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COUP-TFII Revisited: Its Role in Metabolic Gene Regulation

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Abstract

Chicken Ovalbumin Upstream Promoter Transcription Factor II (COUP-TFII) is an orphan member of the nuclear receptor family of transcriptional regulators. Although hormonal activation of COUP-TFII has not yet been identified, rodent genetic models have uncovered vital and diverse roles for COUP-TFII in biological processes. These include control of cardiac function and angiogenesis, reproduction, neuronal development, cell fate and organogenesis. Recently, an emerging body of evidence has demonstrated COUP-TFII involvement in various metabolic systems such as adipogenesis, lipid metabolism, hepatic gluconeogenesis, insulin secretion, and regulation of blood pressure. The potential relevance of these observations to human pathology has been corroborated by the identification of single nucleotide polymorphism in the human *COUP-TFII* promoter controlling insulin sensitivity. Of particular interest to metabolism is the ability of COUP-TFII to interact with the Glucocorticoid Receptor (GR). This interaction is known to control gluconeogenesis, principally through direct binding of COUP-TFII/GR complexes to the promoters of gluconeogenic enzyme genes. However, it is likely that this interaction is critical to other metabolic processes, since GR, like COUP-TFII, is an essential regulator of adipogenesis, insulin sensitivity, and blood pressure. This review will highlight these unique roles of COUP-TFII in metabolic gene regulation.

Keywords

COUP-TFII; GR; Glucose homeostasis; PPAR α ; PEPCK

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1. Introduction

Chicken Ovalbumin Upstream Promoter Transcription Factors (COUP-TFs) were first cloned from a HeLa cell *cDNA* library in 1988 and were found to be members of the steroid/thyroid hormone receptor superfamily. In mammals, there are two COUP-TFs: COUP-TFI (also known as Nuclear Receptor Subfamily 2 Group F Member 1, NR2F1) and COUP-TFII (also known as Nuclear Receptor Subfamily 2 Group F Member 2, NR2F2) [1, 2]. Although COUP-TFII was initially shown to bind the chicken ovalbumin promoter, early independent work isolated the receptor from the apolipoprotein A1 gene promoter and was therefore called Apolipoprotein A1 Regulatory Protein (ARP-1) [3]. COUP-TFs exhibit the classical nuclear receptor structure of an N-terminal domain containing a putative transcriptional activation function, a central DNA binding domain (DBD) containing two zinc fingers in which there is 98% homology between COUP-TFI and COUP-TFII, and a C-terminal ligand binding domain (LBD) in which COUP-TFI and COUP-TFII share 100% and 96% homology, respectively, with the Retinoid X Receptor (RXR) and Retinoic Acid Receptor (RAR) [4]. Though COUP-TFs are generally known as orphan receptors, direct activation by retinoic acid (RA) has been shown [5]. However, the concentration of RA required to activate COUP-TFII is above physiological levels [5].

Despite their near-identical sequence homology, COUP-TFI and COUP-TFII only form homodimers or heterodimers with RXR [6, 7]. Both receptors principally act as transcriptional repressors by binding direct repeat AGGTCA motifs of varying spacing and orientation, and by recruiting the corepressors, nuclear receptor corepressor (NCoR) and the silencing mediator for retinoid or thyroid hormone receptor (SMRT) [6, 8]. Several Type 2 nuclear receptors that also heterodimerize with RXR also bind direct repeat AGGTCA motifs. These include Vitamin D Receptor (VDR), Peroxisome Proliferator-Activated Receptors (PPARs), and Hepatocyte Nuclear Factor-4 (HNF4), all of which principally act as transcriptional activators upon ligand binding [9]. Thus, COUP-TFs can efficiently block activation by these receptors by competitive binding at the AGGTCA motifs and by sequestration of RXR [10, 11]. Previously it has been shown that direct COUP-TFII interaction with the Glucocorticoid Receptor (GR) has been demonstrated, resulting in either repression or promotion of GR activity depending on gene context [7, 12]. Given this array of interactions, it is not surprising that the COUP-TFs are now known to regulate diverse and newly emerging physiological processes.

