A STUDY OF THE SYNTHESIS OF CREATINE BY LIVER PREPARATIONS*

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Creatine is synthesized from guanidoacetic acid and methionine by liver slices from the cat, dog, guinea pig, frog, pigeon, rabbit, and rat (1, 2). Liver slices from adult and embryonic guinea pigs and rabbits are equally effective in the synthesis of creatine (3). On the other hand the capacity of homogenized preparations of liver from various species to methylate guanidoacetic acid is variable. Homogenates of the liver of the adult guinea pig were found capable of synthesizing creatine in the presence of adenosinetriphosphate (ATP); liver homogenates of the rat were shown to be much less effective (4, 5). In a previous report from this laboratory (3), it was noted that liver homogenates from a variety of species and from embryonic guinea pigs also were unable to synthesize creatine at an appreciable rate.

Further studies were made in an effort to determine whether the observed differences in homogenized preparations from adults and embryos were reflections of differences in the transmethylation process itself or in secondary reactions. It has been found that with appropriate additions cell-free preparations from the liver of the rat and embryonic guinea pig are capable of synthesizing creatine. We are reporting some of the properties of the transmethylating systems from various sources.

EXPERIMENTAL

Animals—Adult Sprague-Dawley rats and guinea pigs, obtained commercially, were employed. The animals were fed commercial diets supplemented with liver and lettuce, respectively.

Methods—The methods employed for the preparation of the homoge-
nates, for the incubation of the reaction mixtures, and for the determination of creatine have been described (3). The fractionation of the homogenates was carried out in an International refrigerated centrifuge model PR-1, with a high speed attachment.

**Creatine Synthesis by Whole Liver Homogenates**—Homogenates of liver were prepared (1 part of tissue to 3 parts of buffer) in the buffer of Cohen and Hayano (6), pH 7.4, with use of a glass homogenizer (7). The composition of the buffer was as follows: sodium chloride 0.123 M, potassium chloride 0.005 M, magnesium sulfate 0.0033 M, and sodium phosphate 0.0128 M, pH 7.4.

### Table 1

**Synthesis of Creatine in Whole Liver Homogenates from Adult and Embryonic Guinea Pigs**

The substrate concentrations were guanidoacetic acid 10^{-2} M, L-methionine 10^{-2} M, and ATP 10^{-3} M. The concentration of fumarate, when added, was 10^{-3} M. All solutions were prepared in the buffer of Cohen and Hayano. Incubation time, 1 hour; temperature, 38°; pH, 7.1; final volume, 2 ml.; gas phase, oxygen; tissue concentration, 35 to 40 mg. dry weight per flask.

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Animal</th>
<th>Weight (gm.)</th>
<th>Additions</th>
<th>Creatine synthesized per 10 mg. dry tissue per hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Embryo</td>
<td>50</td>
<td>None</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fumarate</td>
<td>4.4</td>
</tr>
<tr>
<td>2</td>
<td>Adult</td>
<td>805</td>
<td>None</td>
<td>4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fumarate</td>
<td>4.8</td>
</tr>
</tbody>
</table>

The methylation of guanidoacetic acid by methionine in such liver preparations from the adult guinea pig is enhanced by ATP. This was first noted by Borsook and Dubnoff (4) and has been confirmed in this laboratory. The extent to which ATP aids the reaction depends upon the nature of the enzyme preparation used. When freshly prepared liver homogenates from the adult guinea pig were incubated with guanidoacetic acid and L-methionine, the addition of ATP had only a slight effect upon the rate of creatine synthesis (conditions of the incubation are shown in Table I). These results are similar to those reported by Umbreit and Tomházy (5). However, if the homogenate was allowed to age for 2 hours at 0° before the incubation, the rate of synthesis without added ATP decreased 75 to 100 per cent, but was restored to the original level by the addition of ATP.

The homogenate was found to be active between pH 6.0 and 8.0, with maximal activity between pH 6.8 and 7.5. The rate of creatine formation was linear up to 1 hour of incubation and then diminished.

