3-Mercaptopropionic Acid, a Potent Inhibitor of Fatty Acid Oxidation in Rat Heart Mitochondria*

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The effects of several short-chain mercapto acids on the rate of respiration supported by either palmitoyl-carnitine, octanoate, or pyruvate was studied with coupled rat heart mitochondria. 3-Mercaptopropionic acid was found to be a potent inhibitor of respiration sustained by palmitoyl-carnitine or octanoate, whereas under identical conditions respiration with pyruvate as a substrate was unaffected. 2-Mercaptoacetic acid also inhibits palmitoyl-carnitine-supported respiration, but only at much higher concentrations of the inhibitor. 2-Mercaptopropionic acid has virtually no effect. Incubation of mitochondria with 3-mercaptopropionic acid did not cause the irreversible inactivation of any $\beta$-oxidation enzyme. Since 3-mercaptopropionic acid did not inhibit $\beta$-oxidation in uncoupled mitochondria, it appears that this compound must first be metabolized in an energy-dependent reaction before it becomes inhibitory. 3-Mercaptopropionyl-CoA and three of its $S$-acyl derivatives, all of which are likely mitochondrial metabolites of 3-mercaptopropionic acid, were tested for their capacity to inhibit the individual enzymes of $\beta$-oxidation. 3-Mercaptopropionyl-CoA inhibits only acyl-CoA dehydrogenase, whereas $S$-myristoyl-3-mercaptopropionyl-CoA inhibits reversibly several $\beta$-oxidation enzymes. All observations together lead us to suggest that the inhibition of $\beta$-oxidation by 3-mercaptopropionic acid in coupled rat heart mitochondria is most likely a consequence of the reversible inhibition of acyl-CoA dehydrogenase by long-chain $S$-acyl-3-mercaptopropionyl-CoA thioesters and possibly by 3-mercaptopropionyl-CoA.

A prerequisite for elucidating the control mechanisms of fatty acid oxidation in mitochondria is a knowledge of the rate-limiting step or the slow steps of this pathway. Studies carried out in this laboratory have led to the suggestion that the last reaction of fatty acid oxidation catalyzed by 3-ketoacyl-CoA thiolase (EC 2.3.1.15) may be one of the slow steps in $\beta$-oxidation (1, 2). In order to determine the rate of other $\beta$-oxidation reactions relative to the rate of the overall pathway, we are interested in identifying or designing specific inhibitors of $\beta$-oxidation enzymes, especially of acyl-CoA dehydrogenase. Bauché et al. (3) have reported that 2-mercaptoacetic acid administered to rats inhibits fatty acid oxidation, possibly by inhibiting long-chain acyl-CoA dehydrogenase. The same authors also reported the inhibition of $\beta$-oxidation by 2-mercaptopropionic acid in isolated rat liver mitochondria (4, 5). These reports prompted us to study the effects of several short-chain mercapto acids on fatty acid oxidation in isolated rat heart mitochondria. We report in this publication that 3-mercaptopropionic acid is a potent inhibitor of $\beta$-oxidation. 2-Mercaptopropionic acid is a much weaker inhibitor of fatty acid oxidation, while 2-mercaptopropionic acid has no significant effect on this pathway.

EXPERIMENTAL PROCEDURES

Materials—The sources or syntheses of most materials are given in the preceding paper (6). 3-Mercaptopropionic acid, 2-mercaptopropionic acid, 2-mercaptopropionic acid, octanoic acid, L-malate, ADP, and all other standard biochemicals were obtained from Sigma. Sodium pyruvate was purchased from Aldrich. Palmitoyl-carnitine was generously provided by Dr. K. Brendel, University of Arizona, College of Medicine.

Isolation of Mitochondria and Oxygen Uptake Measurements—Rat heart mitochondria were isolated from male, Sprague-Dawley rats (240–260 g) by the procedure of Chappell and Hansford (7). The isolation buffer contained 0.21 M mannitol, 0.07 M sucrose, 5 mM Tris-HCl (pH 7.4), and 1 mM EGTA. Protein concentrations were determined by the biuret method (8). For oxygen uptake measurements, mitochondria (0.5–1 mg/ml) were incubated in 1.9 ml of a basal isotic medium containing 0.11 M KCl, 33 mM Tris-HCl (pH 7.4), 2 mM KPi, 2 mM MgCl2, and 0.1 mM EGTA. To this suspension were added bovine serum albumin (0.5 mg/ml) and 0.5 mM L-malate. After addition of the inhibitor, the mitochondria were preincubated for the indicated periods of time. Respiration was initiated by the simultaneous addition of 1 mM ADP and substrate. Rates of respiration were measured polarographically with a Clark oxygen electrode attached to a Gilson oxigraph. Observed rates of respiration and substrate concentrations are listed in Table 1. When pyruvate served as a substrate, bovine serum albumin was deleted from the incubation mixture.

