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Contribution of serum albumin to the transport of orally administered L-tryptophan into liver of rats with L-tryptophan depletion

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Summary. The role of serum albumin in the transport of orally administered L-tryptophan (Trp) into rat tissues was examined using analbuminemic and Sprague-Dawley (SD) rats with and without α-methyl-DL-tryptophan (AMT)-induced Trp depletion. Trp was orally administered to rats 16 h after AMT or 0.85% NaCl administration, when liver tryptophan 2,3-dioxygenase and protein synthetic activities in AMT-treated rats were similar to those of 0.85% NaCl-treated rats. After oral Trp administration, regardless of the presence or absence of Trp depletion, free serum Trp concentrations were similar in the analbuminemic and SD rats, while total serum Trp concentrations were lower in analbuminemic rats than in SD rats. Although liver, brain, and muscle Trp concentrations after oral Trp administration under Trp depletion were lower in analbuminemic rats than in SD rats, the ratio of the liver Trp concentration in analbuminemic rats to that in SD rats was smaller than that of the brain or muscle Trp concentration. These results suggest that variations in serum albumin levels could affect the transport of orally administered Trp into the liver of rats with Trp depletion.

Keywords: Amino acids – L-Tryptophan – Serum albumin – Transport – L-Tryptophan depletion – α-Methyl-DL-tryptophan – Analbuminemic rat

Introduction

Unlike other amino acids, 80–90% of the total L-tryptophan (Trp) present in the plasma or serum of humans and animals normally occurs in an albumin-bound form, while the remainder (ca. 10 μM) circulates in a free form, i.e., an albumin-unbound form (McMenamy et al., 1957, 1958; Fuller et al., 1973; Saito et al., 1986; Sasaki et al., 1993). Our previous study on the effect of albumin on the disappearance of Trp from the perfusate into isolated perfused rat livers has suggested that under physiological conditions (ca. 100 μM Trp and 4% albumin), serum albumin contributes to the maintenance

of the total serum Trp concentration and to the constant supply of serum Trp to the liver by lessening the change in serum Trp concentration through its binding to the amino acid (Sasaki et al., 1993). Analbuminemic rats lacking genetically in plasma albumin are the mutant strain established from Sprague-Dawley (SD) rats with normal plasma albumin levels (Nagase et al., 1979). We have reported that intravenously administered Trp (100μmol/kg body weight) is cleared from the circulation more rapidly in analbuminemic rats than in SD rats, that the amount of the administered Trp taken up by the liver of analbuminemic rats is larger than that of SD rats, despite there being no differences in the mode and rate of Trp uptake by isolated liver cells, and that there is no difference in the amount of the administered Trp taken up by other tissues such as brain and kidney between analbuminemic and SD rats (Sasaki et al., 1991). Furthermore, we have reported that when Trp (50μmol/kg body weight) with and without albumin is intravenously injected into analbuminemic rats with α-methyl-DL-tryptophan (AMT)-induced Trp depletion in the serum and liver, liver Trp content is higher in the co-injection of Trp and albumin than in the injection of Trp alone under conditions in which liver tryptophan 2,3-dioxygenase (TDO) activity is not altered by the AMT treatment (Sasaki et al., 1992). It has also been shown that the carrier-mediated transport of Trp into isolated perfused rabbit small intestines is stimulated in the presence of serum albumin (Saito et al., 1989). However, the role of serum albumin in the transport of orally administered Trp into rat livers is still unclear.

We, therefore, have attempted to clarify the role of serum albumin in the transport of orally administered Trp into the liver of rats with and without Trp depletion. Specifically, we examined changes in Trp concentrations in the serum, liver, kidney, brain, and muscle of analbuminemic rats with and without AMT-induced Trp depletion following oral Trp administration compared to those of SD rats with and without AMT-induced Trp depletion, respectively.

