Adenylosuccinase activity of rat liver is depressed by prolonged starvation, cortisol administration, high protein diets, and alloxan diabetes. The loss of activity is not due to the accumulation of a dissociable inhibitor or loss of a cofactor. Starvation produces no loss in activity for 1 day; thereafter the activities of the liver and spleen enzyme decay with a half-life of about 0.9 day. Starvation produces no change in the activity of the kidney, brain, and skeletal muscle enzyme. Refeeding restores the activity of the liver enzyme to the fed level, with only a slight overshoot. The recovery of adenylosuccinase activity is equally rapid after refeding a balanced diet, or corn oil, or glucose, and is not influenced by starvation, in contrast to alanine transaminase activity. Recovery is inhibited by cycloheximide, indicating the involvement of protein synthesis. Although adenylosuccinase is depressed in liver of starving rat it is elevated in liver of starving chicken. Starvation depresses malic enzyme activity and elevates alanine aminotransferase activity in both species.

When rats are starved, the rate of de novo synthesis of adenine mononucleotide decreases in spleen and liver but not in kidney, suggesting a regulatory role for adenylosuccinase in purine biosynthesis. The low activity of adenylosuccinase in liver of severely starved rats is inconsistent with the proposal (Moss, K. M., and McGivan, J. D. (1976) Biochem. J. 150, 275–283) that the purine nucleotide cycle plays a major role in ammonia production for urea synthesis, at least under these conditions.

Adenylosuccinate (adenylosuccinate lyase, EC 4.3.2.2) catalyzes two analogous reactions in the de novo synthesis of purine nucleotides, the elimination of fumarate from both aminoimidazole succinocarboxamide ribotide and adenylosuccinate (Reactions 1 and 2) (1, 2).

\[
\text{SAICAR} \rightarrow \text{aminoimidazolecarboxamide ribotide + fumarate (1)}
\]

\[
\text{Adenylosuccinate} \rightarrow \text{AMP + fumarate (2)}
\]

Adenylosuccinase also functions in ammonia production from L-aspartate via the purine nucleotide cycle (3, 4). The operation of this cycle has been demonstrated in extracts of skeletal muscle (5), kidney (6), and brain (7). The three reactions of the cycle also occur in extracts of liver, and it has been proposed that the purine nucleotide cycle is a source of free ammonia for ureogenesis in liver (8). The purine nucleotide cycle has been shown to operate in intact muscle (9) and brain (10) at rates sufficient to account for the rates of ammonia production by these tissues. It may also be involved in nitrogen elimination by ammonotelic teleosts and invertebrates (11, 12).

The regulation of purine biosynthesis has been studied extensively, particularly with regard to the feedback control of 5-phosphoribosyl 1-pyrophosphate amidotransferase activity (13–15). However, few studies have been conducted on the regulation of enzyme levels in this pathway, particularly in higher animals. In uricotelic species, the involvement of hepatic adenylosuccinase in both biosynthetic and catabolic roles requires control mechanisms compatible with both functions. The present paper presents a study of the response of adenylosuccinase activity to different catabolic, dietary, and hormonal influences.

MATERIALS AND METHODS

Animals—Male rats of the Sprague-Dawley strain weighed 120 to 130 g when obtained from Charles River Breeding Laboratories, Wilmington, Mass. The animals were maintained in individual cages in a room with a 12-h light to 12-h dark cycle and had free access to water and diet unless noted otherwise. All animals were maintained on control diets for at least 5 days before starting experimental diets. The control diet containing 22% protein was a commercial Chow obtained from Charles River Breeding Laboratories. The 18% protein diet contained (in per cent by weight): vitamin-free casein, 18; glucose monohydrate, 53; corn oil, 4; salt mixture W, 6; powdered cellulose (Alphacel), 11.8; liver extract concentrate, 2 (all from Nutritional Biochemicals, Cleveland, Ohio), and a commercial vitamin mixture (Pervinal), 0.2. The 72% protein diet was the same except that it contained 72% casein and 5% glucose. Corn oil was fed as a 5% slurry (w/w) with powdered cellulose (Alphacel). Pure glucose was fed as the solid, caked with a minimum amount of water.