Enzyme Assays—All enzyme assays were performed spectrophotometrically at 25 °C. The following assays were used when rat heart mitochondria served as a source of $\beta$-oxidation enzymes. Butyryl-CoA dehydrogenase (EC 1.3.99.2) and acyl-CoA dehydrogenase (EC 1.3.99.3) were assayed at 600 nm as described in principle by Hoskins (9). The assay mixture contained 0.1 M KPi (pH 7.6), 28 $\mu$M 2,6-dichlorophenolindophenol, 0.65 mM phenazine methosulfate, 32 $\mu$M acyl-CoA, 0.18 M N-ethylmaleimide, 0.45 mM KCN, and 0.09% Triton X-100. The reaction was initiated by the addition of phenazine methosulfate. Enolpyruvyl-CoA hydratase (EC 4.2.1.17) was assayed at 263 nm. The assay mixture contained 0.2 M KPi (pH 8), bovine serum albumin (0.2 mg/ml), 0.09% Triton X-100, and either 30 $\mu$M crotonyl-CoA or 30 $\mu$M 2-decenoyl-CoA. L-3-Hydroxyacyl-CoA dehydrogenase was assayed at 340 nm. The assay mixture contained 80 mM KPi (pH 7), 0.12 mM NADH, 50 $\mu$M acetoacetil-CoA, bovine serum albumin (1 mg/ml), and 0.09% Triton X-100. The reaction was started by the addition of acetoacetil-CoA. The activities of both thiolases (EC 2.3.1.9 and EC 2.3.1.16) were determined by measuring the disappearance of acetyl-CoA.

The abbreviations used are: EGTA, ethylene glycol bis(\$\beta$-aminoethyl ether)-N,N,N',N'-tetraacetic acid; Hepes, N-2-hydroxyethylpiperazine-N'-2-ethanesulfonate.

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pearence of the Mg2+-enolate complexes of the substrate at 363 nm. The reaction mixture contained 0.1 mM potassium/Hepes (pH 8.1), 25 mM MgCl2, 90 μM CoASH, bovine serum albumin (0.7 mg/ml), 0.09% Triton X-100, and either 30 μM acetoacetyl-CoA or 20 μM 3-ketodecanoyl-CoA. The assay was started by the addition of CoASH. Exinction coefficients for the Mg2+-enolate complex of acetoacetyl-CoA and 3-oxodecanoyl-CoA were 12,000 M⁻¹ cm⁻¹ and 6,700 M⁻¹ cm⁻¹, respectively.

Purified enzymes of β-oxidation were assayed as described in the preceding paper (6) except that DL-3-hydroxyoctanoyl-CoA or DL-3-hydroxydecanoyl-CoA were used as a substrate in the assay of 3-hydroxyacyl-CoA dehydrogenase. When the effect of S-myrityl-3-mercaptoacyl-CoA on the activity of 3-ketothiolase was determined, Mg2+ was deleted from the assay mixture to avoid precipitation of the long-chain acyl-CoA. The assay mixture contained 0.1 mM Tris-HCl (pH 8.3), 0.1 mM EDTA, 90 μM acetoacetyl-CoA, 178 μM CoA-SH and 3-ketothiolase to obtain a ΔA/min of 0.08. The extinction coefficient used for calculating reaction rates in the absence of Mg2+ was 3,600 M⁻¹ cm⁻¹ (10).

TABLE I

| Substrate           | Concentration | Oxygen uptake (ng atoms O2/min/mg protein) |
|---------------------|---------------|-------------------------------------------|
| Palmitoylcarcetine  | 30 μM         | 242 ± 22 (6)                              |
| Pyruvate            | 2.5 mM        | 268 ± 28 (5)                              |
| Octanoate           | 0.1 mM        | 82 ± 20 (3)                               |

