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CONTROL OF ENZYME ACTIVITIES IN RAT LIVER BY TRYPTOPHAN AND ITS METABOLITES

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Abstract—Tryptophan administration increases the activities of tyrosine and tryptophan transaminases, tryptophan dioxygenase, histidase, serine dehydratase and phosphoenolpyruvate carboxykinase in the livers of fed rats; these increases are blocked by cycloheximide. In fasted rats, the changes are similar except that histidase is unaffected. In diabetic rat liver, only tryptophan dioxygenase and in adrenalectomized rat liver, tyrosine and tryptophan aminotransferases, tryptophan dioxygenase and phosphoenolpyruvate carboxykinase activities are increased after tryptophan. Low doses of both tryptamine and 5-hydroxytryptamine, in the presence of pargyline, increase the activities of tyrosine and tryptophan aminotransferases and phosphoenolpyruvate carboxykinase; these effects are distinct from those of the parent aminoacid. The variation in responses indicates that a number of mechanisms may be involved. Tryptophan is, however, directly effective in increasing tyrosine aminotransferase activity in isolated liver cells.

Of the aminoacids, tryptophan plays a unique role in the maintenance and regulation of hepatic protein synthesis [1–3]. In addition, it may have specific effects on the activities of several hormonally and nutritionally sensitive enzymes, not necessarily related to tryptophan metabolism itself [2, 4–8].

The mechanisms by which tryptophan acts to affect enzyme concentrations remain obscure. It is unlikely [1, 5] that the concentrations of either tryptophan itself or tryptophanyl-tRNA [9] are limiting for protein synthesis. In a few instances, indeed, there are indications that specific regulation by tryptophan involves enzyme degradation rather than synthesis [5, 6]. It has been suggested [10] that a metabolite rather than tryptophan itself may be the actual effector. This is certainly true for tryptophan-induced hypoglycaemia *in vivo* [11] and inhibition of gluconeogenesis *in vitro* [12]. The possibility of a single tryptophan-derived mediator for all actions of the aminoacid is attractive.

Several individual studies of the effects of tryptophan on single enzymes in rat liver have been reported [4–8, 13–15]. The divergences between these reports, and the consequent difficulty of interpretation, may be partially explained by the varying sensitivity to tryptophan in different rat populations [11]. Furthermore, the animals used differed in their nutritional and hormonal status, and were subjected to a range of varying dosages and regimes.

This present study was designed to provide a more systematic investigation of a group of tryptophan-sensitive enzymes, with a view to clarifying the possible principles involved. The data do not support the concept of a single simple mechanism for tryptophan action.

MATERIALS AND METHODS

With the exceptions listed below, all chemicals and biochemicals were from standard suppliers.

Radiochemicals were from the Radiochemical Centre, Amersham, Bucks, U.K. Foetal calf serum and Eagle's minimum essential medium were from Gibco–BioCult, Paisley, U.K. and Flow Laboratories, Irvine, U.K., respectively, and Norit-GSX from Norit Clydesdale Co., Glasgow, U.K. Keto-enol tautomerase (phenylpyruvate keto-enol isomerase, EC 5.3.2.1) [16], ITP [17] and phosphoenolpyruvate [18] were prepared in this laboratory.

Pargyline (*N*-benzyl-*N*-methylprop-2-ynylamine) was from Abbott Laboratories, Queenborough, Kent. MK-486 (Carbidopa: L-α-[3,4-dihydroxybenzyl]-α-hydrazinopropionic acid monohydrate) was kindly given by Merck, Sharp and Dohme Research Laboratories, Rahway, NJ, U.S.A.

All rats were males, Sprague–Dawley CSE/ASH strain (Charles River U.K., LW, Manston, Kent, U.K.), 200–250 g, and were inbred in this laboratory. Unless otherwise specified, all received food (no. 1 maintenance diet; Cooper Nutritional Products, Witham, Essex, U.K.) and water *ad lib.* Adrenal glands were removed by means of a midline dorsal incision under diethyl ether anaesthesia. Adrenalectomized animals were given 1% (w/v) NaCl in place of water and were left for 5–8 days before use. Diabetes was induced by intravenous injection of alloxan (60 mg/kg). Animals were used after 48 hr; diabetes was confirmed by glycosuria (Clinistix; Ames Co., Stoke Poges, Bucks, U.K.) and subsequent measurement of plasma glucose. Rats with a plasma glucose concentration of less than 15 mM were discarded.

All injections were performed using solutions prepared as previously described [11].

