Insulin Action in Hyperthyroidism: A Focus on Muscle and Adipose Tissue

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Hyperthyroidism leads to an enhanced demand for glucose, which is primarily provided by increased rates of hepatic glucose production due to increased gluconeogenesis (in the fasting state) and increased Cori cycle activity (in the late postprandial and fasting state). Adipose tissue lipolysis is increased in the fasting state, resulting in increased production of glycerol and nonesterified fatty acids. Under these conditions, increased glycerol generated by lipolysis and increased amino acids generated by proteolysis are used as substrates for gluconeogenesis. Increased nonesterified fatty acid levels are necessary to stimulate gluconeogenesis and provide substrate for oxidation in other tissues (such as muscle). In the postprandial period, insulin-stimulated glucose uptake by the skeletal muscle has been found to be normal or increased, mainly due to increased blood flow. Under hyperthyroid conditions, insulin-stimulated rates of glycolysis in skeletal muscle are decreased, whereas there is a preferential increase in the rates of lactate formation vs. glucose oxidation leading to increased Cori cycle activity. In hyperthyroidism, the Cori cycle could be considered as a large substrate cycle; by maintaining a high flux through it, a dynamic buffer of glucose and lactate is provided, which can be used by other tissues as required. Moreover, lipolysis is rapidly suppressed to normal after the meal to facilitate the disposal of glucose by the insulin-resistant muscle. This ensures the preferential use of glucose when available and helps to preserve fat stores. (Endocrine Reviews 31: 663–679, 2010)
are mainly proteolysis-derived amino acids and glycerol provided by lipolysis. In the postprandial period, insulin-stimulated rates of glycogen synthesis in skeletal muscle are decreased, whereas there is a preferential increase in the rates of lactate formation vs. glucose oxidation under hyperthyroid conditions. The conversion of glucose to lactate in muscle (and adipose tissue) and the conversion to glucose in the liver represents a cyclic flow of carbon known as the Cori cycle. Increased lactate supply to the liver during the late postprandial and fasting state ensures normal or even slightly increased levels of glucose in plasma.

In this review, we performed a MEDLINE search of the English-language literature using a combination of terms: hyperthyroidism, thyroid hormones, glucose metabolism, insulin resistance, insulin secretion, gastric emptying, intestinal absorption, glucose production, skeletal muscle, adipose tissue, glucose uptake, blood flow, glucose transport, glucose phosphorylation, glycogen synthesis, glycolysis, glucose oxidation, lipid metabolism, and cytokines. We focused on the in vivo studies in humans examining the mechanisms of altered glucose and lipid homeostasis in muscle and adipose tissue in hyperthyroidism. Animal and in vitro studies were used to support findings or to resolve questions that cannot be answered at the in vivo level in man.

II. Gastric Emptying and Intestinal Absorption

Rapid gastric emptying and increased rates of intestinal absorption of glucose have been hypothesized to be responsible for impaired glucose tolerance in hyperthyroidism (4-6). However, in more recent studies, gastric emptying has been found to be decreased (7, 8) or unchanged (9-11). Although increased rates of gastric emptying and intestinal absorption may aggravate postprandial hyperglycemia, it is unlikely that it is the major mechanism to explain the impairment of glucose tolerance in hyperthyroidism.

III. Glucose Production

In hyperthyroidism, the rate of endogenous glucose production is increased and does not respond to the suppressive effects of insulin (12-17).

This effect of thyroid hormones may be explained by: 1) increased rates of gluconeogenesis and glycogenolysis (13, 14, 16, 18-25); 2) increased rates of lactate formation in muscle and adipose tissue (Cori cycle) (26); 3) increased secretion and effects of glucagon and adrenaline on liver cells (13, 21, 27-30); 4) increased proteolysis in muscle, providing increased supply of amino acids to the liver (31); 5) increased concentrations of the GLUT2 glucose transporters in the liver plasma membrane, permitting rapid glucose transport (32, 33); and 6) increased concentrations of free fatty acids in plasma (12, 22, 34, 35). Free fatty acid stimulation of gluconeogenesis has been attributed to the production of: 1) acetyl-coenzyme A derived from free fatty acid oxidation, which allosterically activates pyruvate carboxylase; 2) reduced nicotinamide adenine dinucleotide, which is used for the formation of glyceraldehyde 3-phosphate from 1.3-bisphosphoglycerate; and 3) ATP, which is used as an energy source (36).

