Physiol Rev 94: 355–382, 2014
doi:10.1152/physrev.00030.2013

THYROID HORMONE REGULATION OF METABOLISM

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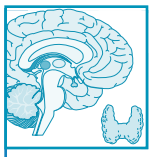


Mullur R, Liu Y-Y, Brent GA. Thyroid Hormone Regulation of Metabolism. *Physiol Rev* 94: 355–382, 2014; doi:10.1152/physrev.00030.2013.—Thyroid hormone (TH) is required for normal development as well as regulating metabolism in the adult. The thyroid hormone receptor (TR) isoforms, α and β, are differentially expressed in tissues and have distinct roles in TH signaling. Local activation of thyroxine (T_4), to the active form, triiodothyronine (T_3), by 5′-deiodinase type 2 (D2) is a key mechanism of TH regulation of metabolism. D2 is expressed in the hypothalamus, white fat, brown adipose tissue (BAT), and skeletal muscle and is required for adaptive thermogenesis. The thyroid gland is regulated by thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH). In addition to TRH/TSH regulation by TH feedback, there is central modulation by nutritional signals, such as leptin, as well as peptides regulating appetite. The nutrient status of the cell provides feedback on TH signaling pathways through epigentic modification of histones. Integration of TH signaling with the adrenergic nervous system occurs peripherally, in liver, white fat, and BAT, but also centrally, in the hypothalamus. TR regulates cholesterol and carbohydrate metabolism through direct actions on gene expression as well as cross-talk with other nuclear receptors, including peroxisome proliferator-activated receptor (PPAR), liver X receptor (LXR), and bile acid signaling pathways. TH modulates hepatic insulin sensitivity, especially important for the suppression of hepatic gluconeogenesis. The role of TH in regulating metabolic pathways has led to several new therapeutic targets for metabolic disorders. Understanding the mechanisms and interactions of the various TH signaling pathways in metabolism will improve our likelihood of identifying effective and selective targets.

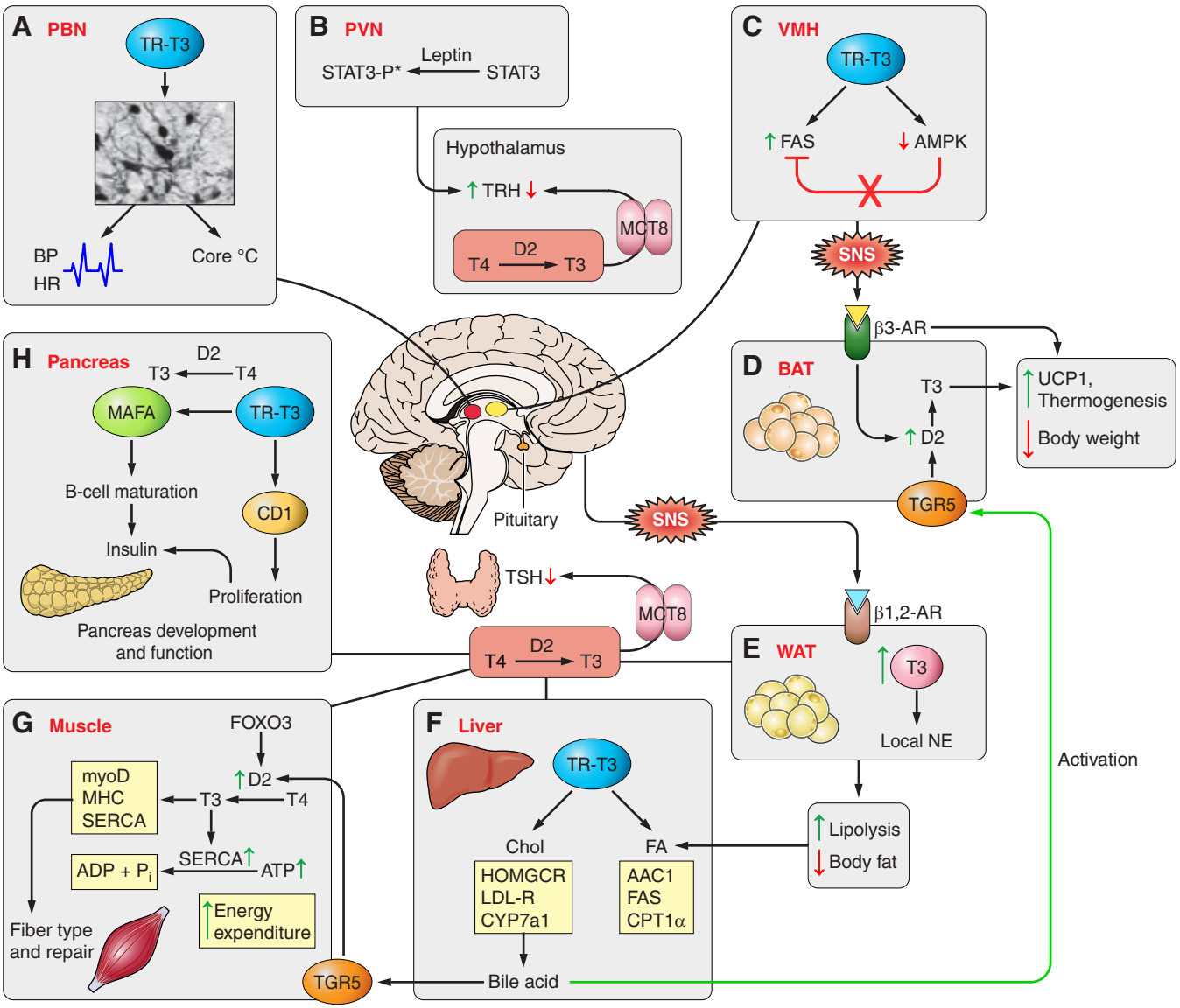
I. INTRODUCTION

Thyroid hormone (TH) regulates metabolic processes essential for normal growth and development as well as regulating metabolism in the adult (28, 40, 189). It is well established that thyroid hormone status correlates with body weight and energy expenditure (80, 127, 143). Hyperthyroidism, excess thyroid hormone, promotes a hypermetabolic state characterized by increased resting energy expenditure, weight loss, reduced cholesterol levels, increased lipolysis, and gluconeogenesis (26, 184). Conversely, hypothyroidism, reduced thyroid hormone levels, is associated with hypometabolism characterized by reduced resting energy expenditure, weight gain, increased cholesterol levels, reduced lipolysis, and reduced gluconeogenesis (27). TH stimulates both lipogenesis and lipolysis, although when TH levels are elevated, the net effect is fat loss (191). TH influences key metabolic pathways that control energy balance by regulating energy storage and expenditure (40, 127, 157). TH regulates metabolism primarily through actions in the brain, white fat, brown fat, skeletal muscle, liver, and pancreas.

A number of recent reviews have focused on specific actions of TH in metabolic regulation (**FIGURE 1, TABLE 1**). These include the molecular mechanisms of TH action (28, 40), lipid regulation (270), cross-talk with nuclear receptors (157), the role of corepressors in metabolic regulation (185), thyroid hormone adrenergic interactions (233), facultative thermogenesis (229), and the metabolic influences on central regulation of TH (117, 163). This review will examine the various sites of TH action and mechanisms that mediate metabolic regulation, focusing on the interaction among the pathways that regulate lipid and carbohydrate metabolism, and the balance of energy storage and energy expenditure. The themes among the interacting TH metabolic pathways include the influence of nutrient feedback, through nuclear receptor crosstalk and epigenetic modifications of histones, the impact of adrenergic signaling, and local ligand availability **(TABLE 2)**. We will conclude with the application of these common mechanisms to therapeutic targets.

We will first examine the mechanisms of TH action that impact pathways important for tissue-specific metabolic regulation, as well as key developmental actions. These mechanisms include variations in thyroid hormone transporter expression, local ligand activation and inactivation, relative expression of thyroid hormone receptor (TR) isoforms, and the activity of receptor corepressors and coactivators (28). In most tissues, there is a combination of these mechanisms that regulate thyroid hormone action. The relative role of most components of the TH signaling pathways has been clarified by the study of mouse models containing gene mutations or inactivation, as well as gene defects identified in human disorders (28). These models include genetic mutations or deletions of each of the TR isoforms, the principle thyroid hormone transporter, monocarboxylate transporter 8 (MCT8), corepressors, and all three deiodinase enzymes (28, 202, 266).

The importance of feedback of the nutritional status of the organism, through epigenetic modification of chromatin, is increasingly recognized as an important level of metabolic regulation (71). Such chromatin modification may be especially important for crosstalk of TR with other nuclear receptors, many of which are nutrient receptors (228), as well as with corepressors (185, 276) and coactivators (53). The nuclear receptor corepressors, nuclear receptor corepressor (NCoR) and silencing mediator for retinoid and thyroid hormone receptor (SMRT), are important metabolic regulators (53, 185, 213). Models with tissue-specific gene inactivation of NCoR in fat (154), and skeletal muscle (273), show enhancement of PPARγ action in metabolism. Differential expression of corepressor variant mRNA provide a further level of regulation for both SMRT (173) and NCoR (98). In the case of NCoR, the mRNA splicing variant NCoRδ stimulates adipogenesis and the variant NCoRω



inhibits it (98). The relative ratio of NCoRδ/NCoRω regulates adipocyte differentiation.

TH has direct and indirect actions on the regulation of cholesterol production, disposal, and efflux (157, 270). Some of the indirect actions include crosstalk with other nuclear receptors including farnesoid X receptor (FXR), liver X receptor (LXR), peroxisome proliferator-activated receptor (PPAR), and PPARγ coactivator (PGC-1α) (157). TH promotes both lipolysis and lipogenesis (191). Bile acid stimulating pathways include direct actions on cholesterol metabolism, but also stimulate 5′-deiodinase type 2 (D2) activity and TH-mediated increase in energy expenditure. These elements also have an impact on carbohydrate metabolism, especially mediating insulin sensitivity in the liver and suppression of gluconeogenesis.

Understanding the integration of the various thyroid hormone pathways remains a challenge. The most significant pathway that interacts with TH regulation of metabolism is adrenergic signaling (233). The central regulation of thyroid hormone production by TRH/TSH integrates signals from nutritional feedback, as well as the adrenergic nervous system (163). Models, such as fasting and illness, provide further information on how TH mediates adaptations to protect energy storage in times of stress to the organism. TH regulates both basal metabolic rate and adaptive thermogenesis, with a significant impact on body weight. Adrenergic stimulation is required for adaptive thermogenesis as a result of direct actions on gene regulation and indirectly by stimulation of D2 activity.

The robust TH regulation of components of lipid and carbohydrate metabolism, as well as energy expenditure, provides attractive therapeutic targets for a range of metabolic disorders (15, 270). A number of thyroid hormone analogs have been developed for cholesterol reduction and weight loss (28, 31, 205, 227). A clearer understanding of the interactions of the various TH-regulated metabolic pathways is essential in the design and development of therapeutic agents.

