Overproduction of Acetyl-CoA Carboxylase Activity Increases the Rate of Fatty Acid Biosynthesis in *Escherichia coli*

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Acetyl-CoA carboxylase (ACC) catalyzes the first committed step of the fatty acid synthetic pathway. Although ACC has often been proposed to be a major rate-controlling enzyme of this pathway, no direct tests of this proposal *in vivo* have been reported. We have tested this proposal in *Escherichia coli*. The genes encoding the four subunits of *E. coli* ACC were cloned in a single plasmid under the control of a bacteriophage T7 promoter. Upon induction of gene expression, the four ACC subunits were overproduced in equimolar amounts. Overproduction of the proteins resulted in greatly increased ACC activity with a concomitant increase in the intracellular level of malonyl-CoA. The effects of ACC overexpression on the rate of fatty acid synthesis were examined in the presence of a thioesterase, which provided a metabolic sink for fatty acid overproduction. Under these conditions ACC overproduction resulted in a 6-fold increase in the rate of fatty acid synthesis.

Fatty acids are an essential component of the cellular membranes of all living organisms excepting the Archaea. Acetyl-CoA carboxylase (ACC) catalyzes the first committed step of the fatty acid synthetic pathway, the formation of malonyl-CoA from acetyl-CoA plus bicarbonate, and ACC has often been postulated to be a rate-controlling step in fatty acid biosynthesis (see, e.g., Refs. 1 and 2). Consistent with this hypothesis, the activity of ACC, the rates of fatty acid synthesis, and the levels of malonyl-CoA are known to be well correlated during hormonal treatments of mammalian tissues (1, 2). However, interpretation of these data is greatly complicated by the recent discovery of a second ACC isozyme present in mitochondria (3). Data obtained by use of ACC inhibitors in isolated chloroplasts are also consistent with a regulatory role for ACC in this fatty acid synthetic system (4), although no data on plastidial malonyl-CoA concentrations were reported. The role of ACC in determining the rate of fatty acid synthesis *in vivo* seems to remain an open question. As first pointed out by Walsh and Kosshland (5), a direct means to approach *in vivo* pathway regulation is to overproduce candidate enzyme(s) and measure the effect on the flux through the pathway. However, we know of no example in any organism where this approach has been utilized for ACC. A test of the rate-controlling nature of ACC *in vivo* requires significantly increased levels of ACC activity as well as a metabolic sink (6) for the overproduced fatty acid molecules. Provision of an appropriate sink precludes the possibility that complex lipid synthesis (or the capacity of cell membrane bilayers) could limit the rate of fatty acid synthesis.

We have chosen the bacterium *Escherichia coli* to test if increased ACC activity results in increased rates of fatty acid synthesis. This organism has several experimental advantages. First, the *E. coli* ACC genes and proteins are well studied (7–13) and the enzyme does not appear to be regulated by small molecules (7). Second, in the presence of high levels of cytosolic thioesterase activity, newly synthesized fatty acids are released into the culture medium in a nonesterified form (as free fatty acids) (14), thus providing an appropriate metabolic sink (6). Third, *E. coli* has only a single ACC and fatty acid synthesis is the only pathway that consumes malonyl-CoA (10). These attributes are demonstrated by the temperature-sensitive growth and fatty acid synthesis of mutant strains having temperature-sensitive mutations in genes encoding ACC subunits (10, 15–18). Finally, the expression levels of the genes encoding the ACC subunits are known to be regulated by the cellular growth rate (12) and the pools of malonyl-CoA and fatty acid synthetic intermediates are extremely small (19, 20). Both of these findings implicate ACC as a possible rate-controlling step.

The ACC reaction consists of two discrete half-reactions (Fig. 1). In the first half-reaction, biotin is carboxylated by bicarbonate in an ATP-dependent reaction to form carboxybiotin, whereas in the second half-reaction, the carboxyl group is transferred from carboxybiotin to acetyl-CoA to form malonyl-CoA (9). In *E. coli* these half-reactions are catalyzed by different components of a large enzyme complex. The bacterial carboxylase component (8, 10), is responsible for the first half-reaction while carboxyltransfer is catalyzed by a complex of two different proteins (called α and β) (11, 13). Although *in vitro* free biotin functions (albeit very inefficiently) in both half-reactions (7–11), *in vivo* function requires that the biotin moiety be covalently attached to a fourth protein, biotin carboxyl carrier protein (BCCP) (7, 9, 10), the sole biotinylated protein of the organism.

