Hormonal and Nutritional Control of the Fatty Acid Synthase Promoter in Transgenic Mice*

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To study the molecular basis of tissue-specific and hormonally regulated expression of the fatty acid synthase (FAS) gene in vivo, we generated lines of transgenic mice carrying 2.1 kilobases of the 5′-flanking region (−2100 to +67) of the rat FAS gene fused to a chloramphenicol acetyltransferase (CAT) reporter gene. This reporter gene construct was strongly expressed in tissues that normally express high levels of FAS mRNA, which include liver and white adipose tissues. In contrast, CAT reporter activity was not detected in appreciable levels in lung, heart, kidney, and muscle tissues, which do not normally show significant levels of FAS activity. The relative levels of the CAT mRNA driven by the rat FAS promoter in various tissues of the transgenic animals approximated those of the endogenous mouse FAS mRNA. We also examined the hormonal and nutritional regulation of the FAS(2.1)-CAT reporter gene in transgenic mice. CAT activity was increased in both liver and white adipose tissue when fasted animals were refed a high carbohydrate, fat-free diet. These changes in CAT activity and CAT mRNA levels occurred in parallel to the changes in endogenous mouse FAS mRNA levels. On the other hand, fasting/refeeding did not change CAT activity appreciably in other tissues, such as muscle and brown adipose tissue. Administration of dibutyryl cAMP at the start of refeeding prevented an increase in CAT activity in liver. However, the cAMP effect was tissue-specific as cAMP treatment did not bring about change in CAT activity in adipose tissue. Next, to examine the effect of insulin, we made the transgenic mice insulin-deficient by streptozotocin treatment. Insulin treatment of the streptozotocin-diabetic mice increased both the CAT activity and CAT mRNA levels. These changes in CAT activity and CAT mRNA levels occurred in parallel to the changes in endogenous mouse FAS mRNA levels. On the other hand, fasting/refeeding did not change CAT activity appreciably in other tissues, such as muscle and brown adipose tissue. Administration of dibutyryl cAMP at the start of refeeding prevented an increase in CAT activity in liver. However, the cAMP effect was tissue-specific as cAMP treatment did not bring about change in CAT activity in adipose tissue. Next, to examine the effect of insulin, we made the transgenic mice insulin-deficient by streptozotocin treatment. Insulin treatment of the streptozotocin-diabetic mice increased both the CAT activity and CAT mRNA levels driven by the rat FAS promoter in liver and white adipose tissue. These changes in CAT expression by insulin paralleled those in endogenous FAS mRNA levels. Administration of glucocorticoids increased CAT activity in all tissues examined: liver, white and brown adipose tissues, lung, heart, and spleen. Overall, the first 2.1 kilobases of the 5′-flanking region of the rat FAS gene appear to contain sequence elements necessary to confer tissue-specific and hormonally regulated expression characteristic of the endogenous FAS gene.

Fatty acid synthase (FAS) plays a central role in de novo lipogenesis in mammals and birds by catalyzing all the reactions in conversion of acetyl-CoA and malonyl-CoA to palmitate. FAS activity is not known to be regulated by allosteric effectors or covalent modification. However, FAS concentration in liver and adipose tissue is highly sensitive to nutritional, hormonal, and developmental states (1–3). When rats are fasted for 1–2 days, the rate of synthesis of FAS declines, while refeeding a high carbohydrate diet increases synthesis of FAS (4). We have previously reported that FAS mRNA was not detectable in livers of fasted mice but dramatically increased upon refeeding a high carbohydrate, fat-free diet (5). This induction of FAS mRNA resulted from increased transcription of the FAS gene (6). Both lipogenic and lipolytic hormones participate in regulating FAS expression. Injection of cAMP prevented increase in FAS mRNA and transcription during fasting/refeeding. FAS expression was very low in diabetic mice, and insulin caused a marked and rapid increase in the FAS mRNA levels and in the transcription rate of the FAS gene (6). Hormonal regulation of FAS expression in adipose tissue, on the other hand, has not been studied extensively. We observed that insulin increased and cAMP decreased FAS mRNA levels in 3T3-L1 adipocytes (5). In these cells, thyroid hormone also stimulated FAS gene transcription, indicating independent effects of insulin, cAMP, and thyroid hormone on FAS gene expression (7). In addition to these various hormones and agents that regulate FAS expression, dietary long-chain polyunsaturated fatty acids (PUFAs) have been reported to have inhibitory effects on FAS expression, while saturated and monounsaturated fatty acids show little to no inhibitory effects (8). The putative cis-acting elements responsible for the hormonal/nutritional regulation of the FAS gene have not been extensively studied. The only reported element is an insulin response sequence at −67 to −52 base pairs of the FAS promoter that we previously defined by transfection of various FAS promoter/luciferase constructs into 3T3-L1 adipocytes (9, 10).

