Tryptophan Catabolism by Tryptophan Pyrrolase in Rat Liver

THE EFFECT OF TRYPTOPHAN LOADS AND CHANGES IN TRYPTOPHAN PYRROLASE ACTIVITY*

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SUMMARY

We investigated how changes in tryptophan pyrrolase activity and tryptophan loads affect the breakdown of tryptophan by tryptophan pyrrolase. Breakdown of tryptophan was estimated by injecting rats with [ring-2-14C]tryptophan and measuring respiratory 14CO2. We concluded, contrary to previous reports, that induction of tryptophan pyrrolase definitely will increase the rate of tryptophan breakdown. Tryptophan loads also increase tryptophan breakdown even in circumstances where there is no increase in tryptophan pyrrolase activity, presumably by increasing the saturation of the enzyme. After a tryptophan load (50 mg per kg) the increase in liver tryptophan concentration lasts only 30 min. The rapid return of liver tryptophan to normal may be due partly to the high turnover rate of liver tryptophan. We estimate that tryptophan pyrrolase degrades tryptophan in vivo at a rate that is equivalent to the whole liver tryptophan concentration in 7.5 min or less.

It is 23 years since Knox (1) showed that tryptophan pyrrolase (L-tryptophan: oxygen oxidoreductase, EC 1.13.11.11) is induced by adrenal cortical hormones. However, it is still uncertain whether or not the increase in enzyme activity brought about by cortisol causes an increase in the rate of tryptophan degradation. The common assumption that a rise in tryptophan pyrrolase activity would increase the rate of tryptophan catabolism was first challenged by Kim and Miller (2). They showed that in the isolated perfused rat liver induction of tryptophan pyrrolase with hydrocortisone did not alter the rate of clearance of a load of tryptophan from the perfusate or increase the rate of accumulation of kynurenine. Also, using the in vivo tryptophan pyrrolase assay of Madras and Sourkes (3), which involves injecting rats with labeled tryptophan and measuring respiratory 14CO2, they found that severalfold increases in tryptophan pyrrolase activity, induced by treatment of rats with cortisol or tryptophan, were associated with at most a 20% increase in the dose of labeled tryptophan that is converted to 14CO2. However, under conditions in which the enzymatic activity was already maximal after a tryptophan load, a further increase in the dose of tryptophan caused a substantial increase in the conversion of labeled tryptophan to 14CO2. They concluded from this that substrate concentration and not enzyme activity was the factor controlling tryptophan catabolism. Their conclusion is supported by work of Powanda and Wannemacher (4) who measured the concentration of NAD, a metabolite of tryptophan down the pathway initiated by tryptophan pyrrolase, in the livers of mice treated with either cortisol or tryptophan. They found that a tryptophan load increased hepatic NAD whereas cortisol did not.

Other reports support the idea that cortisol can increase the rate of tryptophan catabolism. Joseph (5) found an increase in 14CO2 output from labeled tryptophan after cortisol administration. Llamas and Vichido (6) reported that cortisol causes a small but significant increase in mouse liver pyridine nucleotides. Formate derived from tryptophan catabolism is used in purine biosynthesis in the mouse, and cortisol treatment increases the rate of utilization of tryptophan for this process (7).

We have reinvestigated this problem, in order to determine whether changes in tryptophan pyrrolase activity do affect the rate at which the enzyme catabolizes tryptophan and, if possible, to reconcile the apparently contradictory results described above.

MATERIALS AND METHODS

Chemicals—DL-[ring-2-14C]tryptophan and DL-[methylene-14C]tryptophan were obtained from International Chemical and Nuclear Corp. Specific activity was adjusted to 2.0 mCi per mmol, if necessary by addition of cold DL-tryptophan. DL- and L-Tryptophan, αMeTrp,1 hydrocortisone 21-sodium succinate, hereafter referred to as cortisol, and methemoglobin were from Sigma; deuterated globin was from Nutritional Biochemicals Corp.

Animals—Intact and adrenalectomized male Sprague-Dawley rats (120 to 130 g) were obtained from Canadian Breeding Farm and Laboratories, Ltd., St. Constant, Quebec.