Animals were bled after decapitation (always at 0800–0900 hr). The livers were quickly removed, rinsed in ice-cold 0.9% (w/v) NaCl, blotted gently, and weighed. Portions were extracted in various media (see below) with a mechanical tissue disintegrator (Ultra-Turrax, Scientific Instrument Co., London, U.K.).

Assay of fructose 1,6-diphosphatase, glucose 6-phosphatase, hexokinase, glucokinase, phosphofructokinase and pyruvate kinase. Portions of liver were extracted in 4 ml/g. 50 mM-Tris–HCl/0.1 M-KCl/20 mM-

$MgSO_4$/10 mM-2-mercaptoethanol, pH 7.4. Hexokinase (ATP: D-hexose 6-phosphotransferase, EC 2.7.1.1), glucokinase (ATP: D-glucose 6-phosphotransferase, EC 2.7.1.2) and glucose 6-phosphatase (D-glucose 6-phosphate phosphohydrolase, EC 3.1.3.9) were assayed in the crude homogenate [21, 22]. Further portions of the homogenate were centrifuged at 12,000 *g* for 8 min at 4° (Eppendorf 3200). Part of the supernatant was stored at room temperature for assay of pyruvate kinase (ATP: pyruvate 2-*O*-phosphotransferase, EC 2.7.1.40) [23] and the rest in ice for assay of phosphofructokinase (ATP: D-fructose 6-phosphate 1-phosphotransferase, EC 2.7.1.11) [24] and fructose 1,6-diphosphatase (D-fructose 1,6-biphosphate 1-phosphohydrolase, EC 3.1.3.11) [25].

Assay of tyrosine aminotransferase (see also below), tryptophan aminotransferase and tryptophan dioxygenase. Portions of liver were extracted in 3 ml/g. 20 mM-Na phosphate/0.14 M-KCl, pH 7.0 and the homogenates were centrifuged at 38,000 *g* for 40 min at 4°. Supernatants were stored on ice and assayed by standard methods: tyrosine aminotransferase (L-tyrosine:2-oxoglutarate aminotransferase, EC 2.6.1.5) [26], tryptophan aminotransferase (L-tryptophan:2-oxoglutarate aminotransferase, EC 2.6.1.27) [26] and tryptophan dioxygenase (L-tryptophan: oxygen 2,3-oxidoreductase [decyclizing] EC 1.13.11.11) [27].

Assay of other enzymes. Serine dehydratase (L-serine hydrolase [deaminating], EC 4.2.1.13) was extracted in 5 ml/g 50mM-K phosphate/0.154 M-KCl/1 mM-dithiothreitol/0.1 mM-2-mercaptoethanol pH 7.4 and assayed [28] in the 12,000 *g* supernatant. Histidase (L-histidine ammonia-lyase, EC 4.3.1.3) was extracted in 10 ml/g 10 mM-Na pyrophosphate pH 9.2 and assayed [29] in the 12,000 *g* supernatant. Phosphoenolpyruvate carboxykinase (GTP: oxaloacetate carboxylase [transphosphorylating], EC 4.1.1.32) was extracted in 10 ml/g 5 mM-Tris Cl/0.25 M-sucrose/1 mM-2-mercaptoethanol, pH 7.4, and assayed [30, 31] in the 12,000 *g* supernatant. Ornithine decarboxylase (L-ornithine carboxylase, EC 4.1.1.17) was extracted in 5 ml/g 50 mM-Tris Cl pH 7.5 and assayed [32] in the 38,000 *g* supernatant.

Hepatocytes were isolated from fed rats as described elsewhere [9] and were incubated in Eagle's medium supplemented with 10% (v/v) dialysed and charcoal-treated foetal calf serum [20].

In isolated cell experiments, cells were harvested by centrifugation at 50 *g* for 2 min at room temperature. Pellets were frozen and thawed 3 times in 0.2 ml 0.25 M-K phosphate, pH 7.6. Tyrosine aminotransferase and lactate dehydrogenase (L-lactate : NAD^+ oxidoreductase, EC 1.1.1.27) were assayed as previously described [20, 33] in the 10,000 *g* supernatants.

Tryptophan was assayed by a standard procedure [34, 35].

RESULTS AND DISCUSSION

Effect of tryptophan on hepatic enzyme activities in vivo

Tryptophan is known to increase certain enzyme activities and a range of other proteins in rat liver [4, 5, 8, 13–15, 36]. We have examined the specificity of these changes with regard to both the enzymes affected and the chemical character of the effector.