II. THYROID HORMONE ACTION

A. Thyroid Hormone Receptor, Nuclear Receptor Partners, and Response Coregulators

1. Thyroid receptor isoforms

TH action is exerted primarily via the nuclear TR, a member of the superfamily of hormone-responsive nuclear transcription factors that share a similar structure and mechanism of action (28, 40). The structure of the nuclear receptors, such as TR, includes a zinc finger motif DNA binding domain and a COOH-terminal domain that mediates ligand interactions as well as binding of coactivators and corepressors (28, 40). The function of the amino terminus varies among nuclear receptors, but for TR has minimal functional significance. There are two primary isoforms of TR, α and β, which are differentially expressed developmentally and in adult tis-

FIGURE 1. Overview of sites of thyroid hormone regulation of metabolism. *Hypothalamic-Pituitary-Thyroid axis:* thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH) respond primarily to circulating serum T_4, converted in the hypothalamus and pituitary to T_3 by the 5′-deiodinase type 2 (D2). The monocarboxylate transporter 8 (MCT8) is required for T_3 transport into the pituitary and hypothalamus. *A, parvalbuminergic neurons (PBN):* PBN are a population of newly discovered neurons in the anterior hypothalamus that are directly linked to the regulation of cardiovascular function, including heart rate, blood pressure, and body temperature. Thyroid hormone receptor signaling is required for the normal development of PBN neurons linking thyroid hormone to cardiac and temperature regulation. *B, paraventricular nucleus of the hypothalamus (VPN):* leptin, produced in peripheral fat tissue, provides feedback at the VPN, stimulates signal transducer and activator of transcription (STAT)3 phosphorylation ($STAT_3$-P*), which directly stimulates TRH expression. Leptin also stimulates TRH indirectly in the arcuate nucleus by inhibiting neuropeptide Y and agouti-related protein, stimulating proopiomelanocortin (POMC), and the POMC product α-melanocyte stimulating hormone (α-MSH) stimulates CREB in the TRH neuron (indirect pathway is not shown in **FIGURE 1**). *C, ventromedial nucleus of the hypothalamus (VMH):* hyperthyroidism or T_3 treatment stimulates de novo fatty acid synthesis in the VMH, which inhibits AMPK phosphorylation and increases fatty acid synthase (FAS) activity. Increased hypothalamic lipid synthesis is associated with activation of the sympathetic nervous system (SNS) which stimulates brown adipose tissue (BAT). *D, BAT:* adrenergic signaling through the β3-adrenergic receptor (AR) stimulates *UCP1* gene expression, stimulates D2 activity by deubiquitination, and promotes thermogenesis and weight loss. The metabolic signal from bile acid via the G protein-coupled membrane bile acid receptor (TGR5) has been shown in one model to stimulate D2 activity and local T_3 production, which further stimulates BAT lipolysis, UCP1 expression, and thermogenesis. *E, white adipose tissue (WAT):* SNS signals via β1- and β2-AR stimulate WAT lipolysis. T_3 stimulates local production of norepinephrine (NE), increasing lipolysis and reducing body fat. *F, liver*: T_3 is involved in both cholesterol and fatty acid metabolism (see details in **FIGURE 3**). HOMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; ACC1, acetyl-CoA carboxylase 1; CYP7a1, cytochrome *P*-450 7A1; CPT-1α, carnitine palmitoyltransferase 1α; LDL-R, low-density lipoprotein receptor. *G, muscle:* Forkhead box O3 (FoxO3) induces D2 expression, increases local T_3 in skeletal muscle, and promotes T_3-target gene expression; myoD, myosin heavy chain (MHC) and sarcoplasmic reticulum Ca^{2+}-ATPase *(SERCA*). Local T_3 also determines the relative expression level of MHC and SERCA isoforms. Expression level of these isoforms determines muscle fiber types and initiation of repair. *SERCA2a* is primarily expressed in slow-twitch fibers and *SERCA1* in fast-twitch fibers. T_3 stimulates SERCA, which hydrolyzes ATP and increases energy expenditure. *H, pancreas:* T_3 and TR are required for normal pancreatic development and function. In rat pancreatic β cells, expression of TR and D2 are activated during normal development. T_3 treatment enhances *Mafa* (v-maf musculoaponeurotic fibrosarcoma oncogene homolog A) transcription factor gene expression and increases MAFA protein content, the key factor for maturation of β cells to secrete insulin in response to glucose. T_3 stimulates *cyclin D1* (CD1) gene expression and protein level and promotes proliferation. Increasing cyclin D1 activates the cyclin D1/cyclin-dependent kinase/retinoblastoma protein/E2F pathway.

Table 1. *Sites of thyroid hormone action in metabolic regulation*

Process	Elements That Regulate Metabolism	Basic Mechanisms	Examples of Physiological Actions	Reference Nos.
Thyroid hormone action	TR isoforms	TR isoform specificity	Increased basal metabolic rate (BMR)	27, 39, 159, 232
	Corepressor action (NCoR and SMRT)	Histone modification	Stimulate lipolysis/lipogenesis	
	Nutrient feedback	Sumoylation	Increase in adaptive thermogenesis	
	Nongenomic action	Corepressor interactions	Stimulate β-oxidation of fatty acids	
	Tissue-selective thyroid hormone transport	Modulation of signal transduction pathways		
		Stimulation of Na^+-K^+-ATPase and SERCA1		
Central regulation of TRH/TSH	T_4/T_3 feedback	Integration of TRH/TSH regulation with metabolic signals	TSH measurement for the diagnosis of thyroid disease	117, 163
	Leptin	Thyroid hormone transport into the hypothalamus and pituitary (e.g., by MCT8)	And to monitor treatment	
	AMPK activation	Integration of adrenergic signaling	Central adaptation to fasting, illness, and obesity	
	Oxrexigenic/anorectic peptides/appetite regulation			
	Thyronamines (T1AM)			
	Circadian rhythms			
Local ligand activation by D2	D2 expression and activity	Regulation of D2 ubiquitination/deubiquitination	TSH/T4 set point	90, 149
	D2 polymorphisms	Increase in D2 activity with reduction in serum T_4 concentration	T_4/T_3 replacement therapy of hypothyroidism	
	Selenium requirement for deiodinase activity	Developmental and tissue selective deiodinase expression	Stimulates adaptive thermogenesis	
Thermogenesis and body weight	Basal metabolic rate	Integration of adrenergic signaling	Reduces body fat	229
	Adaptive thermogenesis	Central and local adrenergic actions	Increases β-oxidation of fatty acids	
	Body weight and body composition	Stimulation of CPT1α expression	Stimulates adaptive thermogenesis	
	Appetite	Stimulattion of UCP1 expression		
Cholesterol and triglycerides	Cholesterol synthesis	Stimulates LDL-R	Reduces serum cholesterol	145, 157, 270
	Reverse cholesterol transport	Stimulates ABCA1	Reduces serum triglycerides	
	Lipolysis/lipogenesis		Reduces hepatic steatosis	
	Hepatic steatosis			
Carbohydrate metabolism	Pancreatic islet development	TR expression in developing islets	Stimulates gluconeogenesis	49
	Pancreatic islet proliferation	D2 required for developing islets and islet function	Reduces insulin sensitivity	
	Insulin production	Insulin signaling	Increase in insulin metabolism	
	Gluconeogenesis	Stimulation of mitochondrial respiration		
	Insulin sensitivity	Increase in expression of ChREBP, GLUT4, ACC1		
	Insulin metabolism			

ABCA1, ATP-binding cassette transporter A1; ACC1, acetyl CoA carboxylase; ChREBP, carbohydrate response element binding protein; CPT-Iα, carnitine palmitoyltransferase Ia; CYP7A1, cholesterol 7-hydroxylase; D2, 5′-deiodinase type 2; GLUT4, glucose transporter 4; LDL-R, low-density lipoprotein receptor; LXR, liver X receptor; NCoR, nuclear corepressor; PPARα, peroxisome proliferator-activated receptor; RXR, retinoid X receptor; SERCA, sarcoplasmic reticulum calcium ATPase; SMRT, silencing mediator for retinoic and thyroid hormone receptor; T_3, triiodothyronine; T_4, thyroxine; TGR5, G protein-coupled receptor bile acid receptor; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; UCP, uncoupling protein.

sues (28, 167). Both TR α and β undergo posttranslational modification by sumoylation, which is essential for positive and negative gene regulation by TH, including genes important for metabolic regulation (159). Sumoylation of PPARγ is essential for adipogenesis in a SUMO1 gene knockout mouse model (176). TR sumoylation may similarly impact metabolic genes directly regulated by TR and genes regulated by TR crosstalk with other nuclear receptors.

The tissue specificity of the TR isoform expression, and relative expression of each isoform within a tissue, is another pathway of thyroid hormone action specificity in metabolism (76). Each TR isoform has several splice products, for example, TR α1 and α2 and TR β1 and β2 (28, 40). TRα2 does not bind T_3, and acts to reduce T_3 action. TR β2 is predominantly expressed in the brain and pituitary. Developmentally, TRα is expressed first followed by TRβ. The

Table 2. *Common themes integrating thyroid hormone metabolic regulation*

Metabolic Regulatory Themes	Thyroid Hormone Action	Central Regulation of Thyroid Hormone Production	Thermogenesis and Body Weight	Cholesterol and Triglyceride Regulation	Carbohydrate Metabolism
Nutrient feedback	Histone modification (165)	Leptin feedback to arcuate nucleus (117)	T_3 regulation of BMR (137)	Crosstalk with LXR (110)	Crosstalk with LXR (147)
	Sirtuin expression	Selenium required for D2 activity (90)	Fat intake	Crosstalk with PPARα, γ, δ (157, 158)	Fat intake
	Nongenomic signal transduction pathways (34)		Carbohydrate intake	Bile acid and increased thermogenesis (269)	Carbohydrate intake
	Coregulator recruitment (71, 165)		Body composition	TGR5 receptor in white adipose (246)	
Nuclear corepressor action	Mediates basal repression and ligand-induced gene activation or repression (185)	NCoR/HDAC3 and TSH regulation (11, 276)	Modulation of UCP1 expression	Modulation of gene regulation by TR in liver and white adipose (283) Truncated forms of NCoR/SMRT regulate adipocyte differentiation (98)	Modulation of gene regulation by TR in liver and white adipose, BAT, and pancreas
Adrenergic sensitivity	TRα adipocyte lipolysis (160)	Central adrenergic regulation of thermogenesis (163)	D2 activation by stimulating deubiquitinase (212)	T_3 potentiation of catecholamine-induced lipolysis (160)	Suppresses insulin secretion and increases glycogenolysis
	TRα BAT thermogenesis (207)	Central regulation of cardiovascular function in PBN (179)	Synergistic with T_3 in stimulation of UCP1 expression (19)		
Local ligand availability	D2 expression in inner ear and retinal development (186)	D2 activity in the hypothalamus (79)	BAT thermogenesis	Bile acid stimulation of D2 expression (269)	D2 requirement for pancreatic islet function (3)
	Induction of D2 for T3 activation or D3 for inactivation (90, 149)	D2 and T4/TSH set point (116)	Greater weight loss with T_3 replacement compared with T_4 (37)		D2 polymorphisms in diabetes (70, 174)

BAT, brown adipose tissue; D2, 5′-deiodinase type 2; HDAC3, histone deacetylase 3; LXR, liver X receptor; NCoR, nuclear corepressor; PBN, parvalbuminergic neurons in anterior hypothalamus; PPARα, peroxisome proliferator-activated receptor; RXR, retinoid X receptor; SMRT, silencing mediator for retinoic and thyroid hormone receptor; T_3, triiodothyronine; T_4, thyroxine; TGR5, G protein-coupled receptor bile acid receptor; TR, thyroid hormone receptor; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; UCP1, uncoupling protein 1. Reference numbers are in parentheses.

pattern of early TRα expression, followed by expression of TRβ, is seen across all species studied including *Xenopus*, chick, as well as in mammalian development. TRβ has very specific windows of expression during sensory tissue development, including the inner ear and retina (186). TRβ is the predominant TR isoform expressed in the liver and cardiac ventricles. TRα1 is preferentially expressed in brain and white adipose tissue (WAT) as well as the atria, while BAT contains both TR α and β (206).

2. Retinoid X receptor

Retinoid X receptor (RXR) is best characterized as a heterodimer partner that binds with other nuclear receptors to DNA response elements, but it can also be directly stimulated by ligand and regulate gene expression. There are three RXR isoforms: α, β, and γ, which are coded by distinct genes on human chromosomes (9, 6 and 1) and have developmental and tissue-specific patterns of expression (153). RXR can form a homotetramer in solution and bind DNA as a homotetramer or homodimer. RXR can be directly stimulated by the retinoid ligand 9-*cis*-retinoic acid, as well as by a range of other synthetic ligands, several of which have been developed for cancer and metabolic disease treatment (55, 196). Unsaturated fatty acids are natural endogenous ligands for RXR activation, although they bind with relatively low affinity and the authentic endogenous ligand has not been established. There is genetic evidence in mouse models for important RXR isoform-specific functions. The RXRγ knockout mouse is resistant to weight gain when fed a high-fat diet due, in part, to upregulation of skeletal muscle lipoprotein lipase (112).

TR forms a heterodimer complex with RXR which binds to a thyroid response element (TRE), stimulating or inhibiting gene transcription. The response element consists of two hexamer sequences, AGGTCA, with some sequence variation, arranged as direct repeats with a 4-bp gap (28). RXR generally binds the upstream hexamer and TR the downstream hexamer. The response element configuration, with variable spacing of hexamers, is similar to that for the related receptors vitamin D receptor (VDR), retinoic acid receptor (RAR), LXR, and PPAR. These receptors have a number of common features including that they do not bind

heat shock protein, reside predominantly in the nucleus, form heterodimers with RXR that bind to direct repeat DNA response elements, and bind corepressor in the absence of ligand resulting in repression of gene expression (228). The RXR heterodimer nuclear receptor complexes are divided into two groups, depending on RXR ligand influencing the heterodimer, "permissive" (complex can be driven by RXR ligand) and "nonpermissive" (complex driven only by partner ligand) (153, 228). The permissive RXR heterodimer partners, including LXR, FXR, and PPAR, are "feed-forward" ligand receptors, in contrast to ligands regulated by classic feedback inhibition. These receptors respond to a broad range of ligands, in micromolar to nanomolar concentrations, that are generally nutrients or nutrient products. The second group (TR, VDR, and RAR) is referred to as nonpermissive and responds to traditional endocrine hormone ligands that are feedback regulated and act in the nanomolar to picomolar concentration range (228). The shared features among these nuclear receptors that regulate metabolism, such as the response element configuration and interacting with an RXR heterodimer partner, may promote some of the crosstalk observed between TR mediated TH and nutrient pathways (157).