Previously it was reported that homogenates of the liver of embryonic
guinea pigs were much less active in the synthesis of creatine from guanido-
acetic acid, L-methionine, and ATP, than were homogenates prepared from
the liver of adult guinea pigs (3). Now it has been noted, however, that
the addition of a Krebs cycle intermediate, such as fumaric acid, to whole
homogenates of liver from embryonic guinea pigs considerably increased
their activity (Table I). These experiments have been repeated with em-
byros weighing 20, 42, 54, and 63 gm., with almost identical results. Fu-
marate has a much smaller effect on liver homogenates prepared from
adults (cf. (4)).

The results with homogenates are now in accord with those previously
obtained with liver slices from these animals (3) and indicate that under
appropriate conditions the livers from adult and embryonic guinea pigs
are equally effective in the synthesis of creatine.

The addition of members of the Krebs cycle (or related compounds) to
whole homogenates from rat liver resulted in an increased synthesis of
creatine when assayed by the procedure given in Table I. For example,
in eight experiments the synthesis of creatine increased from a base level
of 1.0 $\gamma$ to an average of 2.4 $\gamma$ per 10 mg. of tissue per hour when the
concentration of glutamic acid was raised to $10^{-2}$ M. The range of the
increase extended from 1.4 to 4.0 $\gamma$.

The incorporation of folic acid in the incubation medium invariably
raised the quantity of creatine synthesized to between 4 and 5 $\gamma$. The
addition of folic acid without the Krebs cycle intermediate had little effect.
If the whole homogenate were aged (10 minutes at 25° or 1 hour at 0°),
the addition of the Krebs cycle intermediate had only a slight stimulatory
effect, the synthesis of creatine never exceeding 2.2 $\gamma$ per 10 mg. of tissue,
but the incorporation of folic acid again raised the quantity of creatine
synthesized to above 4 $\gamma$. Typical data are presented in Table II.

The optimal concentration of glutamic acid was found to be approxi-
mately $10^{-2}$ M, and of folic acid, $10^{-3}$ M. The optimal pH for the complete
system was approximately 6.85. Liver homogenates from hamsters also
have been found to respond to folic and glutamic acids in a manner similar
to that described for rat liver homogenates.

The chromogen produced in the presence of glutamic and folic acids was
identified as creatine by the following criteria. No chromogen was pro-
duced when either guanidoacetic acid or L-methionine was omitted from
the reaction mixture. The chromogen appeared only after the mixture
was autoclaved (to convert creatine to creatinine). The chromogen, after
adsorption on Lloyd's reagent and elution by dilute alkali, was destroyed
in the enzymatic procedure of Miller, Allinson, and Baker (8).

The interchangeability of the various members of the Krebs cycle (and
related compounds) in the synthesis of creatine by homogenates of rat liver
is shown in Table III. Cysteine, glutathione, and ascorbic acid were not effective. It should be noted that in order to obtain synthesis in the pres-

Table II

**Effect of Folic and Glutamic Acids on Synthesis of Creatine by Homogenates of Rat Liver**

Whole rat liver homogenates were aged for 10 minutes at 25° before addition to the reaction mixtures. The substrate concentrations were guanidoacetic acid $10^{-3}$ M, L-methionine $10^{-2}$ M, and ATP $10^{-3}$ M. All solutions were prepared in the buffer of Cohen and Hayano. Incubation time, 1 hour; temperature, 38°; pH, 6.85; final volume, 2 ml.; gas phase, oxygen; tissue concentration, 40 mg. dry weight per flask. The values are the averages of six experiments.