Cortisol (hydrocortisone phosphate) was administered subcutaneously (30 mg/kg/day) for 8 days. Glucagon was administered subcutaneously (1.25 mg/kg) every 8 h. Control animals were injected with similar volumes of 0.9% NaCl. Diabetes was induced by a single intraperitoneal injection of alloxan (115 mg/kg body weight) after the animals had been starved 36 h. Animals were considered to be diabetic if blood glucose was greater than 14 mM 10 days later. Rats treated with cycloheximide received an intraperitoneal injection (1.5 mg/kg body weight) at the time of refeeding, and a second injection (0.75 mg/kg body weight) 0.5 h after starting the refeeding.

Two-week-old female chicks of the BUFF-Sex Link strain, weighing 110 to 120 g, initially, were obtained from Lawton Breeding Farms, Foxboro, Mass., and were maintained in individual wire-bottom cages in a room with a 12-h light to 12-h dark cycle. Water and a commercial chick starter mash were available ad libitum. The diet contained approximately 20% protein, 4% fat, 60% carbohydrate, and 4.5% fiber.
Effect of dietary and hormonal treatments on adenylosuccinase of rat liver

Unless otherwise indicated, rats received commercial chow. Two groups of rats received casein-containing diet for 8 days. Cortisol (30 mg/kg) or saline was administered intraperitoneally once a day for 8 days. Diabetes was induced by injection of alloxan (115 mg/kg) and was of 10 days duration. For additional details see "Materials and Methods." Results shown are means ± S.E. for the numbers of animals given in parentheses.

| Treatment           | Adenylosuccinase activity | nmol/g protein/min |
|---------------------|---------------------------|--------------------|
| Saline              | 3.59 ± 0.16 (15)          |
| Cortisol            | 1.89 ± 0.13 (6)           |
| Diabetes            | 2.02 ± 0.22 (6)           |
| 18% Protein diet    | 3.61 ± 0.15 (10)          |
| 72% Protein diet    | 2.63 ± 0.17 (5)           |
| Starved 4 days      | 0.40 ± 0.04 (4)           |

Effect of diet on adenylosuccinase and malic enzyme of rat liver

Rats were fed commercial chow or were starved for 3 days. Thereafter, groups of animals were either starved an additional day or were refed the indicated diet for 24 h. For further details see "Materials and Methods." Results are means ± S.E. for groups of 5 animals.

| Treatment           | n  | Adenylosuccinase | Malic enzyme |
|---------------------|----|-----------------|--------------|
|                      |    | μmol/g fresh weight/min | nmol/g fresh weight/min |
| Fed                 | 4  | 0.46 ± 0.02      | 1.76 ± 0.09   |
| Starved 3 days      | 4  | 0.18 ± 0.05 a    | 0.98 ± 0.05 a |
| Starved 4 days      | 3  | 0.04 ± 0.01 b    | 0.62 ± 0.04 b |
| Starved 3 days, refed chow diet | 3  | 0.34 ± 0.04 c    | 1.80 ± 0.23 c |
| Starved 3 days, refed corn oil | 3  | 0.39 ± 0.04 c    | 1.05 ± 0.11 c |

Effect of Diet and Hormones on Hepatic Adenylosuccinase—Adenylosuccinase activity of liver decreased when rats were subjected to regimes which stimulate amino acid catabolism and gluconeogenesis, namely starvation, cortisol treat-
Adaptive Changes in Adenylosuccinase Activity

TABLE IV

Adenylosuccinase activities in various tissues of chow-fed and starved rats

| Tissue       | Adenylosuccinase activity | Fed       | Starved   | Fed       | Starved   |
|--------------|---------------------------|-----------|-----------|-----------|-----------|
|              | nmol/mg protein/min       | µmol/g fresh weight/min |
| Spleen       | 2.54 ± 0.11               | 0.16 ± 0.05*   | 0.30 ± 0.01   | 0.019 ± 0.006*   |
| Liver        | 3.86 ± 0.14               | 0.44 ± 0.05*   | 0.34 ± 0.01   | 0.06 ± 0.01*   |
| Skeletal muscle | 10.4 ± 0.22            | 10.8 ± 1.16   | 0.52 ± 0.05   | 0.54 ± 0.06   |
| Brain        | 5.74 ± 0.42               | 5.92 ± 0.44   | 0.18 ± 0.01   | 0.19 ± 0.01   |
| Kidney       | 0.78 ± 0.20               | 0.72 ± 0.08   | 0.046 ± 0.01  | 0.044 ± 0.004 |

* Significantly different from chow-fed control, p < 0.01.

