*Minireview*

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# C/EBP and the Control of Phosphoenolpyruvate Carboxykinase Gene Transcription in the Liver*

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In 1989, shortly after the discovery of CAAT/enhancer-binding protein (C/EBP)[1] and in a period before it was clear that there was more than one form of C/EBP, McKnight *et al.* (1) published a review entitled: "Is C/EBP a Central Regulator of Energy Metabolism?" This prediction of a critical metabolic role for this transcription factor was based on the very slim evidence that C/EBP was involved in the transcription of a number of metabolically important genes such as 422/aP2, phosphoenolpyruvate carboxykinase (PEPCK), and fatty acid synthase, in addition to its role in the differentiation of adipocytes (2, 3). Over the decade since this article was published, the prediction has proven to be remarkably accurate. C/EBP is now known to comprise a gene family with a number of closely related members, the biology of which has been detailed in the first minireview in this series by Lekstrom-Himes and Xanthopoulos (4). These C/EBP isoforms can stimulate or inhibit transcription from a growing list of genes in a variety of tissues in animals as diverse as chickens and rats. One of the critical aspects of the biology of C/EBP that has emerged over the past 10 years is the key role that members of the family of transcription factors play in both the development and maintenance of metabolically important processes (1, 5, 6). This review will focus on the effects of C/EBP isoforms on the control of transcription of the gene for the key gluconeogenic enzyme PEPCK (GTP) (EC 4.1.1.32) as a model for its regulation of other genes that code for enzymes of metabolic importance.

## *Transcriptional Regulation of the PEPCK Gene Promoter*

The transcriptional control of the gene for the cytosolic form of PEPCK from the rat (7–9) and chicken (10, 11) has been extensively studied. The promoter regulatory region of the gene from the rat is shown in Fig. 1. Because the sequence of the promoter for the PEPCK gene from the mouse, rat, and human has been remarkably conserved (greater than 95% sequence identity), it is reasonable to assume that the pattern of transcriptional regulation noted from studies with the PEPCK gene promoter from rodents is characteristic of the control in most mammalian species. The PEPCK gene promoter contains several critical regions of transcription factor binding that are required for the regulation of PEPCK gene transcription.

*Region 1*—This region contains a cAMP regulatory element (CRE) (−91 to −84), which is about 60 base pairs 5′ from the TATA box (−29 to −23) and is immediately adjacent to a nuclear factor 1 (NFI)-binding site (−116 to −104). The CRE has been shown to bind members of the leucine zipper family of transcription factors, including C/EBP$\alpha$ (12, 13), C/EBP$\beta$ (14), D-binding protein (15), AP-1 (16), cAMP regulatory element-binding protein (CREB) (17), cAMP regulatory element modulator (CREM) (18), and Jun/Jun homodimers (16). The CRE is required for the full induction of transcription from the PEPCK gene promoter by cAMP (19). Recently, we have demonstrated that NFI inhibits transcription from the PEPCK gene promoter and suggested that an interaction between NFI and CREB-binding protein (CBP) is involved in the control of the basal level of transcription of the PEPCK gene in the liver (20).

*Region 2*—This region contains an hepatic nuclear factor 1 (HNF-1) regulatory element (−190 to −185), which, despite its name, is critical for the expression of the PEPCK gene in the kidney of transgenic mice. There is a C/EBP-binding domain (−234 to −235), termed P3(I), which is required for the liver-specific expression of the PEPCK gene (21); members of the C/EBP family are the only transcription factors that are known to bind to the P3(I) site. This site is involved in the cAMP stimulation of transcription from the PEPCK gene promoter since its deletion results in a 60–70% drop in expression from the promoter in the presence of cAMP in both hepatoma cells (19) and in transgenic mice (21). C/EBP also binds to the P4 site (−282 to −274) (12). A thyroid hormone regulatory element is located at −332 to −316 of the PEPCK gene promoter (22, 23).

*Region 3*—This region contains the glucocorticoid response unit (GRU) composed of two glucocorticoid regulatory elements, three accessory factor-binding sites, and a CRE (24). The entire element lies between −321 and −455 of the PEPCK gene promoter (24). The GRU also contains an insulin regulatory element (IRE) (−414 to −400), which lies within the AF2 domain of the GRU (the AF2 site binds C/EBP and HNF-3) and is responsible for about 50% of the inhibitory effect of insulin on hepatic PEPCK gene transcription (25). However, deletion of the IRE completely inhibits the diabetes-induced increase of PEPCK gene transcription in the liver of transgenic mice and renders the PEPCK gene promoter refractory to induction by glucocorticoids (26).