In Vivo Assay of Tryptophan Pyrrolase—The in vivo assay of tryptophan pyrrolase was performed as described by Madras and Sourkes (3) with the modifications of Young et al. (8). Rats were injected with labeled tryptophan (5 μCi per kg). Respiratory 14CO2 was trapped in an ethylene glycol monomethyl ether-ethanolamine solution and counted. Tryptophan pyrrolase seems to be the rate-limiting factor in the production of 14CO2 from labeled tryptophan (8-10).

In Vitro Assay—Total tryptophan pyrrolase (apoenzyme + holoenzyme) was measured by the method of Knox et al. (11) with the modifications described previously (8). To determine only the enzyme conjugated to heme (holoenzyme) we used the method of Knox and Piras (12). In these assays a fraction of a 25% liver homogenate obtained by centrifugation at 100,000 × g was used.

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1 The abbreviation used is: αMeTrp, DL-α-methyltryptophan.

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was preincubated either with methemoglobin to conjugate apo-
enzyme, or with globin to bind any endogenous heme which might
otherwise conjugate apoenzyme. The appearance of kynurenine
was measured spectrophotometrically. Tryptophan pyrrolase
activity is expressed in units (micromoles of kynurenine formed
per hour per g of liver).

Liver tryptophan was determined by the method of Denekla
and Dewey (13) and liver radioactivity as described previously
(8).

Chromatography of Liver Extracts—Chromatography of liver ex-
tracts was performed as described previously (8). In this method
the liver extract was treated with ethanol to precipitate proteins.
The protein-free extract was concentrated by evaporation under a
stream of nitrogen and spotted on Whatman No. 3MM chroma-
tography paper. Descending chromatograms were run using butan-
el-1/0.1 acetic acid/water (4:1:5). After chromatography the paper
strips were dried and cut into 1-cm lengths which were put in
counting vials with 5 ml of toluene containing 5 g of 2,5-diphenyl-
oxazole per liter.

RESULTS

Effect of Cortisol on Production of Respiratory 14CO2 from Labeled
Tryptophan—When rats were pretreated with cortisol the total
production of 14CO2 from [methylene-14C]tryptophan over 5 hours
was increased by 36%. However, when rates of 14C02 production
were plotted as a function of time (Fig. 1), it was evident that
the effect of cortisol is not uniform over the whole 14CO2 collec-
tion period. Its effect was greatest between 0.5 and 1 hour after
labeled tryptophan administration, when the increase in 14CO2 is
111%. By 3 hours after injection of labeled tryptophan the effect
of cortisol had disappeared.

When the same experiment was repeated with [ring-2-14C]-
tryptophan instead of [methylene-14C]tryptophan the effect of cor-
tisol was greater. The total accumulation over 5 hours in-
creased over the control value by 150% and the rate of 14CO2 pro-
duction between 0.25 and 0.5 hour after labeled tryptophan
administration increased by 170% (Fig 2). While this 170% in-
crease in tryptophan pyrrolase activity over control values
measured in vivo is not as great as the 260% increase in the con-
jugated enzyme measured in vitro after cortisol (Table I), it does
indicate that an increase in tryptophan pyrrolase activity can
increase the rate of tryptophan degradation.

Effect of αMeTrp and Tryptophan Loads on Tryptophan Pyr-
rolase Activity—To investigate further the effect of increases of
pyrrolase activity we used rats that had been pre-
treated with αMeTrp. In this experiment αMeTrp was used to
induce tryptophan pyrrolase because, unlike cortisol, it not only
causes increased synthesis of the enzyme, but also causes enzyme
protein already present to conjugate with heme (14). Tryptophan
has the same effect (14), so a tryptophan load would not be ex-
pected to increase conjugated enzyme in αMeTrp-pretreated
rats, as it would in cortisol-pretreated rats. Nevertheless, some
of these animals were also given tryptophan loads to see how this
might affect their 14CO2 production from labeled tryptophan.
Thus, adrenalectomized rats were pretreated (65 hours) with
αMeTrp (100 mg per kg) or 0.9% NaCl solution. Half of each
group were given a load of tryptophan (50 mg per kg) at zero
time with the labeled tryptophan and 14CO2 was collected for 1
hour. The results are shown in Fig. 3. This experiment was per-
formed on three separate occasions with a total of eight rats.