Recently, a central pathway for modulation of hepatic glucose production by T3 involving the hypothalamic paraventricular nucleus and the sympathetic nervous system has also been reported (37).

IV. The Importance of Cori Cycle

The Cori cycle represents a cyclic flow of carbons manifested by the conversion of glucose to lactate in muscle and adipose tissue and the conversion of glucose in the liver. Lactate is produced by several tissues, but only muscle and adipose tissue are sensitive to insulin and, therefore, are subjected to regulation (26).

In hyperthyroidism, the Cori cycle may have greater physiological significance than just as a “carbon link” between peripheral tissues and the liver because it could be considered as a large substrate cycle; by maintaining a high flux through it, a dynamic buffer of glucose and lactate is provided, which can be used by other tissues as required (1, 26, 38). If the rate of glucose utilization by the tissues is relatively low in comparison with the flux through the Cori cycle, this is equivalent to a high cycling–flux ratio and could provide for precision in regulation of glucose utilization by these tissues (39).

V. Glucose Utilization in Skeletal Muscle and Adipose Tissue

Although hepatic insulin resistance is well established in the hyperthyroid state, information on the effects of insulin on glucose uptake in skeletal muscle and adipose tissue is variable.

A. Skeletal muscle

Skeletal muscle is considered to be the most important tissue for the disposal of glucose in response to insulin. In this tissue, insulin increases the rates of glucose disposal by stimulating blood flow, glucose transport, glucose phosphorylation, glycogen synthesis, glycolysis, and glucose oxidation (26).
Glucose disposal in human hyperthyroidism has been examined with the euglycemic-hyperinsulinemic clamp technique (under these experimental conditions it is likely that glucose uptake occurs mainly in muscle) or with the arteriovenous difference technique across the forearm muscles. In healthy volunteers rendered hyperthyroid with administration of T3 for 2 wk or in patients with hyperthyroidism, the glucose uptake rates at basal and maximal concentrations of insulin were found to be increased, whereas glucose uptake at physiological concentrations of insulin were found to be normal (12, 15, 40–43). At first glance, these results suggest that insulin resistance in hyperthyroidism may be selective on the liver and does not involve peripheral tissues. However, recent studies have examined the hypothesis that increased blood flow rates in hyperthyroidism may mask a defect in intracellular pathways of glucose metabolism (38, 44, 45). These parameters are discussed in detail below.

1. The importance of blood flow

Increased blood flow rates in skeletal muscle are well established in hyperthyroidism (40, 46). The effects of blood flow on muscle glucose uptake were examined in a recent study using the arteriovenous difference technique across the forearm muscles after the consumption of a mixed meal (44). In this study, muscle blood flow (measured with strain-gauge plethysmography) was found to be increased (see Fig. 1). In agreement with the in vitro (38) and in vivo studies (12, 41, 43, 47), in the postprandial period (i.e., in the presence of physiological levels of insulin), net glucose uptake by skeletal muscle (which depends on blood flow) was normal. In contrast, fractional glucose extraction (which is independent of blood flow) was actually decreased (44) (Fig. 1). These results: 1) suggest that in hyperthyroidism, in addition to the liver, skeletal muscle is also resistant to insulin; and 2) support the importance of blood flow in maintaining normal or even increased rates of glucose disposal in muscle tissue in the hyperthyroid state, despite the defects in the intracellular pathways of insulin-stimulated glucose metabolism (see below).

2. Glucose transport

In the soleus muscle removed from rats after short-term (5 d) treatment with T3 (hyperthyroidism of medium severity), 3-O-methylglucose transport was increased at maximal and at basal (fasting) levels of insulin; at physiological levels of insulin, glucose transport rates were normal (38) (Fig. 2). In contrast, long-term treatment of the rats with T3 (10–30 d, severe hyperthyroidism) increased the rates of 3-O-methylglucose transport at basal, physiological, and maximal concentrations of insulin (38, 48); this suggests that severe hyperthyroidism increases the responsiveness of the glucose transport process to insulin (Fig. 2).