We have simultaneously overproduced all four ACC subunit proteins in a coordinated manner and report that overproduction results in a significant increase in the rate of fatty acid synthesis.

**Experimental Procedures**

*Bacterial Strains and Media*—Strain BL21(DE3) containing DE3, a prophage carrying the T7 RNA polymerase gene (21), was used for...
overexpression studies. The medium was rich broth (per liter; 10 g of tryptone, 1 g of yeast extract, 5 g of NaCl). The panD2 allele was transferred into various strains via P1 phage-mediated transduction from strain SJ16 (23, 24). All cultures were grown at 37 °C.

**Plasmid Constructions**—Plasmid pMSD1 was constructed by inserting a 900-base pair pLS182 (10) KpnI-SalI DNA fragment containing the accB gene into the same sites of pFN476 (22). Plasmid pMSD4 resulted from insertion of a 4.2-kilobase pair XhoI-SalI accD DNA fragment from pPJ10 into the same sites of pFN476. Plasmid pMSD6 was made by inserting the 2.8-kilobase pair accBC SacI-XhoI DNA fragment of pLS182 (10) between the same sites of pFN476. A 4.2-kilobase pair XhoI-SalI DNA fragment of pPJ10 containing the accD gene and the downstream folC gene was inserted into the same sites of pMSD6 to give plasmid pMSD7 (accBCD plus folC). The accB gene was inserted into the SphI site of pMSD7 (a second SphI was added by subcloning the pLS151 (11) XhoI-SacI accA gene fragment into an intermediate polylinker plasmid). The final plasmid (pMSD8) has the four acetyl-CoA carboxylase genes in the order accBCDA with folC inserted between the accD and accA genes. Plasmid pMSD15 was constructed by ligation of the HindIII-BamHI vector fragment of the PACYC184 derivative pCY216 (25) to the HindIII-BamHI ‘tesA’ fragment of pHCI22 (14). In later experiments the instability of plasmid pMSD8 was countered by introduction of the compatible lacI plasmid, pREP4 (Qiagen).

**Enzyme Assays**—Cell extracts were prepared by harvesting the cultures by centrifugation, resuspension of the cells in a minimal volume of 0.2 ml) contained 0.1M Tricine-KOH buffer (pH 8.0), 1 mM ATP, 2.5 mM MgCl2, 100 mM KCl, 39 mM NaH14CO3 (1.17 Ci), 1 mM dithiothreitol, 0.3 mM acetyl-CoA, and up to 0.2 mg of cell-free extract protein.

**Analysis of Intracellular CoA Pools**—The CoA metabolite pools were determined, this result suggested that overproduction of abnormal ratios of the four proteins was toxic to cell growth. To counter this apparent toxicity and to obtain stoichiometric production of the ACC subunits, we cloned the four acc genes in a low copy number vector and triggered overproduction by use of the tightly controlled phage T7 transcription system (21). The T7 promoter plasmid, pFN476 (22), was chosen due to its low copy number (1–5 copies/cell). The high transcriptional efficiency (21) of T7 RNA polymerase and the insensitivity of this polymerase to transcriptional polarity and to most E. coli transcriptional terminators (28, 29) were expected to result in equimolar production of the four subunits. Induction by addition of IPTG of this synthetic operon slowed growth of the bacterial strain, but no loss of colony-forming ability was seen. We assayed the relative production of the four ACC subunits by labeling induced cultures with a mixture of 35S-labeled methionine and cysteine in the presence of rifampicin, a specific inhibitor of E. coli RNA polymerase, such that only gene products expressed from a T7 promoter are 35S-labeled (21). The labeled proteins.