TABLE V

Effect of starvation on rat and chick liver enzymes

| Weights          | Rat                            | Chick                         |
|------------------|--------------------------------|-------------------------------|
|                  | Fed       | Starved  | Fed       | Starved  |                      |
| Body weight (g)  | 165 ± 3  | 77 ± 1   | 165 ± 14  | 89 ± 5   |                      |
| Relative liver size (g/100 g body weight) | 5.1 ± 0.1 | 2.8 ± 0.1 | 4.0 ± 0.1 | 3.5 ± 0.1 |                      |
| Enzyme activities|                      |                                |
| Adenylosuccinase | 1.84 ± 0.15 | 0.20 ± 0.06 | 11.8 ± 0.1 | 25.3 ± 1.6 |                      |
| Xanthine dehydrogenase | 1.48 ± 0.06 | 0.48 ± 0.03 | 2.4 ± 0.2 | 12.5 ± 2.1 |                      |
| Alanine ketoglutaric aminotransferase | 597 ± 36 | 1090 ± 87 | 1.4 ± 0.1 | 3.9 ± 0.4 |                      |
| Malic enzyme      | 8.7 ± 0.5 | 1.7 ± 0.1 | 35.4 ± 3.0 | 8.7 ± 0.7 |                      |

FIG. 1. Effect of starving and refeeding rats on adenylosuccinase activity of liver. A, rats were fed the chow diet ad libitum (O) or were starved (O). The results are expressed as means ± SE. The number of rats in each group is shown below the points. B, the decline of adenylosuccinase activity has been replotted on a logarithmic scale. Adenylate deaminase activity is shown for comparison (O).
Adaptive Changes in Adenylosuccinase Activity

0.25

0.20

0.15

0.10

0.05

Time after refeeding (h)

Activity (μmol/g fresh wt/min)

0.0

2 4 6 8 10

FIG. 2. Effect of cycloheximide on induction of hepatic adenylosuccinase by refeeding. Rats were starved for 72 h. They were then injected intraperitoneally with cycloheximide (●) or isotonic saline (○), as described under "Materials and Methods," and refed the chow diet. Values given are means ± S.E. for groups of four animals.

Although adenylosuccinase activity of liver was severely depressed by starvation, the activities of adenylosuccinate synthetase and adenylate deaminase were unaltered. Cytosolic alanine aminotransferase of liver was elevated over 3-fold in the starved rats, in agreement with previous reports (29), while glutamate dehydrogenase activity was unchanged (Table III). Adenylosuccinase activity in spleen of starved rats was also depressed, but no change in its activity was observed in kidney, brain, and leg muscle (Table IV).

Adenylosuccinase activity in liver of fed rat is 1.84 μmol per 100 g body weight per min measured at 30°C (Table V). Assuming a temperature coefficient of 1.8 for the interval from 30 to 38°C, this activity converts to 4.8 mmol per 100 g body weight per day at body temperature. This is adequate to account for the ammonia needed for a daily production of urea by fed rats of 4.8 mmol per 100 g body weight (30). However, adenylosuccinase activity in liver of 4-day starved rats is only 0.20 μmol per 100 g body weight measured at 30°C (Table V), which is equivalent to 0.52 mmol per 100 g body weight per day at 38°C. This activity can account for only 0.52/15.1 = 3.4% of the ammonia needed for a urea production by 4-day starved rats of 15.1 mmol per 100 g body weight (30).

Kinetics of Adenylosuccinase Decay and Induction—The activity of the enzyme in liver of rat began to decline approximately 24 h after withdrawal of food. Thereafter, the degradative half-life of adenylosuccinase was 1 day. When the control diet was restored after 3 days, adenylosuccinase activity recovered rapidly with only a small, transient overshoot (Fig. 1). Administration of cycloheximide to starved rats at the time of refeeding prevented the recovery of adenylosuccinase observed in controls which did not receive the inhibitor (Fig. 2), indicating that recovery of activity is associated with new protein synthesis.