<table>
<thead>
<tr>
<th>Addition</th>
<th>Concentration</th>
<th>Creatine synthesized per 10 mg. dry tissue per hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>$10^{-3}$</td>
<td>1.0</td>
</tr>
<tr>
<td>Folic acid</td>
<td>$10^{-1}$</td>
<td>1.3</td>
</tr>
<tr>
<td>L-Glutamic acid</td>
<td>$10^{-2}$</td>
<td>2.1</td>
</tr>
<tr>
<td>L-Glutamic acid + Folic</td>
<td>$10^{-2}$</td>
<td>4.9</td>
</tr>
<tr>
<td>acid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table III

**Effect of “Energy Source” on Synthesis of Creatine**

Whole rat liver homogenates were aged for 10 minutes at 25° before addition to the reaction mixtures. The substrate concentrations were guanidoacetic acid $10^{-3}$ M, L-methionine $10^{-2}$ M, ATP $10^{-3}$ M, and folic acid $10^{-2}$ M. The “energy sources” were added at a concentration of $10^{-2}$ M. The conditions of incubation are indicated in Table II. The results are expressed as the relative effect upon synthesis of creatine based upon the effect of glutamate as 100. The values are the averages of from two to four experiments.

<table>
<thead>
<tr>
<th>90-100</th>
<th>50-90</th>
<th>10-50</th>
<th>0-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Glutame</td>
<td>Oxalacetate</td>
<td>L-Glutamine</td>
<td>L-Arginine</td>
</tr>
<tr>
<td>L-Proline</td>
<td>Pyruvate</td>
<td>L-Aspartate</td>
<td>L-Histidine</td>
</tr>
<tr>
<td>$\alpha$-Ketoglutarate</td>
<td>Succinate</td>
<td>DL-Alanine</td>
<td>L-Leucine</td>
</tr>
<tr>
<td>Fumarate</td>
<td></td>
<td>Glucose-6-phosphate</td>
<td>Glycine</td>
</tr>
<tr>
<td>L-Malate</td>
<td></td>
<td></td>
<td>Ascorbic acid</td>
</tr>
<tr>
<td>Citrate*</td>
<td></td>
<td></td>
<td>L-Cysteine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glutathione</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Glucose</td>
</tr>
</tbody>
</table>

* When citrate was used, the magnesium ion concentration of the medium was raised to $2 \times 10^{-2}$ M.

ence of citrate it was necessary to raise the concentration of magnesium ions to at least $10^{-2}$ M. In the absence of folic acid the compounds listed in the first column of Table III all slightly enhanced the formation of crea-


dine.
In view of the relationships between folic acid and the synthesis of the methyl group (9), the possibility existed that a synthesis of the methyl group, and not merely a transmethylation, was being observed. The effectiveness of a variety of possible sources of the methyl groups was then examined. Since only L-methionine of the compounds tested (L-methionine, D-methionine, D,L-methionine sulfoxide, D,L-methionine methylsulfonylum chloride, betaine, choline, sodium methyl phosphate, methanol, sarcosine, sodium formate, and formaldehyde) resulted in an appreciable synthesis of creatine, it seemed probable that a direct transmethylation was involved. These results were similar to those originally reported by Borsook and Dubnoff for guinea pig homogenates (4).

The folic acid requirement for the synthesis of creatine in whole homogenates of rat liver could not be satisfied by diphosphopyridine nucleotide (5 X 10⁻⁵ M), triphosphopyridine nucleotide (5 X 10⁻⁵ M), cytochrome c (10⁻⁵ M), pyridoxal phosphate (10⁻⁴ M), vitamin B₁₂ (4), thiamine (10⁻⁵ M), biotin (10⁻³ M), pyridoxine (10⁻³ M), pyridoxal (10⁻³ M), riboflavin (10⁻³ M), nicotinamide (10⁻³ M), nicotinic acid (10⁻³ M), pantothenic acid (10⁻³ M), inositol (10⁻³ M), or thymine desoxyriboside (10⁻³ M).

On the other hand, the folic acid could be replaced by a variety of pteridine derivatives, including 6-pteridylaldehyde, and the folic acid antagonists aminopterin and A-Methopterin (Table IV).

**Creatine Synthesis by Fractionated Liver Preparations**—Homogenates of the liver of adult guinea pigs were prepared and aliquots were then centrifuged at 18,000 X g for 1 hour at 0°. The clear supernatant fluid (SF preparation) and the sedimented material were made up to the original volume of the homogenate, and were tested for their ability to synthesize creatine. The results indicated that all of the transmethylating system is present in the supernatant fluid, with practically none in the residue. The residue, because of the method of preparation, contained cell fragments, nuclei, mitochondria, and a portion of the microsomes.