*Region 4*—This region contains a PPAR$\gamma$ regulatory element (−999 to −987), which is required for the adipose tissue-specific expression of the PEPCK gene in both cultured adipocytes (27) and in adipose tissue of transgenic mice in which the region containing the PPAR$\gamma$ element has been deleted (28).

## *The Role of C/EBP Isoforms in the Regulation of PEPCK Gene Transcription*

Of the C/EBP isoforms, only C/EBP$\alpha$ (6, 23, 29), C/EBP$\beta$ (14), and D-binding protein (15) have been implicated in the control of PEPCK gene transcription; all three of these isoforms of C/EBP bind to the PEPCK gene promoter and can stimulate transcription from the promoter when transfected into hepatoma cells. It is likely that these three transcription factors, either individually or in combination, regulate PEPCK gene transcription in the liver. Wang *et al.* (29) partially resolved the issue of which isoform of C/EBP controls the development of hepatic PEPCK gene transcription when they reported that PEPCK and glucose 6-phosphatase mRNAs were absent in the livers of mice with a deletion in the gene for C/EBP$\alpha$ (C/EBP$\alpha$−/− mice). Subsequently, Flodby *et al.* (30) demonstrated that C/EBP$\alpha$−/− mice also have immature lung development. The complete analysis of those genes whose expression is affected by a deletion in the gene for C/EBP$\alpha$ has not been performed to date, but it is clear from the available data that a

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[1] The abbreviations used are: C/EBP, CAAT/enhancer-binding protein; PEPCK, phosphoenolpyruvate carboxykinase; CRE, cAMP regulatory element; NFI, nuclear factor I; CREB, cAMP regulatory element-binding protein; CBP, CREB-binding protein; GRU, glucocorticoid response unit; HNF-1, hepatic nuclear factor I; IRE, insulin regulatory element; PPAR, peroxisome proliferator-activated receptor; PKAc, catalytic subunit of PKA; PKC, protein kinase C.

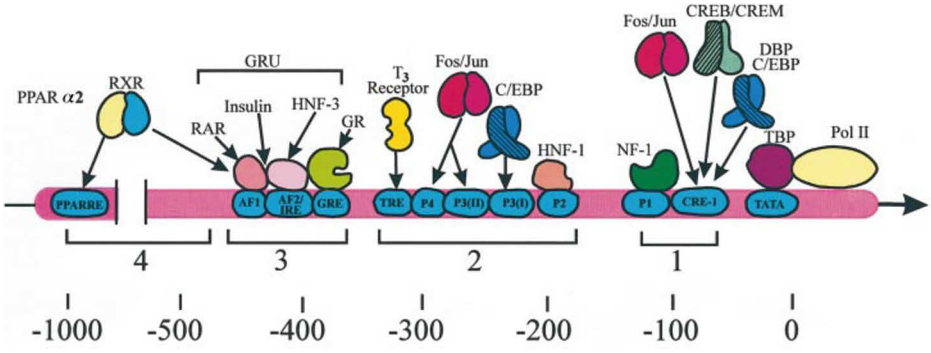


FIG. 1. **Transcriptional regulatory elements of the PEPCK promoter.** The positions of regulatory elements in the PEPCK gene promoter are represented by *ovals,* and the various proteins that regulate transcription of the PEPCK gene are shown relative to their binding sites on the promoter. The abbreviations used are: TRE, thyroid hormone regulatory element; GRE, glucocorticoid regulatory element; TBP, TATA-binding protein(s); PPARRE, PPAR regulatory element; AF-1; accessory factor-1; DBP, D-binding protein; GR, glucocorticoid receptor; RAR, retinoic acid receptor; RXR, retinoic X receptor. This figure is taken from Ref. 37.

number of these genes are involved in integrative metabolic functions (5). These proteins include enzymes involved in gluconeogenesis, glycogen synthesis, and fatty acid synthesis that are markedly altered in the absence of C/EBP$\alpha$. For example, C/EBP$\alpha$−/− mice have no hepatic glycogen at birth (there is no detectable glycogen synthase in the liver), and in the absence of PEPCK and glucose 6-phosphatase, they cannot synthesize glucose to maintain glucose homeostasis in the perinatal period; both brown and white adipose tissues also fail to develop normally (29).