Materials and methods

Male analbuminemic rats were obtained from Clea Japan Co. (Tokyo, Japan) and were bred in our laboratory. Male SD rats were purchased at the age of five weeks from Clea Japan Co. (Tokyo, Japan) and used as a control. These rats were housed in plastic rat cages spread with chips in a controlled room at 25°C and 50% humidity on a 12h:12h dark-light cycle and given rat chow, Oriental NMF (Oriental Yeast Co., Tokyo) and water *ad libitum*. Animals weighing 200g were used. SD or analbuminemic rats received a single intraperitoneal injection of a solution of AMT (Sigma Chemical Co., St, Louis, MO, U.S.A.) dissolved in 0.85% NaCl (1.0mg/ml) at a dose of 5mg/kg body weight. AMT-untreated SD or analbuminemic rats received a single intraperitoneal injection of an equal volume of 0.85% NaCl. Thus, the rats used were divided into the following four groups: Group A, normal SD rats untreated with AMT; Group B, AMT-treated SD rats; Group C, analbuminemic rats untreated with AMT; Group D, AMT-treated analbuminemic rats. All animals were starved with free access to water until the end of experiments after ATM injection. At 16h after the injection, all groups of animals received a single oral administration of a solution of Trp (the highest grade, Wako Pure Chemical Industries Ltd., Osaka, Japan) dissolved in distilled water (50mM) at a dose of

500μmol/kg body weight or an equal volume of distilled water. Animals were sacrificed under ether anesthesia just before or 15, 30, and 60 min after Trp administration, at which time blood was collected from the vena cava caudalis. The collected blood was separated into serum. The liver, kidney, brain (whole brain), and muscle (leg muscle) were removed after collecting the blood. Before removing these tissues, ice-cold 0.15 M KCl was infused from the portal vein for 5 min to remove blood remaining within the tissues, especially the liver. All tissues removed were washed well in ice-cold 0.15 M KCl and then weighed. The separated serum and the removed tissues were stored at -80°C until use.

Serum L-phenylalanine (Phe), L-tyrosine (Tyr), L-leucine (Leu), L-isoleucine (Ile), and L-valine (Val) were determined in a Hitachi L-8500 amino acid analyzer (Hitachi Co., Tokyo, Japan) as described previously (Sasaki et al., 1991). Trp in serum, liver, kidney, brain, and muscle was determined by using high-performance liquid chromatography with electrochemical detection, as described previously (Saito et al., 1986). The preparation of samples for determinations of total Trp and free Trp (protein-unbound Trp) in serum were carried out using Ultrafree C3TK (Millipore Co., Tokyo, Japan) as an ultrafiltration membrane as described previously (Sasaki et al., 1991). Samples for the determinations of liver, kidney, brain, and muscle Trp were prepared as described previously (Sasaki et al., 1991). Liver TDO was assayed in the presence of added hematin (2μM) at 37°C under aerobic conditions with agitation according to the method of Metzler et al. (1982), using fresh 10% homogenates prepared from liver tissues in 0.15 M KCl. This enzyme activity is expressed as micromoles of kynurenine formed per h per g tissue. Liver protein synthetic activity *in vitro* was assayed by the method of Oravec and Sourkes (1970), using liver post-mitochondrial fractions corresponding to 45 mg of fresh rat liver and 18.5 KBq ^{14}C-Leu (Du Pont/NEN Research Products) which was purchased from Daiichi Chemical Co. (Tokyo, Japan). This activity is expressed as the amount of radioactivity incorporated into the protein for 30-min incubation at 37°C.

All values obtained are expressed as means $\pm$ SD. Groups of data were compared using the Student's paired t-test. When multiple comparisons were performed, the data were compared by ANOVA, including Fisher's protected least statistical difference (PLSD) test, using StatView (Abacus Concepts, Berkley, CA, U.S.A.). The level of significance was set at $p < 0.05$.

Results

When Trp concentration was determined in the serum, liver, kidney, brain, and muscle of SD and analbuminemic rats 16 h after injection of AMT (5 mg/kg body weight), the results shown in Table 1 were obtained. The concentrations of total Trp and free Trp (protein-unbound) in the serum of Group B were 48 and 39%, respectively, of those in Group A. The concentrations of total Trp and free Trp in the serum of Group D were 58 and 60%, respectively, of those of Group C. Trp concentrations in the liver, brain, muscle, and kidney of Group B were 41, 54, 66, and 94%, respectively, of those of Group A. Trp concentrations in the liver, brain, muscle, and kidney of Group D were 39, 62, 81, and 95%, respectively, of those of Group C. Thus, Trp depletion was found in the serum, liver, brain, and muscle of Group B and Group D. The concentrations of Phe, Tyr, Val, Leu, and Ile which have been shown to be taken up into liver cells via the transport system common to Trp (Saito et al., 1986; Salter et al., 1986), were also determined in the serum of SD and analbuminemic rats 16 h after AMT treatment. In the serum of Group B, Phe, Leu, Ile, and Val concentrations significantly increased, while in the serum of Group D, only Leu and Val concentrations significantly increased (Table 2).