Here, to investigate the molecular basis for the tissue-specific and nutritional/hormonal regulation of FAS gene expression in an appropriate in vivo physiological context, we generated transgenic mice carrying the 2.1-kb 5′-flanking promoter region of the FAS gene fused to a chloramphenicol acetyltransferase (CAT) reporter gene. Transient transfection into established cell lines is usually employed in defining promoter function. The relevance of cell culture studies to in vivo events, however, is not clear. Transgenic animal studies only will unequivocally demonstrate the presence of a true functional DNA region for tissue-specific expression and for hormonal regulation. In the present study, we show that the 2.1-kb region flanking the 5′-end of the rat FAS gene is sufficient to direct tissue specificity as well as hormonal regulation that mirrors the expression of the endogenous FAS gene.

EXPERIMENTAL PROCEDURES

Plasmid Construction and Production of Transgenic Mice—The 5′-flanking region of the rat FAS gene spanning from 2798 to 5179 was
cloned by PCR from rat genomic DNA using oligonucleotides based on the published sequence for the rat FAS gene (11). The PCR product was subcloned into the pCI vector (Invitrogen) and sequenced using the dye-deoxy chain termination method (12). The FAS(-2100)-CAT plasmid was constructed by ligating the restriction fragment, containing sequences from -2100 to +67 of the rat FAS gene, into the cloning site of the pCI vector pBLCAT3 vector. The construct was obtained from Dr. G. Schutz (Heidelberg, Germany). The 3.8-kb fragment, which has the FAS promoter, CAT, and SV40 polyadenylation sequences from FAS(-2100)-CAT plasmid, was digested with HindIII and KpnI. This 3.8-kb fragment was purified by agarose gel electrophoresis and injected into the pronucleus of fertilized mouse embryos (Harvard Medical School, Brigham Women's Hospital transgenic mice facility). Four founders containing the FAS promoter-CAT gene were produced. Heterozygous transgenic progenies (F1) were obtained by breeding the founders (F0) to C57BL/6 wild type mice. The F1 male and female litter mates were bred back to C57BL/6 wild type mice to produce F2 generation progenies, and the positive F2 generations were used for the studies. Transgenic mice carrying the FAS promoter/CAT gene were identified by PCR amplification of tail DNA using primers 5' - GC-CAAGCTTGACCCCATGT-3' and 5'-TTTATCCGGCCTTATCATT-3', which amplify a 410-base pair region spanning the junction between the FAS promoter and the CAT reporter gene.

Animal Treatment—The animals had access to food pellets containing 58% carbohydrate ad libidum. For PUFA feeding, mice were trained to eat the high carbohydrate, fat-free diet supplemented with 10% triolein (Sigma) from 9 a.m. until 12 noon for 10 days as described previously (13). Butylated hydroxytoluene (Sigma) was added at 0.1% to prevent oxidation of the PUFA diet. One group was maintained on the triolein diet for an additional 5 days, while the other group was switched to a menhaden oil (Zapata-Haynie, Richmond, VA) diet 5 days. Mice were sacrificed 24 h after the last meal. Diabetes was induced by intraperitoneal injections of streptozotocin (20 mg/100 g, body weight) following a 6-h fasting period as described previously (14). Diabetes was confirmed by high blood glucose level (>250 mg/dl) by Dextrostix (Ames). Insulin was administered to diabetic mice at a combined dose of regular insulin (3 units/100 g, body weight; Lilly) intraperitoneally and Lente insulin (10 units/100 g, body weight; Lilly) subcutaneously, as described previously (6). Diabetic mice were studied 85–90 h following streptozotocin treatment. Insulin-treated mice were studied 16 h following insulin treatment. Dibutyryl cAMP (6 mg/100 g, body weight) and theophylline (3 mg/100 g body weight) were given intraperitoneally to the previously fasted mice at the start of the refeeding of a high carbohydrate, fat-free diet (ICN). Mice were injected intraperitoneally with dexamethasone (1.25 mg/100 g, body weight) and sacrificed 5 h later.