The administration of dibutyryl cAMP to C/EBP$\alpha$−/− mice at day 19 of fetal life resulted in a blunted induction of PEPCK mRNA in the liver (about 10% of the control value) but caused a marked increase in the level of C/EBP$\beta$ mRNA in the livers of the C/EBP$\alpha$−/− mice (6). It is thus possible that C/EBP$\beta$ assumes the function of regulating PEPCK gene transcription in the absence of C/EBP$\alpha$. The temporal pattern of expression of the isoforms of C/EBP could be critical for the programmed initiation of gene transcription in the liver. In preliminary studies from our laboratory we have shown that C/EBP$\alpha$−/−/C/EBP$\beta$+/− mice do not survive past day 18 of fetal life,[2] suggesting that the at least one allele for C/EBP$\alpha$ must be present in the mouse to ensure that development proceeds.

The role of C/EBP$\alpha$ in mediating cAMP-stimulated transcription of the PEPCK gene was first demonstrated by Liu *et al.* (19). They reported that a mutant PEPCK gene promoter, in which the CRE has been replaced by the P3(I) site (which binds only C/EBP), is as responsive to the catalytic subunit of PKA (PKAc) as the native PEPCK gene promoter. Recently, Roesler *et al.* (31) demonstrated that C/EBP$\alpha$ (but not C/EBP$\beta$) can substitute for CREB in cAMP-stimulated PEPCK gene transcription and mapped the C/EBP$\alpha$ activation domain to a region between amino acids 176 and 217. In addition, Roesler *et al.* (32) also reported that a dominant repressor of C/EBP$\alpha$, when transfected into hepatoma cells, significantly inhibited induction of transcription from the PEPCK gene promoter by PKAc. Interestingly, the DNA-binding domain of C/EBP$\alpha$ was not required for its effect on PEPCK gene transcription in hepatoma cells but was required in non-hepatoma cells, suggesting that there is an interaction between C/EBP and other factors, which are critical for the full effect of C/EBP$\alpha$ on PEPCK gene transcription.

A major problem in studying the long term effects of a deletion in the gene for C/EBP$\alpha$ in mice is the lethality of the deletion in the perinatal period. Lee *et al.* (33) constructed a conditional knockout allele of C/EBP$\alpha$ using the Cre/*lox*P recombinase system. The Cre recombinase was delivered to the livers of adult mice containing the gene for C/EBP$\alpha$ flanked by *lox*P sites, using a recombinant adenoviral vector carrying the *cre* gene. The hepatic expression of the genes for both C/EBP$\alpha$ and PEPCK was reduced by 90% in the livers of these mice, indicating that C/EBP$\alpha$ is required for maintaining the basal levels of PEPCK in the livers of adult mice. It is surprising that this requirement for C/EBP$\alpha$ could not be compensated for by C/EBP$\beta$ or other C/EBP isoforms, which are abundantly expressed in the liver of adult animals.

Mice homozygous for a deletion in the gene for C/EBP$\beta$ (C/EBP$\beta$−/− mice) were initially generated to study the effects of C/EBP$\beta$ on the interleukin-6 signaling pathway. Screpanti *et al.* (34) reported that the mice developed a pathology similar to animals that overexpress interleukin-6; they have splenomegaly, peripheral lymphadenopathy, enhanced hemopoiesis, and altered T-helper cell function. Despite these problems with the immune system, the mice had no *overt* disruption of glucose homeostasis (34). However, both Screpanti *et al.* (34) and Tanaka *et al.* (35) noted a failure to obtain the expected Mendelian ratio of mice heterozygous for a deletion in the gene for C/EBP$\beta$, although the appropriate number of C/EBP$\beta$−/− mice was present at 20 days of fetal life. In a recent study we reported that there are two phenotypes noted with the C/EBP$\beta$−/− mice (6). Animals with phenotype A live until about 4–6 months of age and die of problems associated with a severely compromised immune system, whereas the other half of the C/EBP$\beta$−/− mice, those with phenotype B, die within the first hour after birth of profound hypoglycemia.