Table 1. Concentrations of serum, liver, kidney, brain, and muscle L-tryptophan (Trp) in Sprague-Dawley (SD) and analbuminemic rats with and without α-methyl-DL-tryptophan (AMT) treatment

	SD rats		Analbuminemic rats	
	Group A (−AMT)	Group B (+AMT)	Group C (−AMT)	Group D (+AMT)
Serum (nmol/ml)				
Total	64.6 ± 2.6	31.3 ± 4.3*	23.7 ± 1.6*	13.7 ± 3.2#§
Free (protein-unbound)	5.7 ± 2.5	2.2 ± 1.3*	20.5 ± 2.6*	12.2 ± 2.9#§
Liver (nmol/g tissue)	44.7 ± 5.5	18.1 ± 3.9*	36.3 ± 3.8*	14.1 ± 2.7#
Kidney (nmol/g tissue)	111.2 ± 26.7	105.5 ± 26.3	117.8 ± 15.5	111.9 ± 16.4
Brain (nmol/g tissue)	29.0 ± 1.2	15.6 ± 1.7*	22.1 ± 2.4*	13.7 ± 1.9#
Muscle (nmol/g tissue)	43.2 ± 8.6	28.5 ± 5.8*	34.2 ± 2.2*	27.6 ± 5.9#

SD and analbuminemic rats were intraperitoneally injected with AMT (5 mg/kg body weight) and sacrificed 16 h after AMT injection. Free serum Trp, i.e., protein-unbound serum Trp, was separated by centrifugation through an ultrafiltration membrane. Trp in serum, liver, kidney, brain, and muscle were determined using high-performance liquid chromatography. Each value is a mean ± S.D. (n = 4–10). *$p < 0.05$ (vs. Group A); §$p < 0.05$ (vs. Group B); #$p < 0.05$ (vs. Group C).

Table 2. Concentrations of serum L-phenylalanine, L-tyrosine, and branched-chain amino acids is Sprague-Dawley (SD) and analbuminemic rats with and without α-methyl-DL-tryptophan (AMT) treatment

	SD rats		Analbuminemic rats	
	Group A (−AMT)	Group B (+AMT)	Group C (−AMT)	Group D (+AMT)
	nmol/ml			
L-Phenylalanine	86.1 ± 3.4	102.5 ± 6.9*	125.2 ± 14.9*	126.6 ± 17.9
L-Tyrosine	96.4 ± 17.0	95.3 ± 12.0	84.5 ± 13.8	72.5 ± 8.8
L-Leucine	203.0 ± 8.4	272.9 ± 17.5*	241.5 ± 24.6*	295.8 ± 36.7#§
L-Isoleucine	147.8 ± 5.7	176.1 ± 8.2*	187.5 ± 19.6*	198.8 ± 25.7
L-Valine	234.7 ± 20.1	335.9 ± 13.4*	275.2 ± 27.2*	332.8 ± 36.6#

SD and analbuminemic rats were intraperitoneally injected with AMT (5 mg/kg body weight) and sacrificed 16 h after AMT injection. Serum L-phenylalanine, L-tyrosine, and branched-chain amino acids were determined in an amino acid analyzer. Each value is a mean ± S.D. (n = 5). *$p < 0.05$ (vs. Group A); §$p < 0.05$ (vs. Group B); #$p < 0.05$ (vs. Group C).

The rates of increases in serum Leu and Val concentrations in Group D were 120% each, and the rates of increases in serum Leu, Ile, Val, and Phe concentrations in Group B were between 110 and 140% (Table 2). In addition, serum Phe, Leu, Ile, and Val concentrations in Group C were significantly higher than those in Group A; serum Phe, Leu, Ile, and Val concentrations in Group C were 1.5-, 1.2-, 1.3-, and 1.2-fold, respectively, higher than those in Group A. As shown in Table 3, liver TDO and protein synthetic activities were similar

Table 3. Liver tryptophan 2,3-dioxygenase (TDO) and protein synthetic activities in Sprague-Dawley (SD) and analbuminemic rats with and without α-methyl-DL-tryptophan (AMT) treatment