CAT Activity Measurement—The animals were killed by cervical dislocation. Tissues were isolated by rapid dissection and frozen in liquid nitrogen. The frozen tissues were pulverized using a ceramic mortar. 250 μl of 0.1 M Tris, pH 7.4, and 2 μl NaCl were added to the powdered tissue, and this suspension was freeze-thawed three times at -70°C. The suspension was centrifuged at 12,000 × g for 10 min at 4°C. The protein concentration was determined by the Bio-Rad coomassie dye binding assay using bovine serum albumin as the standard (15). CAT activity from 30 to 500 μg of protein extracts was measured as described by Gorman et al. (16). Chloramphenicol and its acetylated products were separated after 2 h of incubation by silica gel 1B thin layer chromatography (TLC) plates (Baker). TLC plates were exposed to Fuji RX film.

RNA Extraction and Northern Blot Analysis—Tissues were excised and frozen in liquid nitrogen. Total RNA from tissues was extracted with guanidinium thiocyanate and centrifuged over CsCl (17). For Northern blot analysis, RNA was size fractionated on a 1% agarose gel in 2.2 M formaldehyde, 20 mM MOPS, pH 7.0, 1 mM EDTA, stained with ethidium bromide, and transferred to Hybond (Amersham). Some of the membranes were stained with ethidium bromide as indicated according to the procedure of Herrin and Schmidt (18). Following prehybridization for at least 3 h in 50% formamide, 5 × SSC, 5 × Denhardt’s solution, 0.5% SDS, and 50 μg/ml herring sperm DNA at 42°C, filters were hybridized at 42°C for 16–20 h under identical conditions with the addition of at least 1 × 106 cpyml of 32P random-primed probes (19). Final washes were for 1 h in 0.1 × SSC, 0.1% SDS at 65°C. Filters were exposed with intensifying screen to Fuji RX film.

RESULTS AND DISCUSSION

Tissue Specificity of FAS Promoter/CAT Fusion Gene Expression in Transgenic Mice—To investigate the tissue-spe-
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murine FAS mRNA levels, high levels in adipose tissue and liver compared to other tissues, determined by Northern blot analysis using the same RNA prepared from these tissues. This is in agreement with the fact that FAS activity is high in lipogenic tissues such as liver, adipose tissue, and lactating mammary tissue (1–3). Although two different founders show high level expression of CAT in both liver and adipose tissue, the relative levels of CAT activity between these two tissues were somewhat different in these two founders. The reason for this variation may be due to the differences in food consumption and therefore, induction of the FAS gene by fasting/refeeding, since these mice were fasted and subsequently refed a high carbohydrate diet before sacrifice. Mice that were fed a normal chow diet showed higher CAT activity in adipose tissue than in liver (as indicated in Fig. 5), but the magnitude of induction by fasting/refeeding in liver was higher than that in adipose tissue. The results indicate that the 2.1 kb of the 5′-flanking region of the rat FAS gene is sufficient to confer tissue-specific expression, i.e. high level expression in liver and adipose tissue.