Animals with the B phenotype have normal levels of hepatic glycogen but do not mobilize this glycogen and do not initiate hepatic PEPCK gene transcription, which is characteristic of the neonatal period (36). However, PEPCK gene transcription and glycogen mobilization from the liver can be induced during the perinatal period in C/EBP$\beta$−/− mice by the administration of dibutyryl cAMP.[2] It is possible that C/EBP$\beta$−/− mice are less responsive to cAMP and are thus not able to maintain the level of glucose in the blood by either glycogenolysis or gluconeogenesis. C/EBP$\beta$−/− mice have about 25% of the total hepatic cAMP, and the administered dose of glucagon to adult C/EBP$\beta$−/− mice (A phenotype) does not cause the same level of increase in the concentration of cAMP as with C/EBP$\beta$+/+ mice.[3] C/EBP$\beta$−/− mice (A phenotype) also have a diminished ability of the liver and adipose tissue to respond to glucagon and epinephrine administration.[3] The rate of glucose production by the liver after glucagon administration is less than control mice, and the rate of free fatty acid release from adipose tissue *in vitro* after the addition of epinephrine is greatly reduced. It thus seems likely that the inability of C/EBP$\beta$−/− mice with the B phenotype (mice die immediately after birth) to maintain the appropriate level of hepatic cAMP is responsible for the failure of these animals to initiate glucose homeostasis at birth. We are currently investigating the mechanism(s) responsible for the lower level of cAMP in the livers of these mice.

C/EBP$\beta$−/− mice (A phenotype) also are less responsive to administered glucocorticoids.[2] Dexamethasone induces transcription of the gene for PEPCK in the kidney of C/EBP$\beta$−/− mice (A phenotype) to about 10% of the level noted in control mice. There is, however, no defect in the cAMP induction of PEPCK gene transcription, indicating that C/EBP$\beta$, although critical for the full response of metabolically important genes to hormones such as glucocorticoids, glucagon, and epinephrine, is not required for the induction of PEPCK by cAMP.

The reason there are two different phenotypes noted with the C/EBP$\beta$−/− mice is not clear. We assume that there are factors produced in the mice with phenotype A that allows them to transcribe genes critical for survival during the perinatal period. These "modifier genes" are expressed as a result of the genetic background of the mice, which are not inbred. This possibility is sup-

[2] C. Croniger and R. W. Hanson, unpublished results.

[3] S. Liu, C. Croniger, J. Ren, M. Shiba, V. Poli, R. W. Hanson, and J. E. Freedman, submitted for publication.

ported by preliminary experiments in which mice homozygous for a deletion the gene for C/EBP$\beta$ were backcrossed with C57/BL6 mice; no C/EBP$\beta$−/− offspring from these matings survived after birth.[4] One simple explanation for this result is that the gene(s) for other C/EBP isoforms are up-regulated in mice with the A phenotype, permitting their survival through the perinatal period. However, there is no apparent up-regulation in the expression of the gene for C/EBP$\alpha$ or C/EBP$\delta$[4] in the livers of the C/EBP$\beta$−/− mice; the level of expression of the genes for the other members of the C/EBP family has not as yet been investigated in detail in these mice.

### *Mechanism of the Effect of C/EBP on PEPCK Gene Transcription; Interaction with CBP/p300*

C/EBP isoforms bind to three major sites on the PEPCK gene promoter, the CRE, the P3(I) site, and the AF2 element; all three are critical for the regulated transcription of the PEPCK gene in the liver. A deletion in the CRE or the P3(I) site results in 70% loss of transcriptional induction from the PEPCK gene promoter by cAMP, whereas mutating both sites virtually eliminates the inductive effects of the cyclic nucleotide (19). In addition, mice containing a transgene with the PEPCK gene promoter lacking the P3(I) site (only isoforms of C/EBP are known to bind to this site) have a greatly diminished level of expression of the transgene in the liver (21). A deletion in the AF2 site in the PEPCK gene promoter eliminates the stimulatory effect of diabetes on transcription from that promoter when it is introduced into transgenic mice.[5] The results of gene deletion studies outlined above offer further support for the importance of C/EBP isoforms in both the liver-specific expression of the PEPCK gene and the cAMP-regulated transcription from the PEPCK promoter. The mechanism by which C/EBP regulates transcription from the PEPCK gene promoter remains to be determined. There are, however, a number of recent research studies, and work in our own laboratory now sheds some light on this critical question.