**RESULTS AND DISCUSSION**

**Overexpression of the Acc Proteins**—The accA, accB, accC, and accD genes encode the four ACC subunits: carboxyltransferase α, BCCP, biotin carboxylase, and carboxyltransferase β, respectively. The accB and accC genes comprise a bicistronic operon (10, 12), whereas the genes encoding the carboxyltransferase subunits are far removed both from these genes and one another (11). In order to overexpress ACC activity, we constructed a synthetic operon containing all four genes under control of a bacteriophage T7 promoter (21). A fifth unrelated gene, folC, which lies adjacent to accD in the genome, was included as an internal standard for protein production. We chose to express the acc genes from a phage T7 promoter rather than the native promoters or other E. coli promoters for several reasons. First, in preliminary work we had found that transformation of two compatible high copy number plasmids, one carrying accA and accD and the other accB and accC, into the same host strain was very inefficient (data not shown). Since transformants carrying either plasmid alone were readily obtained, this result suggested that overproduction of abnormal ratios of the four proteins was toxic to cell growth. To counter this apparent toxicity and to obtain stoichiometric production of the ACC subunits, we cloned the four acc genes in a low copy number vector and triggered overproduction by use of the tightly controlled phage T7 transcription system (21). The T7 promoter plasmid, pFN476 (22), was chosen due to its low copy number (1–5 copies/cell). The high transcriptional efficiency (21) of T7 RNA polymerase and the insensitivity of this polymerase to transcriptional polarity and to most E. coli transcriptional terminators (28, 29) were expected to result in equimolar production of the four subunits. Induction by addition of IPTG of this synthetic operon slowed growth of the bacterial strain, but no loss of colony-forming ability was seen. We assayed the relative production of the four ACC subunits by labeling induced cultures with a mixture of 35S-labeled methionine and cysteine in the presence of rifampicin, a specific inhibitor of E. coli RNA polymerase, such that only gene products expressed from a T7 promoter are 35S-labeled (21). The labeled proteins.

**Analysis of Intracellular CoA Pools**—The CoA metabolite pools were labeled with [3-3H]alanine by use of a panD strain (19, 22, 23) which greatly facilitates detection and quantitation. Strains were grown overnight in minimal E salts enriched with 0.2% vitamin-free casein hydrolysate, 0.4% glucose, and 1 mM [3-3H]alanine. The cultures were centrifuged and the cells resuspended in fresh medium and grown until mid-log phase. The cultures were then either treated with cerulenin (0.1 mg/ml) or IPTG (1 mg/l) or both. As described previously (23), following induction the cells were treated with trichloroacetic acid; a mixture of unlabeled CoA, malonyl-CoA, and acetyl-CoA were added as internal standards (these were detected by UV absorption); and the CoA compounds were separated and quantitated. Intracellular malonyl-CoA concentrations were calculated from the efficiency of counting and cell numbers.

**Assay of Lipid Synthesis**—Labeling of lipids with [1-14C]acetate and thin layer chromatography were performed as described previously (27), followed by PhosphorImager analysis.
were then separated by SDS-polyacrylamide gel electrophoresis, and the radioactivity in each band was quantitated using the FluorChem protein as an internal standard. The relative molar values obtained for the four ACC subunits were: AccB, 1.0; AccC, 0.99; AccA, 1.13; and AccD, 0.95. It should be noted that another enzyme is required for ACC activity, the biotin protein ligase that attaches the biotin moiety of BCCP (25). In some experiments we overexpressed the E. coli biotin protein ligase from a compatible plasmid prior to induction of ACC overexpression. This gave only a modest increase in ACC specific activity, indicating that ligase was not severely limiting during the brief induction of ACC overexpression, and thus the biotin ligase plasmid was omitted in order to simplify the experiments.