3. Nuclear receptor coregulators

Coactivators associate with liganded nuclear receptors and enhance gene transcription (53). Examples of coactivators include the steroid receptor coactivators 1, 2 and 3, members of the p160 family, that interact broadly with steroid receptors. Some coactivators, such as PGC-1α, are more selective, interacting predominantly with a single type of receptor. cAMP response element binding protein (CREB) binding protein (CBP) interacts with essentially all transcription factors and enhances gene transcription by relaxing chromatin structure by virtue of its intrinsic histone acetyltransferase (HAT) activity.

Coactivator recruits enzymes that acetylate histones and promote transcription, a process sensitive to the metabolic state of the cell (71, 165). Genome-wide studies have demonstrated that nuclear receptors regulate gene expression by direct DNA binding, but that nuclear receptors can also assist in opening chromatin at noncanonical sites and influence gene expression in ways distinct from direct DNA binding (71). Many histone modifying enzymes are influenced by nutrient signals in the cell, including NAD^+/NADH influencing sirtuin histone deacetylase, acetyl-CoA is a donor for AHT-mediated histone acetylation, and a low ATP/AMP ratio activates AMPK, which phosphorylates histones (165).

In the liganded state, the TR complex recruits coactivators, such as members of the SRC family, to stimulate the transcription of T_3-regulated genes (53). In several studies of T_3 action, SRC1 was shown to be important for the increase in TSH in response to hypothyroidism as well as thyroid hormone-dependent repression of TSH (6, 247). SRC1, however, influenced only a few genes related to peripheral action of thyroid hormone, such as Spot 14 in the liver (247).

Corepressors bind to nuclear receptors in the unliganded state and promote gene repression. In the unliganded state, the TR complex associates with a corepressors, such as NCoR or SMRT, to decrease gene transcription of T_3-regulated genes and antagonize the action of other nuclear receptor complexes (7, 28, 185) **(FIGURE 2)**. Corepressors recruit histone deacetylases (HDACs) to the promoters of target genes to promote repression by unliganded TR (119). NCoR interactions with HDAC3 modulates expression of genes both positively and negatively regulated by thyroid hormone, as shown by a study with an NCoR mutation (276). The HDAC3 interacting domain site in NCoR, the deacetylase activating domain (DAD), was mutated in mice and liver and pituitary gene expression analyzed in euthyroid, hypothyroid, and hyperthyroid mice. As expected, genes positively regulated by TH were no longer repressed in the absence of ligand, but they also reported that genes negatively regulated by T_3, such as TSHα, were upregulated, regardless of thyroid status. The global physiological role of repression by the unliganded TR bound to a positive TRE was demonstrated in vivo by a mouse model without expression of TR α or β (100). The phenotype of these mice with no TR was much milder than a hypothyroid mouse, with no ligand but intact TR. This is consistent with the importance of corepressor-mediated repression by the unliganded TR in hypothyroidism. Eliminating TR expression largely "rescues" the abnormal phenotype associated with hypothyroidism. These observations, coupled with the profound developmental and metabolic impact of corepressors gene knockouts in mice, highlight the importance of corepressor action as a key factor in thyroid hormone regulation of metabolism (9, 10, 119, 213).

NCoR plays an essential role in PPARγ signaling (213), which may be linked to TH signaling. The global NCoR knockout is an embryonic lethal resulting in defects in multiple organs. Selective inactivation of NCoR in adipose tissue resulted in a phenotype similar to activation of PPARγ with an agonist: increased insulin sensitivity, improved glucose tolerance, and activation of PPARγ-regulated genes (154). Selective inactivation of NCoR expression in skeletal muscle, where PPARδ and estrogen-related receptor (ERR) are expressed, produced an increase in mitochondrial content, oxidative metabolism, and muscle fiber size (273). This is generally consistent with the actions from PPARδ activation. It was further noted in this study that a high-fat diet reduced NCoR levels in fat and muscle. Regulation of corepressor expression may be a significant mechanism of regulation. One mechanism of metabolic regulation is that high fat intake reduces NCoR expression, promotes PPARγ-δ activation by interaction with coactivator, and

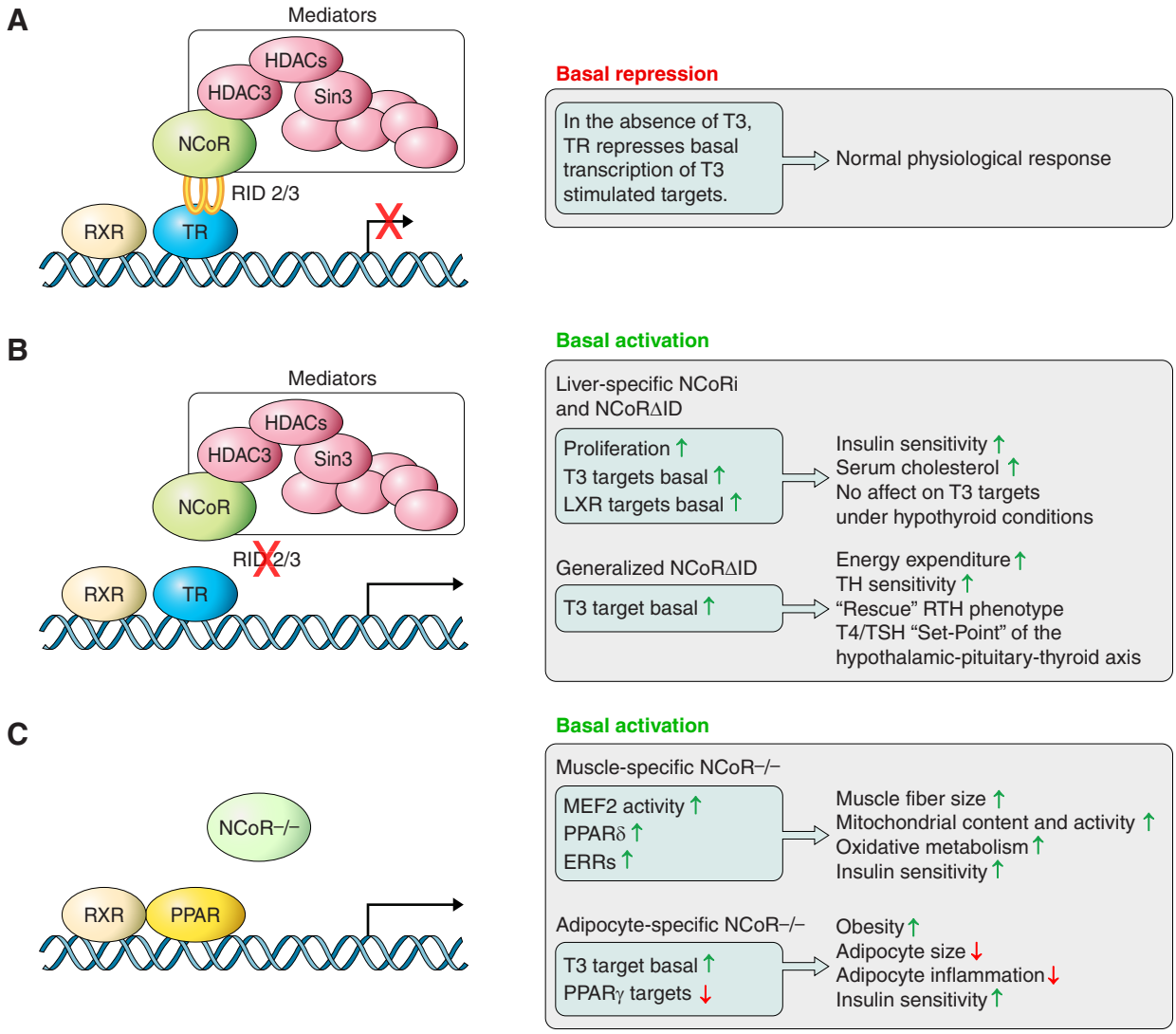


FIGURE 2. Role of corepressors in metabolic regulation. NcoR has three receptor interacting domains (RIDs) located in the COOH terminus. Unliganded TR interacts with RID 2 and 3 and recruits histone deacetylase 3 (HDAC3) to assemble a mediator complex, resulting in basal transcription repression. *A*: deletion of all three RID (NCoRi) or only RID2–3 (L-NCoRΔID) results in a corepressor that can no longer be recruited to unliganded-TR, although the repression mediator complex can still be assembled since the repression domains are intact. Without NCoR interaction, basal transcription is activated. This activation induces hepatocyte proliferation and T_3- and LXR-target genes activation in liver. *B*: global expression of the NCoRΔID enhances metabolic actions, such as energy expenditure, and can rescue the RTH phenotype produced by TRβ mutations and increase TH sensitivity. *C*: the conditional NCoR knockout in specific tissues demonstrates tissue-specific actions of NCoR. After NCoR knockout, basal transcription is activated. Muscle-specific NCoR inactivation enhanced metabolic actions of PPARδ and estrogen-related receptors (ERRs); MEF2, myocyte enhancer factor-2. Adipocyte-specific NCoR$-/-$ enhanced PPARγ actions, inhibited NCoR phosphorylation, leading to constituitive activity, enhanced insulin sensitivity, reduced inflammation, and promoted obesity, consistent with the actions of a PPARγ agonist.

promotes lipogenesis in fat and lipid oxidation and mitochondrial biogenesis in skeletal muscle (213). Although thyroid pathways were not directly assessed or discussed in these studies, a similar stimulation of lipogenesis and oxidative metabolism is mediated by TR and would likely be activated by a reduction in NCoR expression. Unliganded TR favors interaction with NCoR, and TR has been shown to influence PPARα (158), and LXR (110), signaling.

The ligand-dependent corepressor (LCOR) has been identified as a regulator of TR induction of lipogenic genes and hepatic lipid accumulation. LCOR was first identified as a corepressor for estrogen receptor which bound to the LXXLL motif, also referred to as the nuclear receptor (NR) box. LCOR expression was reduced in fatty livers of leptin-deficient (*ob/ob*) mice and diet-induced obese mice (243). Overexpression of LCOR re-

presses TH induction of lipogenic genes by reducing recruitment of the coactivator SRC to TR and is a key regulator of hepatic lipogenesis.

4. Resistance to TH

The recognition of TR isoform-specific actions has come from animal models of TR gene mutations and inactivation as well as the phenotype of individuals with TR gene mutations (28, 29) **(TABLE 3)**. TR isoform specificity has also been probed by TR isoform-selective agonists. TR isoform selective actions are likely due to both the timing and location of TR expression as well as subtle different properties between the major receptor isoforms TRα and -β.

Resistance to TH (RTH) has been studied extensively as a disorder in which TRβ has reduced affinity for binding T_3 and corepressor binding is not reversed by ligand (202). Patients generally have an elevated serum T_4 and T_3 concentration, but "inappropriately normal" or slightly elevated serum TSH, since the elevated serum T_4 and T_3 concentration should suppress TSH, but do not because of the defective TRβ. The associated clinical features include goiter and general euthyroidism, except for tachycardia, consistent with the unopposed action of the elevated serum T_4 and T_3 stimulating TRα in the atria. Other clinical features, which vary among affected individuals, include reduced linear growth, impaired hearing, defects in bone formation, and attention deficit disorder (203). Genetic studies of multiple families revealed defects in the ligand binding domain of the TRβ gene, which correlate with the clinical features seen in RTH patients, impaired TRβ action in the brain and liver, and preserved TRα activity in the heart. Metabolic characterization of individuals with RTH due to TRβ mutations demonstrate an enhanced metabolic rate and hyperphagia, presumably due to the actions of high levels of TH mediated by TRα (178). Animal models generally show a similar phenotype as that observed in humans (28). The role of the corepressor, NCoR, has been demonstrated by crossing mice with RTH due to a TRβ mutation with a mouse expressing NCoR with a mutation in the domain that interacts with TR, NCoRΔID (81). The RTH phenotype was largely rescued in this setting, indicating that the irreversible interaction of the mutant TR with NCoR, an interaction not present when the NCoRΔID is expressed, is a significant mechanism for resistance.