RESULTS

Effects of Short-chain Mercapto Acids on the Respiration of Rat Heart Mitochondria—All respiration measurements were performed with coupled rat heart mitochondria that exhibited respiratory control ratio values between 5 and 10. Palmitoylcarnitine and pyruvate each supported high rates of respiration in these mitochondria (see Fig. 1, A and D). Since lower rates of respiration were observed when the mitochondria were preincubated with ADP in the absence of a respiratory substrate, ADP and the substrate were added simultaneously. Preincubation of mitochondria in the presence of 178 μM 3-mercaptoacipropionic acid caused virtually complete inhibition of palmitoylcarnitine-supported respiration (see Fig. 1B). After a slight and short-lived oxygen consumption, the rate of respiration was identical with the rate observed in the absence of substrate (see Fig. 1, B and C). The result shown in Fig. 1C also demonstrates that 3-mercaptoacipropionic acid, itself, does not support respiration. Preincubation of mitochondria with 178 μM 3-mercaptoacipropionic acid for 5 min did not affect respiration supported by pyruvate (see Fig. 1, D and E). These observations lead to the conclusion that 3-mercaptoacipropionic acid inhibits fatty acid oxidation directly, and not indirectly by an inhibition of either the citric acid cycle or oxidative phosphorylation.

The degree to which fatty acid oxidation was inhibited depended on the concentration of 3-mercaptoacipropionic acid (see Fig. 2A). Inhibition by 50% after 3 min of preincubation was observed with 27 μM of the inhibitor when the concentration of rat heart mitochondria was 0.5 mg/ml. No significant inhibition of respiration supported by pyruvate was detected at concentrations of the inhibitor up to 0.7 mM. Usually, a slight stimulation of pyruvate-supported respiration was observed at low concentrations of 3-mercaptoacipropionic acid. Since the magnitude of the stimulation was similar to the standard deviation of the measurements, no attempt was made to quantitate the stimulation or to study it in any detail.

Respiration sustained by octanoate, which enters mitochondria independent of the acylcarnitine uptake system (11), was also inhibited by 3-mercaptoacipropionic acid, although to a lesser degree (see Fig. 2A). The possible competition between 3-mercaptoacipropionate and octanoate for the same activating enzyme in the mitochondrial matrix may be the cause for the less severe inhibition of octanoate-supported respiration as compared to the inhibition of palmitoylcarnitine-supported respiration. Since the inhibition of octanoate-supported respiration could also be the consequence of the competitive inhibition of octanoate activation by 3-mercaptoacipropionic acid, the effect of this inhibitor on octanoate oxidation cannot be interpreted unambiguously. However, the observed inhibition of octanoate oxidation is expected if 3-mercaptoacipropionic acid inhibits the β-oxidation cycle. The inhibition of β-oxidation by 3-mercaptoacipropionic acid as a function of time is shown in Fig. 2B. The rate of fatty acid oxidation was decreased by 50% after 30 s of preincubating mitochondria with 178 μM of 3-mercaptoacipropionic acid. After the standard 3-min preincubation period the residual rate of β-oxidation was close to zero. With pyruvate as a substrate, respiration was only slightly (approximately 5%) depressed after 3 min, but it declined to approximately 80% within 6 min. Thus, even pyruvate-supported respiration is inhibited by 3-mercaptoacipropionic acid after prolonged preincubation with the inhibitor.

The effects of 2-mercaptoacetate and 2-mercaptoacipropionoic acid on respiration with either palmitoylcarnitine or pyruvate as substrates are shown in Fig. 3. The inhibition of palmitoylcarnitine-supported respiration by 2-mercaptoacetic acid first reported by Bauche et al. (3-5) is confirmed. The concentration of this inhibitor which caused 50% inhibition was close to 0.4 mM. This value is approximately 15 times
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FIG. 2. Effect of 3-mercaptopropionic acid on mitochondrial respiration. A, rate of respiration as a function of the concentration of 3-mercaptopropionic acid (3-MPA). Coupled rat heart mitochondria were preincubated for 3 min with 3-mercaptopropionic acid and assayed for palmitoylcarnitine-supported respiration (○), octanoate-supported respiration (■), and pyruvate-supported respiration (▲). B, rate of respiration as a function of the preincubation time. Coupled rat heart mitochondria were preincubated with 178 \( \mu \)M 3-mercaptopropionic acid and assayed for palmitoylcarnitine-supported respiration (○) and pyruvate-supported respiration (▲).