Table I

|                      | Control | Cortisol pretreatment | % of Control | P  |
|----------------------|---------|-----------------------|--------------|----|
| 14CO2 release at 0.5 hr (%/hr) |         |                       |              |    |
| Conjugated trypto-
| phan pyrrolase (units) | 0.56 ± 0.08 | 2.04 ± 0.06 | 360 <0.001 |
| Injected 14C (%/g liver) | 0.119 ± 0.009 | 0.128 ± 0.010 | 106 >0.05   |
| Tryptophan (μg/g liver) | 8.18 ± 0.41 | 5.12 ± 0.18 | 63 <0.001   |

* Probability of difference between treated and control rats.

** Units are micromoles of kynurenine formed per hour per g of liver (wet weight).
formed with adrenalectomized rats to decrease the variability of results. When it was repeated with normal rats that had been starved for 15 hours before the experiment, similar results were obtained (Fig. 4). The only differences were that, as expected, \(^{14}\text{CO}_2\) production was slightly greater and the standard errors were larger.

As in the experiment in which cortisol was given, an increase in tryptophan pyrrolase caused increased tryptophan catabolism, when the labeled tryptophan was administered either alone or with a tryptophan load. A tryptophan load also causes elevated \(^{14}\text{CO}_2\) production both in rats with normal amounts of tryptophan pyrrolase and in those with elevated concentrations owing to the \(\alpha\)-MeTrp treatment.

**In Vitro Measurements of Tryptophan Pyrrolase, Tryptophan, and Radioactivity in Rat Liver**—The rate of tryptophan degradation is not the only factor that might affect \(^{14}\text{CO}_2\) production. The uptake of labeled tryptophan into the liver and the specific activity attained will also be of importance. To see how much the variations in \(^{14}\text{CO}_2\) output described above could be attributed to these different factors we performed an experiment similar to the one described above. Adrenalectomized rats were pretreated with \(\alpha\)-MeTrp or saline solution. Half of each group received a tryptophan load, including the labeled amino acid. The rats were killed 1 hour after receiving the labeled tryptophan, the collection of \(^{14}\text{CO}_2\) being omitted. Tryptophan pyrrolase and radioactivity were measured in the livers. Tryptophan was also measured in the livers of rats pretreated with saline solution. It was not possible to measure tryptophan in the \(\alpha\)-MeTrp-pretreated rats because \(\alpha\)-MeTrp, as well as tryptophan, is detected by the method of Denckla and Dewey (13). The results are shown in Table II.

In rats pretreated with either saline solution or \(\alpha\)-MeTrp, a tryptophan load did not increase the total (apo + holoenzyme) tryptophan pyrrolase within an hour. However, in saline-pretreated rats there was an increase in the conjugated enzyme. This was not so in \(\alpha\)-MeTrp-pretreated rats, where the \(\alpha\)-MeTrp had already increased the extent of conjugation maximally. A tryptophan load also increased the radioactivity found in the liver in both groups of rats.

When rats pretreated with \(\alpha\)-MeTrp and saline solution, respectively, were compared, again \(\alpha\)-MeTrp increased both total and conjugated tryptophan pyrrolase. In these rats with high tryptophan pyrrolase there is also significantly more \(^{14}\text{C}\) in the livers. However, the increase is small, of the order of 23%.

It may be noted that a tryptophan load does not cause a significant increase in liver tryptophan at least at 1 hour (Table II). However, the increased conjugation of tryptophan pyrrolase

![](image1.png)

**Fig. 3.** The effect of \(\alpha\)-MeTrp and tryptophan loads on \(^{14}\text{CO}_2\) production from \([\text{ring-2-}\text{14C}]\text{tryptophan in adrenalectomized rats. Adrenalectomized rats were given a tracer dose of } [\text{ring-2-}\text{14C}]\text{tryptophan 65 hours after intraperitoneal injections of either saline solution} (---) or \(\alpha\)-MeTrp (100 mg per kg) (-----). Other groups of rats received a tryptophan load (50 mg per kg) with the labeled tryptophan 65 hours after the saline solution (---) or \(\alpha\)-MeTrp (-----). The \(^{14}\text{CO}_2\) was collected as described under "Materials and Methods." Each point represents the mean for six rats ± standard error.