Administration of glucagon to starved rats at the time of refeeding inhibits induction of malic enzyme (31). When rats that had been starved for 3 days were injected with glucagon (1.25 mg/kg body weight) at 8-h intervals beginning 30 min after refeeding the chow diet, induction of malic enzyme but not of adenylosuccinase was inhibited (Fig. 3).

Effect of Starvation on Activity of Spleen Enzymes—Decline in the activity of adenylosuccinase of spleen began approximately 24 h after the withdrawal of food (Fig. 4A). Thereafter, the degradative half-life was 0.8 day (Fig. 4A, inset). Xanthine dehydrogenase activity expressed per g of spleen increased during starvation. However, no change in enzyme activity was noted when the data were expressed as...
Adaptive Changes in Adenylosuccinase Activity

units per 100 g body weight (Fig. 4B), indicating that the spleen conserves existing xanthine dehydrogenase while the tissue is decreasing in size.

Effect of Starvation on Adenylosuccinase from Chicken Liver—In contrast to rat, adenylosuccinase activity of chick liver was more than doubled after starving the animals for 4 days (Table V). Presumably this increase in activity occurs to facilitate the SAICAR lyase function of adenylosuccinase (see Equations 1 and 2) and reflects the different function of the enzyme in chicken as compared to rat. Xanthine dehydrogenase activity was also increased substantially in liver of starving chicks, but was depressed in liver of starving rats. However, malic enzyme and cytosolic alanine aminotransferase showed parallel changes in chick and rat liver.

Adenylosuccinase activity in liver of fed and starved chick is 11.8 and 25.3 μmol per 100 g body weight per min measured at 30°C (Table V). Assuming a temperature coefficient of 2.0 for the interval from 30 to 42°C, these activities convert to 34.0 and 72.9 mmol per 100 g body weight per day, respectively. These activities are more than adequate to account for the elevated rates of uric acid production observed in chicken fed high protein diets. Rates of uric acid production by chicks fed 75% protein diet and adult chicken fed 60% protein diet are only 7.3 and 13.4 mmol per 100 g body weight per day, respectively (32, 33). Rates of uric acid excretion in fasted chicks were not determined in the present study; however, they are unlikely to be substantially greater than the rates observed on the high protein diets.

Effect of Starvation on Purine Biosynthesis in Rat Tissues—The adaptive behavior of adenylosuccinase in liver and spleen of rat raises the possibility that its activity may be one of the rate-limiting factors of purine biosynthesis in these organs. The effect of starvation on purine biosynthesis was determined by measuring [14C]formate incorporation into adenine, which involves adenylosuccinase-catalyzed reactions twice, into guanine plus hypoxanthine, which involves an adenylosuccinase-catalyzed reaction once, and into FGAR which does not involve an adenylosuccinase-catalyzed reaction.

Incorporation of [14C]formate into FGAR by spleen of rats starved for 3 days was 26% of that found in fed animals (Table VI), in agreement with previous reports (26). However, incorporation of [14C]formate into guanine plus hypoxanthine of starved animals was only 16%, and incorporation of [14C]formate into adenine was only 6.4% of the amounts found in the fed group (Table VI). Thus in starvation there is a progressive reduction in the rate of operation of the pathway subsequent to FGAR formation. Incorporation of [14C]formate

![Graph A](image1)

**Fig. 4.** Effect of starvation on adenylosuccinase and xanthine dehydrogenase activities of rat spleen. A, adenylosuccinase activity is expressed as units per mg of cytosolic protein (○) or per g of spleen (■). In the inset the decline of adenylosuccinase has been replotted on a logarithmic scale. B, xanthine dehydrogenase activity is expressed as units per mg of cytosolic protein (○), per g of spleen (■), and per 100 g body weight (■). Values given are means and the S.E. for four to eight animals.

| Organ   | Animals | [14C]Formate incorporated into | Adenine | Guanine + hypoxanthine | FGAR | Serine |
|---------|---------|--------------------------------|---------|------------------------|------|--------|
|         |         | 10⁻¹ × dpm/g fresh weight     |         |                        |      |        |
| Spleen  | Fed     | 323 ± 39                       | 74.9 ± 6.0 | 290 ± 49               | 120 ± 23|
|         | Fasted  | 20.8 ± 4.0                     | 12.0 ± 1.5 | 72 ± 11                | 158 ± 25|
| Liver   | Fed     | 5.20 ± 0.49                    | 1.56 ± 0.21 |                        |      |        |
|         | Fasted  | 2.07 ± 0.15                    | 1.45 ± 0.10 |                        |      |        |
| Kidney  | Fed     | 37.9 ± 3.1                     | 8.0 ± 2.0  |                        |      |        |
|         | Fasted  | 16.9 ± 3.0                     | 3.5 ± 5.8  |                        |      |        |

* Significantly different from fed group, p < 0.01.