	SD rats		Analbuminemic rats	
	Group A (−AMT)	Group B (+AMT)	Group C (−AMT)	Group D (+AMT)
TDO activity (μmol kynurenine/h/g tissue)	3.25 ± 0.57	3.58 ± 0.31	3.41 ± 0.49	3.44 ± 0.64
Protein synthetic activity (dpm × 10^{-3}/g tissue)	5,961 ± 1,161	5,800 ± 650	5,139 ± 439	5,000 ± 789

SD and analbuminemic rats were intraperitoneally injected with AMT (5 mg/kg body weight) and sacrificed 16 h after AMT injection. TDO activity in liver homogenates and protein synthetic activity in liver post-mitochondrial fractions were assayed in the presences of added haematin (2 μM) and [^{14}C]-L-leucine (18.5 KBq), respectively, at 37°C. Each value is a mean ± S.D. (n = 4–5).

in Group A and Group C, and there were no differences in both activities between Group A and Group B or between Group C and Group D.

When Trp (500 μmol/kg body weight) were orally administered to Group A and Group C, the pattern of increase in the total serum Trp concentration 15, 30, or 60 min after the administration was similar in both groups (Fig. 1). But, the total serum Trp concentration at 15, 30, or 60 min after Trp administration was significantly lower in Group C than in Group A, and there was a significant difference between the two groups in the rate of increase in total serum Trp concentration at 15 or 60 min after the administration (Fig. 1). There was no significant difference in free serum Trp concentration at 15, 30, or 60 min after Trp administration between Group A and Group C (Fig. 1). However, there was a significant difference in the rate of increase in free serum Trp concentration at 15, 30, or 60 min after the administration between both groups (Fig. 1). There were no differences in liver, brain, and muscle Trp concentrations and in the rates of increases in liver, brain, and muscle Trp concentrations at 15, 30, or 60 min after Trp administration between Group A and Group C (Fig. 2). But, there were significant differences in liver, brain, and muscle Trp concentrations determined just before the administration between both groups (Fig. 2).

When Trp (500 μmol/kg body weight) was orally administered to Group B and Group D, the pattern of increase in the total serum Trp concentration over a 60 min period after the administration was similar in both groups, but the rate of increase in total serum Trp concentration in Group D was much smaller than that in Group B (Fig. 3). There was no significant difference in the free serum Trp concentration after Trp administration between Group B and Group D, although there was a significant difference in total serum Trp concentration after the administration (Fig. 3). Liver Trp concentration and