![](image2.png)

**Fig. 4.** The effect of \(\alpha\)-MeTrp and tryptophan loads on \(^{14}\text{CO}_2\) production from \([\text{ring-2-}\text{14C}]\text{tryptophan in normal rats. This experiment was performed in the manner described in Fig. 3 except that normal rats were used instead of adrenalectomized."

**Table II**

**Effect of \(\alpha\)-MeTrp and tryptophan on rat liver tryptophan pyrrolase activity and tryptophan concentrations**

Adrenalectomized rats were injected intraperitoneally with saline solution or \(\alpha\)-MeTrp (100 mg per kg) 65 hours before labeled tryptophan. Tryptophan loads (50 mg per kg) were given with the labeled tryptophan. Half an hour after the labeled tryptophan the rats were killed and the liver tryptophan pyrrolase, radioactivity, and tryptophan concentrations were measured as described under "Materials and Methods." All values are given as mean ± standard error (six determinations).

|                      | Control | Tryptophan load | Control | Tryptophan load |
|----------------------|---------|-----------------|---------|-----------------|
| **Tryptophan pyrrolase (units)** |         |                 |         |                 |
| Total                | 2.15 ± 0.20 | 2.42 ± 0.08 | 6.05 ± 0.62 | 6.53 ± 0.38 |
| Conjugated           | 0.45 ± 0.07 | 0.84 ± 0.16 | 2.01 ± 0.01 | 2.27 ± 0.41 |
| % conjugated         | 21       | 35              | 30       | 29              |
| Administered \(^{14}\text{C}\) (%/g liver) | 0.162 ± 0.004 | 0.294 ± 0.008 | 0.197 ± 0.012 | 0.368 ± 0.018 |
| Tryptophan (µg/g liver) | 8.67 ± 0.70 | 9.13 ± 0.21 |

* Units are micromoles of kynurenine formed per hour per g of liver (wet weight).
found of 6.1 =t 0.2 g (12 determinations) we can calculate that the whole liver will contain 0.50% of the administered r4C as labeled tryptophan. This is being broken down to 14C02 which, in turn, is being expired at the rate of 1.95% of the administered 14C per hour. Thus, in 15 min the amount of 14CO2 expired will be equal to the total [14C]tryptophan content of the liver.

The normal tryptophan content of the liver is 8.18 μg per g (Table I), which gives a total liver tryptophan content of 49.8 μg. Thus, if the rate of tryptophan degradation is equivalent to the tryptophan content of the liver per 15 min this gives a rate of tryptophan degradation in vivo of 3.3 μg per min for the total liver tryptophan pyrrolase. This estimate is probably too low, as some of the [14C]formate released from the tryptophan by the action of tryptophan pyrrolase and formamidase (aryl-formylaminoaminohydrolase, EC 3.5.1.9) will be incorporated into the 1-carbon pool. We have found that about one-half of the 14C in labeled formate injected into a rat is released as 14CO2 (8). If we assume that one-half of the labeled formate derived in metabolism from tryptophan is released as 14CO2, the rate of tryptophan degradation in the whole rat liver would be about 7 μg per min (35 nmol per min). This activity would consume an amount of tryptophan equal to the total of liver tryptophan content in 7.5 min.

We chose this interval as it was the time of maximum 14C02 production. In cortisol-pretreated rats the r4C in the liver was not significantly changed, but there was a significant decrease in the liver tryptophan concentration.

Liver Content of [ring-2-14C]Tryptophan—Measurement of the liver content of tryptophan and 14C will not, alone, give a measure of the specific activity of liver tryptophan, as we have shown previously that not all the 14C is associated with tryptophan (8). Therefore, rats were treated as described in the previous section except that they received 30 μCi per kg instead of 5 μCi per kg. Liver extracts were chromatographed as described under "Materials and Methods." In this case the experiment was performed in the same way as the in vivo cortisol experiment except that the rats were killed 0.5 hour after the injection of labeled tryptophan.

We chose this interval as it was the time of maximum 14C02 production. In cortisol-pretreated rats the r4C in the liver was not significantly changed, but there was a significant decrease in the liver tryptophan concentration.