In skeletal muscle and adipose tissue, basal glucose uptake depends on the activity of the GLUT1 glucose transporters, whereas insulin-stimulated glucose uptake depends on the activity of GLUT4 and GLUT3 glucose transporters on the plasma membrane (49). Thyroid hormones may be important for the transition (GLUT4 induction and GLUT1 repression) from fetal to neonatal levels (50).

The increases in the basal rates of glucose transport in hyperthyroidism (i.e., in the presence of basal concentrations of insulin) are explained by increases in the total
concentrations of the GLUT1 glucose transporters, but also by fractional partitioning of the GLUT4 glucose transporters to the plasma membrane (51, 52).

Reports in skeletal muscle isolated from hyperthyroid rats with severe hyperthyroidism have shown increases in the total number of the GLUT4 glucose transporters and increased translocation of these transporters from the intracellular pool to the plasma membrane in response to insulin (51, 53). Similar findings have been described in the cardiac muscle of hyperthyroid rats: insulin-stimulated glycolytic rates and lactate efflux rates were increased, mediated by an increased insulin-stimulated translocation of the GLUT4 glucose transporters to the sarcolemma (54).

In humans with hyperthyroidism, the translocation of GLUT4 glucose transporters in response to insulin has been examined only in peripheral monocytes; basal concentrations of GLUT4 glucose transporters on the monocyte plasma membrane were indeed increased in the hyperthyroid state, but insulin-stimulated translocation of these glucose transporters from intracellular pools to the cell surface was actually decreased (55). In hyperthyroidism, glucose uptake in the presence of insulin may depend mostly on the translocation of GLUT3 glucose transporters to the plasma membrane (55). This explanation is most probable because the expression of GLUT3 glucose transporters increases to several times basal values during metabolic stress and increased tissue energy demand; under these conditions, this glucose transporter may become primarily responsible for the increase in cellular glucose transport and utilization (56).

Increased transcription rates of the genes encoding these glucose transporters resulting in increased synthesis of the specific proteins may be required for these effects of T3 to be manifested (52, 53).

These results suggest that insulin-stimulated glucose transport in muscle in hyperthyroidism is either normal or increased.

3. Glucose phosphorylation

The increase in glucose transport may not be the only effect of insulin on glucose uptake in muscle under hyperthyroid conditions. This possibility was examined in soleus muscle isolated from rats made hyperthyroid after administration of T3 for 10 d, by incubating the muscles with 2-deoxyglucose, a glucose analog that is transported and phosphorylated like glucose but not further metabolized. These experiments showed that, in muscle, the rate of glucose phosphorylation in response to insulin is increased in hyperthyroidism (38).

After the 10-d treatment of the rats with T3, the intracellular content of free 2-deoxyglucose in muscle remained unaltered, but the rate of phosphorylation of 2-deoxyglucose increased when insulin was increased from 10 to 100 mU/liter (38) (Fig. 3). These findings suggest that, under conditions of thyroid hormone excess, insulin stimulates the rate of glucose phosphorylation not only by its effects on glucose transport but also by increasing the activity of hexokinase (38). This effect may be caused, at least in part, by the direct effect of insulin on the enzyme (38, 57).

4. Glycogen synthesis

Administration of T3 to rats for 2 d (mild hyperthyroidism) or for 5 (hyperthyroidism of medium severity) or 10 d (severe hyperthyroidism) in a dose that increased its concentration in plasma to levels usually found in patients with hyperthyroidism decreased the sensitivity of glycogen synthesis to insulin in the isolated soleus muscle to about the same extent (38, 45, 58) (Fig. 4).