Even though COUP-TFI and COUP-TFII share nearly identical sequence homology, these two receptors differ significantly in respect to their gene locus, function and transcriptional regulation of their targets. The COUP-TFI gene resides on chromosome 5 in humans and chromosome 13 in mice, while COUP-TFII is located on chromosome 15 in humans and chromosome 7 in the mice [13]. In rats, *Coup-TFI* is found in chromosome 2 and *Coup-TFII* is found in chromosome 1 [14, 15]. Both homologs of COUP-TFs are expressed early during embryonic development, with COUP-TFI appearing at E7.5 primarily in neural ectoderm, while COUP-TFII appears at E8.5 primarily in visceral mesoderm [16]. Though *Coup-TFII*^{-/-} homozygous knockout mice die before E10 [16]. The contribution of COUP-TFII to metabolic processes has been emerging. Although many expert reviews on COUP-TFII exist, most only superficially cover metabolism and energy homeostasis [2, 17, 18].

Therefore, in this review, we focus on the COUP-TFII contribution to glucose homeostasis, adipogenesis, energy balance, and gene function in various metabolic active organs (Fig. 1).

2. COUP-TFII Role in Energy Regulation and Adipogenesis

Metabolic homeostasis requires precise control of food intake and energy expenditure [19]. Extensive research has expanded our understanding of metabolic flux and how metabolic remodeling contributes to the pathogenesis of diabetes, metabolic syndrome and cardiovascular disease, including hypertension [20, 21]. Numerous candidate proteins are currently being investigated for their role in metabolic regulation [20, 22]. COUP-TFII is one of these due to its involvement in energy metabolism. Studies conducted using *Coup-TFII*^{+/-} mice models demonstrated that *Coup-TFII*^{+/-} mice maintain a lean body mass phenotype and are found to be resistant to obesity when compared to wild-type mice maintained on high-fat diet [23]. Further, under high-fat diet fed conditions, *Coup-TFII*^{+/-} mice displayed normal glycemic clearance during the glucose tolerance testing, along with improved insulin resistance during the insulin tolerance test as compared to wild-type mice [23]. Aging is associated with both weight gain and insulin resistance, which can lead to diabetes and cardiovascular complications [24, 25]. Interestingly aged *Coup-TFII*^{+/-} mice raised on standard lab chow showed a leaner phenotype, as well as improved glucose tolerance when compared to the wild-type aged mice [23].

COUP-TFII also plays a role in regulating energy expenditure [23]. Energy balance is the net result of energy intake versus expenditure. Energy intake can merely be measured by food intake. Indirect calorimetry measures energy expenditure by calculating the rates of oxygen consumption (VO_{2max}) and CO₂ production (VCO_{2max}). Studies were done using *Coup-TFII*^{+/-} mice demonstrated increased VO_{2max} and VCO_{2max} in both the light and dark phases of daily activity compared to wild-type mice [23]. Furthermore, *Coup-TFII*^{+/-} mice also showed an increase in heat generation, as evidenced by an increase in respiratory exchange ratio (RER) when compared to wild-type mice [23]. An increase in energy expenditure may be the result of an increase in mitochondrial uncoupling protein 1 (UCP1) [26]. Mitochondria are enriched in heart tissue due to its high-level energy requirement for its continuous muscle contraction and relaxation. Studies have shown that, mitochondrial dysfunction can modify the electron transport chain function, causing leakage of electrons, which interact with molecular oxygen to form superoxide radicals, which in turn leads to oxidative stress, macromolecular damage, and apoptosis [27, 28]. A study conducted by Wu et al (2015) reported that an increase in heart *Coup-TFII* levels represses the expression of critical mitochondrial genes, which increases the risk for developing oxidative stress while also disrupting energy homeostasis [27]. Implications of oxidative stress in many pathophysiological conditions have been heavily investigated [29-31]. However, further investigations of COUP-TFII function in mitochondrial bioenergetics and oxidative stress using both *in vitro* and *in vivo* approaches will be needed to fully delineate the involvement of this transcriptional master regulator in disease progression arising from imbalances of energy expenditure.