The SF preparation was inactive in the absence of ATP. The activity was completely restored by the addition of ATP, but not by adenosine-5'-phosphate.

Magnesium ions are required for the synthesis of creatine. The magnesium may be partially replaced by manganese ions (which are approxi-

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1 The pyridoxal phosphate and the thymine desoxyriboside were kindly furnished by Dr. W. W. Umbreit and Dr. E. E. Snell, respectively. The diphosphopyridine nucleotide "90," triphosphopyridine nucleotide "65," and the cytochrome c were obtained from the Sigma Chemical Company.

2 We wish to thank Dr. J. M. Ruesegger, Dr. J. M. Smith, and Dr. E. L. R. Stokstad, of the American Cyanamid Company, and Dr. R. Anker for the pteridine derivatives used in this study.
SYNTHESIS OF CREATINE BY LIVER

nearly 80 per cent as effective), but not by calcium, cobalt, nickel, iron, or zinc ions. In these experiments the homogenates and all other solutions were prepared in the buffer of Cohen and Hayano, with omission of the magnesium sulfate and sodium phosphate. (The phosphate was omitted owing to the insolubility of the phosphates of some of the cations added.) The pH of all the solutions was adjusted to 7.4 with dilute sodium hydroxide. The SF preparation was then tested for its ability to synthesize creatine in the presence of the various cations, at a concentration of 0.0033 M, added either as the chloride or sulfate.

**Table IV**

Specificity of Folic Acid in Synthesis of Creatine

Whole rat liver homogenates were aged for 10 minutes at 25° before addition to the reaction mixtures. The substrate concentrations were guanidoacetic acid 10^-2 M, L-methionine 10^-2 M, ATP 10^-4 M, and glutamic acid 10^-2 M. The conditions of incubation are indicated in Table II. The results are expressed as the relative effect upon the synthesis of creatine based upon the effect of folic acid as 100. The values are the results of from two to four experiments.

<table>
<thead>
<tr>
<th>Addition</th>
<th>Effect (as % of folic acid)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folic acid</td>
<td>100</td>
</tr>
<tr>
<td>10-Formylfolic acid</td>
<td>90–100</td>
</tr>
<tr>
<td>Aminopterin</td>
<td>60–90</td>
</tr>
<tr>
<td>A-Methopterin</td>
<td>60–90</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>40–60</td>
</tr>
<tr>
<td>Pteroic acid</td>
<td>20–50</td>
</tr>
<tr>
<td>Pteroyltetraglutamic acid</td>
<td>20–30</td>
</tr>
<tr>
<td>p-Aminobenzoic acid</td>
<td>0</td>
</tr>
<tr>
<td>p-Aminobenzoylglutamic acid</td>
<td>0</td>
</tr>
<tr>
<td>6-Pteridylaldehyde</td>
<td>90–100</td>
</tr>
<tr>
<td>Xanthopterin</td>
<td>10–20</td>
</tr>
</tbody>
</table>

The SF preparation may be dialyzed for periods up to 4 hours in the cold against the buffer of Cohen and Hayano with no loss in activity. If the magnesium sulfate is omitted from the buffer, the dialyzed preparation shows no activity. The addition of magnesium ions to the incubation mixture restores the original activity.

The abilities of SF preparations made from the livers of adult guinea pigs, embryonic guinea pigs, and adult rats to synthesize creatine were then compared. Typical results are shown in Table V. These effects have been confirmed in three experiments with adult animals and with embryos weighing 42 and 63 gm. The SF preparations from embryonic and adult guinea pigs behave almost identically. Similar amounts of creatine are synthesized at all concentrations of ATP. The SF preparation from rat liver can synthesize creatine at approximately the same rate as guinea pig.
preparations, but requires a much higher concentration of ATP. When rat and guinea pig preparations are compared at high concentrations of ATP ($9 \times 10^{-3} \text{ M}$), the amounts of creatine synthesized are similar, but, when compared at a concentration of ATP of $10^{-3} \text{ M}$, rat preparations show practically no activity, whereas guinea pig preparations show almost maximal activity.