These results agree with findings in healthy subjects rendered hyperthyroid after administration of T3 for 2 wk (12) or in patients with hyperthyroidism (42); rates of glycogen synthesis were measured with indirect calorimetry during a euglycemic-hyperinsulinemic clamp (12) or by the arteriovenous difference technique across the forearm muscles after an oral glucose tolerance test (42). In these studies, the sensitivity of glycogen synthesis to insulin in muscle was also found to be decreased in the hyperthyroid state.
5. Glycolysis, lactate formation, and glucose oxidation

It has been previously reported that glucose uptake in muscle tissue in the hyperthyroid state is normal or even increased mainly due to increased blood flow rates (12, 38, 44). Given that insulin-stimulated rates of glycogen synthesis are decreased in muscle, glucose residues are redirected toward glycolysis, lactate formation, and glucose oxidation (12, 38, 45, 59). Indeed, the sensitivity of lactate formation to insulin was markedly increased in skeletal muscle isolated from rats made hyperthyroid (45) (Fig. 4). In addition to this, an increase in insulin from physiological (10 or 100 μU/liter) to maximal levels (1000 μU/liter) did not change the content of glucose 6-phosphate, although the rate of glucose phosphorylation and the flux through glycolysis were both increased (38) (Fig. 3). These results suggest, under these conditions, insulin may stimulate 6-phosphofructokinase activity, possibly via an increase in fructose 2,6-bisphosphate. Indeed, the content of fructose 2,6-bisphosphate in muscle isolated from hyperthyroid rats was increased in the presence of insulin (38) (Fig. 3). Fructose 2,6-bisphosphate, a potent activator of 6-phosphofructokinase, is neither a substrate nor an intermediate of glycolysis or of any other pathway but a metabolic signal. Therefore, extracellular messengers such as hormones could control its concentration in muscle.

Hyperthyroidism has been shown to increase the insulin-stimulated rates of glucose oxidation in muscle in vitro (measured in the soleus muscle isolated from hyperthyroid rats and incubated with [14C]glucose) (38, 45). In one of these studies (45), the rats were treated with T3 for 2, 5, or 10 d; although the sensitivity of glycogen synthesis to insulin was clearly decreased and that of lactate formation was increased under all three experimental conditions, the sensitivity of glucose oxidation to insulin was increased
only after 5 or 10 d of treatment (Fig. 4). These results suggest that, in hyperthyroidism, there is a preferential increase in lactate formation relative to glucose oxidation in skeletal muscle (45). This is supported by a study in rats reporting that, in the fed state, hyperthyroidism increased glucose utilization in skeletal muscle but decreased the activity of the pyruvate dehydrogenase complex, a key enzyme for the regulation of glucose oxidation (58). Pyruvate dehydrogenase complex inactivation is facilitated by increases in pyruvate dehydrogenase kinase isoform (PDK4) expression in skeletal muscle (65).

These results are in agreement with in vivo studies in hyperthyroid subjects using indirect calorimetry during euglycemic hyperinsulinemic clamps (12) or after an oral administration of glucose (42). In these studies, rates of lactate formation and glucose oxidation were both increased in the presence of insulin.

Thyroid hormones have been recognized as major regulators of oxidative energy metabolism at the level of mitochondria (66, 67). Increases in mitochondrial enzyme activities likely contribute to the ATP production capacity by permitting increased energy flux through the oxidative pathway (66).

Hyperthyroidism is associated with an increase and hypothyroidism with a decrease in the secretion of GH and glucocorticoids in vivo (68–70). It has been firmly established that a change in the levels of these hormones in plasma affects glucose homeostasis; an excess of GH or glucocorticoids induces glucose intolerance by interfering with insulin action in liver and peripheral tissues (71, 72).

In skeletal muscle, GH and glucocorticoids inhibit the stimulation of glucose metabolism (glycogen synthesis and glucose utilization) in response to insulin (73–76). Administration of small (replacement) doses of cortisone or GH to hypothyroid rats and measurements of glycogen synthesis and glycolysis in the presence of insulin suggested that the changes seen in the sensitivity of glucose utilization to insulin in muscle in altered thyroid states are unlikely to be caused by changes in plasma concentrations of these hormones and may be due to changes in thyroid hormone levels per se (38).