Recent case reports have described patients with a dominant negative TRα mutation, analogous to TRβ RTH mutations, with clinical features of short stature, developmental delay, bony deformities, and chronic constipation, but no impairment in TRβ-mediated processes (21, 258). The elevated cholesterol and increased BMI seen in these patients suggest reduced activity of some metabolic processes. Since TRH/TSH feedback is primarily mediated by TRβ, the pituitary in the RTH TRα mutant patients responds normally to TH feedback, so serum TSH and T_4 levels are normal. These patients, therefore, do not compensate for the mutant TRα, so they have more of a phenotype of hypothyroidism. Serum T_3 levels are elevated relative to

Table 3. *Metabolic manifestations in resistance to thyroid hormone*

	Genetic Defect	Hypothalamic-Pituitary-Thyroid Axis	General Manifestations	Metabolic Manifestations	Reference Nos.
RTH ß	Most commonly a mutation or deletion in ligand binding domain of TRβ, generally producing reduced ligand binding and irreversible interaction with corepressors	In most cases resistance to thyroid hormone feedback at the pituitary (mediated by TRβ)	Goiter	Enhanced metabolic rate	28, 178, 202
		Elevated serum T_4 and T_3, "inappropriately" normal range serum TSH	Generally euthyroid, except for tachycardia (unopposed action of the elevated serum T_4 and T_3 stimulating TRα in the atria)	Hyperphagia	
		Elevated T_4/T_3 "compensate" for resistance to thyroid hormone	In some models; reduced linear growth, impaired hearing, defects in bone formation, and attention deficit disorder		
RTH α	In the few reported cases, a mutation in ligand binding domain of TRα, analogous to those found in TRβ, generally producing reduced ligand binding and irreversible interaction with corepressors	Pituitary is predominantly TRβ, pituitary normally sensitive to feedback	Short stature	Elevated cholesterol	21, 258
		Normal T_4, T_3, and TSH	Developmental delay	Elevated BMI	
		Elevated serum T_3/T_4 ratio compared with normal	Bony deformities		
			Chronic constipation		

serum T_4, although the mechanism is not established (278). On the basis of animal models, the elevated T_3 may be due to both increased 5′-deiodinase type 1 (D1) activity and reduced 5-deiodinase type 3 (D3) activity (278). It has previously been shown that TRα is the primary regulator of D3 expression, so it is expected that a TRα mutation would lead to reduced D3 (14). Characterization of two TRα RTH mutation patients, on and off thyroxine treatment, indicate some of the metabolic actions of TRα. Thyroxine treatment in TRα mutant patients was associated with normalization of lipoproteins, suppression of TSH, normalization of T_4, and improvement in nerve conduction and symptoms of constipation (259). There was no improvement, however, in cognitive or fine motor skills. The difference in phenotype between individuals with the TRα and TRβ mutations highlights the tissue specificity and distinct roles of TR isoforms in metabolic regulation.

5. TR crosstalk

TH signaling, especially in metabolic regulation, involves TR crosstalk with other nuclear hormone receptors including PPARα, PPARγ, and LXR (157). These ligand-activated nuclear receptors recognize and bind to DNA response elements that are arranged as hexameric half-sites with direct repeats, although the spacing of the hexamers varies among the different receptors. The nuclear receptors all form heterodimers with RXR, and in some cases may compete for limiting amounts of RXR (120). Mouse models with TR mutations have shown crosstalk of TH signaling with PAPRα (158), as well as with LXR (110). Thyroid hormone has also been shown to directly stimulate LXR expression (111). The role of LXR as a coordinator of both lipid and carbohydrate metabolism suggests the potential for interactions with TR (16, 147). A recent study demonstrated that LXR is important for hepatic lipid deposition (16). In *ob/ob* mice with an LXR gene knockout, hepatic lipogenesis was reduced, excess fat was deposited in adipose tissue rather than the liver, and insulin sensitivity was improved (16). The differential actions of LXR in liver lipogenesis and fat are similar to those of TR. Such examples of crosstalk and interaction will be discussed in greater detail while characterizing the role of TR in lipid, cholesterol, and carbohydrate metabolism.

B. Role of Deiodinases

The intracellular action of TH is regulated by the amount of local T_3 available for receptor binding (90, 149). The iodothyronine deiodinases include two activating enzymes, D1 and D2, and one inactivating enzyme, D3, which are differentially expressed developmentally and in adult tissues. Developmentally, D3 is generally expressed first, followed by D2, and D1 is expressed last. D1 is expressed at high levels in the liver, kidney, and thyroid; D2 in brain, pituitary, thyroid, and BAT; and D3 in the skin, vascular tissue, and placenta. The deiodinase enzymes also differ in subcellular localization, with D1 and D3 expressed on the cell membrane and D2 in the endoplasmic reticulum. D1 is not essential for TH action in the euthyroid mouse as was studied in a D1 gene knockout mouse (220). D1 functions predominantly as a scavenger enzyme that deiodinates sulfated TH while being cleared in the bile and urine (220). D1, therefore, may be important for the adaptation to iodine deficiency and to diminish the impact of elevated thyroid hormone levels in hyperthyroidism. D3 is expressed in the placenta, where it can protect a developing fetus from excessive maternal TH, as well as in the skin and vascular tissue. D3 expression is stimulated in hypoxia as mediated by hypoxia-inducible factor (HIF-1) (236). All of the deiodinases require selenium for catalytic activity, and defects in the synthesis of selenoproteins can lead to abnormal thyroid hormone metabolism and defects in the hypothalamic pituitary feedback mechanism (65). Defects in the selenocysteine insertion sequence binding protein 2 (SECISBP2) is associated with a range of defects, including azoospermia, myopathy, and reduced T-cell proliferation (221). Nutritional selenium deficiency is also associated with reduced deiodinase activity (90).

D2 is the primary enzyme responsible for the rapid increases in intracellular T_3 in specific tissues as well as the primary producer of serum T_3 in humans (166). The D2 enzyme has a short half-life due to ubiquitination and proteasome degradation (8, 90). Deubiquitination, which increases D2 activity, is stimulated by adrenergic activation or by low levels of serum T_4 (91, 212). D2 is expressed in key thyroid-responsive tissues, such as brain, skeletal muscle, and brown fat, which preserves T_3 in these tissues as serum T_4 levels fall. The T_3 generated intracellularly by D2 is transferred to the nucleus and then regulates gene transcription. D2 activity is critical for the synergism of TH and signaling in regulating thermogenesis in BAT (233).

D2 activity has been shown in one study to be stimulated by bile acids, through activation of the G protein-coupled receptor for bile acids (TGR5) receptor, which potentially links TH action with bile acid signaling (269). Administration of bile acids to mice resulted in increased energy expenditure in BAT, prevented obesity, and improved insulin sensitivity. This action was independent of the FXR but required D2 gene expression. D2 and TGR5 are coexpressed in key metabolic tissues, and this may be relevant for the regulation of energy expenditure. Bile acids may have an action in addition to bile acid homeostasis to function more broadly in metabolism (269). The TGR5 receptor is expressed in human adipose tissue, and its expression was correlated with basal metabolic rate (246).

A further link of D2 to a metabolic phenotype has come through studies of associations with D2 gene polymorphisms. Polymorphisms in the D2 gene have been associated with type 2 diabetes, insulin resistance, and obesity in

some (70, 174), but not all (42, 175), studies. In those studies with a positive association between D2 polymorphisms and metabolic disease, it is strongest when combining the D2 gene polymorphism with a polymorphism in a gene from another interacting metabolic pathway, such as the β3 adrenergic receptor (174), or PPARγ (70). These findings also support the importance of the interaction of TH signaling with other metabolic pathways.

A recent study in hypothyroid patients found that those with a specific D2 gene polymorphism had improvement of symptoms on T_4/T_3 combined therapy compared with T_4 monotherapy (192). This suggests that individuals with reduced T_4 to T_3 conversion due to D2 gene polymorphisms may benefit from the addition of the active form of TH, T_3, to their replacement therapy. Recently, a direct crossover comparison of monotherapy with T_4 to desiccated thyroid extract, which contains both T_4 and T_3, was made in hypothyroid patients (115). The serum TSH was kept in the reference range for patients while on both forms of thyroid replacement therapy. Patients, while on desiccated thyroid, had a modest, but significant, weight loss compared with the time period when they were on T_4 monotherapy.

C. Intracellular Transport

It had generally been assumed that thyroid hormone, due to its hydrophobicity, enters cells via passive diffusion. In vitro studies have identified multiple transporters with the ability to transport thyroid hormone, including the monocarboxylate and organic ion transporter families; however, the physiological significance was not known (130). On the basis of association of a transporter defect with a clinical disorder, it was shown that thyroid hormone transport is required in specific tissues, especially the brain (135, 265). The genetic disorder Allan-Herndon-Dudley Syndrome, with serum thyroid hormone abnormalities, low serum T, and elevated serum T_3, and severe neurologic deficits, was shown to be due to a mutation in the monocarboxylate transporter 8 (MCT8) gene. This proved an important role for the MCT8 transporter in normal human brain development. Thyroid hormone transporters are expressed in a specific temporal and spatial pattern in the developing brain (224, 256, 265). The MCT8 gene is located on the X chromosome (66, 84), and males with MCT8 gene mutations have neurologic abnormalities including dystonia and developmental delay, with progression to quadriplegia (18).

Mouse models of MCT8 gene knockout show thyroid function study changes similar to those in patients with Allan-Herndon-Dudley Syndrome, but modest changes in brain function (67, 255, 265). Mice likely have redundant thyroid hormone transporters, such that the MCT8 gene inactivation does not have the same consequences as is seen in humans. MCT8 is highly expressed in the hypothalamus, resulting in impaired central regulation and blunted thyroid hormone feedback when mutated (5). Without a functioning MCT8 transporter in the brain, specific brain areas become hypothyroid. Conversely, the liver remains sensitive to TH action when MCT8 is inactivated, such that the excess hormone produced due to impaired negative feedback in the hypothalamus results in tissue-specific hyperthyroidism and hypermetabolism and profound weight loss (114). Treatment with diiodothyropropionic acid (DITPA), in animal models and humans with inactivation or mutation in the MCT8 gene, results in reduction in serum TSH and serum T_3, and an improvement in hypermetabolism with weight gain and reduced caloric needs (60, 262). There was, however, limited improvement in cognitive or developmental delay in the human studies. The robust metabolic response to treatment that lowers serum T_3 in these patients shows the important role T_3 plays in hypermetabolism, but also that the tissues that mediate T_3 action in metabolism remain sensitive to TH even in the absence of the MCT8 transporter.

D. Nongenomic Actions

TH hormone action is not limited to nuclear receptor mediated T_3 actions that increase or decrease gene transcription, but include nongenomic actions (40). These nongenomic actions, shown with both in vitro and in vivo models, include interaction of TH with membrane integrin receptors, as well as TR effects in the cytoplasm modulating the activity of signal transduction pathways (40). Nongenomic mechanisms have been identified through which TH regulates growth, development, and metabolism via phosphorylation and activation of kinase pathways and neural proteins. Studies in human fibroblasts revealed activation of phosphatidylinositol 3-kinase (PI3K) via a liganded TR resulting in downstream phosphorylation and activation of PKB/Akt, mTOR and $p70^{S6K}$ (34). The RTH associated TR mutant with a COOH-terminal deletion, TRβPV, binds directly to the p85 subunit and results in a constitutively active PI3K (86). Another mechanism of nongenomic action involves interaction with the plasma membrane protein, integrin $\alpha v\beta 3$, which has been identified as a TH receptor that activates both the PI3K and ERK1/2 pathways (17). This cell surface receptor binds TH at two sites, S1 and S2, which result in different intracellular actions (54). The $\alpha v\beta 3$ S1 site only binds T_3 at physiological concentrations, resulting in phosphorylation and activation of PI3K, and nuclear accumulation of TRα (155). The $\alpha v\beta 3$ S2 site preferentially binds T_4 and activates the ERK1/2 pathway. The metabolic consequences of T_4 binding to the S2 site of $\alpha v\beta 3$ include proliferation of cancer cell lines (156), TRβ accumulation in the nucleus (155), and increased angiogenesis (17).

TH action by these nongenomic pathways activates PI3K or ERK1/2 and stimulates gene transcription. One gene induced by T_3 via a nongenomic pathway, important in metabolic regulation, is hypoxia inducible factor (HIF)-1α (181). HIF-1 is a key mediator of angiogenesis and adapta-

tion to hypoxia in tumor cells that results in expression of glycolytic enzymes and glucose transporters (222). HIF-1α is a potent stimulator of D3, which inactivates thyroid hormone by converting T_3 to reverse T_3 (236). A number of studies have identified a nongenomic role for TH in the phosphorylation of proteins. TH stabilizes and promotes protein phosphorylation in synaptosomes and intermediate filaments in both the mature and developing cytoskeleton in the cerebral cortex (216, 277). In addition, T_3 alters the phosphorylation status of several kinases, including p38, in a tissue-specific manner in vivo, with resulting cardiac hypertrophy, mitochondrial biogenesis, and osteoblast activation (125, 138). AMP-activated protein kinase (AMPK) has a wide range of actions including inhibition of inflammation and oxidative stress and stimulation of fatty acid oxidation and autophagy, all of which promote insulin sensitivity (210). Reduced activity of AMPK has been associated with the metabolic syndrome. Within 2 h of T_3 treatment of a rat, AMPK activity was reduced in the liver, increased in skeletal muscle, and not changed in the heart (123).