Tryptophan causes large increases in phosphoenolpyruvate carboxykinase activity ([31]; Table 1). In animals given tryptophan (750 mg/kg) 12 hr before killing, no changes at all were seen in the activities of other key enzymes of carbohydrate metabolism: glucokinase, hexokinase, phosphofructokinase, pyruvate kinase, fructose 1,6-diphosphatase and glucose 6-phosphatase. Since, over such a short period as 12 hr, enzymes with slow rates of turnover would show little change in activity in any case, we also examined ornithine decarboxylase activity (t = 11 min; [37]), but again found no effect of tryptophan (data not shown).

Tryptophan (750 mg/kg) increased the activities of all six enzymes listed in Table 1 within 6 hr. After 1 hr, only tryptophan dioxygenase and phosphoenolpyruvate carboxykinase activities were increased, the latter by a distinct short-term mechanism independent of protein synthesis [31, 38]. Dose-dependence studies (not shown) revealed that only tyrosine aminotransferase, tryptophan dioxygenase and, to a lesser extent, phosphoenolpyruvate carboxykinase showed increased activity in animals given 100 mg/kg tryptophan. Conversely, histidase was increased only at 750 mg/kg. Serine dehydratase and tryptophan aminotransferase were intermediate, being increased 100–200 per cent at 200 mg/kg.

When given intraperitoneally, tryptophan is taken up readily into rat tissues [39]. When the aminoacid is given at a dose of 750 mg/kg, the plasma concentration declines linearly (Fig. 1) but remains approximately 4 times that in control animals at 6 hr.

All tryptophan-induced increases in activity were, with the possible exception of serine dehydratase, substantially inhibited by pretreatment with cycloheximide, indicating the importance of protein turnover in these effects (Table 1). This agrees with several (e.g. [10, 14, 38, 39]), but not all [4, 40] reports. The apparent "induction" of tyrosine aminotransferase activity by cycloheximide may be attributed to inhibition of protein turnover at a time when enzyme activity, in its diurnal rhythm, was near its maximum [41].

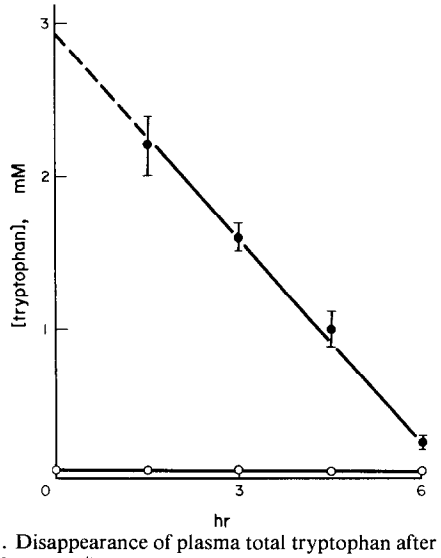

Fig. 1. Disappearance of plasma total tryptophan after injection of 750 mg/kg into 48 hr starved rats. Results are means ± S.E.M. for 4 observations; where not shown, error bars are within the symbols. Open circles, control values; closed circles, treated animals.

Table 1. Effect of tryptophan and cycloheximide on hepatic enzyme activities in fed rats *

	Control (A)	Tryptophan (B)	Cycloheximide (C)	Cycloheximide + Tryptophan (D)	P A vs B	P A vs C	P B vs D	P C vs D
Tyrosine aminotransferase	0.91 ± 0.09	7.6 ± 0.17	2.6 ± 0.13	2.9 ± 0.13	<0.001	<0.001	<0.001	NS
Tryptophan aminotransferase	0.03 ± 0.005	0.11 ± 0.006	0.06 ± 0.004	0.05 ± 0.003	<0.001	<0.01	<0.001	NS
Tryptophan dioxygenase	0.10 ± 0.005	0.30 ± 0.04	0.084 ± 0.002	0.12 ± 0.02	<0.01	NS	<0.01	NS
Histidase	0.14 ± 0.04	0.27 ± 0.01	0.18 ± 0.01	0.20 ± 0.01	<0.02	NS	<0.01	NS
Serine dehydratase	1.4 ± 0.20	2.7 ± 0.30	2.3 ± 0.20	2.2 ± 0.20	<0.02	<0.02	NS	NS
Phosphoenolpyruvate carboxykinase	5.2 ± 0.80	12.9 ± 1.2	3.4 ± 0.30	4.5 ± 0.60	<0.001	NS	<0.001	NS

* Animals were killed 6 hr after receiving tryptophan (750 mg/kg, i.p.). Cycloheximide (5 mg/kg, i.p.) was given 30 min before tryptophan. Control animals received appropriate volumes of 0.9% (w/v) NaCl. Activities are μmoles.min^{-1} (g liver)$^{-1}$ at 37° (phosphoenolpyruvate carboxykinase) or 30° (others), and are means ± S.E.M. of 4 observations. P, significance of the difference of the mean between groups; NS, not significant.

