substances: free (ultrafiltrable) serum, total (acid-soluble) serum and brain tryptophan, brain 5-hydroxytryptamine, serum glucose (for references, see Badawy *et al.*, 1980) and serum albumin (Doumas *et al.*, 1963), corticosterone (Glick *et al.*, 1964) and NEFA (Mikac-Dević *et al.*, 1973). Brain 5-hydroxyindol-3-ylacetic acid concentration could not be determined, because of loss of the relevant extract. Results were analysed statistically by using Student's *t* test.

There were no significant differences in body weight gains between rats maintained on any of the five diets. Serum glucose concentration was also not significantly altered by the corn oil, tallow, sucrose or starch diet (in comparison with values observed in rats given the 41B diet). Of the former four diets, only corn oil caused a significant increase (31%; $P < 0.01$) in serum corticosterone concentration.

As shown in Table 1, free serum tryptophan concentration was significantly increased by the corn oil, tallow, sucrose and starch diets by 28, 28, 26 and 26% respectively, whereas that of total serum tryptophan was decreased by these four diets by 29, 18, 23 and 26% respectively. The percentage free serum tryptophan (an expression of tryptophan binding to serum proteins) was therefore increased by the four diets by 80, 57, 64 and 71% respectively. These four diets also increased the concentrations of brain tryptophan (by 35, 26, 23 and 24% respectively) and brain 5-hydroxytryptamine (by 28, 40, 40 and 40% respectively). None of the mean values of any of the above five parameters differed significantly between the four experimental dietary groups. These results therefore provide not only additional support to the concept that brain tryptophan concentration is governed mainly by that of the free, rather than the protein-bound, amino acid in serum, but also an explanation of the failure of Lawson *et al.* (1981) and Cousins *et al.* (1982) to demonstrate the ability of high-fat (and also high-carbohydrate) diets to increase tryptophan availability to the brain. We (Badawy *et al.*, 1980) have shown that the failure of some investigators to demonstrate the enhancement of cerebral 5-hydroxytryptamine synthesis by chronic ethanol administration is due to their use, as control treatments, of chronic isocaloric doses of glucose or

Abbreviation used: NEFA, non-esterified fatty acids.

sucrose, both of which also enhance this synthesis.

An increase in free serum tryptophan concentration either in the absence of an increase, or in the presence of a decrease, in that of total serum tryptophan usually indicates a decrease in binding of the amino acid to serum proteins. This could be due to a decrease in serum albumin concentration, an increase in that of serum NEFA (or the presence of another direct displacer) or both. The results in Table 1 are consistent with a NEFA-mediated displacement. The ability of the high-carbohydrate diets to increase NEFA concentration and, hence, free tryptophan availability to the brain represents an additional mechanism whereby carbohydrates (via glucose) increase brain tryptophan concentration; the other two mechanisms being participation of insulin and inhibition of liver tryptophan pyrrolase activity (see Badawy *et al.*, 1980).

Because liver tryptophan pyrrolase activity is a major determinant of tryptophan availability to the brain and is known to be inhibited by chronic administration of glucose, sucrose (Badawy *et al.*, 1980) and high-fat diets (Chiancone, 1964), it was considered of interest to see if the diets used in the present work could also exert a similar effect. That this is so is shown by the results in Table 1, but it is difficult to assess the possible influence of such inhibition on tryptophan availability to the brain in the presence of concurrent tryptophan displacement by NEFA. The mechanism of the pyrrolase inhibition by glucose has previously been exam-

ined (Badawy & Evans, 1976), whereas that by the high-fat diets requires investigation.

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Table 1. Effects of chronic consumption by rats of various diets on tryptophan metabolism and disposition and on serum albumin and non-esterified fatty acid concentrations

Experimental details and references to methods are given in the text. Liver tryptophan pyrrolase activity is expressed in μmol of kynurenine formed/h per g wet wt., whereas concentrations of serum albumin and NEFA are given in g/l and mM respectively. All other values (except the percentage free serum tryptophan) are in $\mu\text{g}/\text{ml}$ of serum or per g wet wt. of brain. Values are means \pm S.E.M. for each group of four (pyrrolase activities) or six (all other determinations) rats. The four experimental dietary groups have been compared with themselves and with the control group (that maintained on the standard 41B diet) and the significance of the differences is indicated as follows: $\dagger P < 0.05$; $\dagger\dagger P < 0.025$; $\dagger\dagger\dagger P < 0.02$; $*P < 0.01$; $**P < 0.005$; $***P < 0.001$.

Test	Diet . . .	41B (I)	Corn oil (II)	Tallow (III)	Sucrose (IV)	Starch (V)
Free serum tryptophan		0.88 \pm 0.01	1.13 \pm 0.03***	1.13 \pm 0.04***	1.11 \pm 0.04***	1.11 \pm 0.04***
Total serum tryptophan		29.10 \pm 0.53	20.73 \pm 0.85***	23.88 \pm 1.14***	22.42 \pm 0.78***	21.47 \pm 1.21***
Free serum tryptophan (%)		3.02 \pm 0.09	5.45 \pm 0.24***	4.73 \pm 0.26***	4.95 \pm 0.24***	5.17 \pm 0.38***
Brain tryptophan		3.54 \pm 0.12	4.78 \pm 0.24***	4.46 \pm 0.22**	4.34 \pm 0.26†††	4.39 \pm 0.08***
Brain 5-hydroxytryptamine		0.60 \pm 0.024	0.77 \pm 0.033**	0.84 \pm 0.028***	0.84 \pm 0.054**	0.84 \pm 0.071*
Serum NEFA		0.31 \pm 0.04	0.88 \pm 0.05***	0.59 \pm 0.04***	0.68 \pm 0.03***	0.62 \pm 0.05***
Serum albumin		39.20 \pm 0.70	38.20 \pm 0.90	40.40 \pm 0.50	39.10 \pm 0.90	38.20 \pm 0.90
Liver tryptophan pyrrolase						
Holoenzyme activity		1.60 \pm 0.06	1.60 \pm 0.06	1.50 \pm 0.06	1.70 \pm 0.05	1.60 \pm 0.06
Total enzyme activity		3.20 \pm 0.07	2.30 \pm 0.14**	1.80 \pm 0.09***	2.50 \pm 0.11**	2.50 \pm 0.04***
Apoenzyme activity		1.60 \pm 0.10	0.70 \pm 0.12**	0.30 \pm 0.04***	0.80 \pm 0.14**	0.90 \pm 0.09**
				II vs. III**	II vs. IV*	II vs. V**
				III vs. IV†	III vs. IV**	III vs. V***
				II vs. III††	III vs. IV**	III vs. V***
				II vs. III†††	III vs. IV†††	III vs. V***