III. CENTRAL REGULATION OF THYROID HORMONE PRODUCTION

A. Hypothalamic-Pituitary-Thyroid Axis

TH is secreted from the thyroid gland under the regulation of the hypothalamic-pituitary axis **(FIGURE 1)**. TRH, secreted from the hypothalamus, acts upon the pituitary gland, binding to G protein-coupled TRH receptors on the thyrotrope, resulting in an increase in intracellular cAMP, and subsequent thyrotropin (TSH) release (113). Hormone signals that have modulatory effects on TSH secretion include dopamine (219), somatostatin (250), and leptin (223), which function as a point of central regulation of thyroid hormone release (93). TSH secretion, and its sensitivity to TRH stimulation, is affected by renal failure, starvation, sleep deprivation, depression, and hormones, including cortisol, growth hormone, and sex steroids (89, 128).

The importance of the adrenergic nervous system in central TRH/TSH regulation is being increasingly recognized (163). The combination of central nutritional and hormonal signals, including leptin, adrenergic signaling, and cortisol, integrate information regarding overall nutritional status, circadian rhythms, as well as acute stress, to modulate thyroid hormone production (93, 117). A central regulator of circadian rhythms, the RevErbAα/RevErbAβ nuclear receptors, are activated by BMAL-1, which then suppresses BMAL-1 transcription (74). RevErbAα is transcribed from the strand opposite the TRα gene and binds heme.

TSH binds to a G protein-coupled TSH receptor on the thyroid follicular cell, stimulating the production and release of TH. T_4, a prohormone, is the primary secretory product of the thyroid gland, which utilizes MCT8 for secretion (59). Local conversion of T_4 to T_3, by D2, provides negative feedback at the level of both thyrotrophs in the pituitary and tanycytes in the hypothalamus (79, 90, 149). This results in reduction in TRH and TSH secretion in response to adequate tissue levels of TH. Polymorphisms in the D2 gene have been associated with interindividual variation in the TSH-free T_4 "set point" (116). The corepressor NCoR is also required for negative regulation by thyroid hormone (11, 276). Tight regulation of this feedback loop is the key to using a serum TSH measurement for the diagnosis and management of primary thyroid disease, both hypothyroidism and hyperthyroidism, since small changes in serum T_4 are amplified by changes in serum TSH.

B. Integrating Signals Regulating TRH/TSH

The sympathetic nervous system (SNS) and TH regulate a number of metabolic processes in a complementary fashion (233). The earliest observations of central sympathetic nervous system regulation of TH action came from clinical management of patients with hyper- and hypothyroidism. Thyrotoxic patients have normal plasma norepinephrine (NE) levels, while hypothyroid patients have elevated plasma NE levels, perhaps to compensate for reduced adrenergic sensitivity (48). Epinephrine levels were not different in hyperthyroid or hypothyroid patients compared with normal (48). Direct measurement of epinephrine secretion shows no difference in hyperthyroid or hypothyroid patients (47). Follicular cells of the thyroid gland are also innervated by sympathetic fibers containing NE, which can influence the mitotic response to TSH stimulation (245). Catecholamines increase T_4 to T_3 conversion, by stimulating activity of a specific deubiquitinase that acts on the D2 protein, upregulates D2 activity, and increases T_3 levels in the nucleus (90). The synergism between the SNS and TH is best characterized in studies of facultative thermogenesis in BAT (207). The role of TH within the central nervous system is evolving and now includes alterations in neuroendocrine peptides with relation to energy intake, adipokines, nongenomic actions of TH within the hypothalamus, and the action of decarboxylated and deiodinated analogs of TH (163).

In rats, fasting has been shown to decrease pituitary D2 levels and liver D1 levels, and correlates with reduced peripheral T_3 isolated from liver homogenates (22, 23). Despite this reduction in pituitary and liver T_3, hypothalamic D2 activity is actually increased with fasting, resulting in an increase in the orexigenic proteins neuropeptide Y (NPY) and agouti-related peptide (AgRP) from the arcuate nucleus. Thus, despite fasting associated reductions in peripheral TH levels, there is still a localized increase in T_3 within the hypothalamus during fasting with a marked increase in orexigenic signals, which in turn act upon the paraventricular nucleus to decrease TRH production. This is thought to

be the mechanism for most such patients having a normal serum TSH despite a reduced serum T_4 concentration. Humans who are anorexic or undergo severe caloric restriction exhibit similar reductions in TH levels, which likely functions to protect energy stores (148, 204, 268). The administration of leptin (51), or α-MSH (73), can abolish the fasting-induced reductions in TRH.

Leptin is an adipokine that circulates in both the free and bound forms, and the serum concentration is proportional to body fat content. While both leptin and TH regulate signaling in the arcuate nucleus and reflect changes in energy stores, data regarding the correlation between leptin levels and hypo- and hyperthyroidism are inconsistent. In hypothyroid and hyperthyroid patients, followed before and after treatment, leptin levels were elevated in hypothyroidism and reduced in hyperthyroidism, correlating with BMI and with TSH levels (190). Adipocytes and preadipocytes express the TSH receptor, and acute administration of recombinant TSH in thyroid cancer patients has been shown to have an acute stimulatory effect on serum leptin, and the increase was proportional to the fat mass (215). In an obese animal model, and obese humans, there is an increase in free leptin with an increase in BMI (118). Within the hypothalamus, leptin is a known regulator of TRH and TSH secretion via direct action on the paraventricular nucleus and indirect action on the arcuate nucleus (223). In the direct pathway, leptin stimulates TRH neurons by inducing signal transducer and activator of transcription (STAT)3 phosphorylation, and regulating prepro-TRH transcription. In the indirect pathway, leptin inhibits NPY and AgRP and stimulates proopiomelanocortin (POMC). The POMC product α-MSH stimulates CREB in the TRH neuron. However, in the obese state, there is a significant amount of leptin resistance in the arcuate nucleus of the hypothalamus such that the indirect pathway of leptin stimulation of TRH is not active. This leptin resistance allows for maintenance of euthyroidism in the setting of diet-induced obesity (195).

The role of T_3 in adrenergic-mediated thermogenesis is thought to be due primarily to direct actions on BAT tissue. A recent study, however, has supported an important central role for T_3 in stimulating adrenergic-mediated thermogenesis. Rats given T_3 systemically or administered centrally in the cerebral ventricles showed reduced TRH/TSH, significant weight loss despite hyperphagia, and increased BAT thermogenesis (164). Within the hypothalamus, T_3 treatment selectively reduced AMPK phosphorylation, which was colocalized with TRα within the hypothalamus, and reduced activity (164). This resulted in increased lipogenesis and sympathetic output to BAT with a net effect of increased thermogenesis and energy expenditure (164). This action was blocked by selective expression of a mutant TR in the ventral medial hypothalamus, establishing a significant central role for T_3 in thermogenesis. The importance of TRα in mediating local adrenergic action in vivo in white fat and BAT was previously shown using an isoform-selective agonist (207), and a TRα mutant mouse model (158).

The influence of TH on central regulation of the autonomic nervous system has recently been localized to a previously unknown population of parvalbuminergic neurons (PBN) located in the anterior hypothalamus (179). These neurons are required for regulation of cardiovascular function and ablation results in hypertension and temperature-dependent tachycardia. Both TR isoforms are required for normal development of these neurons in the hypothalamus.

Thyroid hormone influences appetite and feeding through several pathways. T_3-treated rats have reduced POMC expression, accumulation of malonyl-CoA, and inactivation of CPT1 in the hypothalamus, which should produce anorexia, but the rats were resistant to this signal and remained hyperphagic (164). The increased energy demand may override the anorexic stimuli (164). Local TH metabolism also plays a role in appetite regulation. In the arcuate nucleus, D2 expressed in glial cells increase T_3 production during fasting, which stimulates UCP2 and mitochondrial proliferation in orexigenic NPY/AgRP neurons and stimulates rebound feeding after food deprivation (46).

C. Thyronamines

The metabolic effects of TH are also influenced by thyronamines, such as 3-iodothyronamine (T_1AM) and fully deiodinated thyronamine (T_0AM), which are decarboxylated and deiodinated analogs of thyroid hormone (197). Although these analogs have peripheral actions, the focus of their metabolic regulation activity appears to be centrally acting. The thyronamines bind to G protein-coupled trace amino acid associated receptor 1 (TAAR1) and adrenergic receptor α2 (24, 197). T_1AM is not a metabolite of T_3 degradation, but like TH, requires the sodium-idodie symporter (NIS) and thyroid peroxidase for synthesis (105). T_1AM circulates bound to a high-affinity binding protein, apolipoprotein B-100 (209). Circulating T_1AM levels are lower than those found in tissues, but T_1AM has been measured in both humans (88) and mice (106). Variations in measurement of endogenous T_1AM may be significantly influenced by the method used, tandem mass spectroscopy measuring lower levels compared with radioimmunoassay (217).

In response to a single dose of T_1AM, rodents develop hypothermia, bradycardia, and hyperglycemia (183). The rapid response has been related to changes seen in hibernation and has been used in an animal model of stroke to preserve brain function (64). The receptor for T_1AM, TAAR1, is expressed in the arcuate nucleus, and intracerebroventricular administration of T_1AM decreased food intake in rats by a reduction in AgRP (183). In the Djungarian hamster, administration of a single dose of T_1AM resulted

in a rapid switch from carbohydrate to lipid fuel source (25). These mice had reduced metabolism, followed by hypothermia, thought secondary to the reduced metabolism. The hypothermia induced by T_1AM was less than that typically seen in hybernation, and the switch in fuel source from carbohydrate to fat was the change that persisted the longest after a single T_1AM treatment.

IV. THERMOGENESIS AND BODY WEIGHT

TH plays a significant role in energy expenditure through both central and peripheral actions. TH maintains basal metabolic rate, facilitates adaptive thermogenesis, modulates appetite and food intake, and regulates body weight.

A. Basal Metabolic Rate

Basal metabolic rate (BMR) is the primary source of energy expenditure in humans, and reductions in BMR can result in obesity and weight gain (201). TH is a key regulator of BMR, but the targets are not clearly established (137). BMR correlates with lean body mass (132) and thyroid hormone levels (52, 230). Cold and heat intolerance are hallmark clinical features of patients with hypothyroidism and hyperthyroidism, respectively. In addition, resting energy expenditure (REE) is remarkably sensitive to TH, especially in athyreotic individuals (4).

TH stimulates BMR by increasing ATP production for metabolic processes and by generating and maintaining ion gradients (82, 104, 231). TH stimulates metabolic cycles involving fat, glucose, and protein catabolism and anabolism, but these are minor contributions to BMR. The two ion gradients that TH stimulates, either directly or indirectly, are the Na^+/K^+ gradient across the cell membrane and the Ca^{2+} gradient between the cytoplasm and sarcoplasmic reticulum. TH can alter the levels of Na^+ within the cell and K^+ outside of the cell, thus requiring ATP consumption in the form of Na^+-K^+-ATPase to maintain the gradient. In addition, TH directly stimulates the Na^+-K^+-ATPase, but this effect has more impact on BMR in hyperthyroidism than in euthyroid or hypothyroid individuals (44, 68, 126). TH also regulates the expression of the sarcoplasmic/endoplasmic reticulum Ca^{2+}-dependent ATPase (SERCA) in skeletal muscle (235, 237, 284). Stimulation of the Ca^{2+}-ATPase produces heat during ATP hydrolysis (57). TH increases the amount and activity of ryanodine receptors in heart and skeletal muscle, which then stimulates Ca^{2+} efflux into the cytosol, requiring more ATP to return the Ca^{2+} to the sarcoplasmic reticulum (131).

TH maintains BMR by uncoupling oxidative phosphorylation in the mitochondria (107), or reducing the activity of shuttle molecules that transfer reducing equivalents into the mitochondria (72, 109). In skeletal muscle, TH increases the leak of protons through the mitochondrial inner membrane, stimulating more oxidation to maintain ATP synthesis, since the proton-motive force driving ATP production is compromised. The presence of uncoupling protein (UCP) 2 and 3 in skeletal and cardiac muscle initially suggested that these proteins were mediators of the TH-stimulated proton leak. Further investigation revealed that TH treatment produced upregulation of UCP2 and UCP3, but this was not associated with changes in the proton gradient in human muscle (13). Clinically, when transitioning from hypothyroidism to euthyroidism, TH induced energy expenditure results in heat production without a significant increase in ATP generation. In hyperthyroidism, there is an increase in both ATP synthesis and heat production (108). T_3 also regulates the efficiency of ATP synthesis induction of mitochondrial glycerol-3-phosphate dehydrogenase (mGPD), a shuttle enzyme that contributes to the generation of ATP by transferring reducing equivalents generated in the cytoplasm into the mitochondrial membrane. Mice homozygous for a GPD gene knockout have higher levels of T_4 and T_3 and impaired ability to maintain core body temperature, consistent with a defect in thermogenesis (63). T_3 induction of UCP3 in skeletal muscle may play a role in thermogenesis. In mice lacking beta 1, 2, and 3 adrenergic receptor (beta-less), which are cold intolerant, T_3 treatment during cold exposure resulted in maintenance of body temperature (77). T_3 treatment of UCP3 knockout mice, compared with wild-type, had slightly less thermogenesis, indicating that T_3 induction of UCP3 may be important for thermogenesis in some settings (77).