Regulation of the FAS Promoter/CAT Fusion Gene Expression by Fasting/Refeeding—We have previously reported that FAS mRNA levels were dramatically increased in the livers of previously fasted mice fed a high carbohydrate diet and that this induction was controlled at the transcriptional level by increasing the transcriptional rate of the FAS gene (6). FAS activity is known to be induced by refeeding of a high carbohydrate diet not only in liver but also in adipose tissue (1–3). We have previously reported that FAS induction in adipose tissue is also at the pretranslational level by increasing FAS mRNA levels in white adipose tissue. 2 To assess the nutritional regulation of the FAS(2.1)-CAT reporter gene, transgenic mice from two different founders were fasted for 48 h followed by 24 h of refeeding of a high carbohydrate, fat-free diet. CAT activity was low but detectable in liver of fasted mice but, refeeding resulted in a 5-fold increase in CAT activity. CAT mRNA was not detectable in fasted mice but was induced dramatically in refeed mice (Fig. 2). The increase in CAT mRNA was parallel to that of the endogenous FAS mRNA. The relative levels of CAT activity in fasted mice did not appear to quantitatively reflect the CAT mRNA or the endogenous FAS mRNA levels. The reason for this discrepancy in CAT activity and CAT mRNA levels is not known, but it may reflect higher sensitivity of CAT activity measurement than the Northern blot analysis for CAT mRNA levels. It may also be possible that CAT protein was stabilized in fasted mice. We also examined changes in CAT activity by fasting/refeeding in white and brown adipose tissues and in muscle. As shown in Fig. 2, there was a similar induction in CAT activity in white adipose tissue as in liver. On the other hand, there was no increase in CAT activity in brown adipose tissue or skeletal muscle. These experiments, therefore, indicate that induction of FAS gene transcription occurs in lipogenic tissues, i.e. liver and white adipose tissue only, and the 2.1-kb 5′-flanking region of the rat FAS gene is sufficient for the induction of the FAS gene by fasting/refeeding. Recently, investigators reported a site hypersensitive to DNase I present in the first intron of the rat FAS gene in the liver but not in the spleen (20, 21), in contrast to Roder et al. (22) who did not find a DNase I hypersensitive site in this region. An E-box sequence has been located in this region that could bind in vitro USF/MLTF, a transcription factor responsible for glucose regulation of the L-pyruvate kinase and S14 gene (23–26). In addition, Towle and co-worker (26) showed that this E-box sequence from the FAS gene could confer glucose responsiveness to a heterologous promoter when transiently transfected into primary hepatocytes. Foufelle et al. (20) concluded, therefore, that this site present in the first intron might be the glucose-response element of the FAS gene. Regardless, our transgenic experiments clearly demonstrate that the first 2.1-kb FAS promoter region that does not include the first intron is sufficient for the transcriptional activation of the FAS gene during fasting/refeeding. The present results, therefore, indicate that a functional glucose response element is present in the first 2.1 kb of the promoter region of the FAS gene.

Hormonal Regulation of the FAS Promoter/CAT Fusion Gene in Transgenic Mice—In addition to the increased glucose levels, increased insulin and decreased glucagon levels in circulation brought about by the nutritional manipulation of fasting/refeeding contribute to the changes in FAS gene expression. We previously reported transcriptional effects of the FAS gene by insulin and cAMP in mice liver. Therefore, we examined whether the 2.1-kb FAS promoter/CAT fusion gene was capable of responding to these hormones in transgenic mice. To examine the insulin regulation of the 2.1-kb FAS promoter/CAT gene, we compared CAT expression in streptozotocin-diabetic and insulin-treated streptozotocin-diabetic transgenic mice. Insulin treatment resulted in an order of magnitude increase in the CAT expression directed by the 2.1-kb 5′-flanking region of the rat FAS gene. The increase in

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CAT activity accompanying insulin treatment was observed in both liver and white adipose tissue but not in brown adipose tissue (Fig. 3). We determined CAT mRNA levels in liver of these mice by Northern blot analysis. The CAT mRNA was not detectable in diabetic transgenic mouse liver, but its level was increased dramatically by insulin, the increase being parallel to that of the endogenous FAS mRNA. These results indicate that the 2.1-kb 5′-flanking sequence of the rat FAS gene is sufficient for insulin responsiveness in vivo and that insulin regulation is in liver and white adipose tissue but not in other tissues such as brown adipose tissue and kidney. We have previously demonstrated by transient transfection into 3T3-L1 adipocytes that an insulin response element is present between −67 to −52 base pairs of the FAS promoter (10).

We next studied the effect of cAMP on FAS promoter/CAT gene expression. Fasted transgenic mice were refeed with a high carbohydrate, fat-free diet for 9 h to induce FAS/CAT fusion gene expression. Dibutyryl cAMP was administered at the start of refeeding. As shown in Fig. 4, both lipogenic tissues, liver and white adipose tissue, showed high levels of CAT activity after 9 h of refeeding of a high carbohydrate diet. cAMP administration at the start of the refeeding prevented this increase in CAT activity in liver driven by the 2.1-kb 5′-flanking region of the FAS gene. The present result is in agreement with our previous observation that cAMP prevents increase in FAS gene transcription that accompanies refeeding in mice (6). However, the effect of cAMP appears to be tissue specific. Unlike in liver, there was no change in CAT activity in adipose tissue. Our observation may explain a previous report that glucagon decreased FAS activity in liver but not in adipose tissue (27). On the other hand, we previously reported that cAMP decreased FAS mRNA levels in 3T3-L1 adipocytes in culture. We do not know the reason for this discrepancy. It is possible that cAMP has a dominant negative effect during fasting/refeeding only in liver, and the hormonal and nutritional milieu of cultured 3T3-L1 adipocytes is different from that of adipose tissue in vivo. Further studies are necessary to elucidate cAMP effects on the FAS gene transcription in different tissues. Nevertheless, our result clearly indicates that the 2.1-kb 5′-flanking sequence of the FAS gene is sufficient for dominant suppressive effect of cAMP on FAS gene transcription in liver during fasting/refeeding.