* Not significantly different from fed group, p > 0.05.
into serine was unaffected by starvation (Table VI), demonstrating the absence of interfering effects on the radioactive precursor pool and on the folate-dependent enzymes associated with formate metabolism. Incorporation of \( ^{14}C \)formate into guanine plus hypoxanthine by liver of rats starved for 3 days was unaltered; however, a 45% reduction in \( ^{14}C \)formate incorporation into adenine was observed (Table VI), indicating a specific, starvation-sensitive step between IMP and adenine nucleotide. Kidney, in which adenylosuccinase activity is not decreased by starvation (Table IV), displayed identical reduction of both adenylosuccinase and guanine plus hypoxanthine synthesis (Table VI). The total adenine, guanine, and hypoxanthine contents of liver and kidney were not altered by starvation; however, in spleen starvation decreased the total adenine content from 2.93 ± 0.12 to 1.75 ± 0.10 µmol/g dry weight, increased the total guanine content from 0.37 ± 0.02 to 0.47 ± 0.02 µmol/g dry weight, and increased the total hypoxanthine content from 0.12 ± 0.01 to 0.20 ± 0.01 µmol/g dry weight.

**DISCUSSION**

The present study demonstrates species-specific effects of diet on adenylosuccinase activity in higher animals. Little information is available regarding factors that control the expression of enzymes in the pathway of purine biosynthesis, particularly in eucaryotes. In prokaryotes several of these enzymes are repressed by adenine and guanine nucleotides (34, 35). Exogenous adenine and guanine compounds also repress purine synthesis by cultured mammalian cells. Recovery of purine synthesis after removal of the compounds from the culture medium involves synthesis of a specific protein; however, the activities of adenylosuccinase and other enzymes of purine synthesis are not affected (36, 37). Prolonged starvation has no effect on 5-phosphoribosyl 1-pyrophosphate amidotransferase activity of rat liver (38), but the inhibition of purine synthesis in spleen that occurs upon starvation involves a step prior to FGAR formation and is rapidly reversed upon refeeding (26).

Prominent metabolic adaptations to starvation in both mammalian and avian species include an increase in gluconeogenesis from amino acids and a decrease in lipogenesis. These changes are mediated in part by adjustments in the levels of several enzymes involved in these metabolic processes (39). Thus, alanine aminotransferase and malic enzyme respond to starvation in opposite fashion in both the rat and the chick (Table V). Similar hormonal regulatory mechanisms probably mediate these effects in both species. The adaptation to starvation of urea cycle enzymes in rat liver (39) probably has its parallel in the adaptation to starvation of uric acid synthesis enzymes in chicken liver. Starvation-induced increases in the activities of chicken liver 5-phosphoribosyl 1-pyrophosphate amidotransferase (38), the first enzyme in the pathway, and xanthine dehydrogenase (40) have been reported previously. An intermediate enzyme in the purine biosynthesis pathway, adenylosuccinase, is also elevated substantially in liver of starving chicks (Table V). It seems likely that other enzymes in the pathway are also induced coordinately.