Emerging evidence suggests that white adipose tissue (WAT) is an important organ for COUP-TFII regulation of energy expenditure [23]. COUP-TFII is highly expressed in

mesenchymal cells and mature adipocytes [23]. *Coup-TFII*^{+/-} mice showed significantly less WAT mass compared to wild-type mice under both regular and high-fat diet conditions, as well as better glucose homeostasis and increased energy expenditure [23]. WAT tissue of *Coup-TFII*^{+/-} mice had increased mitochondrial respiration resulting from upregulation of *Pgc-1α* and *Ucp1*, along with increased mitochondrial density [23]. Overall, these studies suggest that COUP-TFII plays a significant role in energy expenditure in WAT and further understanding of this process will strengthen our knowledge about the overall COUP-TFII function in adipocytes.

3. Insulin and COUP-TFII

The endocrine pancreas plays a significant role in metabolic regulation through several hormones secreted by pancreatic islets [32-34]. Islets contain four main cell types: α cells, which release glucagon, β cells, which release insulin, δ cells, which release somatostatin, and γ cells, which release pancreatic polypeptide. Proper functioning of β-cell functions is dependent on many transcription factors that are needed for genes involved in glucose sensing, insulin synthesis, and insulin secretion [35-37]. Changes in the levels of these transcriptional regulators or mutations in any of them can have significant impacts on various pathophysiological complications, such as diabetes and obesity [38]. The accumulating evidence now suggests that COUP-TFII is vital to β-cells and insulin secretion. Immunohistochemistry has revealed that COUP-TFII is expressed in all four-islet cell types in both embryonic and adult mice [39]. In β-cells, negative regulation of *Coup-TFII* mRNA and protein expression by glucose and insulin has been demonstrated *in vivo* and *in vitro* [39]. Similarly, Perilhou et al (2008) demonstrated that high-carbohydrate diet represses *Coup-TFII* expression in pancreas and liver [39]. Conversely, *Coup-TFII* can also regulate insulin secretion. Tissue-specific knockdown of *Coup-TFII* in β-cells of mouse pancreas tissue showed an abnormal pattern of insulin secretion in which insulin secretion was higher under low glucose but was significantly decreased in response to glucose stimulation [39]. Interestingly, glucose repression of *Coup-TFII* occurs by an autocrine mechanism in which secreted insulin binds to its β-cell insulin receptor [39]. Further, the authors also showed reciprocal regulation of insulin and *Coup-TFII* is mediated by the forkhead box protein O1 (FOXO1) transcription factor. In β-cells, nuclear FOXO1 regulates *Coup-TFII* gene expression either directly or indirectly [39]. Insulin signaling, however, results in activation of the phosphatidylinositol 3-kinase (PI3K)-Akt pathway, leading to phosphorylation of FOXO1 which inactivates the factor and causes it to leave the nucleus. Thus, insulin represses *Coup-TFII* expression by inhibition of FOXO1 (Fig. 2). Lastly, important confirmation that the insulin/*COUP-TFII* relationship may apply to humans was provided by analysis of the DESIR cohort of normoglycemic, middle-aged French citizens, which identified a single nucleotide polymorphism (rs-3743462) in the *COUP-TFII* gene (*NR2F2*) distal glucose responsive promoter that is significantly associated with insulin sensitivity. The SNP allelic change from T to C enhances COUP-TFII binding to its own promoter that is associated with insulin sensitivity in DESIR study [40].