B. Facultative Thermogenesis

Homeothermic species have developed a nonshivering or facultative thermogenesis to maintain core body temperature after cold exposure and increase energy expenditure after eating. The primary site of this adaptive thermogenesis in rodents is in BAT (33). Both the SNS and TH are required for maintenance of core body temperature (234). Hypothyroid rodents develop marked hypothermia with cold exposure, and T_4 treatment reverses this via induction of BAT activity (35). Expression of UCP1 is required for BAT thermogenesis, and UCP1 is synergistically regulated by both NE and T_3. While T_3 and NE each increase UCP1 expression by 2-fold separately, there is a 20-fold induction of UCP1 when both agents are combined (19). The UCP1 gene contains several cAMP response elements (CRE) that enhance the responsiveness of adjacent TREs to T_3 (234). It is important to note that while TRβ regulates UCP1 expression in BAT, TRα mediates sensitivity to adrenergic simulation (207). This demonstrates TR isoform specificity in metabolic regulation within a single tissue, and both TR isoforms are required for a normal thermogenic response. A recent study showed that TH induced UCP1 expression in WAT via TRβ and increased both mitochondrial biogenesis and the oxygen consumption rate (151).

UCP1 expression is critical to BAT thermogenesis, although it is now well established that D2 activity, required for the local conversion of T_4 to T_3, is also essential (56). D2KO mice develop hypothermia and must rely on shivering to maintain core body temperature (56). In addition, with cold exposure, D2KO mice preferentially oxidize fat. They are resistant to diet-induced obesity and have normal glucose tolerance due to increased sympathetic tone. The evaluation of D2 knockout mice provided an important insight into difference between rodents and humans with respect to the thermoneutral temperature. Mice, raised at room temperature 22°C, activate heat production pathways since this is colder than their thermoneutral temperature of 30°C (36). When thermal stress is eliminated by raising D2 knockout animals to be raised in an environment at 30°C, they develop obesity, glucose intolerance, and hepatic steatosis that is the result of impaired BAT T_3-induced thermogenesis (36).

There is both visceral and subcutaneous BAT in humans, which may have specific functions that relate to the anatomical location (211). Until recently, human BAT was considered to be important in neonates, but not likely to be important in the adult. Recent studies utilizing PET and CT imaging have shown a significant amount of BAT, especially in the subscapular and chest region (50, 257). In general, there is more BAT in younger and leaner individuals, and it is induced by cold. Treatment with β-adrenergic blockers reduces BAT activity, due to the importance of catecholamines for the development and regulation of BAT.

The relative importance of BAT for metabolic regulation in adults remains controversial, although significant effort has been focused on agents that stimulate BAT activity in humans, as well as the ability to convert white fat to more metabolically active "beige" or brown fat (211, 264). A recent study showed that direct biopsy of adipose tissue from the supraclavicular areas, thought to contain BAT tissue, had increased oxidative capacity and increased expression of UCP-1 (263). Activation of BAT in humans has been reported after overnight exposure to 19°C compared with those exposed to 24°C (39). Resting energy expenditure, as well as functional imaging by PET scan, was performed to demonstrate BAT activation.

C. Skeletal Muscle

Skeletal muscle has been recognized as a key TH target for contractile function, regeneration, and transport as well as for metabolism and glucose disposal (237, 238). TH stimulation favors transition to fast-twitch fibers and transition to a faster myosin heavy chain (MHC) form. The significant regulation of D2 is a key factor that modulates T_3 levels in skeletal muscle. In skeletal muscle development and regeneration after injury, FoxO3 stimulates D2 expression (170). Skeletal muscle injury is associated with a twofold increase in local T_3 levels, not seen in D2 knockout animals. There has also been interest in the common Myf 5 expressing precursor cell for both skeletal muscle and brown adipose tissue (150). The zinc finger protein, PRDM16, directly represses white fat genes and activates brown fat genes (133). D2 levels are higher in slow-twitch compared with fast-twitch muscle fibers and are stimulated by hypothyroidism, but not by cold exposure (169).

D. Regulation of Body Weight

It is well established that thyroid status, either hypothyroidism or hyperthyroidism, is associated with changes in weight and REE. In healthy individuals, variations in serum TSH, even within the reference range, are associated with body weight and body weight change in both men and women (80, 143). Individuals with serum TSH levels in the upper quintiles have higher BMIs and lower quintiles a lower BMI. Interestingly, reestablishing euthyroidism with T_4 treatment is associated with reductions in body weight and increase in REE in hypothyroid individuals, but fat mass is unchanged and weight loss is primarily excretion of excess body water (134). It is possible that increased caloric intake, stimulated by TH, is responsible for this discrepancy. In addition, given the impact of central regulation of TH on orexigenic neuropeptides (78), variable regulation of the HPT axis with altered leptin levels also could be responsible for this metabolic abnormality (20). Hyperthyroid patients have increased intake of carbohydrates, which reverses after treatment of the hyperthyroidism (199). The stimulation of a preference for carbohydrate intake is thought to be due to central adrenergic stimulation. A study comparing treatment of hypothyroid patients with T_3 or T_4 monotherapy showed that T_3 treatment resulted in significant weight loss and reduction in total cholesterol and apolipoprotein B, compared with T_4 treatment, without adverse cardiovascular outcomes (38). This study also noted a nonsignificant trend effect in decreasing fat mass with T_3 therapy. While there was no significant change in REE, it is likely that the weight reduction seen in T_3 therapy is a result of an increase in metabolic rate. The greatest weight change associated with thyroid disease is the body weight increase seen after treatment of hyperthyroidism (161). Most patients regain more weight than they had prior to having Graves' disease, sustaining the higher energy intake associated with hyperthyroidism, even when they become euthyroid. This study also examined body composition and found that weight loss in hyperthyroidism was due to loss of both fat and lean body mass.

V. CHOLESTEROL AND TRIGLYERIDE METABOLISM

TH regulation of lipid metabolism is primarily dependent on liver-specific actions of T_3, TRβ, and nuclear hormone receptor crosstalk **(FIGURE 3)**. The metabolic activity of fat is also becoming increasingly recognized and is a significant site of TH action (208).

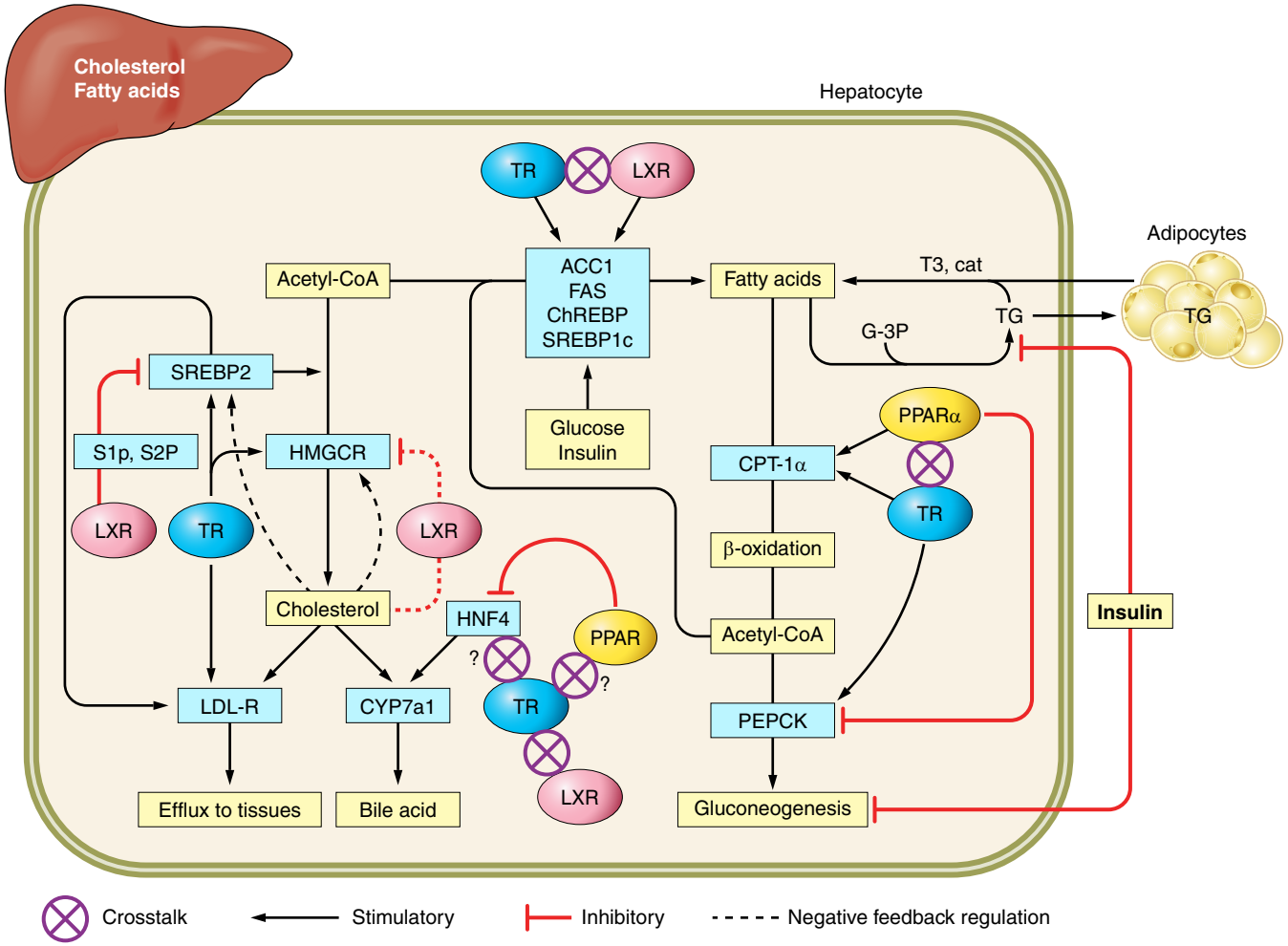


FIGURE 3. Lipid homeostasis in liver is coordinately regulated by direct actions of T_3 and indirect crosstalk with nutrient-activated nuclear receptors. HMG-CoA reductase, a rate-limiting enzyme in cholesterol synthesis, and sterol response element binding protein (SREBP2) are stimulated by T_3. HMG-CoA reductase is subject to feedback inhibition by cholesterol. The SREBP2 and LXR pathways respond to changes in cellular sterols. When cholesterol levels are low, SREBP2 is activated by LXR-mediated maturation by site 1 and site 2 proteases (S1P and S2P), then transported to the nucleus for activation of its target gene, HMG-CoA reductase. When cellular cholesterol is high, LXR inhibits S1P and S2P resulting in inactive SREBP2, which triggers sterol concentration-dependent HMGCR degradation. This then reduces cholesterol synthesis. CYP7a1 is a rate-limiting enzyme in bile acid synthesis. TR directly stimulates CYP7a1 gene expression in human liver. In mouse, both TR and LXR regulate *CYP7a1* expression. Hepatocyte nuclear factor 4 (HNF4) also plays an important role in CYP7a1 gene expression. PPARγ reduces CYP7a1 gene expression by inhibiting HNF4 gene expression. Both TR and LXR play a role in fatty acid synthesis by regulating the expression of acetyl CoA carboxylase (ACC1), fatty acid synthase (FAS), carbohydrate response element binding protein (ChREBP), and SREBP1c. This regulation is mediated by similar DR4 response elements in these gene promoters. Fatty acid β-oxidation is controlled by the rate-limiting enzyme CPT-1α, which transports long-chain fatty acid into the mitochondria for oxidation. A functional TRE and PPRE are located in close proximity (50 bp apart) in the CPT-1α promoter. The mechanism of crosstalk between PPARα and TRα on the CTP-1α promoter has been previously characterized (151). Phosphoenolpyruvate carboxykinase (PEPCK) catalyzes the key step initiating gluconeogenesis and is regulated by hormones at the transcriptional level, including T_3. In liver, PPARα ligand inhibits PEPCK mRNA expression. In adipocytes, PPARγ induces PEPCK expression to promote fat storage (not shown in figure). In the presence of glyceraldehyde-3-phosphate (G-3P), triglyceride is synthesized and transported to adipocytes. When energy is needed, there is central activation of the sympathetic nervous system and release of catecholamines, which acts on adipocytes to hydrolyze TG. T_3 increases β-AR expression in adipocytes, which promotes catecholamine-induces lipolysis.