Despite the parallel responses to starvation in the activities of adenylosuccinase, malic enzyme, and xanthine dehydrogenase in rat liver (Table V), it is clear that coordinate regulation is not involved. Administration of glucagon to starved rats at the time of refeeding with chow diet does not affect induction of adenylosuccinase but blocks induction of malic enzyme (Fig. 3). Diets high in fat inhibit induction of lipogenic enzymes (41). Refeeding starved rats with corn oil completely restores adenylosuccinase activity within 24 h, but has no effect on malic enzyme activity (Table II). Refeeding starved rats with glucose leads to recovery of both adenylosuccinase and malic enzyme (Table II). Last, induction of adenylosuccinase does not result in an overshoot of the control activity, which is typical of malic enzyme (Fig. 3). In the rat either glucose or corn oil alone can replace a balanced diet in eliciting the refeeding response of adenylosuccinase. In this species the effect may be mediated through a diet-sensitive hormonal factor, possibly insulin. The level of insulin is elevated not only by glucose but also by refeeding starved animals fats without carbohydrates (42) and by infusing oleate (43) or ketones (44). Alternatively, synthesis of adenylosuccinase may be particularly sensitive to a variable such as the cellular ATP concentration, which declines during starvation (45). Requirement for a specific dietary factor appears to be ruled out because a variety of different nutrients are able to restore the activity of the enzyme (Table IV).

The effect of starvation on adenylosuccinase activity from chicken liver is the opposite of that observed in rat (Table V), although malic enzyme and alanine aminotransferase levels are apparently controlled similarly in both species. In this regard it is worth noting that the plasma insulin concentration in chick is unaltered by starvation, in contrast to rat (46).

The organ specificity (Table III) of the effect of starvation on adenylosuccinase activity suggests that differential tissue sensitivity to hormonal factors may be involved. For example, the specificity may reside in the hormone receptors or may be mediated through tissue-specific isozymes of adenylosuccinase that differ in sensitivity to hormonal influences.

The decline in adenylosuccinase activity of rat liver and spleen that occurs during starvation is of functional significance. FGAR biosynthesis in rat spleen was previously shown to be depressed during starvation (26). The progressive inhibition of purine biosynthesis from FGAR to adenine in spleen of starving rat (Table VI) is consistent with starvation-sensitive steps in the pathway subsequent to FGAR. The greater inhibition of \( ^{14}C \)formate incorporation into adenine (93.6%), compared to hypoxanthine plus guanine (84%), suggests that adenylosuccinase may become partially rate-limiting for purine biosynthesis under these conditions. It is probable, however, that additional enzymes in the pathway, not assayed in the present study, also decline during starvation and contribute to the reduction in purine biosynthesis.

In liver of rats starved 45% reduction of \( ^{14}C \)formate incorporation into adenine, but no change in its incorporation into hypoxanthine plus guanine. This indicates a decrease in the capacity of the liver to convert IMP to AMP.

Adenylosuccinate synthetase activity of liver was not altered by starvation (Table III). Thus it seems reasonable to attribute the decrease in adenine biosynthesis to the decline of adenylosuccinase activity. IMP dehydrogenase activity increases 2-fold on starving rats for 3 days (47). Although the ATP content of liver declines in starving rat (45), this has no apparent effect on purine biosynthesis up to the level of IMP (Table VI). Prolonged starvation does not decrease significantly the aspartate content of liver (48).

Purine biosynthesis is not limited by adenylosuccinase activity in kidney of starved rat, and starvation has no effect on the activity of adenylosuccinase in this organ (Table IV). Incorporation of \( ^{14}C \)formate into adenine and into guanine plus hypoxanthine are inhibited to the same extent in this tissue (Table VI), presumably due to suppression of an earlier step in the pathway.

Urea cycle enzymes are induced in rat liver by prolonged starvation (30, 49), as are amino acid-degrading enzymes (29). The enzymes of the purine nucleotide cycle do not display
parallel adaptive responses (Table III). Hadacidin, an inhibitor of adenylosuccinase synthetase (50), is without effect on urea synthesis by isolated rat hepatocytes (51). Experimental conditions which promote the deamination of AMP to IMP in rat liver result in a prolonged depression of its adenine nucleotide content, with some conversion of IMP to uric acid (52, 53), rather than in the rapid reamination of IMP observed in rat skeletal muscle (9).

Adenylosuccinase activity declines upon starvation (Table I), while urea synthesis increases under these conditions. A comparison of the results shown in Table V with daily urea production indicates that adenylosuccinase activity in liver of fed rats is sufficient for the daily production of urea; however, in the case of severely starved rats it can account for only about 3% of the needed ammonia. Sufficient activity to account for the observed rate of urea production in fed rats does not prove involvement of adenylosuccinase in urea production. However, the activity of adenylosuccinase in liver of starved rats accounts for only about 3% of the needed ammonia.}

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