4. COUP-TFII Regulates Hepatic Gluconeogenesis and Fatty Acid β -Oxidation

Like the pancreas, expression of *Coup-TFII* in the liver is inhibited by glucose and insulin both *in vitro* and *in vivo* [39, 41]. Not surprisingly, in mice the *Coup-TFII* expression is up-regulated under fasting condition and down-regulated upon re-feeding [42]. Coordination of *Coup-TFII* expression in the liver during fasting condition suggests that it participates in hepatic glucose production through upregulation of gluconeogenic enzymes and β -oxidation pathway genes [42]. This would allow, COUP-TFII to play a significant role in the regulation of hepatic gluconeogenesis that is essential to the maintenance of glucose homeostasis [42]. Hepatic glucokinase (hGK) is an insulin-regulated kinase that converts glucose to glucose-6-phosphate for entry in the glycolytic and glycogen deposition pathways. Thus, it plays a central role in hepatic glucose metabolism [39]. Previously, it was shown that the *Coup-TFII* expression was upregulated in fasted *hGK*^{-/-} mice compared to the wild-type mice [39]. However, upon re-feeding, the wild-type mice showed a decrease in *Coup-TFII* expression, whereas the *hGK*^{-/-} mice showed no reduction of *Coup-TFII* [39]. Thus, it was concluded that active glucose metabolism within the liver is required for inhibition of COUP-TFII expression [42]. Results such as these additionally suggest that repression of *Coup-TFII* is required for robust induction of the glycolytic and lipogenic pathways in the fed state. An important mediator of the fed state is the carbohydrate-responsive element-binding protein (ChREBP). ChREBP is a transcription factor vital to the promotion of glycolysis and lipid metabolism [43-45]. Leptin-deficient (ob/ob) mice that are obese, hyperglycemic and hyperinsulinemia are commonly used as models for type 2 diabetes [46]. It has been reported that these mice have elevated levels of ChREBP that can inhibit COUP-TFII expression in hepatocyte cultures and livers of ob/ob mice [39]. Under high glucose levels, ChREBP is also known to bind the carbohydrate-response element region in the promoter region of L-type pyruvate kinase (*L-PK*) gene. L-PK is activated by glucose and insulin and serves to promote hepatic lipogenesis under conditions of caloric excess by converting phosphoenolpyruvate to pyruvate [47]. During fasting, L-PK is repressed by glucagon via the cAMP [47] and by COUP-TFII, thus repressing glycolysis and allowing gluconeogenesis to proceed.

In INS-1 β cells, genetic ablation of *Foxo1* decreases *Coup-TFII* levels, whereas overexpression of *Foxo1* increases *Coup-TFII* levels. Further, *Coup-TFII* expression levels increase in parallel with *Foxo1* levels in fasted mouse liver [39, 42]. In turn, COUP-TFII acts as an accessory component in the coordinated upregulation of gluconeogenic gene products, such as phosphoenolpyruvate carboxykinase (*Pepck*), which ultimately leads to elevated glucose production in hepatic tissue [7, 48]. Hepatic *Coup-TFII* expression is low in postnatal mice but reaches normal adult levels between 3-13 days of age. Upon glucagon injection, an increase in *Coup-TFII* and *Pepck* mRNA levels is observed in the livers of mice [42]. Hepatic *Coup-TFII* levels also correlate with *Hnf4a* and *Ppara* levels [42, 49]. This correlation is not a coincidence because the direct interaction of COUP-TFII with PPAR α and HNF4 α has been documented. The interaction occurs at the promoters of various gluconeogenic and β -oxidation pathway genes via direct repeats of AGGTCA binding sites (DR1) spaced throughout each promoter [49]. In the case of HNF4 α , the COUP-TFII

interaction can be either inhibitory or synergistic depending on gene and tissue context. At the hepatic *Pepck* gene promoter, HNF4 α and COUP-TFII interact synergistically to drive glucose production [13].