**Mechanism of Activation of Creatine Synthesis by Pteridine Derivatives—**

We have no clear understanding of the mechanism by which folic acid enhances the ability of whole liver homogenates from the rat to synthesize creatine. Folic acid, with or without a Krebs cycle intermediate, has no appreciable effect in enhancing the ability of the SF preparation (from the rat) to synthesize creatine from guanidoacetic acid and L-methionine with concentrations of ATP varying from $10^{-3} \text{ M}$ to $9 \times 10^{-3} \text{ M}$. It would thus appear that the folic acid is not concerned directly with the enzyme system responsible for the transmethylation.

The activating effect of folic acid on whole homogenates may be duplicated with a combination of the SF preparation (rat) and mitochondria isolated from rat liver by the procedure of Schneider and Hogeboom (10). The mitochondria, after the final washing with 0.25 M sucrose, were suspended in the buffer of Cohen and Hayano and added to the SF preparation

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**TABLE V**

**Synthesis of Creatine in Soluble Liver (SF) Preparations**

The preparation of the enzyme is indicated in the text. The substrate concentrations were guanidoacetic acid $10^{-3} \text{ M}$ and L-methionine $10^{-2} \text{ M}$. The concentrations of ATP employed are indicated in the table. The conditions of incubation are indicated in Table I. The tissue concentrations were 15 to 18 mg. dry weight per flask.

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Animal</th>
<th>Weight</th>
<th>ATP added</th>
<th>Creatine synthesized per 10 mg. dry tissue per hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adult guinea pig</td>
<td>805</td>
<td>0</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>10.0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>9.5</td>
</tr>
<tr>
<td>2</td>
<td>Embryonic guinea pig</td>
<td>50</td>
<td>0</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>8.5</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>8.5</td>
</tr>
<tr>
<td>3</td>
<td>Adult rat</td>
<td>155</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9</td>
<td>9.5</td>
</tr>
</tbody>
</table>
SYNTHESIS OF CREATINE BY LIVER

in amounts which approximated their concentration in whole liver homogenates. These results are presented in Table VI. It should be noted that in the presence of mitochondria, folic acid, and fumaric acid much less ATP \((10^{-3} \text{ M})\) is required in the synthesis than when the SF preparation is tested by itself (Table V). It thus seemed possible that the folic acid was functioning in some manner to maintain a relatively high level of ATP during the 1 hour of incubation.

The rate of synthesis of creatine by SF preparations from the rat was the same whether the gas phase was oxygen or nitrogen. On the other hand, oxygen was required for the synthesis when whole homogenates were used; no synthesis occurred when nitrogen was substituted for oxygen.

**Table VI**

*Synthesis of Creatine by Fractions of Rat Liver*

Supernatant (SF) preparations and mitochondrial suspensions were employed. The substrate concentrations were guanidoacetic acid \(10^{-3} \text{ M}\), L-methionine \(10^{-2} \text{ M}\), and ATP \(10^{-3} \text{ M}\). When added, the concentration of folic acid was \(10^{-3} \text{ M}\) and fumaric acid \(10^{-2} \text{ M}\). The conditions of incubation are indicated in Table II. The tissue concentrations of the SF preparation were 20 mg. per flask. The mitochondria were added in amounts which approximated their concentration in whole liver homogenates.

<table>
<thead>
<tr>
<th>Tissue preparation</th>
<th>Addition</th>
<th>Creatine synthesized per flask</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Experiment 1</td>
</tr>
<tr>
<td>SF</td>
<td>Folic acid + fumaric acid</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>&quot; &quot; + &quot; &quot;</td>
<td>0.0</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>None</td>
<td>2.1</td>
</tr>
<tr>
<td>SF + mitochondria</td>
<td>Fumaric acid</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>Folic acid + fumaric acid</td>
<td>15.2</td>
</tr>
</tbody>
</table>

In these experiments the substrate concentrations were guanidoacetic acid \(10^{-3} \text{ M}\) and L-methionine \(10^{-2} \text{ M}\). When SF preparations were used, the concentration of ATP was \(9 \times 10^{-3} \text{ M}\). With whole homogenates, the concentration of ATP was \(10^{-3} \text{ M}\), of folic acid \(10^{-3} \text{ M}\), and of fumaric acid \(10^{-2} \text{ M}\).