B. Adipose tissue

In adipocytes isolated from rats or patients with hyperthyroidism, the sensitivity of glucose transport and utilization to insulin has been found to be normal (77), increased (78, 79), or decreased (80–85). The disagreement between studies may be due, at least in part, to regional differences in the metabolic characteristics and function of the isolated adipocytes (86).

The effects of thyroid hormones on glucose uptake in the adipose tissue have been recently examined in vivo with the arteriovenous difference technique across the abdominal sc adipose tissue in subjects with hyperthyroidism after the consumption of a mixed meal (34). Blood flow rates in the adipose tissue (measured by the clearance of $^{133}$Xe) were increased. In this study, the net glucose uptake (which depends on blood flow) and the fractional glucose extraction (which is independent of blood flow) in the adipose tissue were normal in the face of hyperinsulinemia, suggesting resistance of glucose uptake to insulin (34) (Fig. 5). The suppression of lipolysis by insulin after the meal may be an additional mechanism facilitating the uptake of glucose by the insulin-resistant adipose tissue.

VI. Lipid Metabolism in Adipose Tissue

In addition to effects on glucose metabolism, thyroid hormones stimulate synthesis, degradation, and mobilization of lipids (12, 87, 88).

Adipose tissue is the tissue with the highest activity of lipoprotein lipase, the enzyme responsible for clearance of
plasma triglycerides, particularly in the postprandial state (89). Hormone-sensitive lipase is the intracellular enzyme regulating the release of lipid energy from fat stores into the circulation as nonesterified fatty acids and has a major role in determining the circulating lipid fuel supply for the whole body (90). In 2004, a new lipase—adipose triglyceride lipase—has been identified (91). Hormone-sensitive lipase is the major lipase catalyzing the rate-limiting step in stimulating lipolysis in humans, whereas adipose triglyceride lipase catalyzes the initial step in the hydrolysis of stored triglycerides in coordination with hormone-sensitive lipase (92).

Insulin effects on lipolysis, lipoprotein lipase action, and nonesterified fatty acids fluxes in hyperthyroid subjects were studied with the arteriovenous difference technique across the abdominal subcutaneous adipose tissue after a mixed meal (34). The pattern of triglycerides was unusual because fasting levels were not significantly different from those in euthyroids (93–96), but late postprandial levels were decreased (34) (Fig. 6). These changes are consistent with a higher triglyceride turnover (95). The late postprandial lowering of plasma triglycerides was not secondary to an increased rate of removal by the two major tissues expressing lipoprotein lipase, adipose tissue, and muscle because postprandial lipoprotein lipase activity was low or unchanged in these tissues (34).

The possibility that increased adipose tissue blood flow was responsible for the late postprandial drop of triglycerides was also unlikely because this can only be achieved through increased lipoprotein lipase action and triglyceride clearance (97, 98) and yet both were blunted in the hyperthyroid subjects (34). Could increased triglyceride removal by the liver account for the postprandial triglyceride reductions? Experiments in humans have suggested that hyperthyroidism enhances the capacity of the liver for complete particle uptake of the remnants of triglyceride-rich lipoproteins (93), but this may only partly explain our results because the liver primarily removes remnant particles that are low in triglycerides (99).