Inhibition of \( \beta \)-Oxidation in Rat Heart Mitochondria by Metabolites of 3-Mercaptopropionic Acid—In an attempt to identify the \( \beta \)-oxidation reaction(s) that is (are) inhibited by 3-mercaptopropionic acid, we preincubated rat heart mitochondria with 178 \( \mu \)M inhibitor for 3 min and assayed the activities of the individual \( \beta \)-oxidation enzymes. The enzyme activities presented in Table II prove that none of the enzymes were irreversibly inhibited by 3-mercaptopropionic acid. Since mitochondria were lysed with Triton X-100 in the assay mixture and their contents were diluted at least 10\(^4\)-fold, a reversible inhibition of any of the enzymes would not have been detected. When mitochondria were uncoupled with 2,4-dinitrophenol, 3-mercaptopropionic acid did not inhibit respiration supported by palmitoylcarnitine. This observation suggests that a metabolite of 3-mercaptopropionic acid, formed in an energy-requiring reaction, may be a reversible inhibitor of one or several \( \beta \)-oxidation enzymes.

Elucidation of the mechanism by which 3-mercaptopropionic acid inhibits \( \beta \)-oxidation in coupled rat heart mitochondria was attempted by studying the effects of chemically synthesized metabolites of 3-mercaptopropionic acid on the activities of purified enzymes of \( \beta \)-oxidation. As expected, 3-mercaptopropionic acid itself at concentrations up to 200 \( \mu \)M did not affect the activity of any of the \( \beta \)-oxidation enzymes. 3-Mercaptopropionyl-CoA, the first mitochondrial metabolite of 3-mercaptopropionic acid, had no effect on the activities of enoyl-CoA hydratase and 3-hydroxyacyl-CoA dehydrogenase. However, this compound is a good analog of CoASH in thiolase-catalyzed reactions and a poor substrate of medium-chain acyl-CoA dehydrogenase (6). A kinetic study proved 3-mercaptopropionyl-CoA to be a competitive inhibitor \( (K_i = 5 \mu M) \) of medium-chain acyl-CoA dehydrogenase with respect to butyryl-CoA. Since 3-mercaptopropionyl-CoA can substitute for CoASH in thiolase-catalyzed reactions and a poor substrate of medium-chain acyl-CoA dehydrogenase, this compound is a good analog of CoASH in thiolase-catalyzed reactions and a poor substrate of medium-chain acyl-CoA dehydrogenase (6). A kinetic study proved 3-mercaptopropionyl-CoA to be a competitive inhibitor \( (K_i = 5 \mu M) \) of medium-chain acyl-CoA dehydrogenase with respect to butyryl-CoA. Since 3-mercaptopropionyl-CoA can substitute for CoASH in thiolase-catalyzed reactions and a poor substrate of medium-chain acyl-CoA dehydrogenase, this compound is a good analog of CoASH in thiolase-catalyzed reactions and a poor substrate of medium-chain acyl-CoA dehydrogenase (6).

Further studies showed that 3-mercaptopropionate can be converted intramitochondrially to S-acetyl-3-mercaptopropionyl-CoA thioesters in which the acetyl residue can be an acetyl group or any other acyl group derived from fatty acids by \( \beta \)-oxidation. We have studied the effects of three of these possible metabolites of 3-mercaptopropionyl-CoA on the activities of the enzymes of \( \beta \)-oxidation. The results presented in Table III show S-acetyl-3-mercaptopropionyl-CoA and S-

FIG. 3. Effect of 2-mercaptoacetic acid or 2-mercaptopro- pionic acid on mitochondrial respiration. Coupled rat heart mitochondria were preincubated for 3 min with either 2-mercaptoacetic acid (○, △) or 2-mercaptopropionic acid (●, ▲) and then assayed for palmitoylcarnitine-supported respiration (○, ●) and pyruvate-supported respiration (▲, △).

higher than the concentration of 3-mercaptopropionic acid necessary to bring about the same degree of inhibition. 2-Mercaptopropionic acid, at concentrations between 0.5 and 5 mM, depressed respiration with palmitoylcarnitine as a substrate by only 20%. In contrast, pyruvate-supported respiration was stimulated 20–50% by 2-mercaptoacetic acid at concentrations up to 0.5 mM and by 2-mercaptopro- pionic acid at concentrations between 0.5 and 5 mM. 2-Mercaptopropionic acid at concentrations higher than 0.5 mM, caused an inhibition to 70% of the control level.
hexanoyl-3-mercaptopropionyl-CoA to have little or no effect on the β-oxidation enzymes. However, S-myristoyl-3-mercaptopropionyl-CoA, a long-chain acyl derivative of 3-mercaptopropionyl-CoA, inhibits enoyl-CoA hydratase (crotonase) moderately and is a strong inhibitor of 3-ketoacyl-CoA thiolase, 3-hydroxyacyl-CoA dehydrogenase, and long-chain as well as medium-chain acyl-CoA dehydrogenase.