The addition of folic acid to homogenates of either the adult or embryonic guinea pig, containing guanidoacetic acid, L-methionine, ATP, and fumarate, did not result in any significant increase in the synthesis of creatine. As noted previously, whole homogenates of the liver of hamsters behaved in a manner similar to that of liver homogenates from the rat.

**DISCUSSION**

The embryo of the guinea pig is well endowed with the ability to synthesize creatine from guanidoacetic acid and L-methionine. The differences
which have been observed between whole liver homogenates of embryonic and adult guinea pigs apparently do not reside in the system directly responsible for the transmethylation, since centrifuged (SF) preparations are equally effective. Possibly homogenates from the adult liver possess a greater capacity to maintain adequate levels of ATP.

Centrifuged liver preparations from the adult rat required considerably more ATP for the synthesis of creatine than did similar preparations from the guinea pig. Whether this is due to a more rapid inactivation of the ATP by the rat preparation, or to an actual difference in the ATP requirements of the systems in the two species, is not known.

It is not possible, from the data at hand, to delineate a mechanism for the activation of the synthesis of creatine in rat liver homogenates by pteridine derivatives. The failure of folic acid to affect appreciably the synthesis of creatine by the supernatant preparations from rat liver homogenates indicates that it is not, in this system, directly concerned in the transmethylation or in the synthesis of the methionine-ATP compound reported by Cantoni (11). Since the pteridine derivatives are effective only in the presence of an intermediate of the Krebs cycle, one possibility is that the pteridine derivatives are acting by enhancing the effect of these Krebs cycle members. The response of whole homogenates can be duplicated by a combination of the supernatant preparation and a mitochondrial preparation. Oxygen is required for the synthesis of creatine in this system. It thus seems probable that a function of Krebs cycle intermediates is the regeneration of ATP. It would be of interest to see whether these pteridine derivatives also aid other reactions in rat liver homogenates which require ATP, and whether tissue preparations from folic acid-deficient animals can utilize the Krebs cycle intermediates.

The known effects of various pteridine derivatives on enzyme systems in vitro include the inhibition of xanthine and pteridine oxidase (12), the inhibition and subsequent enhancement of the oxygen uptake of liver homogenates (13), the activation of choline oxidase (14, 15), the increase in methionine formation in liver homogenates from betaine and homocystine (16), and an increased synthesis of methyl groups from radioformate in liver slices of folic acid-deficient rats (17). Whether the effects reported in the present paper are related to these previous observations remains to be demonstrated.

SUMMARY

1. The synthesis of creatine by whole homogenates of the liver from a variety of sources has been studied. Homogenates from guinea pigs can synthesize creatine in the presence of guanidoacetic acid, L-methionine, and ATP. Whole homogenates from the livers of embryonic guinea pigs require, in addition, the presence of a member of the tricarboxylic acid
cycle. The formation of creatine by whole homogenates of the liver of adult rats was enhanced by the combined presence of a member of the Krebs cycle and of a pteridine derivative such as folic acid, aminopterin, or 6-pteridylaldehyde.

2. Soluble preparations may be obtained from the livers of adult guinea pigs, embryonic guinea pigs, and adult rats, all of which are able to synthesize creatine in the presence of guanidoacetic acid, L-methionine, and ATP. The preparations from adult and embryonic guinea pigs are similar with respect to their requirements for ATP. A much higher level of ATP is necessary for the formation of creatine by the preparations from rat liver.

3. The synthesis of creatine by whole homogenates of rat liver, but not by the soluble preparation, required oxygen. L-Methionine serves as a specific methyl donor in the reaction.

4. The soluble liver preparation obtained from adult guinea pigs may be dialyzed without loss of activity. Magnesium ions are required for the synthesis.

BIBLIOGRAPHY

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