Although lipoprotein lipase may contribute to the nonesterified fatty acid pool, the majority of nonesterified fatty acid appearance after a meal derives from lipolysis of stored triglycerides (89, 97, 100, 101). In a recent study (34), rates of lipolysis and nonesterified fatty acid release in the adipose tissue of hyperthyroid subjects were both increased in the fasting and late postprandial state, but were rapidly suppressed to normal shortly after the beginning of the meal (Fig. 7). These results suggest that hyperthyroidism induces resistance to lipolysis to insulin, which however is evident at low (basal) levels of insulin; this rate is rapidly suppressed when insulin is increased after the meal. It is noteworthy that lipolysis is extremely sensitive to insulin; the half-maximal suppression in euthyroid humans in vivo (102, 103) or in isolated adipocytes in vitro (82) ranges from 2–11 μU/ml. Because the venoarterial differences of plasma nonesterified fatty acids across the adipose tissue in the hyperthyroid subjects were both increased in the fasting and late postprandial state, but were rapidly suppressed to normal shortly after the beginning of the meal (Fig. 7). These results suggest that hyperthyroidism induces resistance to lipolysis to insulin, which however is evident at low (basal) levels of insulin; this rate is rapidly suppressed when insulin is increased after the meal. It is noteworthy that lipolysis is extremely sensitive to insulin; the half-maximal suppression in euthyroid humans in vivo (102, 103) or in isolated adipocytes in vitro (82) ranges from 2–11 μU/ml. Because the venoarterial differences of plasma nonesterified fatty acids across the adipose tissue in the hyperthyroid subjects were similar to those in euthyroids, the fluctuations in the rates of lipolysis may be due to those in blood flow and not to a decreased sensitivity of hormone-sensitive lipase and adipose tissue triglyceride lipase to insulin (34). These results correspond well with observations in adipocytes isolated from hyperthyroid patients and incubated in vitro; the suppression of glycerol release was decreased at insulin levels less than 10 μU/ml but was normal at insulin levels between 10 and 100 μU/ml (82). These results are in agreement with a
study in hyperthyroid patients in vivo, examining insulin effects on glycerol release from the sc adipose tissue, using microdialysis and euglycemic-hyperinsulinemic clamps (104); basic glycerol release from the adipose tissue was higher in the hyperthyroid subjects than in controls but was suppressed to the same extent (50%) in both groups when insulin was infused.

Recent studies (105, 106) suggest that thyroid hormones regulate lipolysis by affecting local norepinephrine concentrations and/or adrenergic postreceptor signaling.

At the hepatic level, lipogenesis has been found increased in the fasting state in human hyperthyroidism (owing mostly to an increased delivery of nonesterified fatty acids to the liver) (95, 100, 107). This stimulation of fatty acid incorporation into triglycerides occurs simultaneously with increased lipolysis and lipid oxidation rate (47, 108, 109). The parallel stimulation of synthesis and degradation of triglycerides represents another enhanced metabolic cycle that could contribute to the increased energy expenditure of hyperthyroid subjects (107). Cholesterol synthesis has also been found increased in hyperthyroidism; however, plasma cholesterol levels are decreased in hyperthyroid subjects probably due to an increased clearance rate (107) and/or an increased biliary excretion of cholesterol (110).

As a result, in hyperthyroidism, adipose tissue lipolysis is increased in the fasting state resulting in increased production of glycerol and nonesterified fatty acids. Under these conditions, increased glycerol generated by lipolysis and increased amino acids generated by proteolysis are used as substrates for gluconeogenesis. Nonesterified fatty acid levels are necessary to stimulate gluconeogenesis and provide substrate for oxidation in other tissues (such as muscle). However, lipolysis is rapidly suppressed to normal after the meal to facilitate the disposal of glucose by the insulin-resistant muscle (34). This ensures the preferential use of glucose when available and helps to preserve fat stores (34, 111).
VII. The Role of Cytokines

Adipose tissue is an active endocrine organ that, in addition to regulating fat mass and nutrient homeostasis, releases a large number of cytokines, modulating glucose and lipid metabolism, inflammation, energy balance, and body weight (112–114). An interaction between thyroid hormones and adipose tissue-produced cytokines would be important for two reasons. First, thyroid hormones have marked effects on adipose tissue metabolism (1, 12). And second, because thyroid hormones induce insulin resistance (1, 34), an effect on production rates and plasma levels of these cytokines could provide an insight into the responsible mechanism(s).

A. Adiponectin

Adiponectin stimulates glucose uptake and reduces glucose production by increasing the sensitivity of muscle and liver to insulin (113). Measurements of adiponectin in hyperthyroidism have shown conflicting results: these levels have been found to be normal (115–117) or increased (118–121). A possible explanation of these discordant results might be related to the etiology of hyperthyroidism. In the majority of the studies that have shown increased circulating adiponectin levels, the patients had autoimmune hyperthyroidism (122). Indeed, in a recent study in Graves’ disease patients, increased serum adiponectin levels have been found to be related to the degree of hyperthyroidism and the autoimmune process (121).