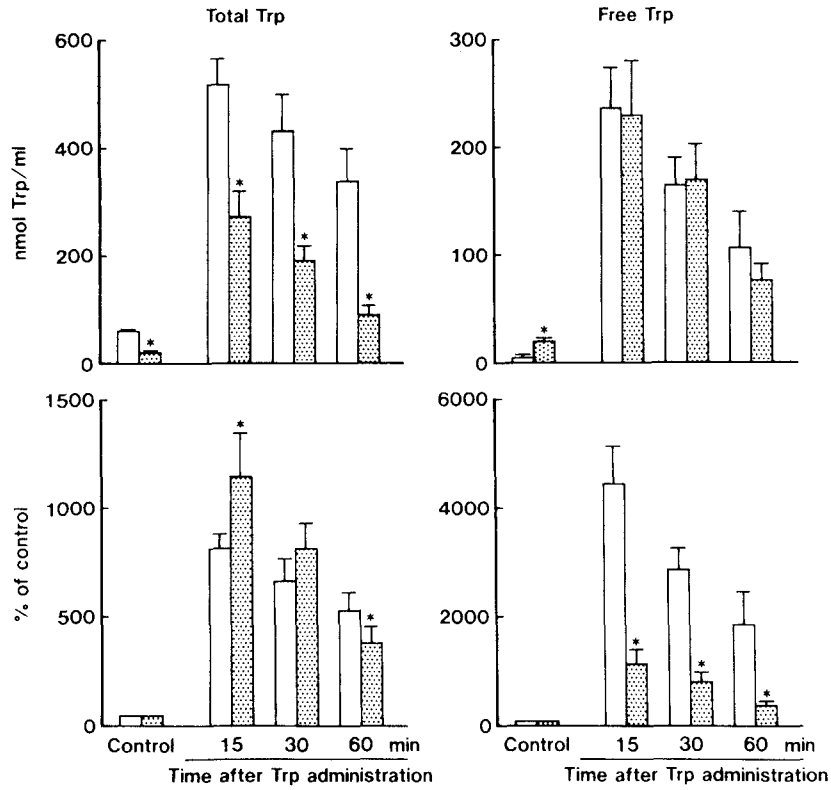

Fig. 1. Changes in total and free L-tryptophan (*Trp*) concentrations in the serum of Sprague-Dawley (SD) and analbuminemic rats after oral Trp administration. Group A of Trp-undepleted SD rates (open bar) and Group C of Trp-undepleted analbuminemic rats (dotted bar) were orally administered with Trp (500μmol/kg body weight). Total and free (protein-unbound) Trp in the serum were determined using high-performance liquid chromatography. Each value is a mean ± SD (n = 4–10). *, $p < 0.05$ (Vs. Group A)

the rate of increase in that concentration at 15, 30, or 60min after Trp administration were significantly less in Group D than in Group B (Fig. 4). Brain Trp concentration at 15, 30, or 60min after Trp administration was significantly less in Group D than in Group B and the rate of increase in that concentration at 30min after the administration was significantly less in Group D than in Group B (Fig. 4). Muscle Trp concentration and the rate of increase in that concentration at 30 or 60min after Trp administration were significantly less in Group D than in Group B (Fig. 4). The ratio of brain or muscle Trp concentration at 15, 30, or 60min after Trp administration in Group D to the corresponding Trp concentration after the administration in Group B was between 0.70 and 0.78 (Fig. 4). In contrast, the ratio of liver Trp concentration at 15, 30, or 60min after Trp administration in Group D to the corresponding Trp concentration after the administration in Group B was between 0.48 and 0.64 (Fig. 4). Thus, the ratio for brain or muscle Trp concentration after Trp administration was larger than that for liver Trp concentration after the administration.

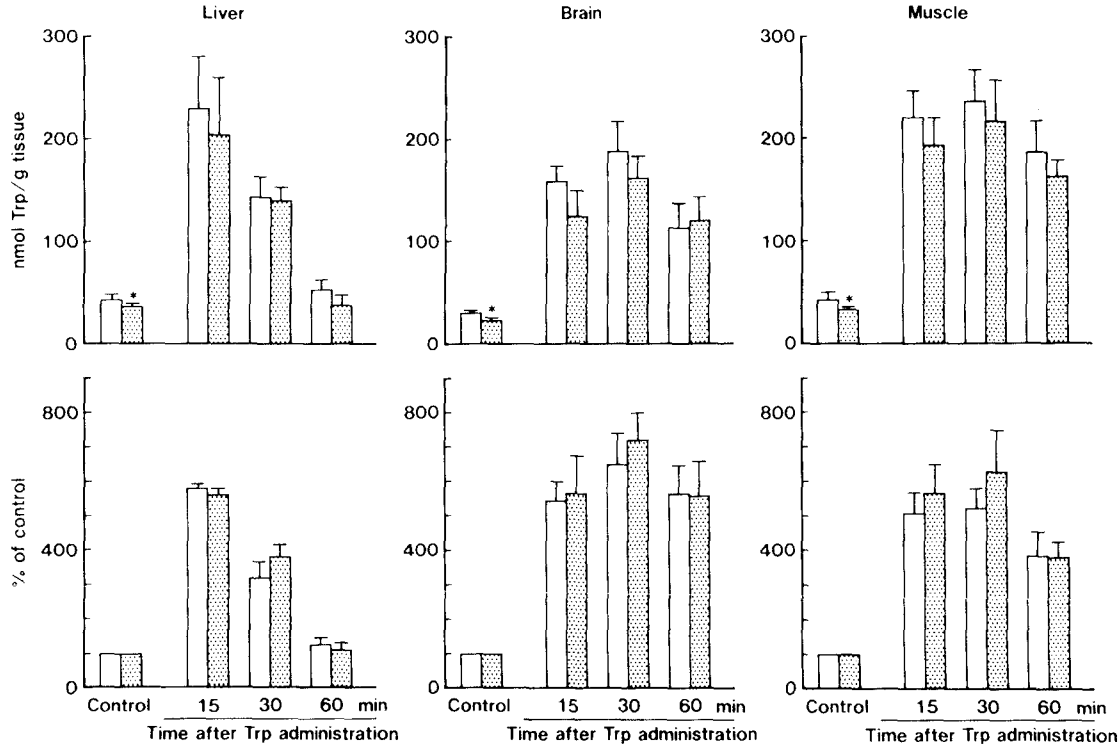

Fig. 2. Changes in L-tryptophan (*Trp*) concentrations in the liver, brain, and muscle of Sprague-Dawley (SD) and analbuminemic rats after oral Trp administration. Group A of Trp-undepleted SD rats (open bar) and Group C of Trp-undepleted analbuminemic rats (dotted bar) were orally administered with Trp (500μmol/kg body weight). Trp in the liver, brain, and muscle was determined using high-performance liquid chromatography. Each value is a mean ± SD (n = 3–6). *, $p < 0.05$ (Vs. Group A)