A. Regulation of Cholesterol Synthesis

TH regulates cholesterol synthesis through multiple mechanisms. A major pathway is TH stimulation of transcription of the LDL-R gene resulting in increased uptake of cholesterol and enhanced cholesterol synthesis (162). This has been a major pathway of T_4-mediated cholesterol lowering after T_4 treatment of patients with hypothyroidism (139).

Another regulator of the LDL-R gene is the sterol response element binding protein (SREBP)-2 (97). SREBP-2 is a member of a family of transcription factors that regulate glucose metabolism, fatty acid synthesis, and cholesterol metabolism. Specifically, TH induces SREBP-2 gene expression that in turn modulates LDL-R expression. In hypothyroid rats, SREBP-2 mRNA is suppressed, but this is reversed when T_3 levels are restored (226). This nuclear coregulation is further highlighted by the fact that several genes have a tandem arrangement of the TRE and SREBP response element (SRE) (282). Other nuclear hormone receptors, such as PPARα, have opposing effects on LDL and cholesterol synthesis (144), which underscore the role of nuclear crosstalk in TH regulation of metabolism (157). The isoform-specific induction of LDL-R highlights the role of T_3 action in the liver.

TH also reduces cholesterol through non-LDL receptor-mediated pathways. Mice with hypercholesterolemia due to LDL-receptor gene knockouts were treated with high dose T_3 or 3,5-diiodo-L-thyronine (T_2) (95). Under these conditions, the reduction in LDL-cholesterol was linked to reductions in apolipoprotein (apo) B48 and apoB11. Hepatic triglyceride production was increased. The high doses of T_2 used were associated with cardiac toxicity and increased heart weight, but these findings suggest mechanisms for T_3, in addition to stimulation of the LDL-receptor, for cholesterol lowering.

B. Cholesterol Efflux

Reverse cholesterol transport is a complex process that results in transfer of cholesterol to the liver for elimination as bile acids or neutral steroids. ATP-binding cassette transporter A1 (ABCA1) is required for high-density lipoprotein (HDL) assembly and carriage of esterified cholesterol back to the liver for excretion. ABCA1 utilizes two separate promoters that are responsive to LXR and SREBP-2, both of which increase ABCA-1 transcription (249). The LXR-response element (LXRE) also permits TR binding. Cotransfection of the human ABCA1 promoter and an expression vector for TRβ resulted in suppression of the ABCA1 promoter in the presence of T_3 (122). In addition, TR competes with LXR for binding, resulting in T_3-induced inhibition of ABCA-1 and decreased HDL levels (122). ABCA1 mRNA is induced by overexpression of SREBP-2, but is completely absent in hepatic cells that are SREBP-2 null (272).

C. Bile Acid Synthesis

The conversion of cholesterol to bile acids is required to maintain cholesterol homeostasis. This cholesterol clearance pathway is regulated by a number of nuclear receptors that control the expression of cholesterol 7-hydroxylase (CYP7a1), the rate-limiting step in bile acid synthesis (41). Human and murine CYP7a1 are regulated by different nuclear receptors and their ligands (157). In murine models of impaired TRβ action, LXR is induced with a high-cholesterol diet that stimulates CYP7a1 gene expression and bile acid synthesis (103, 110). LXR has no effect on human CYP7A1 mRNA levels (2); however, T_3 treatment reduces CYP7A1 mRNA and cholic and chenodecoycholic acid synthesis in human hepatocytes (69). While there is no role for LXR in human CYP7A1 expression, both PPARα and hepatic nuclear factor (HNF) 4α have response elements that are located in close proximity to the TRE. In addition, HNF4α positively regulates CYP7A1 gene expression while PPARα inhibits HNF4α activity resulting in lower CYP7A1 levels (194).

Bile acids are now recognized as a regulatory pathway, stimulating both the TGR5 membrane receptor and the nuclear receptor FXR, as well as other related nuclear receptors including VDR, PXR, and CAR (279). Bile acids bind the TGR5 receptor on enteroendocrine L cells in the small intestine, which stimulates production of the incretin GLP-1 improving insulin sensitivity and increasing satiety. In BAT, as previously described, bile acids bind TGR5 and stimulate expression of D2 increasing energy expenditure and promoting resistance to diet-induced obesity (251, 269). Bile acids combine with the nuclear FXR receptor and stimulate target genes regulating cholesterol and bile acid metabolism (279). A recent clinical study in both healthy and cirrhotic subjects revealed that bile acid synthesis correlated positively with energy expenditure, and postprandially, serum TSH decreased in both groups (188), suggesting that the bile acid serum level influences the thyroid pituitary axis set point.

Bile acids are increasingly linked to glucose homeostasis mediated by both the TGR5 and FXR receptors. Animals studies have shown that a TGR5 agonist, EMCA, increases intracellular ATP/ADP, stimulates GLP-1, and attenuates diet-induced obesity (252). Activation of FXR by bile acids also improves diabetes in animal models. An FXR knockout mouse model resulted in glucose intolerance and insulin insensitivity (280). Treatment of diabetic mice with a synthetic FXR agonist repressed hepatic gluconeogenesis and enhanced liver sensitivity to insulin (280). Bile acids, like thyroid hormone, impact the metabolism of lipids and glucose and are linked by activation of D2 in specific tissues.

D. Fatty Acid Metabolism

TH stimulates both lipolysis and lipogenesis, although the direct action is lipolysis with lipogenesis thought to be stimulated to restore fat stores (191). A time course study in rats carefully measured whole body lipid content and thermogenesis after T_3 treatment and concluded that the TH-induced lipogenesis is primarily to maintain fat loss that occurs with TH-induced lipolysis (191). Fatty acids produced

from TH-induced lipolysis are the substrate for the increase in thermogenesis (191). T_3 regulation of these divergent metabolic pathways is subject to nuclear receptor crosstalk, ligand-binding, nutritional status, and competition for RXR heterodimers (157). TH plays a significant role in the conversion of preadipocytes to adipocytes (187).

Malonyl CoA production in the liver promotes lipogenesis and directly inhibits carnitine palmitoyl transferase (CPT)-Iα, which converts long-chain fatty acyl-CoAs to acylcarnitines for translocation from the cytosol into inner mitochondrial matrix where β-oxidation occurs (172). T_3 also induces the transcription of acetyl CoA carboxylase (ACC)-1, which generates malonyl CoA from acetyl CoA. ACC-1 is regulated by TR, LXR, and SREBP-1 (121). While LXR can directly stimulate ACC-1 (248), TR and SREBP1 must form a complex that stabilizes SREBP-1 on the binding site (275). SREBP-1 action is also enhanced by a PPARα agonist, which can potentiate SREBP-1c nuclear activity (142).

CPT-Iα mRNA and enzyme activity is greatly increased in the livers of hyperthyroid animals, and a functional TRE and CCAAT enhancer binding protein (C/EBP) are both necessary for T_3 induction of CPT-Iα (129). The PPARα and TR response elements are in close proximity on the CPT-Iα gene. A PPARα agonist can induce CPT-Iα mRNA and reduced serum triglyceride levels after high fat feeding (177). PPARγ coactivator PGC-1α enhances both PPARα and TR induction of CPT-Iα (281). In vivo studies of a mutant TRα mouse model demonstrated crosstalk between PPARα and T_3 signals in CPT-Iα regulation. The TRα-P398H mutant mouse model has impaired fatty acid oxidation because the mutant TRα occupies the CPT-Iα PPRE and inhibits PPARα-induced CPT-Iα expression (158). Another in vivo study demonstrated nuclear crosstalk via treatment with polyunsaturated fatty acids. These fatty acids induce hepatic TRβ expression and decreases both serum cholesterol and serum triglycerides; however, in the hypothyroid state, polyunsaturated fatty acid failed to induce TRβ, but stimulate PPARα expression, resulting in decreased serum cholesterol, but persistent hypertriglyceridemia (244).

Finally, the actual mobilization of lipid droplets into the hepatocyte, termed "lipophagy," has been shown to be T_3 regulated (239). Impairment of this process is associated with hepatic steatosis and insulin resistance (274). T_3-mediated autophagy is tightly coupled with β-oxidation to promote ketosis, is T_3 dependent, and in the unliganded state is repressed by NCoR (241).

E. Hepatic Steatosis

Nonalcoholic fatty liver disease (NAFLD) is associated with diminished thyroid action. The TRα mutation analogous to a resistance to thyroid hormone (RTH)-associated mutation in TRβ, TRα-P398H mutant, with impaired fatty acid metabolism, also had evidence of hepatic steatosis (158). There is significant evidence for nuclear hormone crosstalk in the development and treatment of hepatic steatosis. In fact, subclinical hypothyroidism, with TSH levels in the upper normal range, were found to be associated with NAFLD, with greater TSH elevations correlated with more extensive steatosis (43). In a gene expression array study of human hepatic steatosis samples, there was downregulation of T_3-responsive genes in the steatosis samples compared with normal liver (198). In a diabetic rat model, a TRβ selective analog was effective at reducing hepatic steatosis (32). These findings suggest that NAFLD is associated with impaired TH signaling. A recent study showed that a general, GC1, and liver-selective TRβ agonist, KB-2115, reduced hepatic steatosis, but both impaired insulin sensitivity by different pathways (260). GC1 treatment was associated with increased endogenous glucose production and KB-2115 with reduced insulin-stimulated glucose uptake in skeletal muscle due to reduced GLUT4 expression.

Fibroblast growth factor (FGF)-21 is expressed primarily in the liver, adipose tissue, and pancreas and is regulated by T_3 in a PPARα-dependent manner (1). FGF-21 stimulates glucose uptake in fat and enhances mitochondrial oxidation through AMPK activation. Transgenic mice overexpressing FGF21 in liver have reduced plasma triglyceride concentrations and are resistant to weight gain after high-fat feeding. In addition, treatment with FGF21 in diet-induced obesity mice led to increased β-oxidation, improved serum lipid concentrations, and decreased hepatic triglycerides (136). FGF21 expression is known to be downstream of the nuclear receptor PPARα, and fibrate treatment, the PPARα ligand, causes an increase in FGF21 expression in rodents (12). T_3 treatment in mice acutely induces hepatic expression of FGF21, but this induction is abolished in PPARα knockout mice (1).

In a study of healthy adults, 12 h of cold exposure at 24 or 19°C resulted in an increase in plasma FGF21 and enhanced lipolysis and energy expenditure (152). In a study of serum FGF-21 levels in obese youth with steatohepatitis, FGF-21 levels were elevated compared with control and correlated with hepatic fat content (94). In these patients with obesity and liver damage, the elevated FGF-21 levels may not be adequate to increase energy expenditure, although this was not directly studied.

One of the mechanisms that links the metabolic syndrome with hepatic steatosis is insulin stimulation of lipogenesis, which can lead to fatty liver and worsening insulin resistance, leading to greater stimulation of lipogenesis (182). The lipogenic transcription factor, SREBP-1c, is a mediator of this cycle and is itself influenced by a range of nuclear receptors, including CAR, TRβ, LRH-1, ERα, and FXR/SHP (182). Nu-

clear receptors have the potential to suppress SREBP-1c, which is a pathway that promotes insulin sensitivity.