The graphs show the counts per min in 1-cm lengths of paper chromatogram obtained by chromatographing liver extracts of rats that had been injected with cortisol (50 mg per kg) (above) or saline solution (below) 4.5 hours previously and with [ring-2-14C]tryptophan 0.5 hours previously. Experimental details are given under "Materials and Methods."

### Table III

| Pretreatment          | Compound       | Time  | Tryptophan load | Radioactivity as tryptophan |
|-----------------------|----------------|-------|-----------------|-----------------------------|
| Normal                | Saline         | 65    | -               | 65                          |
| Adrenalectomized      | Saline         | 65    | +               | 34                          |
| Adrenalectomized      | aMeTrp         | 65    | -               | 35                          |
| Adrenalectomized      | aMeTrp         | 65    | +               | 18                          |
| Normal                | Saline         | 4     | -               | 70                          |
| Normal                | Cortisol       | 4     | -               | 50                          |
The in vitro assay of tryptophan pyrrolase gives the activity of the conjugated enzyme as 0.45 unit (micromoles of kynurenine formed per hour per g of liver). This is equivalent to a total tryptophan catabolizing capacity for the liver of about 10 μg per min (50 nmol per min).

**DISCUSSION**

One of the aims of this work was to determine if an increase in tryptophan pyrrolase activity will lead to an increase in tryptophan breakdown. Our results clearly indicate that tryptophan breakdown is increased in rats whose tryptophan pyrrolase has been induced with cortisol. Although this conclusion is in disagreement with that of Kim and Miller (2) we do not dispute their results. Kim and Miller found that cortisol-treated rats converted 20% more [methylene-14C]tryptophan to 14CO2 than control rats, over 6 hours. Collecting the 14CO2 over 5 hours we found a somewhat larger, although qualitatively similar value of 36% (Fig. 1). When we used [ring-2-14C]tryptophan this value increased to 100% with a peak rate of 14CO2 production half an hour after the labeled tryptophan injection of 170% more than the control (Fig. 2).

We feel that results obtained with the ring-labeled tryptophan are more appropriate to answer the question of the relation of pyrrolase activity to the rate of tryptophan catabolism in vivo than those obtained with the compound labeled in the side chain because the ring-14C has a much shorter pathway to 14CO2. Thus, the 14C in [ring-2-14C]tryptophan is converted to labeled formate by the action of tryptophan pyrrolase and formamidase. The pathway from formate to CO2 is not firmly established, but liver homogenates can oxidize formate to CO2 in a system that requires Mg2+, ATP, NADP+, and tetrahdrofolic acid (15). The pathway from [methylene-14C]tryptophan is much longer. The 14C is split off kynurenine or 3-hydroxykynurenine as the methyl group of alanine. This is then transaminated to pyruvate which is oxidized to CO2.

We also suggest that results obtained at short time intervals after labeled tryptophan administration are more valid than those obtained by collecting 14CO2 over long periods. Our calculations indicate that there is a high rate of turnover of tryptophan in the liver. In such a situation the estimate of the rate of 14CO2 production at long time intervals after labeled tryptophan injection would probably depend more on the specific activity of the liver tryptophan than on the rate of tryptophan catabolism.

Results obtained using [ring-2-14C]tryptophan and 14CO2 collection for only half an hour indicate that cortisol does increase tryptophan breakdown. However, after cortisol administration the rate of CO2 production does not increase as much as the conjugated tryptophan pyrrolase activity measured in vitro. This may be due partly to the decline in liver tryptophan concentration (Table I). The normal liver tryptophan concentration of 8.18 μg per g of liver is equivalent to about 50 μM. However, in vitro tryptophan pyrrolase does not reach saturation until the tryptophan concentration is above 1 mM (16).

The experiments in Figs. 3 and 4 show that tryptophan loads, as well as increases in tryptophan pyrrolase activity, raise the rate of tryptophan catabolism. Some of the rats that received tryptophan loads had been pretreated with αMeTrp, a compound which promotes conjugation of the enzyme with heme (14). Thus, the tryptophan load does not increase the conjugation of the enzyme any further after αMeTrp (Table II). Despite this, tryptophan degradation is increased (Fig. 3). Hence we agree with Kim and Miller (2) when they concluded that tryptophan loads could increase tryptophan breakdown even under circumstances in which tryptophan pyrrolase did not increase.