Discussion

As described in the Introduction, the role of serum albumin in the transport of orally administered Trp into rat livers has not yet been clarified. In the present study, therefore, we attempted to clarify the role of serum albumin in the transport of orally administered Trp into the liver of rats with and without Trp depletion.

It has been shown that in SD rats injected with AMT, liver TDO activity is increased through inhibition of the degradation of the enzyme, resulting in Trp depletion in the liver, brain, and blood (Moran and Sourkes, 1963; Oravec and Sourkes, 1970; Sourkes et al., 1970). It is also known that inhibition of liver protein synthesis occurs in SD rats treated with a large dose of AMT (above 2mg/kg body weight, i.p.) (Oravec and Sourkes, 1970). We have also reported that in Wistar rats treated with AMT (2mg/kg body weight, i.p.), Trp depletion occurs in the serum and liver without changes in TDO and protein synthetic activities in the liver at 16h after the treatment (Ohta et al., 1992). In addition, our previous report has demonstrated that in analbuminemic rats treated with AMT (5mg/kg body weight, i.p.), Trp depletion occurs in the

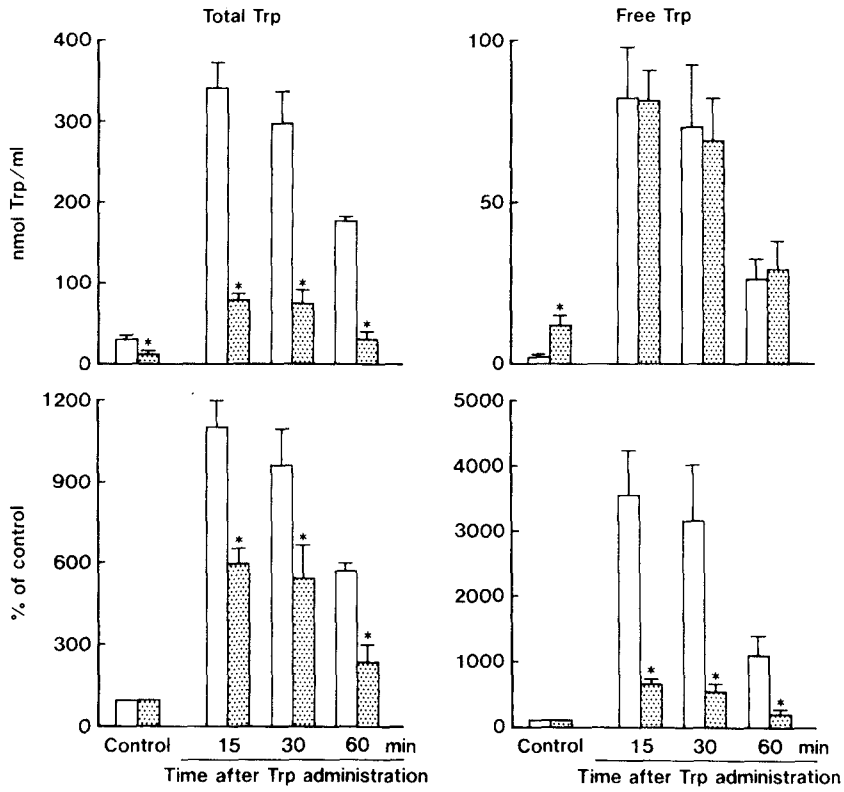

Fig. 3. Changes in total and free L-tryptophan (*Trp*) concentrations in the serum of Sprague-Dawley (SD) and analbuminemic rats after oral Trp administration under Trp depletion. Trp depletion was induced by treatment with α-methyl-DL-tryptophan (AMT) (5 mg/kg body weight, i.p.). Group B of AMT-treated SD rats (open bar) and Group D of AMT-treated analbuminemic rats (dotted bar) were orally administered with Trp (500 μmol/kg body weight). Total and free (protein-unbound) Trp in the serum was determined using high-performance liquid chromatography. Each value is a mean ± SD (n = 3–5). *, $p < 0.05$ (Vs. Group B)