The overproduced ACC proteins were highly active in both half-reactions (Table I). We also compared extracts of induced cultures that overproduced subsets of the ACC proteins. The biotin carboxylase activities observed upon overexpression of accC alone or in combination with the other subunits were several orders of magnitude greater than those of non-overproducing strains, and increased activities were observed when several subunits were overexpressed; these results are consistent with formation of a protein complex. Similar results were obtained for the carboxyltransferase activity. The most striking result was seen when the overall ACC reaction, conversion of acetyl-CoA to malonyl-CoA, was assayed (Table I). Extracts of strains that overproduced all four subunits had readily detectable ACC activities, whereas, in agreement with prior work (7, 8, 30), no activity could be detected in extracts of wild type strains (the ACC complex is believed to be unstable at the low subunit concentrations of crude extract). Extracts of strains that overproduced only one or two subunits also had no detectable ACC activity. Surprisingly, a strain that overproduced only the AccB, AccC, and AccD proteins had ACC activity despite the lack of AccA overproduction (Table I). The product of these reactions was identified as malonyl-CoA by HPLC analysis (see below) and its function as a substrate for rat liver fatty acid synthase, resulting in mislabeling the isotope. A dual label experiment was performed to determine if ACC overproduction altered the specific activity of the acetyl-CoA pool synthesized in the presence of [1-14C]acetate. The experiment of Fig. 2 was repeated except that cultures were grown with β-[3H]alanine and briefly labeled with [1-14C]acetate in the presence or absence of ACC overproduction and the (3H:14C) ratios of the two isotopes were determined for the acetyl-CoA produced. The ratio for cells having normal levels of ACC was 1.15 to 1, while cells that overproduced ACC had a virtually identical (3H:14C) ratio (1.11 to 1). These data indicated that the rate of incorporation of this precursor was a valid measure of the rate of fatty acid synthesis under these conditions.

The enzyme activities were assayed as described under “Experimental Procedures.” All activities are given as nanomoles of 14CO2 fixed (for biotin carboxylase and acetyl-CoA carboxylase activities) or of 14CO2 released (for the carboxyltransferase back reaction) min 1 mg 1 of protein. Each assay was repeated at least twice on independently grown cultures.

**Table I**

| Plasmid-borne acc genes | Biotin | Carboxylase | Carboxyltransferase | Acetyl-CoA carboxylase |
|-------------------------|--------|-------------|---------------------|-----------------------|
| None                    | 0.004  | 0.021       | <0.01               |<0.01                  |
| A                       | NT*    | NT          | <0.01               |<0.01                  |
| B                       | 0.002  | 0.022       | <0.01               |<0.01                  |
| C                       | 2.94   | <NT>        | <0.01               |<0.01                  |
| D                       | NT     | 14.87       | <0.01               |<0.01                  |
| BC                      | NT     | NT          | 0.01                |0.01                   |
| AD                      | NT     | 25.01       | <0.01               |<0.01                  |
| BCD                     | 4.23   | NT          | 0.11                |0.11                   |
| ABCD                    | 4.63   | 28.37       | 0.50                |0.50                   |

* NT, not tested.

As expected, cultures that overproduced ACC also overproduced malonyl-CoA (Fig. 2). A readily detectable level of malonyl-CoA (17.7% of the total CoA compounds, a calculated intracellular concentration of 13.3 μmol) was observed upon overproduction (Fig. 2C), whereas strains having normal ACC levels contained barely detectable malonyl-CoA levels (0.01% of the total CoA metabolite pool) (Fig. 2A). Similarly low levels of malonyl-CoA in wild type E. coli cells were reported by Heath and Rock (19), who also reported accumulation of much larger pools of malonyl-CoA when fatty acid synthesis is blocked by addition of cerulenin. This inhibitor specifically blocks 3-ketoacyl-ACP synthases I and II, the enzymes primarily responsible for addition of malonate-derived carbon atoms to the elongating fatty acyl chains. Addition of cerulenin to strains having normal ACC levels increased the malonyl-CoA pools to 10% of the total CoA compounds (Fig. 2B). In contrast, addition of cerulenin to cultures induced for ACC overproduction gave a very large increase in malonyl-CoA at the expense of acetyl-CoA, such that malonyl-CoA comprised more than half (55.1%) of the total CoA metabolites (Fig. 2D). These results indicate that the overproduced ACC proteins are active in vivo. Moreover, the increased malonyl-CoA levels observed upon blocking fatty acid synthesis in cells overproducing ACC suggested that, in the absence of cerulenin, malonyl-CoA was consumed by fatty acid synthesis at an accelerated rate.