Since S-myristoyl-3-mercaptopropionyl-CoA is a long-chain acyl-CoA thioester, it may be a nonspecific inhibitor of many enzymes as are the CoA derivatives of long-chain fatty acids. To evaluate the specificities of the observed inhibitions we have compared the effectiveness of S-myristoyl-3-mercaptopropionyl-CoA and palmitoyl-CoA as inhibitors of 3-ketoacyl-CoA thiolase and 3-hydroxyacyl-CoA dehydrogenase. Acyl-CoA dehydrogenases were not included in this evaluation because palmitoyl-CoA is a good substrate of both the medium-chain and long-chain enzyme (12). As shown in Fig. 4, both 3-ketoacyl-CoA thiolase (Fig. 4A) and 3-hydroxyacyl-CoA dehydrogenase (Fig. 4B) are inhibited by both acyl-CoA thioesters with nearly equal effectiveness. At inhibitor concentrations of 10-20 μM, both enzymes are completely inhibited. However, the addition of bovine serum albumin to the inhibited enzymes resulted in their reactivation. Hence, the inhibitions are reversible. Since 3-hydroxyacyl-CoA dehydrogenase and 3-ketoacyl-CoA thiolase are strongly inhibited by palmitoyl-CoA, which is present at substantial concentrations in the matrix of mitochondria actively oxidizing fatty acids (13), the inhibition of these two enzymes by S-myristoyl-3-mercaptopropionyl-CoA in whole mitochondria is unlikely.

In view of these findings our studies were concentrated on the inhibition of medium-chain acyl-CoA dehydrogenase by S-myristoyl-3-mercaptopropionyl-CoA. As illustrated in Fig. 5, this compound is an effective inhibitor of the dehydrogenase. A kinetic study of this enzyme with octanoyl-CoA as a substrate yielded an inhibition constant of 0.8 μM for S-myristoyl-3-mercaptopropionyl-CoA (data not shown). It appears that long-chain derivatives of 3-mercaptopropionyl-CoA at low micromolar concentrations can effectively inhibit medium-chain acyl-CoA dehydrogenase.

Since 3-mercaptopropionionic acid has only a slight effect on respiration supported by pyruvate (see Fig. 2), it was concluded that the inhibition of β-oxidation by the same compound is not due to the inhibition of the tricarboxylic acid cycle, the respiratory chain, or oxidative phosphorylation. However, we have not ruled out the indirect inhibition of β-oxidation by S-acyl-3-mercaptopropionyl-CoA thioesters which are formed only when 3-mercaptopropionic acid and fatty acids are metabolized simultaneously. Apparent evidence for an indirect inhibition of β-oxidation is the observed 80% inhibition of respiration with pyruvate as a substrate in mitochondria preincubated with 0.5 mM 3-mercaptopropionic acid, malate, ADP, P₅, and palmitoylcarnitine. However, the addition of 50 mM L-carnitine restored pyruvate-dependent respiration to 45% of its control value, whereas respiration supported by palmitoylcarnitine was not stimulated by the addition of L-carnitine. We conclude that the inhibition of β-oxidation by long-chain S-acyl-3-mercaptopropionyl-CoA thioesters results in the sequestration of free CoASH as acyl-CoA, thereby preventing pyruvate metabolism. The addition of carnitine leads to the regeneration of CoASH and therefore results in the stimulation of pyruvate-supported respiration. Thus, none of the reactions subsequent to the β-oxidation cycle appears to be responsible for the inhibition of this pathway.

**DISCUSSION**

Since 3-mercaptopropionic acid inhibits palmitoylcarnitine-supported respiration, but hardly affects respiration sus-

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**TABLE II**

**Effect of 3-mercaptopropionic acid on the enzymes of β-oxidation**

Mitochondria were preincubated for 3 min with or without 178 μM 3-mercaptopropionic acid (3-MPA) and assayed for the enzymes of β-oxidation as described under "Experimental Procedures."