The role of glucocorticoids in regulating FAS activity or FAS gene expression in different tissues has not been studied. Moreover, contradictory results were reported on glucocorticoid effects on fatty acid synthesis (28, 29). Therefore, we examined the regulation of the 2.1-kb FAS promoter/CAT reporter gene by glucocorticoids in transgenic mice. As shown in Fig. 5, the basal CAT activity of transgenic animal on a normal chow diet was highest in adipose tissue as discussed in Fig. 1. On the other hand, CAT activity was difficult to detect in other tissues from normal chow-fed transgenic animal. Administration of synthetic glucocorticoids, such as dexamethasone, caused an increase in CAT expression in all tissues examined such as liver, white and brown adipose tissues, lung, heart, and spleen. Therefore, we conclude that glucocorticoids increase FAS expression in all tissues. Our observation that glucocorticoids up-regulate FAS gene agrees with a recent report on glucocorticoid stimulation of FAS gene transcription in fetal lung (30). On the other hand, a previous report showed that FAS activity was decreased in adipose tissue, and adrenalectomy produced an increase in FAS activity that correlated with changes in fatty acid synthesis (27). These changes, however, were tissue specific in that neither the glucocorticoid injection nor the adrenalectomy affected hepatic FAS activity. In those studies, the animals were on a high carbohydrate, fat-free diet, and the effects observed may partly reflect glucocorticoid effect during FAS induction by refeeding. Regardless, our data indicate that 2.1 kb of the FAS 5′-flanking sequence is sufficient for the transcriptional activation of FAS gene by glucocorticoids.

It has been known that, although their molecular basis is not clear, dietary PUFAs can suppress expression of several genes involved in hepatic lipid metabolism, including FAS (8). It was also shown that PUFAs suppressed expression of FAS mRNA levels in liver was at the transcription level (13). In adipose tissue, however, although both saturated and unsaturated fatty acids depressed de novo fatty acid synthesis, dietary saturated and polyunsaturated fat had only a slight suppressive effect on FAS mRNA levels (8). We, therefore, compared the effects of triolein con-
taining essentially oleic acid (C18:1) and menhaden oil enriched in long chain n-3 fatty acids (e.g. eicosapentaenoic acid (C20:5ω3) and docosahexaenoic acid (C22:6ω3)) on the regulation of the 2.1-kb FAS promoter/CAT gene of these transgenic mice. First, we carried out Northern blot analysis to determine the effect of these oils on the endogenous FAS mRNA levels. In both liver and adipose tissue, FAS mRNA levels were dramatically suppressed in both liver and adipose tissue of mice fed the menhaden oil diet as compared to those fed the triolein diet (Fig. 6). However, CAT activity in these tissues was only 2-fold lower than that of the mice on the menhaden oil diet. It is possible that multiple elements are present for suppression of the FAS gene transcription by PUFAs and that one such element exists in the first 2.1 kb of the 5'-flanking region of the FAS gene. Another possibility is that FAS may also be regulated by PUFAs at the level of mRNA stability as well as at the transcriptional level.

In summary, a 2.1 kb region flanking the 5'-end of the rat FAS gene appears sufficient to direct tissue-specific expression of a reporter gene in transgenic mice. In addition to being sufficient for conferring tissue-specific expression in transgenic animals, the 2.1 kb FAS promoter fragment also displays appropriate hormonal control characteristic of the endogenous mouse FAS mRNA. Most of these studies were performed in at least two transgenic founder lines and gave similar results, indicating that the site of chromosomal integration did not influence expression. Additional FAS promoter-reporter constructs expressed in transgenic mice will be necessary to further define DNA sequences responsible for tissue-specific and regulated expression of the FAS gene in vivo.

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