serum and liver without changes in liver TDO activity at 16 h after the treatment (Sasaki et al., 1992). In the present study, SD and analbuminemic rats treated with AMT (5 mg/kg body weight, i.p.) showed Trp depletion in the serum, liver, brain, and muscle, but not the kidney, at 16 h after the treatment. Furthermore, as with the Trp-undepleted condition, no differences were observed in liver TDO and protein synthetic activities between SD and analbuminemic rats under this AMT-induced Trp depletion. This finding indicates that in both SD and analbuminemic rats, administered Trp is similarly metabolized and utilized for protein synthesis in the liver regardless of the presence or absence of Trp depletion in the tissue.

We first attempted to clarify the role of serum albumin in the transport of orally administered Trp into the liver of rats without Trp depletion. There were no differences in free serum Trp concentrations determined over a 60 min period after the oral administration of Trp (500 μmol/kg body weight) between SD and analbuminemic rats. The total serum Trp concentrations

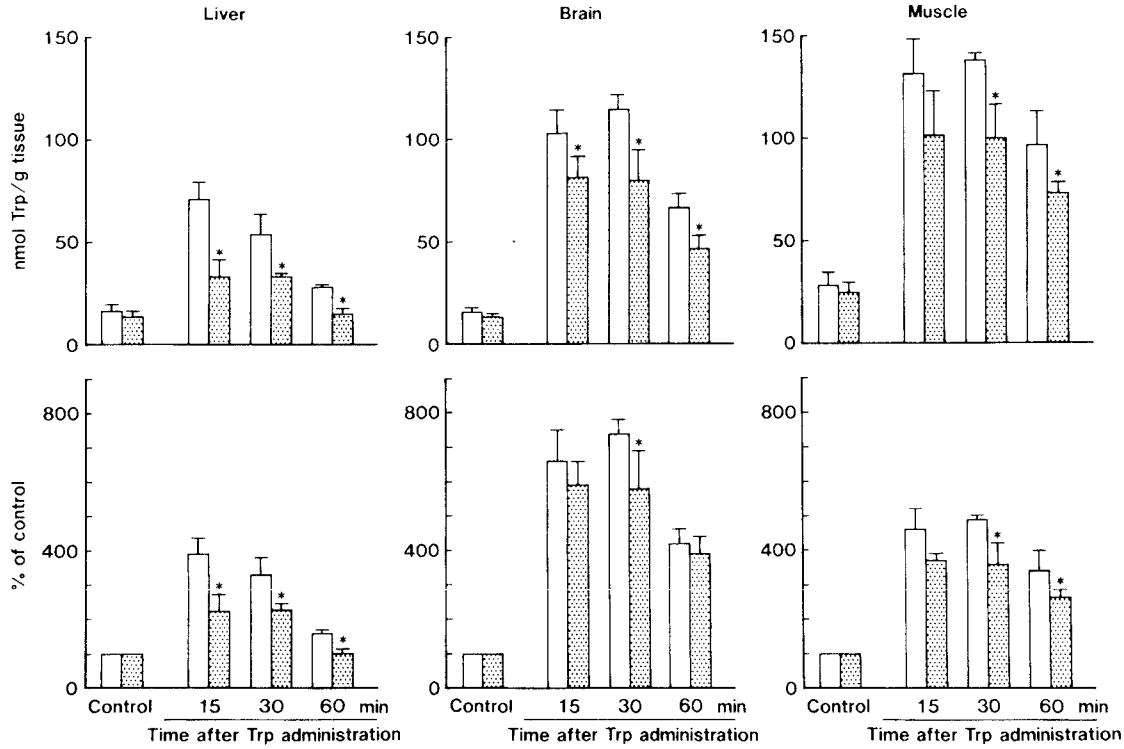

Fig. 4. Changes in L-tryptophan (*Trp*) concentrations in the liver, brain, and muscle of Sprague-Dawley (SD) and analbuminemic rats after oral Trp administration under Trp depletion. Trp depletion was induced by treatment with α-methyl-DL-tryptophan (AMT) (5 mg/kg body weight, i.p.). Group B of AMT-treated SD rats (open bar) and Group D of AMT-treated analbuminemic rats (dotted bar) were orally administered with Trp (500 μmol/kg body weight). Trp in the liver, brain, and muscle was determined using high-performance liquid chromatography. Each value is a mean $\pm$ SD (n = 3–8). *, $p < 0.05$ (Vs. Group B)