C/EBP isoforms have been shown to bind to the dyad-symmetric sequence ATTGCGCAAT (38). The sequences for the CRE and the P3(I) sites in the PEPCK gene promoter are not identical to this consensus sequence, which is consistent with the varying affinity of C/EBP for different gene promoters. Phosphorylation of C/EBP$\alpha$ by protein kinase C (PKC) results in an attenuation of its binding to DNA (39, 40). PKC inhibits transcription from the PEPCK gene promoter in hepatoma cells (41), suggesting a connection between C/EBP$\alpha$ and the signaling pathways involved in the cellular effect of PKC on the PEPCK gene.

The various isoforms of C/EBP have been shown to bind to a number of other transcription factors (42) and also can interact with the glucocorticoid receptor to regulate gene transcription (43). For example, both C/EBP$\alpha$ and C/EBP$\beta$ form a heterodimeric complex with ATF-2, a transcription factor that binds to the CRE of a number of gene promoters and activates transcription (42). C/EBP$\alpha$ diminishes the inductive effect of ATF-2 on transcription from a hybrid promoter, containing the thymidine kinase minimal promoter and a C/EBP-binding site, when expression vectors with genes coding for both proteins are transfected into Fao hepatoma cells; this supports a functional interaction of C/EBP$\alpha$ and ATF-2. Recently, Mink *et al.* (44) reported that the transcriptional co-activator CBP binds C/EBP$\beta$ at a region from amino acids 1752 to 1859 of CBP and that this domain, when transfected into cells in culture, was a dominant-negative inhibitor of C/EBP$\beta$-induced transcription. CPB can stimulate the synergy between C/EBP$\beta$ and the transcription factor Myb for binding to a minimal promoter-containing binding sites for both transcription factors. The amino-terminal region of C/EBP$\beta$ binds to CBP; this region contains several stretches of amino acids that are conserved in the various isoforms of C/EBP, suggesting that other members of the C/EBP family of transcription factors bind to CBP via this site.

CBP/p300 is the designation of a group of co-activator proteins of which CBP and p300 are the prototypes (45, 46). CBP and p300 are highly related proteins, with 75% similarity and 63% sequence identity across the entire length of the protein (see Ref. 47 for a review). CBP from the mouse is composed of 2440 amino acids; the genes for both CBP and p300 in this species have been deleted by homologous recombination (48). Mice homozygous for a deletion in the gene for p300 (p300−/− mice) die between embryonic days 9 and 11, exhibiting defects in neurulation, cell proliferation, and heart development (48). Interestingly, mice that are heterozygous for a deletion in the gene for p300 also show increased lethality, whereas mice that are heterozygous for a deletion in genes for *both* CBP and p300 die as embryos (48). Not all of the functions of CBP and p300 are similar; fibroblasts prepared from p300−/− mice (normal CBP) were defective in their response to retinoic acid but responded normally to CREB (48). These results strongly support the critical role of both CBP and p300 in mammalian cell proliferation and development.

CBP/p300 has a number of discrete functions in regulating gene transcription. It binds to RNA polymerase II and can integrate regulatory signals from transcription factors and chromatin by virtue of its intrinsic acetyltransferase activity (49). CBP/p300 can itself be phosphorylated on serine and threonine residues during retinoic acid-induced differentiation of F9 embryonal carcinoma cells (50), suggesting that phosphorylation of the protein by a cyclin-dependent kinase can control its transcriptional activity. At the present time there are more than 30 proteins known to bind to CBP/p300, and the list is growing (47). Nakajima *et al.* (51) have suggested a model in which CREB is phosphorylated by PKA and then binds to CBP, resulting in an association of CBP with TFIIB and RNA polymerase II. Because isoforms of C/EBP can also bind to CBP (but at a different location), it is reasonable to assume that they act in the same manner in controlling the transcription of a subset of cAMP-responsive genes such as PEPCK, acetyl-CoA carboxylase, and glucose-6-phosphatase. These genes are expressed at high levels in the liver, where the concentration of C/EBP is highest and the level of CREB is relatively low. However, there are no data indicating that PKA phosphorylation of C/EBP$\alpha$ results in activation of transcription so that some mechanism involving the direct phosphorylation of CBP may be responsible for induction of PEPCK gene transcription by cAMP.