B. Leptin

Leptin is considered to play a role in the maintenance of energy balance and body weight by neuroendocrine mechanisms. In addition, leptin has been shown to improve hepatic and skeletal muscle sensitivity to insulin (113). In hyperthyroidism, circulating leptin levels have been found to be normal (116, 118, 123–125) or decreased (115, 126). Interestingly, leptin has been shown to increase peripheral type 2 deiodinase activity so that more T₃ is available to peripheral tissues (127, 128); thus, leptin may play a role in raising levels of T₃, thereby worsening hyperthyroidism (2).

C. Interleukin-6

IL-6 has been reported to reduce insulin-dependent hepatic glycogen synthesis (129, 130) and glucose uptake in adipocytes (131), whereas it enhances insulin-dependent glycogen synthesis and glucose uptake in myotubes (132, 133). In previous studies in hyperthyroidism, IL-6 plasma levels have been found to be increased (123, 134–137) or unchanged (138, 139). Adipose tissue secretion of IL-6 levels has been previously studied with sc fat biopsies, in vitro in hyperthyroid subjects with Graves’ disease (123); in this study, serum concentrations as well as adipose tissue release of IL-6 were increased, both before and during antithyroid treatment as compared with euthyroid subjects. In a recent study in patients with hyperthyroidism of nonautoimmune origin, increased abdominal sc venous IL-6 levels were positively associated with the homeostasis model of assessment index, suggesting a possible link between IL-6 production from sc adipose tissue and the development of insulin resistance in the hyperthyroid state (136).

D. Tumor necrosis factor

In previous studies focusing mainly on Graves’ disease, TNFα plasma levels have been found to be increased (135, 138–140) or unchanged (123, 134). In a recent study in patients with hyperthyroidism of nonautoimmune origin, arterial TNFα levels were found to be increased and positively associated with arterial plasma nonesterified fatty acid levels, suggesting a possible link between increased TNFα levels and the development of insulin resistance in lipolysis (136). This is in accordance with previous observations in euthyroid subjects showing that TNFα inhibits lipoprotein lipase activity and increases lipolysis (114, 141, 142). Given that there was no secretion of TNFα by the sc adipose tissue depot (136), it is possible that TNFα produced by other tissues or cells could influence lipolysis through endocrine mechanisms.

E. Resistin

Measurements of resistin in hyperthyroidism have shown conflicting results; these levels have been found to be normal (121), increased (118, 143) or decreased (115). However, even in studies that showed increased levels of resistin (143), there was no association between these levels and body weight, body fat, waist circumference or body mass index, which makes it unlikely that resistin plays a crucial role in thermogenesis and energy homeostasis in the hyperthyroid state.

F. Visfatin

Visfatin exerts insulin-mimetic effects in various tissues, and its administration has been shown to lower plasma glucose levels in mice (144). Previous studies have shown that plasma visfatin levels are correlated with type 2 diabetes (145) and obesity (146). Other studies, however, did not confirm an association of visfatin and visceral adipose tissue or parameters of insulin sensitivity in humans (147). Only two studies have evaluated visfatin levels in hyperthyroidism so far. The first study showed increased plasma visfatin concentration in hyperthyroid patients and a decrease after treatment; however, these levels were not associated with indices of insulin resistance (148). These findings contrast with the results of the sec-
ond study in hyperthyroid patients that found low visfatin levels that were increased after antithyroid therapy (149).

VIII. Insulin Secretion

Although several studies have found decreased insulin secretion (77, 150–159), most of the studies have reported normal or even increased levels of insulin in the peripheral blood of normal glycemic hyperthyroid patients (Fig. 8); these changes are abolished after treatment (12, 27–29, 34, 160–169).

These discrepancies can be explained by the finding that, in hyperthyroidism, increased secretion of insulin may be masked by increased degradation of insulin (12, 47, 170). Interestingly, in one of these studies performed in patients with Graves’ disease, increased insulin secretion and metabolic clearance rate of insulin were positively correlated with plasma free T₄ levels (170).