The prime role of PPAR α in the liver is to drive β -oxidation of fatty acids derived from adipose tissue in times of fasting. There is now evidence that Coup-TFII augments this process [42]. In *Ppara*^{-/-} mice, fasting-induced upregulation of acyl-CoA oxidase (*Aco*) gene expression in the liver was significantly reduced and this correlated with *Coup-TFII* levels that were reduced by half [42]. This suggests that PPAR α promotes *Coup-TFII* expression during fasting in the liver. In studies using adenoviral delivery to the liver of mutant *Coup-TFII* (*Coup-TFII*-DN) unable to bind the DR1 response element, the mice were found to have a profound induction of hypoglycemia, along with a reduction of ketone body concentrations, and rise in triglyceride concentration [42]. Although these physiological effects could be partially explained by the COUP-TFII role in regulating *Pepck* gene expression. In addition to *Pepck* gene expression other genes involved in β -oxidation pathways were also down-regulated (carnitine palmitoyltransferase 1 (*Cpt1*), mitochondrial 3-Hydroxy-3-Methylglutaryl-CoA reductase (*mHMG-CoA*), lipoprotein lipase (*Lpl*), fatty acid transporters (*Cd36*), and fatty acid-binding protein 1 (*Fabp1*)) in *Coup-TFII*-DN mice [7, 42]. This list suggests that the *Coup-TFII*-DN mutant is altering cooperativity with *Ppara*. It has also been demonstrated that overexpression of wild-type *Coup-TFII* leads to mitochondrial dysfunction and affects crucial metabolic pathways, such as fatty acid β -oxidation, glycolysis, glucose uptake via altered expression of glucose transporter type 4 (*Glut4*), and glycolysis via altered hexokinase 2 (*Hk2*) and phosphofructokinase (*Pfkfb*) [27]. Additionally, *Coup-TFII* overexpression in mice also produced severe defects in electron transport chain activity and an increase in the reactive oxygen species production. This creates a highly oxidizing environment, which can cause deleterious effects including protein oxidation, lipid peroxidation, and DNA damage [27]. Taken as a whole, these observations show that COUP-TFII exerts critical and diverse roles in the liver to control glucose homeostasis, lipid metabolism, and oxidative stress.

5. COUP-TFII in Hepatic Bile Acid Production

Cholesterol 7 α -hydroxylase (*Cyp7a1*) is the rate-limiting enzyme in the catabolism of cholesterol to bile acid in liver [50]. The CYP7A1 enzyme serves to eliminate cholesterol from the body and maintain proper cholesterol homeostasis. COUP-TFII has been found to increase transcription of the *Cyp7a1* gene by binding at the promoter to the direct repeat AGGTCA as a homodimer or as a heterodimer with RXR, HNF4 α , or GR [7, 49-51]. The *Cyp7a1* gene promoter contains a sequence nt -149 to -118 which is mainly responsible for controlling its transcription activity [49]. HNF4 α purified from rat liver nuclear extracts was shown to bind oligomers homologous to the nt -146 to -134 of *Cyp7a1*. COUP-TFII was found to bind an overlapping region nt -139 to -128 in the *Cyp7a1* promoter and does not interfere with HNF4 α binding [50, 51]. This is consistent with data showing that HNF4 α has a high affinity for nt -146 to -134 and COUP-TFII has a low affinity for nt -139 to -128. However, there is a strong affinity for COUP-TFII to bind to nt -72 to -57 of the *Cyp7a1* promoter, which may function as an auxiliary site for HNF4 α transactivation [49-51]. In addition, a COUP-TFII variant lacking the DBD (*Coup-TFII* V2) failed to drive

expression of *Cyp7a1* by physically interacting with endogenous COUP-TFII and inhibiting its DNA binding ability [50]. Therefore, it may be concluded that protein/protein interaction between COUP-TFII and HNF4 modulate the expression of the *Cyp7a1* gene to control bile acid metabolism in the liver [49, 52].

6. COUP-TFII Interaction with the Glucocorticoid Receptor

The steroidal glucocorticoid hormones (GCs) that include cortisol in humans and corticosterone in rodents are essential regulators of metabolism, promoting lipolysis in adipose tissue, protein degradation in muscle and gluconeogenesis in liver [53, 54]. In liver, GR is also known to cooperate with PPAR α to control lipid metabolism. Like COUP-TFII, the GR is a nuclear receptor that functions to control the transcriptional regulation of target genes. A direct interaction between GR and COUP-TFII has been demonstrated with a variety of effects on their respective transcriptional activities [7, 55]. Through yeast two-hybrid screening, it was found that the DBD of COUP-TFII interacts with the human forms of GR α and GR β -splicing-variant [48]. Conversely, GR α and GR β bind to COUP-TFII between amino acid 75 and 163, a region that spans the carboxy-terminal end of the GR-DBD and the hinge region of COUP-TFII [7, 48] (Fig. 3). Functional studies went on to show that COUP-TFII suppressed the steroidal (dexamethasone)-induced GR transactivation of an MMTV reporter construct which contains a glucocorticoid-responsive element in a dose-dependent manner in both HeLa and CV-1 cells [7]. In contrast, GR α , but not GR β , served to enhance *Coup-TFII* stimulated *Cyp7a1* promoter activity [7, 48]. At present, little more is known about functional consequences of the COUP-TFII/GR β interaction. However, we now know that the COUP-TFII/GR α interaction can be either antagonistic or synergistic depending on gene and tissue context.