The CRE of the PEPCK promoter lies immediately adjacent to an NFI-binding domain (12), and NFI inhibits the induction of transcription from the PEPCK gene promoter by PKAc (20). However, it has been demonstrated in gene transfection studies that the NFI-binding site of the PEPCK gene promoter is not required for the effect of NFI. This suggests that there is an interaction between NFI and another protein(s), neither of which need to bind to the PEPCK gene promoter to form a productive complex. Recently, Leahy *et al.*[6] provided evidence that this interaction is with CBP, because co-transfection of CBP with NFI overcomes the strong negative effect of NFI on transcription from the PEPCK gene promoter. This effect is concentration-dependent for both CBP and NFI. Preliminary data suggest that NFI binds to the CREB-binding domain of CBP. In support of the role of CBP in the regulation of PEPCK gene transcription is our observation that E1A, the adenoviral early protein, strongly inhibits cAMP-induced transcription from the PEPCK gene promoter (52).[6] Because E1A binding to CBP/p300 is well characterized as a major mechanism by which adenovirus controls host cell function, it is likely that CBP/p300 is also a critical factor in the transcriptional response of PEPCK to hormones (see Fig. 2).

### *Model for the Control of PEPCK Gene Transcription*

Our current model (Fig. 2) for the role of C/EBP isoforms in the control of PEPCK gene transcription is from Leahy *et al.*[6] and shows the PEPCK gene promoter arranged to stress the role of CBP in coordinating the transcriptional response of cAMP, glucocorticoids, and insulin. C/EBP, which binds to both the CRE and the P3(I) site of the PEPCK gene promoter, interacts with CBP, probably in response to stimulation by PKA. The effect of glucocorticoids on PEPCK gene transcription is also exerted via the interaction of the glucocorticoid receptor with its well characterized binding site on CBP. It is also likely that insulin exerts its effect on PEPCK gene transcription by interfering with this interaction. The removal of the AF2 domain in the PEPCK gene promoter results in

[4] V. Poli, unpublished observations.
[5] P. S. Lechner, C. Croniger, and R. W. Hanson, unpublished observations.
[6] P. Leahy, D. R. Crawford, G. Grossman, A. Chaudhry, R. Gronostajski, and R. W. Hanson, submitted for publication.

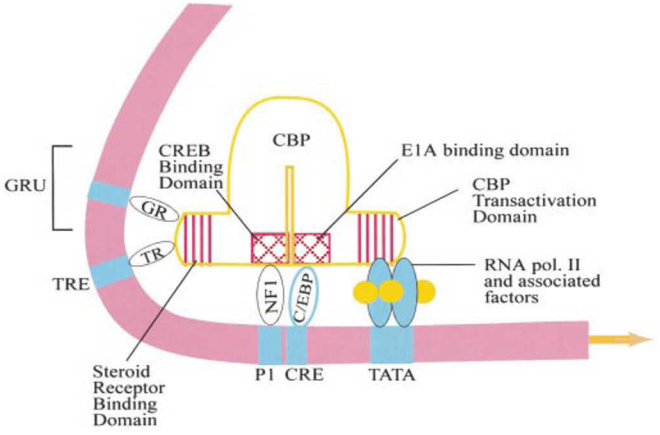


FIG. 2. **Interaction of transcription factors involved in the control of PEPCK gene transcription.** The PEPCK gene promoter is shown emphasizing the role of the transcriptional co-activator CBP in integrating the action of several transcription factors, which regulate PEPCK gene transcription. The binding site of E1A on CBP is shown schematically, whereas the glucocorticoid receptor and the thyroid hormone receptor are shown binding to both the PEPCK gene promoter and the co-activator CBP. NFI binds to the CREB-binding domain of CBP whereas C/EBP binds to the E1A region of CBP (see text for details). The abbreviations are the same as those used in Fig. 1 except: Pol II, RNA polymerase II; TR, thyroid receptor. This figure is taken from Leahy *et al.*[6]

a total loss of transcriptional induction from the promoter in livers from diabetic mice.[4] Although the glucocorticoid receptor does not bind to the AF2 region of the PEPCK gene promoter (24) it may exert its effect on transcription via an interaction with CBP. Other hormonal effectors of PEPCK gene transcription, such as the thyroid hormone receptor or the retinoic acid receptor, also are known to bind to CBP at well characterized sites (47) and most likely influence PEPCK gene transcription via that mechanism. Finally, NFI interacts with CBP to maintain PEPCK gene transcription in the liver at a low basal level in the absence of PKA-mediated phosphorylation of either C/EBP$\alpha$ or CBP.[6] The mechanism by which phosphorylation of either or both of these proteins alters transcription of the PEPCK gene remains to be determined.

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