Table 2. Effect of tryptophan on hepatic enzyme activities in 48 hr starved rats *

	Control (A)	Tryptophan (B)	Starved (C)	Starved + tryptophan (D)	P A vs B	P A vs C	P B vs D	P C vs D
Tyrosine aminotransferase	0.51 ± 0.06	3.9 ± 0.40	0.50 ± 0.13	7.4 ± 0.60	<0.001	NS	<0.01	<0.001
Tryptophan aminotransferase	0.024 ± 0.002	0.09 ± 0.006	0.027 ± 0.003	0.17 ± 0.005	<0.02	NS	<0.001	<0.001
Tryptophan dioxygenase	0.07 ± 0.006	0.25 ± 0.03	0.08 ± 0.006	0.25 ± 0.034	<0.001	NS	NS	<0.001
Histidase	0.11 ± 0.02	0.18 ± 0.01	0.31 ± 0.01	0.30 ± 0.02	<0.001	<0.001	<0.01	NS
Serine dehydratase	0.58 ± 0.15	1.3 ± 0.14	3.3 ± 0.30	5.2 ± 0.20	<0.02	<0.001	<0.001	<0.01
Phosphoenolpyruvate carboxykinase	6.5 ± 0.40	23.5 ± 2.3	8.3 ± 0.80	20.6 ± 1.7	<0.001	NS	NS	<0.001

* Tryptophan (750 mg/kg, i.p.) was given 12 hr and 6 hr before killing. Activities are μmoles.min^{-1} (g liver)$^{-1}$ at 37° (phosphoenolpyruvate carboxykinase) or 30° (others), and are means ± S.E.M. of 4 observations. P, significance of the difference of the mean between groups; NS, not significant.

Table 3. Effect of tryptophan on hepatic enzyme activities in alloxan-diabetic rats*

	Control (A)	Tryptophan (B)	Diabetic (C)	Diabetic + Tryptophan (D)	P A vs B	P A vs C	P B vs D	P C vs D
Tyrosine aminotransferase	0.63 ± 0.08	4.6 ± 0.6	2.2 ± 0.4	4.3 ± 1.0	<0.001	<0.01	NS	NS
Tryptophan aminotransferase	0.02 ± 0.002	0.12 ± 0.02	0.11 ± 0.04	0.11 ± 0.04	<0.01	<0.1	NS	NS
Tryptophan dioxygenase	0.083 ± 0.005	0.56 ± 0.05	0.11 ± 0.014	0.41 ± 0.06	<0.001	NS	NS	<0.01
Histidase	0.11 ± 0.01	0.20 ± 0.01	0.21 ± 0.02	0.30 ± 0.03	<0.001	<0.01	<0.05	<0.05
Serine dehydratase	0.75 ± 0.11	2.3 ± 0.15	6.2 ± 0.61	5.4 ± 0.70	<0.001	<0.001	<0.01	NS
Phosphoenolpyruvate carboxykinase	3.8 ± 0.30	15.1 ± 1.10	16.0 ± 1.40	17.8 ± 0.90	<0.001	<0.001	NS	NS

*Tryptophan (750 mg/kg, i.p.) was given 12 hr and 6 hr before killing. Activities are μmoles.min^{-1} (g liver)$^{-1}$ at 37° (phosphoenolpyruvate carboxykinase) or 30° (others), and are means ± S.E.M. of 4 observations. P, significance of the difference of the mean between groups; NS, not significant.