To test this indirect indication of increased fatty acid synthesis, we directly measured fatty acid synthesis. Incorporation of [1-14C]acetate is the preferred method for quantitation of fatty acid synthetic rates in vivo, but since acetyl-CoA is a central metabolic intermediate, these pools can change upon metabolic manipulations (31). Alterations of the endogenous acetyl-CoA pool would then change the effective specific activity of the acetyl-CoA utilized in fatty acid synthesis, resulting in misleading synthetic rates. A dual label experiment was performed to determine if ACC overproduction altered the specific activity of the acetyl-CoA pool synthesized in the presence of [1-14C]acetate. The experiment of Fig. 2 was repeated except that cultures were grown with β-[3H]alanine and briefly labeled with [1-14C]acetate in the presence or absence of ACC overproduction and the (3H:14C) ratios of the two isotopes were determined for the acetyl-CoA produced. The ratio for cells having normal levels of ACC was 1.15 to 1, while cells that overproduced ACC had a virtually identical (3H:14C) ratio (1.11 to 1). These data indicated that the rate of incorporation of this precursor was a valid measure of the rate of fatty acid synthesis under these conditions.

**Increased ACC Activity Results in Increased Rates of Fatty Acid Synthesis**—As noted above, a valid test of the effects of ACC overproduction on the rate of fatty acid synthesis requires that the products can accumulate without limitation. We therefore uncoupled fatty acid synthesis from phospholipid synthesis by overproduction of a mutant form of E. coli thioesterase I (14). Thioesterase I (encoded by the tesA gene) is normally a periplasmic enzyme, but the mutant protein (called TesA) lacks the leader peptide, thereby blocking export of the enzyme to the cellular periplasm. The 'TesA' enzyme remains in the cytosol, where it cleaves the long chain acyl-ACP intermediates of fatty acid synthesis (14). The resulting free fatty acids are found in the culture medium (14); hence, production of the mutant thioesterase would direct any overproduced fatty acids to an ideal (6) high capacity metabolic sink, the culture medium.

In these experiments the 'TesA' thioesterase was induced by addition of arabinose (14). ACC overproduction was subsequently induced and the rate of fatty acid synthesis was fol-
Fig. 2. Analysis of the intracellular pools of CoA and its thioesters. The strains used were made by transformation of a pnonD2 derivative of E. coli BL21 (DE3) with either the vector plasmid, pFN476 (panels A and B), or the ACC overproduction plasmid, pMSD8, which encodes all four ACC subunits (panels C and D). The strains were labeled with $\beta$-[3H]alanine before and after IPTG induction of ACC overproduction. After 1 h of induction, the two cultures were each split in half. One half of each culture was treated with cerulenin (0.1 mg/ml final concentration) to block long chain fatty acid synthesis, and the remaining half was left untreated. After a 5-min incubation, the CoA pools were extracted and analyzed by HPLC. The chromatographic peaks are malonyl-CoA (M), CoA (C), and acetyl-CoA (A). Panel A, CoA metabolites from the strain carrying vector pFN476 without cerulenin treatment; panel B, CoA metabolites from the strain carrying vector pFN476 following cerulenin treatment; panel C, CoA metabolites from the strain carrying the ACC overproduction plasmid pMSD8 without cerulenin treatment; panel D, CoA metabolites from the strain carrying the ACC overproduction plasmid pMSD8 following cerulenin treatment. The radioactivity (cpm) of the [3H]-labeled compounds determined by an in-line scintillation counter is plotted versus the retention time (note the slightly differing scales of the upper and lower panels).

Fatty acid synthesis results from cleavage of the fatty acid synthetic pathway and become incorporated into phospholipids. The Guanosine Alarmones Do Not Inhibit Fatty Acid Synthesis—Amino acid starvation—P. citronellolis triggers a complex pattern of metabolic adjustments called the stringent response, which results in inhibition of phospholipid synthesis as well as other processes such as stable RNA synthesis (32). This response is mediated by the rapid accumulation of the guanosine alarmones, guanosine-5'-triphosphate-3'-diphosphate and guanosine-5'-diphosphate-3'-diphosphate, collectively called (p)ppGpp. Polaskis and co-workers (33) have attributed the inhibition of phospholipid synthesis during amino acid starvation to inhibition of ACC by the guanosine alarmones since (p)ppGpp was found to inhibit the carboxyltransferase half-reaction in vitro (the overall ACC reaction was not tested). Moreover, guanosine 5'-diphosphate 3'-diphosphate inhibition of the P. citronellolis ACC reaction has been reported (30). The physiological relevance of these observations has been questioned, most recently by Heath and co-workers (35), who showed that overproduction of sn-glycerol 3-phosphate acyltransferase, the first enzyme of phospholipid synthesis, substantially restored the rate of phospholipid synthesis in cells containing high concentrations of (p)ppGpp. However, in that study phospholipid synthesis was not completely restored and thus an effect on fatty acid synthesis remained possible.