GR α contains two transactivation domains, TAF-1 and TAF-2, which mediate of RNA polymerase-2 activity at target genes by recruiting co-activators, co-repressors or chromatin modulators. TAF-1 is localized to the N terminal domain (NTD) of the receptor, while TAF-2 is found in the LBD and is responsible for ligand-dependent transcriptional regulation. It was found that TAF-1 (but not TAF-2) was required for enhancement of COUP-TFII-induced transcriptional activity of the *Cyp7a1* promoter in a glucocorticoid-dependent manner [7]. This effect at the *Cyp7a1* promoter presumably occurs through recruitment of co-activators (perhaps PGC1 α), although the precise co-activators involved have not been identified. COUP-TFII is known to directly suppress the transcriptional activity of many genes by recruiting corepressors, such as SMRT, to the last 35 amino acids of the receptor [7, 48, 56]. In the case of some GR-regulated genes, suppression occurs by recruitment of the COUP-TFII/SMRT complex to the TAF-1 domain of promoter-bound GR.

Perhaps the most studied metabolic gene with respect to the GR/COUP-TFII interaction is PEPCK. PEPCK is a rate-limiting enzyme in hepatic and renal gluconeogenesis and glyceroneogenesis in adipose tissue [57]. In the fasted state, GCs promote upregulation of *Pepck*, particularly in the liver, to increase glucose production to supply the needs of peripheral organs, especially muscle and brain [7, 48]. In contrast, fasting promotes GC mediated down-regulation of *Pepck* expression in the adipose tissue to block triglyceride storage and cause fatty acid release as an additional caloric source. We now know that

COUP-TFII cooperates with GR to facilitate these tissue-specific processes by augmenting GR-induced *Pepck* expression in liver and GR-mediated *Pepck* repression in adipose [48, 58]. This dual effect of GR and COUP-TFII on *Pepck* gene regulation is mediated by a set of promoter elements collectively known as the Glucocorticoid Response Unit (GRU) at which a variety of transcription factors can bind, including GR and COUP-TFII [13]. This unit spans 100-bp, which includes two GR binding sites (GR1 and GR2) and at least two accessory factor binding sites (AF1 and AF2) [13]. Direct binding of COUP-TFII to AF1 in liver and adipose has been demonstrated, while GR binds at GR1 and GR2. Although GR and COUP-TFII have distinct binding sites within the GRU, physical interaction between COUP-TFII and GR was found from an *in vitro* glutathione transferase pull down assay. COUP-TFII interacted via its DBD with the hinge region of GR [7]. This physical interaction of the two receptors at the promoter appears to be necessary for hormonal (dexamethasone) activation of GR and *Pepck* expression in the liver (Fig 3). Both down-regulation of *Coup-TFII* by siRNA and expression of mutant COUP-TFII unable to bind GR results in complete blockage of dexamethasone-induced *Pepck* expression [7, 48]. In adipose tissue, the exact mechanism of synergistic repression of *Pepck* by GR and COUP-TFII is less clear. A prevailing hypothesis suggests that each receptor occupying the AF1 and GR-1/2 sites serve to block occupancy by PPAR γ and/or CEBP transcription factors, both of which promote *Pepck* expression and glyceroneogenesis in adipose tissue [57]. Taken as a whole, the above observations suggest that the physical interaction of COUP-TFII with GR is vitally important to the coordinated control of lipid and carbohydrate metabolism in liver and adipose tissue.