Table 4. Effect of tryptophan on hepatic enzyme activities in adrenalectomised rats*

	Control (A)	Tryptophan (B)	Adrenalectomy (A)	Adrenalectomy + tryptophan (D)	P A vs B	P A vs C	P B vs D	P C vs D
Tyrosine aminotransferase	0.77 ± 0.06	1.7 ± 0.2	0.42 ± 0.05	0.94 ± 0.1	<0.01	<0.01	<0.02	<0.01
Tryptophan aminotransferase	0.018 ± 0.001	0.053 ± 0.008	0.017 ± 0.001	0.04 ± 0.002	<0.01	NS	NS	<0.001
Tryptophan dioxygenase	0.10 ± 0.01	0.23 ± 0.03	0.06 ± 0.001	0.12 ± 0.01	<0.01	<0.01	<0.02	<0.001
Histidase	0.2 ± 0.009	0.19 ± 0.03	0.14 ± 0.03	0.14 ± 0.02	NS	NS	NS	NS
Serine dehydratase	0.7 ± 0.18	1.43 ± 0.2	0.47 ± 0.08	0.58 ± 0.06	<0.05	NS	<0.01	NS
Phosphoenolpyruvate carboxykinase	4.0 ± 0.1	7.8 ± 0.5	4.4 ± 0.1	7.2 ± 0.6	<0.001	NS	NS	<0.01

*Tryptophan (200 mg/kg, i.p.) was given 6 hr before killing. Activities are μmoles.min^{-1} (g liver^{-1}) at 37° (phosphoenolpyruvate carboxykinase) or 30° (others), and are means ± S.E.M. of 4 observations. P, significance of the difference of the mean between groups; NS, not significant.

Table 5. Effect of tryptamine and 5-hydroxytryptamine on hepatic enzyme activities in pargyline-pretreated fed rats*

	Pargyline	Pargyline + tryptamine	Pargyline	Pargyline + 5-hydroxytryptamine
Tyrosine aminotransferase	0.43 ± 0.10	1.7 ± 0.1§	0.62 ±0.20	2.5 ± 0.7†
Tryptophan aminotransferase	0.023 ± 0.002	0.06 ± 0.005§	0.023 ± 0.004	0.08 ± 0.002§
Tryptophan dioxygenase	0.13 ± 0.01	0.23 ± 0.01§	0.15 ± 0.03	0.16 ± 0.01
Histidase	0.19 ± 0.04	0.2 ± 0.02	0.19 ± 0.04	0.23 ± 0.01
Serine dehydratase	1.9 ± 0.3	2.1 ± 0.20	2.2 ± 0.20	2.6 ± 0.30
Phosphoenolpyruvate carboxykinase	7.0 ± 0.5	9.9 ± 0.6‡	7.0 ± 0.5	10.6 ± 0.8‡

* Animals were given pargyline (75 mg/kg, i.p.) 45 min before tryptamine or 5-hydroxytryptamine (both 5 mg/kg, i.p.), and were killed a further 6 hr later. Activities are μmoles.min^{-1} (g liver)$^{-1}$ at 37° (phosphoenolpyruvate carboxykinase) or 30° (others), and are means ± S.E.M. of 4 observations. P (significance of the difference of the mean between groups); † <0.05, ‡ <0.01, § <0.001.

Table 2 shows that tryptophan remains effective in 48 hr-starved rats. Histidase activity, increased by starvation, is not, however, further increased by tryptophan. Serine dehydratase activity, by contrast, is increased in starvation, and further elevated by tryptophan. Atypically [31], phosphoenolpyruvate carboxykinase activity was not significantly increased in the fasted animals, but remained tryptophan-sensitive.

Effect of hormonal insufficiency on response of liver enzymes to tryptophan administration

In acutely alloxan-diabetic rats (Table 3), tryptophan elicits increases only in the activities of tryptophan dioxygenase and histidase. In the latter case, the effect is additive with that seen with diabetes alone; this suggests that insulin plays no important role in this specific action of the aminoacid. The insensitivity of serine dehydratase and tyrosine aminotransferase together with the evidence that at least one form of each enzyme is insulin-sensitive [42, 43], is, on the other hand, consistent with a requirement for an insulin-dependent factor in normal rats. Similarly, the *in vitro* effect of tryptophan in fasted rat liver, together with the absence of such an effect in the diabetic animal *in vivo* [44] suggests that insulin deficiency *per se* may not be the sole factor involved.

In this population of rats, tryptophan at this dosage produced a profound hypoglycaemia, maximal at 6 hr [11]. Throughout this period, plasma insulin concentrations remain unchanged (P. Lloyd and C. I. Pogson, unpublished work). In the diabetic rats, however, the hypoglycaemia was insignificant [11], and was thus unlikely to be related to the effects on enzyme activities.