| Enzyme                          | Substrate          | Control  | + 3-MPA Remaining activity | %       |
|---------------------------------|--------------------|----------|-----------------------------|---------|
| Acyl-CoA dehydrogenase          | Butyryl-CoA        | 0.061    | 0.061                       | 100     |
| Enoyl-CoA hydratase             | Decanoyl-CoA       | 0.044    | 0.044                       | 100     |
| Long-3-Hydroxyacyl-CoA dehydrogenase | Crotonyl-CoA       | 4.7      | 4.55                        | 97      |
|                                 | 2-2-Decenoyl-CoA   | 2.2      | 2.24                        | 102     |
| Thiolase                        | Acetoacetyl-CoA    | 1.36     | 1.38                        | 101     |
|                                 | 3-Ketodecanoyl-CoA | 0.44     | 0.42                        | 96      |

**TABLE III**

The effects of S-acyl-3-mercaptopropionyl-CoA thioesters on the activities of β-oxidation enzymes

The assay conditions are described in the preceding paper (6). The concentrations of all S-acyl-3-mercaptopropionyl-CoA thioesters were 20 μM. The substrates used for assaying the β-oxidation enzymes are: butyryl-CoA, octanoyl-CoA, and palmitoyl-CoA for the short-chain, medium-chain, and long-chain acyl-CoA dehydrogenases, respectively; crotonyl-CoA for crotonase; DL-3-hydroxyoctanoyl-CoA for 3-hydroxyacyl-CoA dehydrogenase; and acetoacetyl-CoA for 3-ketoacyl-CoA thiolase.

| Compound                        | Remaining activity | Acyl-CoA dehydrogenase | Crotonase | 3-Hydroxyacyl-CoA dehydrogenase | 3-Ketoacyl-CoA thiolase |
|---------------------------------|--------------------|------------------------|-----------|-------------------------------|-------------------------|
| S-Acetyl-3-mercaptopropionyl-CoA| 100                | 100                    | 96        | 100                           | 92                      |
| S-Hexanoyl-3-mercaptopropionyl-CoA | 100            | 100                    | 94        | 100                           | 96                      |
| S-Myristoyl-3-mercaptopropionyl-CoA | 92               | 28                     | 55        | 6                             | 0                       |

* SC, short-chain; MC, medium-chain; LC, long-chain.
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We therefore conclude that 3-mercaptopropionic acid or a compound derived from it inhibits one or several of the β-oxidation enzymes in a reversible manner. Since β-oxidation is not inhibited in uncoupled mitochondria, the inhibition is energy-dependent possibly because 3-mercaptopropionic acid must first be converted to its CoA derivative.

Our study of the metabolism of 3-mercaptopropionic acid provides strong evidence for the formation of 3-mercaptopropionyl-CoA and S-acyl-3-mercaptopropionyl-CoA thioesters in the mitochondrial matrix (6). Since these metabolites are likely to be present at low concentrations only, no attempt was made to identify them directly and to quantitate them. Instead, we have used chemically synthesized metabolites of 3-mercaptopropionic acid and tested them for their inhibitory effects on individual enzymes of β-oxidation. The conclusion of this evaluation is that 3-mercaptopropionyl-CoA is an inhibitor of medium-chain acyl-CoA dehydrogenase and presumably of butyryl-CoA dehydrogenase. More importantly, long-chain acyl derivatives of 3-mercaptopropionyl-CoA are effective inhibitors of several enzymes of β-oxidation. The inhibitions of 3-ketoacyl-CoA thiolase and 3-hydroxyacyl-CoA dehydrogenase are not believed to be physiologically significant, because these two enzymes are inhibited to nearly the same extent by palmitoyl-CoA which is present at concentrations of 100 μM and higher in mitochondria which actively oxidize fatty acids (13). It seems likely that the inhibition of β-oxidation is a consequence of the inhibition of long-chain and medium-chain acyl-CoA dehydrogenase by long-chain S-acyl-3-mercaptopropionyl-CoA thioesters and 3-mercaptopropionyl-CoA. Although direct proof for the proposed mechanism by which 3-mercaptopropionic acid inhibits β-oxidation in coupled mitochondria is lacking, the data presented in this and the preceding paper (6) agree best with the suggestion that the inhibition of β-oxidation is a consequence of the reversible inhibition of the first step in the pathway.

It is of interest to note that 3-mercaptopropionic acid is a known convulsant agent (14) which has been suggested to cause seizures by depressing the levels of γ-aminobutyric acid in brain (15). The data presented in this and the preceding paper (6) greatly enhance our understanding of the metabolism and the biological activities of 3-mercaptopropionic acid and thus may aid future studies about the biochemistry of chemically induced convulsions.
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