7. COUP-TFII Role in Heart and Skeletal Muscle

Metabolic remodeling serves as a critical role in the pathogenesis of heart failure [22, 27]. In some cases, metabolic remodeling precedes structural changes and may be what initiates the structural remodeling in cardiac and skeletal muscle [59]. This metabolic control relies on many co-regulators such as the *Pgc-1 α* and *Pgc-1 β* [60, 61]. PGC-1 α and COUP-TFII are known to interact and control key genes involved in energy homeostasis and active aerobic respiration [62]. Metabolic dysfunction has been significantly associated with hypertension [21, 63, 64]. Previously, we have shown that targeted disruption of the *Coup-TFII* locus (*Nr2f2*) in the Dahl salt-sensitive rat (SS) decreases blood pressure, proteinuria, and improved vascular response compared to wild-type SS rats [15]. Another study provided evidence that overexpression of *Coup-TFII* in mice significantly reduced cardiac performance, which was observed through a decrease in fractional shorting, reduced relative wall thickness and reduced mean survival time of the mice [17].

COUP-TFII is expressed in multiple tissues and organs, which suggest that its role in metabolism may not be limited to the liver and pancreas [65]. Skeletal muscle accounts for a substantial portion of total body mass and energy expenditure. Skeletal muscle is one of the most metabolically active tissues; thus there is a need for proper regulatory mechanisms for fuel handling, i.e., fatty acid β -oxidation and glucose production to satisfy their energy demand [66]. siRNA mediated knockdown of *Coup-TFII* expression in the mouse C2C12 myoblast cell line resulted in the reduction of essential genes, such as *Ppara*, *Fabp3*, and *Cpt1* involved in the fatty acid β -oxidation pathway [35]. In the same study, reduced

expression was noted for genes involved in thermogenesis *Ucp1* and in cholesterol transport (ATP-binding cassette transporter, *Abca1*; ATP Binding Cassette Subfamily G Member 1, *Abcg1*) [35]. Additionally, it has been demonstrated that in mice COUP-TFII levels in skeletal muscle regulate the levels of *Glut4* expression [67]. Recently it was shown that COUP-TFII was also found to play an important role in myogenesis [68]. Using an in-vivo approach in which *Coup-TFII* was ectopically expressed during the myogenesis process demonstrated that a reduction in COUP-TFII is necessary for the expression of genes involved in myoblast differentiation such as Nephronectin, (*Npnt*), Caveolin 3 (*Cav3*), and integrin-focal adhesion kinase (*Fak*) [68]. Through ChIP-seq data, it was found that COUP-TFII directly binds to the promoter region on *Npnt* and *Cav3*, which may inhibit transcription and inhibit myogenesis [68, 69].

8. Coup-TFII Role as Energy Sensor in the Hypothalamus

In addition to its role in metabolic tissues, COUP-TFII is expressed in the brain, specifically in neurons of the ventromedial nucleus (VMN) of the hypothalamus [70]. Loss of the *Coup-TFII* in the hypothalamus, which results in growth retardation in mice [71]. The VMN is known for its role in metabolic regulation through its ability to measure changes in the extracellular concentrations of glucose, insulin, and leptin [70, 72, 73]. A heterozygous mouse model with *Coup-TFII* inactivation in the VMN neurons displayed a leaner phenotype with improved insulin sensitivity [70]. These mice also showed better-altered glucagon secretion lead to hypoglycemia [70]. These mutant mice were more likely to develop hypoglycemic-associated autonomic failure. In addition, both mRNA and protein levels of *Coup-TFII* are upregulated in the VMN during fed state in mice, as opposed to *Coup-TFII* levels in the liver and pancreas during fed state [74]. It is believed that the upregulation of *Coup-TFII* in the VMN is due to the activation of the melanocortin pathway by an increase of insulin levels upon feeding [74]. However, activation of the melanocortin pathway in the liver and pancreas repress *Coup-TFII* levels [74]. In peripheral tissue, insulin is known for its anabolic activity; however, insulin's effect in the central nervous is catabolic [74]. This catabolic activity in the brain can lead to a decrease in food intake and weight [74]. These opposite regulation of *Coup-TFII* expression in different organs is needed for whole body glucose homeostasis.