We tested the effects of the stringent response on fatty acid synthesis per se by generating high intracellular levels of (p)ppGpp by use of a plasmid that overexpressed (p)ppGpp synthase I, the relA gene product, under a tac promoter. The plasmid used was compatible with the plasmids used for ACC overproduction and for TeaA production, and thus various combinations of plasmids could be tested. First, overproduction of ACC failed to reverse the inhibition of phospholipid synthesis resulting from induction of (p)ppGpp accumulation (detected by inhibition of growth). However, since this result could be...
E. coli the mutant thioesterase. The strains were Lanes 1 and 2, no plasmids; lanes 3 and 4, pMSD8 (overproduction of AccABCD); lanes 5 and 6, pMSD8 and pMSD15 (overproduction of AccABCD and TesA); lanes 7 and 8, pMSD8 and pMSD15 (overproduction of AccBCD and TesA); lanes 9 and 10, pMSD15 and pMSD1 (overproduction of Acc and TesA). The doublot in the free fatty acid region is due to partial conversion of the free acids (lower spot) to methyl esters during extraction and chromatography. The phospholipid species are (in ascending order) phosphatidylethanolamine, phosphatidylglycerol, and cardiolipin.

CONCLUSIONS

Our finding that the rate of fatty acid synthesis can be increased by overexpression of ACC does not agree with the increased by overexpression of ACC does not agree with the

due to the reported effect on sn-glycerol 3-phosphate acyltransferase (35), we introduced the TesA production plasmid and examined free fatty acid production during the stringent response in the presence or absence of ACC overproduction (Fig. 4). The accumulation of (pppGpp) had no detectable effect on the rate of free fatty acid synthesis either in the presence or absence of ACC overproduction. We therefore conclude that the in vitro inhibition of ACC by the guanosine alarmones is not physiologically relevant. A plausible explanation for the observed enzyme inhibition (30, 33) is that (pppGpp) may compete with the substrate CoA esters since adenosine 5′-monophosphate-3′-monophosphate, a molecule structurally similar to (pppGpp), is a potent inhibitor of many enzymes that utilize CoA and its thioesters.

Our finding that the rate of fatty acid synthesis can be increased by overexpression of ACC does not agree with the
strict tenants of metabolic control analysis (6, 36). This analytical approach holds that the control of a pathway is spread among the component enzymes such that increased activity of one enzyme will not result in increased flux through a pathway (6, 36). Metabolic control analysis has done a valuable service in countering the classical idea of a rate-limiting step in which one enzyme determines the rate of a pathway. However, in addition to the present case, there are several well-documented examples in which increased activity of one or two enzymes does increase the flux through a pathway in *E. coli*. In early work, Walsh and Koshland (5) showed that increased citrate synthase activity increased the flux through the tricarboxylic acid cycle. More recently, succinate production by *E. coli* was shown to increase upon overproduction of phosphoenolpyruvate carboxylase (37) and increased rates of glycolytic flux resulted from increased pyruvate kinase levels (38). Similar results have been obtained for the aromatic amino acid synthetic pathway (39). Therefore, it seems that there are pathways including fatty acid synthesis in which the situation is intermediate between the two extreme views: that of the classical rate-limiting step and that of metabolic control analysis.

It should be noted that metabolic control analysis stipulates that small (<10%) changes in enzyme levels (relative to the wild type levels) are required to calculate accurate flux control coefficients (6), and thus we are unable calculate such values from the present data. Technical limitations preclude a fine level of control within the range of the enzyme levels of wild type cells. We are limited to phage promoters such as that of phage T7 since ACC overproduction requires stoichiometric overproduction of the individual proteins of the enzyme complex. These promoters use a simple form of RNA polymerase that is immune to transcriptional polarity thus avoiding the polarity characteristic of *E. coli* RNA polymerase. However, the cost of use of phage T7 promoters is that they are very strong and are controlled only indirectly via synthesis of T7 RNA polymerase, which does not allow fine levels of control.
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