during the same period, however, were much lower in analbuminemic rats than in SD rats. Emori et al. (1983) have also reported similar changes in total plasma Trp concentrations after the oral administration of Trp (200 mg/kg body weight) in SD and analbuminemic rats. In the present study, it was found that there were no differences in liver, brain, and muscle Trp concentrations determined over a 60 min period after oral Trp administration between SD and analbuminemic rats. However, liver, brain, and muscle Trp concentrations measured just before the Trp administration were slightly lower in analbuminemic rats than in SD rats. These results indicate that variations in the serum albumin level have little influence on the transport of orally administered Trp into the liver of rats without Trp depletion.

We next attempted to clarify the role of serum albumin in the transport of orally administered Trp into the liver of rats with Trp depletion. There were no differences in free serum Trp concentrations determined over a 60 min period after the oral administration of Trp (500 μmol/kg body weight) between SD and analbuminemic rats under the above-described AMT-

induced Trp depletion. But, the total serum Trp concentrations during the same period were much lower in analbuminemic rats than in SD rats. In contrast with the case without Trp depletion, liver, brain, and muscle Trp concentrations determined over a 60 min period after oral Trp administration under Trp depletion were significantly lower in analbuminemic rats than in SD rats. In addition, the ratio of liver Trp concentration in Trp-administered analbuminemic rats to that concentration in Trp-administered SD rats was smaller than that of brain or muscle Trp concentration. These results suggest that in rats with Trp depletion, variations in the serum albumin level could affect the transport of orally administered Trp into the liver more strongly than that into the brain or muscle.

It is known that aromatic amino acids such as Phe and Tyr or branched-chain amino acids such as Leu, Ile, and Val are transported into the liver via the transport system common to Trp (Saito et al., 1986; Salter et al., 1986). In the present study, Phe, Leu, Ile, and Val concentrations in the serum of analbuminemic rats were found to be 1.5-, 1.2-, 1.3-, and 1.2-fold, respectively, higher than those in SD rats in a Trp-undepleted condition. This result was not consistent with that reported by Emori et al. (1983), which showed no differences in concentrations of serum aromatic and branched-chain amino acids between SD and analbuminemic rats in a Trp-undepleted condition. The reason for this discrepancy is not clear at present. Under the above-described AMT-induced Trp depletion, serum Leu and Val concentrations were increased by 20% in analbuminemic rats, while serum Phe, Leu, Ile, and Val concentrations were increased by 10 to 40% in SD rats. As described above, there were no differences in free serum and liver Trp concentrations after oral Trp administration in a Trp-undepleted condition between SD and analbuminemic rats, although analbuminemic rats had 1.2- to 1.5-fold higher concentrations of serum aromatic and branched-chain amino acids than did SD rats. These findings may allow use to assume that in both SD and analbuminemic rats, the increases in concentrations of serum aromatic and branched-chain amino acids found under AMT-induced Trp depletion do not have a large influence on the transport of orally administered Trp into the liver.

It appears possible that differences in the rate and/or mode of intestinal absorption of orally administered Trp and/or of hepatic uptake of the absorbed Trp between SD and analbuminemic rats under Trp depletion result in different increases in serum (total), liver, brain, and muscle Trp concentrations after oral Trp administration. Emori et al. (1983) have demonstrated that the passage of Trp through the intestinal wall and its transport in the blood are similar in SD and analbuminemic rats in a Trp-undepleted condition. We have shown that the rate and mode of Trp uptake by isolated liver cells are similar in SD and analbuminemic rats in a Trp-undepleted condition (Sasaki et al., 1991). Accordingly, it is conceivable that under Trp depletion, the rate and/or mode of intestinal absorption of orally administered Trp and/or of hepatic uptake of the absorbed Trp are similar in SD and analbuminemic rats. However, further investigation is necessary to clarify this matter.

In conclusion, the results obtained in the present study suggest that variations in serum albumin levels could affect the transport of orally administered Trp into the liver of rats with Trp depletion, but not without Trp depletion, probably through its binding to the amino acid.

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