Therefore, in lean euglycemic hyperthyroid subjects (34), increased rather than decreased secretion of insulin is manifested, which, however, is insufficient to suppress hepatic glucose output. This has also been reported in overweight euglycemic hyperthyroid subjects in whom β-cell response to hyperglycemia has been found not to be impaired (171); this is in contrast to what has been observed in patients with early type 2 diabetes (172).

However, the significance of decreased insulin secretion may increase during long-term severe thyrotoxicosis: treatment of rats with high doses of T₄ causes marked decrease of both pancreatic insulin content and rate of secretion (173–175).

IX. Concluding Remarks

Hyperthyroidism leads to an enhanced demand for glucose (Fig. 9). Because net glucose disposal evoked by insulin has been found to be either normal or increased in skeletal muscle in the hyperthyroid state both in vivo (12, 15, 40–43) and in vitro (38, 48), the elevated plasma glucose levels in this condition may be explained by increased rates of hepatic glucose production, due to increased gluconeogenesis (in the fasting state) and increased Cori cycle activity (in the late postprandial and fasting state) (38).

Thus, in hyperthyroidism, it may be of primary importance to increase the rate of lactate formation by muscle relative to glucose oxidation in the postprandial period to increase Cori cycle activity (1, 38, 45). This will be achieved primarily by a decrease in glycogen synthesis and an increase in glycogenolysis in muscle (45, 60). When
hyperthyroidism progresses in severity, increases in the responsiveness of glucose transport to insulin and in the activity of hexokinase and 6-phosphofructokinase may also be involved (38). Increases in muscle and adipose tissue blood flow in hyperthyroidism may play an important role in maintaining normal rates of glucose disposal in the presence of hyperinsulinemia in these tissues (34, 44). Moreover, in hyperthyroidism, peripheral tissues may increase the sensitivity of glucose utilization to IGF-I (176). These parameters help to explain the paradox of normal or even increased overall glucose metabolism at the skeletal muscle level with insulin resistance.

The hepatic resistance to insulin in hyperthyroidism may serve a beneficial effect in preventing the development of hypoglycemia (1, 38). Increased energy demands from peripheral tissues (such as muscle and adipose tissue) in hyperthyroidism necessitate an increase in substrate availability. If production of glucose did not match the increased demand for muscle lactate formation and glucose oxidation and if muscle glycogen formation were not decreased, the plasma glucose concentration would have to decrease; this would activate counterregulatory mechanisms and enhance an already catabolic state (1, 38). As long as the pancreatic β-cell can adapt to this insulin resistance and to an associated increase in insulin degradation with an appropriate increase in insulin secretion, normal glucose homeostasis can be maintained; when the β-cell capacity for adaptation is exceeded, glucose tolerance will deteriorate and diabetes mellitus may eventually develop.

In hyperthyroidism, adipose tissue lipolysis is increased in the fasting state, whereas postprandially this rate is rapidly suppressed to normal (34). The significance of the changes in lipid fluxes in the hyperthyroid subjects becomes apparent from the transcapillary flow of nonesterified fatty acids. In the fasting state, due to insulin resistance, there is an increased outflow of nonesterified fatty acids from the adipose tissue into the capillaries—necessary to stimulate gluconeogenesis and provide nonesterified fatty acids for oxidation in other tissues (such as muscle)—which, however, quickly subsides after the meal to facilitate the disposal of glucose by the insulin-resistant muscle (34). This ensures the preferential use of glucose when available and helps to preserve fat stores (34, 111). This conclusion is supported by previous experiments with indirect calorimetry in hyperthyroid patients showing increased whole-body lipid oxidation in the fasting and late postprandial states and carbohydrate oxidation shortly after the meal (42, 177). These changes may be required to relieve tissues from the increase of nonesterified fatty acids after the meal, thus facilitating muscle glucose disposal by insulin.

From a clinical point of view, hyperthyroid patients should be screened for glucose and lipid abnormalities. Similarly all diabetic patients should be screened for thyroid dysfunction because correcting hyperthyroidism may improve glucose homeostasis.

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