9. Conclusion

COUP-TFII has been known for its transcriptional regulation of many vital developmental processes, such as organogenesis, angiogenesis, and neuronal development. In the current review, we highlighted the emerging role of COUP-TFII in metabolic homeostasis. It is now clear that COUP-TFII is an important regulator of metabolic processes in the liver that include, gluconeogenesis, fatty acid oxidation and cholesterol processing, and that COUP-TFII achieves this, in part, by interacting with the glucocorticoid receptor. In addition to its role in liver, COUP-TFII exerts key effects in adipose tissue by promoting adipogenesis and in β -cells of the pancreas by regulating insulin secretion. It is not surprising, therefore, that changes in dietary sugar levels can significantly affect COUP-TFII expression in various organs. More importantly, rodent models have now shown that COUP-TFII deficiency correlates with reduced adipose tissue mass, improved glucose tolerance and less insulin

resistance. In addition, mice lacking COUP-TFII are less likely to develop cardiovascular complications, such as hypertension. These facts point to COUP-TFII as a viable target for the potential treatment of metabolic disorders and underline the need for further investigations into the COUP-TFII roles in metabolism.

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Highlights

- Coup-TFII, a transcription factor that is found to play an important role in adipogenesis and energy regulation.
- High levels of glucose and insulin suppress the expression of Coup-TFII in the pancreas.
- Human patients with a SNP in the promoter region of COUP-TFII was linked with insulin sensitivity.
- Upregulation of Coup-TFII in the liver has been correlated with an increase in gluconeogenesis and β - oxidation genes.
- A mutation in the hinge region on Coup-TFII in the Dahl SS rats leads to an improvement in blood pressure regulation.

Figure 1: The COUP-TFII roles in metabolism.

The COUP-TFII transcription factor controls metabolism at several organs. In the liver, it regulates glucose, lipid and cholesterol metabolism, in part, by upregulating the expression of gluconeogenic enzymes (e.g., *Pepck*), fatty acid oxidation genes (e.g., *Hmg-CoA*), and the rate-limiting enzyme in conversion of cholesterol to bile acids (*Cyp7a1*). In the pancreas, COUP-TFII modulates insulin secretion in response to glucose, although the genes involved are currently unknown. In heart muscle, COUP-TFII is involved in cardiac remodeling, possibly by upregulating the expression of *Pgc-1α* and *Ucp1*. Interestingly, in adipose tissue COUP-TFII suppresses *Pgc-1α* and *Ucp1* expression to blunt energy expenditure. In the brain, COUP-TFII expression in the ventromedial nucleus (VMN) of the hypothalamus (not shown) has been shown to regulate systemic glucose homeostasis.

Figure 2: The glucose/insulin pathway regulates COUP-TFII expression in pancreatic β -cells. Under low glucose conditions, COUP-TFII expression is promoted by the FOXO1 transcription factor. Elevated COUP-TFII levels will then modulate insulin secretion by a still undefined mechanism (not shown). In response to high glucose, insulin is secreted from β -cells. By autocrine signaling, insulin targets its own receptor on β -cells to activate the phosphoinositide 3-kinase (PI3K) pathway, leading to activation of AKT and phosphorylation of FOXO1, driving down COUP-TFII expression.

Figure 3: The GR/COUP-TFII interaction drives expression of phosphoenolpyruvate carboxykinase (PEPCK).

Hepatic PEPCK expression is controlled by a set of promoter elements collectively known as the Glucocorticoid Response Unit (GRU) at which a variety of transcription factors can bind, including GR and COUP-TFII. Within the GRU, GR binds at two glucocorticoid response elements (GRE1 and GRE2), while COUP-TFII binds at accessory factor-binding elements (AF sites). Although each receptor can independently bind the GRU, a full response to glucocorticoid hormones (GCs) requires expression of COUP-TFII and GR capable of directly binding COUP-TFII. Thus, GR/ COUP-TFII interaction at the GRU is required for robust induction of hepatic gluconeogenesis in response to glucocorticoid hormones.