The conclusions reached above depend on the acceptance of 14CO2 evolution from [ring-2-14C]tryptophan as an index of tryptophan breakdown by tryptophan pyrrolase. Although this has been commonly assumed there is another factor in addition to the rate of tryptophan catabolism that could affect 14CO2 production. This is the specific activity of the liver tryptophan, which will depend on the uptake of the radioactive tryptophan into the liver, and its dilution by endogenous cold tryptophan. For this reason we measured the concentrations of tryptophan and radioactivity in the liver (Tables I and II). We also determined by paper chromatography the portion of the label that was attributable to unmetabolized tryptophan (Fig. 6). This decreases with increasing 14CO2 production (Table III). The fact that a higher percentage of the radioactivity is associated with metabolic products when 14CO2 release is high is additional evidence that 14CO2 release is an index of tryptophan breakdown.

Thus, in cortisol-treated rats, 0.5 hour after the labeled tryptophan injection, 67% more of the radioactivity is due to metabolites than in controls. This supports the conclusion that cortisol does increase tryptophan breakdown.

In adrenalectomized rats a tryptophan load causes a significant increase (p < 0.001) in the liver radioactivity (Table II). However, using the values in Table III for the portion of radioactivity that is due to labeled tryptophan, the controls of Table II would have 0.11%, the tryptophan-treated rats 0.10% of the administered 14C per g liver as tryptophan. As there is no change in the radioactive tryptophan or in the tryptophan concentration, the specific activity of the tryptophan remains unchanged. The same is true for the effect of cortisol on normal rats. In this case cortisol decreases both the liver tryptophan and labeled tryptophan concentrations. The specific activity remains the same, and thus 14CO2 output alone is a valid index of tryptophan breakdown in both these situations.

From our results we calculated a rate of tryptophan breakdown by tryptophan pyrrolase in normal rats, under the circumstances of our experiments of about 7 μg per min (35 nmol per min). This value will be only approximate because of assumptions made in calculating it. The main assumption is the percentage of endogenously derived formate that is converted to 14CO2; this could well be less than 50%. Thus our value will set an approximate lower limit for the rate of tryptophan catabolism. It is likely that tryptophan is being broken down in the liver at a rate equal to its content in the whole liver every 7.5 min or faster. This means that the liver tryptophan must have a very high turnover rate.

After a tryptophan load the liver tryptophan concentration is back to normal within 30 min (Fig. 5) in contrast to the brain tryptophan which has not started to decline by 1 hour (17). The functional tryptophan pyrrolase activity will be increased after a tryptophan load both by an increase in the conjugation with heme and by an increase in saturation with substrate. In view of the high rate of tryptophan breakdown in the liver relative to its total tryptophan content it may be that the excess tryptophan in the liver is rapidly broken down. After cortisol treatment tryptophan pyrrolase is elevated and the liver tryptophan declines. Further work will be necessary to determine how much of this decline is due to an increased rate of catabolism and how much to other factors.

The liver tryptophan concentration can affect tryptophan pyrrolase activity, and this work indicates that the enzyme may affect the concentration of its substrate. These two effects would act to stabilize the liver tryptophan concentration. Thus a high
liver tryptophan concentration increases the enzymic activity to speed tryptophan breakdown, while a high tryptophan pyrrolase activity may lower the liver tryptophan concentration, thus decreasing both the rate of tryptophan catabolism and the active enzyme concentration.

Understanding the factors that control tryptophan breakdown in the liver should help in determining under what circumstances tryptophan pyrrolase can affect other metabolic processes. Thus Bloxam, Warren, and White (18) have shown that the stimulation of gluconeogenesis during starvation (19) is accompanied by a decrease in the liver tryptophan concentration. As tryptophan metabolites can inhibit gluconeogenesis (20, 21) they contend that this is consistent with a regulatory role for tryptophan in gluconeogenesis. Thus, this is one area in which tryptophan pyrrolase may be important. Other possible areas are control of brain 5HT (22), regulation of liver NAD concentration (4), and, as tryptophan is the least abundant amino acid in the pool available for protein synthesis (23), also protein synthesis.

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