F. TR Isoforms as Therapeutic Targets

TR isoform agonists have been the primary target for drug development, especially for the treatment of hypercholesterolemia and obesity (270) **(TABLE 4)**. TRβ agonists have shown significant promise in the treatment of hypercholesterolemia, hepatic steatosis, and weight loss, without generating cardiac toxicity or accelerated bone loss (83, 145). In a clinical study of patients who did not reach serum LDL cholesterol targets on HMG CoA reductase inhibitors alone, addition of the TRβ selective agonist eprotirome resulted in serum LDL cholesterol reduction of up to 30%, including reduction of serum Lpa and triglycerides at the higher dose of eprotirome (145). Treatment for 10 wk with a liver-targeted TRβ-selective agonist pro-drug, MB07811, was effective at reducing hepatic steatosis in diabetic rats and reduced serum triglycerides and free fatty acids (32). The compound MB07811 is activated in the liver by cytochrome *P*-450 3A4 and may result in more selective action in the liver compared with other TRβ selective agonists. Animal studies, however, found that long-term use of eprotirome was associated with cartilage breakdown (227). This finding has discouraged development of these agents for broader clinical use despite their effectiveness in direct metabolic actions. The T_4 analog DITPA, originally studied for

Table 4. *Metabolic properties of natural and synthetic thyroid compounds*

	Mechanism of Action	General Actions	Metabolic Actions	Reference Nos.
		Naturally occurring		
Thyroxine (T_4)	Requires conversion by D1 or D2 to T_3 for activity at nuclear receptor Binds integrin $\alpha v\beta 3$ membrane receptor	May activate PI3K and ERK1/2 pathways	Cell proliferation and angiogenesis	28, 40, 155, 156
Triiodothyronine (T_3)	Active form of thyroid hormone that binds nuclear TR	Ligand activating thyroid hormone actions in brain, bone, liver, muscle, and heart	Weight loss Cholesterol and triglyceride reduction	28, 38, 40
Triac	Binds to the nuclear TR	TSH suppression Does not require MCT8 transporter	Reduction in LDL cholesterol Increased bone turnover Increase SHBG from liver	225
DITPA	Binds to the nuclear TR	Does not require MCT8 transporter Enhances cardiac function	LDL cholesterol lowering Body weight loss	96
T_1AM	Binds to G protein-coupled trace amino acid associated receptor 1 (TAAR1)	Hypothermia Bradycardia	Transition from carbohydrate to lipid fuel source Hyperglycemia	25, 88, 217
		Synthetic		
GC1	Binds to the nuclear TR, TRβ selective	Preference for TRβ Preferential liver distribution and action Reduced activity bone and heart	Reduce serum LDL cholesterol Reduce serum triglycerides	260, 270
Eprotirome (KB-2115)	Binds to the nuclear TR, TRβ	Preference for TRβ Preferential liver distribution and action Reduced activity bone and heart	Reduce serum LDL cholesterol Reduce serum triglycerides	260, 270
MB07811	Binds to the nuclear TR Activated in the liver by cytochrome *P*-450 3A4	Preference for TRβ Preferential liver distribution and action	Reduces LDL cholesterol Reduces hepatic steatosis	32, 270

BAT, brown adipose tissue; D1, 5′-deiodinase type 1; D2, 5′-deiodinase type 2; HDAC3, histone deacetylase 3; SHBG, sex hormone binding globulin; T_3, triiodothyronine; T_4, thyroxine; TR, thyroid hormone receptor; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; UCP1, uncoupling protein 1.

its property to enhance cardiac function (96), was found in human trials to have potent actions stimulating metabolism and promoting weight loss (146). The patients treated with DITPA for 6 mo had a reduction in serum total and LDL cholesterol, but also had evidence of increased bone turnover, suggestive of the complications seen with eprotirome. Although DITPA is a potent agent mediating weight loss, there is concern that at the doses required for the metabolic effects, the skeletal actions may limit its usefulness for metabolic disorders.

The action of TRα in mediating adrenergic sensitivity, centrally and peripherally, suggests that it would be an attractive target for promoting energy expenditure and weight loss in metabolic disorders. Studies with TRα agonists in an amphibian model demonstrated a selective role for TRα in neuronal development and proliferation (58). In vivo studies of TRα agonists in mouse brain, however, did not produce a gene expression profile that differed from T_3 treatment, indicating that TR isoform specificity was not reproduced in the mammalian brain (101). The most significant concern with a selective TRα agonist is that stimulation of bone turnover and cardiac stimulation could limit its use for metabolic targets.

VI. CARBOHYDRATE METABOLISM

Thyroid disease has well-documented effects on glucose homeostasis. Thyroid hormone actions in the liver, white adipose tissue, skeletal muscle, and pancreas influence plasma glucose levels, insulin sensitivity, and carbohydrate metabolism. Reduced activity of mitochondria has been a link between a well-described action of thyroid hormone and a defect in type 2 diabetes (49).

A. Gluconeogenesis

It has been previously established that T_3 stimulates gluconeogenesis, especially in the hyperthyroid state, and that hypothyroidism is associated with reduced gluconeogenesis (45). Treatment with T_4 increases alanine transport into hepatocytes, increasing production of metabolic intermediate of the gluconeogenic pathway and ultimately conversion of alanine into glucose (240). Evaluation of T_3 treatment on target genes in the liver reveals that there is an increase in genes regulating glycogenolysis and gluconeogenesis (75). Specifically, regulation of phosphoenolpyruvate carboxykinase (PEPCK), the rate-limiting step in gluconeogenesis, is critical for glucose homeostasis and has been shown to be regulated by TRβ and CCAAT enhancer-binding protein in the liver (193). In thyrotoxic rats, hepatic PEPCK mRNA was stimulated 3.5-fold, and they were resistant to insulin suppression of hepatic glucose production compared with euthyroid rats (141). The hepatic insulin resistance was mediated by sympathetic stimulation. In a follow-up study, administration of T_3 to the hypothalamic paraventricular nucleus, through interaction with the SNS, increases glucose production via sympathetic input to the liver, showing that the T_3 effect was central (140).

Rodents with the RTH-associated Δ337T mutation in TRβ, conferring a dominant negative TR, have impaired gluconeogenesis with lower levels of PEPCK mRNA compared with wild-type (214). These animals are more sensitive to insulin and became hypoglycemic after an insulin injection that did not produce hypoglycemia in the wild-type animals.

B. Insulin Production and Action

Several studies have linked thyroid hormone action with pancreatic islet cell development and function. Pancreatic islets contain TRα1 and TRβ1 which are important for normal islet development (3). T_3 acts by stimulating the islet transcription factor Mafa. T_3 is required for the transition of islets to glucose-responsive insulin-secreting cells. In pancreatic islet cells studied in culture, T_3 and TRα promote proliferation (87). Inactivation of D2 gene is associated with insulin resistance and diet-induced obesity (168). Thyroid hormone acts to impair glucose-stimulated insulin release, despite increased islet glucose utilization and oxidation. Hyperthyroidism and high-fat feeding result in significant impairment of islet function (85). In contrast, physiological T_3 treatment prevents streptozocin-induced islet deterioration and maintains islet structure, size, and consistency (261). T_3 induces these anti-apoptotic effects via nongenomic activation of the AKT signaling pathway.

Hepatic glucose output is increased in hyperthyroidism due to increased gluconeogenesis. The rates of insulin-stimulated glucose disposal in peripheral tissues, therefore, must be altered to maintain euglycemia. In the hyperthyroid state, skeletal muscle glucose uptake is increased to overcome a depletion in glycogen stores (62). A TRE has been characterized in the promoter region of the GLUT-4 gene (271). T_3 treatment in rats increased GLUT-4 mRNA in skeletal muscle and, possibly through posttranscriptional splicing, and also augmented the levels of GLUT-4 protein in skeletal muscle. Similar results were reproduced in Zucker rats, but a notable finding was that T_3 treatment reversed hyperinsulinemia, but not hyperglycemia, in obese animals (254).

A study in rats supports a dissociation of thyroid hormone effects on BAT thermogenesis from glucose uptake and control (171). This group had previously shown in the streptozotocin (STZ)-induced uncontrolled diabetic rat that intracerebroventricular administration of leptin returned glucose to normal, restored BAT glucose uptake, and normalized serum T_4 and BAT UCP1 mRNA levels (92). Treatment of the STZ rat with T_3, or the selective TRβ agonist

GC1, however, stimulated energy expenditure, but did not increase BAT glucose uptake (171). Although thyroid hormone can influence glucose levels, the primary action in the context of this rat diabetes model was on energy expenditure, which did not influence the hyperglycemia.

C. Thyroid Status and Diabetes

The interaction of thyroid status and diabetes is complex. Patients with type 1 diabetes have an increase in prevalence rates of autoimmune thyroid disorders compared with the nondiabetic population, especially among women (267). This is thought to be due to similar genetic susceptibility to both autoimmune conditions (253). Studies investigating the interaction of type 2 diabetes and thyroid dysfunction, however, have not shown a consistent association (61, 99, 124). Abnormal serum TSH concentrations were seen in ~30% of poorly controlled type 2 diabetic patients (37). Among those patients with an abnormal low or high TSH levels, who were negative for thyroid autoantibodies, serum TSH normalized in all but one patient when their glucose level was controlled for ~2 mo (37). Conversely, in severely thyrotoxic patients, the calculated metabolic clearance rate of insulin is markedly higher than control patients, contributing to hyperglycemia in the thyrotoxic state (200). In a recent case report, a patient with severe insulin resistance improved dramatically after suppressive dose levothyroxine for thyroid cancer (242). Imaging of the patient when hypothyroid and then after replacement was restored showed induction of BAT, highlighting the role of TH in insulin sensitivity and energy expenditure.

D. Factors Contributing to Diabetes

TH induces HIF-1α via the PI3K/ERK pathways, as well as by direct induction. The known HIF-1α target genes include the glucose transporter 1 (GLUT1), phosphofructokinase (PFKP), and monocarboxylate transporter 4 (MCT4), which regulate cellular glucose metabolism by controlling glucose uptake, glycolysis, and lactate transport, respectively (181). These genes are induced by physiological doses of T_3, and pretreatment with a PI3K inhibitor abolishes this effect (180). HIF-1α also induces expression of D3 gene leading to reduced T_3 and increased rT_3 production (236).

Systemic administration of T_1AM rapidly increases endogenous glucose production, glucagon, and corticosterone but does not increase plasma insulin (218). Central administration of T_1AM resulted in a much more profound effect on endogenous glucose production and hyperglucagonemia and reduced plasma insulin (218). The effects of T_1AM on glucose and insulin, like the effects of TH, likely vary with the mode and duration of exposure.

VII. CONCLUSION AND FUTURE PERSPECTIVES

Significant progress has been made in understanding TH targets that mediate metabolic regulation. Several themes have emerged which coordinate these signaling pathways, including nutrient feedback at the cellular and central level, nutrient nuclear receptor crosstalk, local ligand activation, and adrenergic stimulation. This has led to mechanistic insights, especially understanding those factors that modulate multiple TH-regulated pathways. A number of these mechanisms are actively being evaluated as therapeutic targets for metabolic diseases. Although several thyroid hormone analogs have shown significant success in reducing serum LDL cholesterol and producing weight loss, the broad effects of these compounds have limited their clinical application.

A. Integrating Mechanisms of Thyroid Hormone Regulation of Metabolism

TH directly regulates metabolic rate, body weight, and cholesterol metabolism **(TABLE 2)**. TH regulates the expression of target genes directly through TR binding to specific TREs, as well as nongenomic modification of cell signaling. New evidence highlights the coordinate roles of central and peripheral regulation of TH in modulating metabolic pathways. TH interacts with the SNS in a synergistic and complementary fashion to maintain homeostasis. In addition, adipokine and neuropeptide regulation of the HPT axis and thermogenesis integrates information on energy availability, storage, and utilization to gauge the regulation of appetite, basal metabolic rate, and body weight. TR nuclear hormone crosstalk with other metabolic pathways, especially the nuclear receptors PPARα, LXR, and PGC-1α, is essential for the T_3 regulation of cholesterol metabolism and transcription of lipogenic and lipolytic genes. Bile acid stimulation of D2 and local thyroid hormone activation is another unexpected signaling link. Interference with thyroid hormone signaling is associated with obesity and hepatic steatosis. Finally, emerging evidence identifies a role for TH in glucose metabolism including actions in pancreatic islet development, gluconeogenesis, and insulin signaling.

B. Therapeutic Targets for Metabolic Disorders

An improved understanding of the mechanism underlying the actions of TH on lipid metabolism and thermogenesis has led to several useful compounds targeting TR for treatment of metabolic disorders (30, 183, 205) **(TABLE 4)**. The thyroid hormone-related thyronamine signaling is a novel pathway to consider for treatment of obesity and metabolic disturbances (88, 217). The thyronamines are measurable

in normal human sera and tissues (88). Acute T_1AM treatment in animals induces hypothermia and reduces metabolism, similar to torpor in hibernating mammals. Although the factors that regulate endogenous T_1AM levels are not known, this is a pathway that could potentially be antagonized to raise metabolic rate. T_1AM, however, also has the property of rapidly converting an animal from carbohydrate to exclusive fat metabolism, which persists after acute T_1AM stimulation (25). Selective augmentation of this T_1AM action is an attractive target for the treatment of metabolic disorders.

Nuclear receptors play a key role in metabolic regulation and are attractive therapeutic targets for metabolic disorders. A significant limitation of their use, however, is unintended metabolic consequences of these agents as well as adverse effects at other sites (102). An example of this is the class of PPARγ agonists, which improve insulin sensitivity, but are associated with weight gain, fluid retention, and adverse cardiac events. TRβ agonists lower LDL cholesterol, lipoprotein(a), and reduce hepatic steatosis, but promote insulin resistance through various mechanisms (260). TR agonists at doses sufficient for favorable metabolic action, such as weight loss and cholesterol lowering, have been associated with adverse action on bone, cartilage, and the heart (146). Ultimately, more selective and specific agents targeting TH signaling pathways, based on improved mechanistic understanding, will be needed to effectively and selectively target metabolic diseases.

ACKNOWLEDGMENTS

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GRANTS

This work was supported by Veterans Affairs Merit Review Funds and National Institute of Diabetes and Digestive and Kidney Diseases Grant RO1 DK98576.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

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