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***AN ALTERNATELY SPLICED
FORM OF CHREBP ACTS AS A
DOMINANT NEGATIVE***

Carbohydrate Response Element Binding Protein (ChREBP) is a transcription factor that activates the expression of genes encoding enzymes of de novo lipogenesis, the conversion of carbohydrate into triglycerides. Under conditions of increased glucose uptake and metabolism, ChREBP is activated in the liver, helping to store excess carbohydrate in the preferred energy storage form of triglycerides. A better understanding of the regulation of ChREBP may establish whether ChREBP is a target for the treatment of obesity and related metabolic disorders. The carboxy terminal end of ChREBP contains the DNA binding domain and the site of interaction with its binding partner Mlx. Regions responsible for glucose regulation, including nuclear localization and shuttling sequences, are localized in the amino terminal end. Recently, an alternatively spliced isoform of ChREBP, designated theta, was found in mouse kidney. This form removes amino acids 58-79 in the glucose control region. To evaluate whether the theta isoform is functional, I constructed a plasmid expressing the theta ChREBP variant and transfected it into primary hepatocytes. A reporter gene assay indicated that theta ChREBP was inactivate under both low and high glucose conditions, indicating that amino acids 58-79 of ChREBP are critical for glucose regulation. I hypothesized that ChREBP theta might function as a dominant negative to the full length protein. Indeed, transfecting increasing levels of the theta isoform into primary hepatocytes inhibited endogenous ChREBP activity. Assessment of adult mouse liver, skeletal muscle and adipose by reverse transcriptase-PCR failed to detect theta mRNA in these tissues. I conclude that theta ChREBP acts as a repressor of the full-length protein and that its expression is highly restricted in the animal.

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