Previous suggestions [7, 45] that tryptophan acts through changes in adrenal steroids prompted experiments with adrenalectomized animals. As previously noted [6], such rats are considerably more sensitive than intact animals towards tryptophan, and tolerated only a single dose of 200 mg/kg (Table 4). Under these circumstances, histidase activity was unchanged throughout. The other enzyme activities, with the exception of serine dehydratase, exhibited a relative sensitivity to tryptophan little different from that of fed animals. The failure of serine dehydratase to respond may indicate that corticosteroid is specifically important, although steroid and tryptophan are reported to induce separate and distinct isoenzymic forms of the enzyme [7].

Role of tryptophan metabolites in the alteration of hepatic enzyme activities

Lardy's group [46] suggested that the effects of tryptophan on gluconeogenesis might be mediated through formation of quinolinate, a metabolite known to accumulate in liver under these conditions [47]. Quinolinate at 750 mg/kg in our hands had no effect on the activities of the enzymes tested (data not shown). This agrees with [6], but not with [48].

Other reports indicate that 5-hydroxytryptamine may play a role in mediating these effects [6, 10]. Neither tryptamine nor 5-hydroxytryptamine affected enzyme activity by themselves (data not shown). When their breakdown by monoamine oxidase (amine: oxygen oxidoreductase (deaminating) (flavin-containing); EC 1.4.3.4) was inhibited with pargyline (75 mg/kg) significant changes were observed in some enzyme activities at relatively low doses (Table 5). Maximal inhibition of monoamine oxidase activity is produced by this dose of pargyline [10], but no effect of pargyline on the basal activities of any of the enzymes was observed. 5-Hydroxytryptamine, added exogenously, is, nevertheless, clearly different in its actions from that generated intracellularly [11, 49]. When rats were pretreated, however, with MK-486, which blocks aromatic aminoacid decarboxylation [50], or with *p*-chlorophenylalanine which blocks tryptophan 5-monooxygenase (EC 1.14.16.4; [51]), the effects of tryptophan were undiminished (data not shown). This does not support the hypothesis [10] that tryptophan acts through its conversion to the amines, and is more consistent with a more complex mechanism whereby a number of compounds may independently act as effectors [6, 52, 53]. This lack of specificity is further suggested by experiments with endotoxin-treated animals. Endotoxin, a lipopolysaccharide component of the cell wall of several bacterial species [58], at low doses itself increased tyrosine aminotransferase activity; tryptophan, which also increased enzyme activity, did not give an additive response with endotoxin (Table 6).

When isolated liver cells from fed rats are incubated for 6 hr with 2.5 mM-tryptophan, tyrosine aminotransferase activity is significantly increased above controls (controls 0.49 ± 11; tryptophan-treated 0.92 ± 0.21 (μmoles/min/g wet cells); means ± S.E.M. of seven paired observations; P < 0.005 [54]). Together with data from Tables 2 to 4, and the lack of consistent changes in circulating insulin concentrations with tryp-

Table 6. Effect of endotoxin and tryptophan on hepatic tyrosine aminotransferase activity*

	Treatment		Tyrosine aminotransferase (μmoles.min^{-1} (g liver)$^{-1}$)	P
	Endotoxin	Tryptophan		
I	–	–	1.45 ± 0.40	
II	+	–	2.81 ± 0.17	vs I : <0.05
III	–	+	4.89 ± 0.57	vs I : <0.01
IV	+	+	5.63 ± 0.24	vs II : <0.001 vs III : not significant

* Rats were starved for 48 hr. 12 hr before killing, experimental animals received 1 mg/kg endotoxin from *Salmonella typhimurium*; in 0.9% (w/v) NaCl intraperitoneally. Tryptophan (750 mg/kg, i.p.) was given 3 hr before killing. Controls were given appropriate injections of 0.9% NaCl. Results are means ± S.E.M.; 3 observations in each group.

tophan, this suggests that a direct action of tryptophan on the liver cell may play a part in the mechanisms *in vivo*.

General discussion

Whether these effects are important physiologically is open to question, since large doses are required to elicit appreciable responses. Nevertheless, these concentrations are achieved therapeutically, and smaller doses, equivalent to the amount normally present in the diet will increase tyrosine aminotransferase activity [39]; the aminoacid may be the regulator *in vivo* responsible for the diurnal rhythmicity of the same enzyme [55] and tryptophan dioxygenase [56].

It is clear, however, that no single simple mechanism will fit all the data pertaining to enzyme activities, and that there is little in common with the tryptophan-sensitive controls of carbohydrate metabolism [11]. These experiments show that, even in the same individual animal, enzymes may respond differently to the same stimulus; these differences are not readily explicable by the variations in the respective half-lives [57].

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