Abstract

Hyperthyroidism affects glucose metabolism via several mechanisms. Increased plasma glucose levels in this condition may be explained mainly by resistance of the liver to insulin due to enhanced gluconeogenesis. In skeletal muscle in hyperthyroidism: (1) glucose uptake is resistant to insulin, but this defect is masked by an increase in blood flow; (2) insulin-stimulated glucose phosphorylation is increased; (3) insulin-stimulated glycogen synthesis is decreased, whereas glycolysis and lactate formation are increased; (4) glycogenolysis is increased due to increased responsiveness to β-adrenergic stimulation; and (5) although insulin-stimulated glucose oxidation is increased, there is a preferential increase in lactate formation relative to glucose oxidation. In adipose tissue in hyperthyroidism: (1) in the fasting state, lipolysis is increased and is necessary to provide nonesterified fatty acids for oxidation in other tissues (such as muscle) and for stimulating gluconeogenesis, and (2) postprandially, increased rates of lipolysis subside to facilitate the disposal of glucose by the insulin-resistant muscle.

Thyroid hormones play a critical role in differentiation, growth and physiological cell function. Moreover, it has been known for decades that thyroid hormones are important regulators of glucose and lipid metabolism. Our previous studies, more than 40 years ago, demonstrated the presence of abnormal glucose metabolism and insulin resistance in overt hypothyroid patients [1]. In these patients, treatment with thyroid hormones resulted in normalization of glucose utilization and insulin secretion [1]. Interestingly, insulin resistance is a common finding in hyperthyroidism too [2, 3]. Various mechanisms have been suggested to explain the impairment of glucose tolerance in the hyperthyroid state, including those described in the following.
**Gastrointestinal System**

In hyperthyroidism, rapid gastric emptying, enhanced intestinal glucose absorption and increased portal venous blood flow have been hypothesized to contribute, at least in part, to postprandial hyperglycemia [4].

**Insulin Secretion**

Insulin secretion in hyperthyroidism has been found to be increased, normal or decreased [5]. These discrepancies can be explained by the finding that, in hyperthyroidism, increased secretion of insulin may be masked by increased degradation of insulin [6, 7]. Therefore, decreased secretion of insulin is not the primary mechanism explaining impaired glucose tolerance in hyperthyroidism. Its significance, however, may increase during long-term severe thyrotoxicosis, which has been shown to cause beta cell dysfunction resulting in reduced pancreatic insulin content, poor insulin response to glucose and a decreased rate of insulin secretion [7].

**Endogenous Glucose Production**

Hyperthyroidism is a hypermetabolic state leading to an increased demand for glucose, which is primarily provided by increased rates of hepatic glucose production via the following mechanisms: (1) increased rates of gluconeogenesis and glycogenolysis; (2) increased secretion and effects of glucagon and adrenaline on liver cells; (3) increased concentrations of free fatty acids in plasma; (4) increased proteolysis in muscle, providing an increased supply of amino acids to the liver; (5) increased concentrations of glucose transporter (GLUT) 2 in the liver plasma membrane, which allows increased glucose efflux to occur without accumulation of intracellular glucose, which would limit hepatic glucose production; and (6) a central pathway for modulation of hepatic glucose production by triiodothyronine, involving the hypothalamic paraventricular nucleus and the sympathetic nervous system [2, 5, 8, 9].

**Glucose Utilization**

**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 rate of glucose disposal by stimulating glucose transport, glucose phosphorylation, glycogen synthesis,
glycolysis and glucose oxidation. The effects of thyroid hormones on insulin-stimulated rates of glucose uptake in skeletal muscle have been examined in vitro and in vivo.

**Glucose Uptake**

3-O-methylglucose is transported across the plasma membrane like glucose but not metabolized, and therefore its accumulation in muscle is an accurate measure of the rate of this process. In the soleus muscle removed from rats after short-term (5-day) treatment with triiodothyronine (hyperthyroidism of medium severity), 3-O-methylglucose transport was increased at maximal and at basal levels of insulin; at physiological levels of insulin, the glucose transport rates were normal [10]. In contrast, long-term treatment of the rats with triiodothyronine increased the rates of 3-O-methylglucose transport at basal, physiological and maximal concentrations of insulin [10]; this suggests that chronic increases in the levels of triiodothyronine in plasma increase the responsiveness and sensitivity of the glucose transport process to insulin. This is consistent with the results on muscle glucose uptake obtained in human hyperthyroidism with the hyperinsulinemic euglycemic 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 by administration of triiodothyronine for 2 weeks or in patients with hyperthyroidism, the glucose uptake rates at basal and maximal concentrations of insulin were found to be increased, while glucose uptake at physiological concentrations of insulin were found to be normal [11].

These results from in vitro and in vivo experiments suggest that insulin resistance in hyperthyroidism may be selective on the liver and does not involve peripheral tissues. However, it must be pointed out that glucose uptake by peripheral tissues depends (a) on the cellular mechanisms of glucose transport, and (b) on the rate of blood flow. These mechanisms have been investigated both in vitro and in vivo.

**Cellular Mechanisms of Glucose Transport**

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 GLUT1, but also by fractional partitioning of GLUT4 to the plasma membrane [12]. Reports regarding skeletal muscle isolated from hyperthyroid rats with severe hyperthyroidism have shown increases in the total number of GLUT4 and increased translocation of these transporters from the intracellular pool to the plasma membrane in response to insulin [12].

However, recent findings in isolated human monocytes have suggested that GLUT4 may not be the major transporter involved in insulin-stimulated glucose uptake in hyperthyroidism: basal concentrations of GLUT4 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 [13]. In hyperthyroidism, glucose uptake in the presence of insulin may depend mostly on the translocation of GLUT3 on the plasma membrane [13]. This explanation is most probable, since the expression of GLUT3 increases to several times the 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.

**Blood Flow**

Increased blood flow rates in skeletal muscle are well established in hyperthyroidism. 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 [14]. In this study, muscle blood flow (measured with strain-gauge plethysmography) was found to be increased. In agreement with the in vitro and in vivo studies [10, 11], in the postprandial period, the net glucose uptake by skeletal muscle (which depends on blood flow) was normal. In contrast, fractional glucose uptake (which is independent of blood flow) was actually decreased [14]. These results (a) suggest that in hyperthyroidism, in addition to the liver, skeletal muscle is also resistant to insulin, and (b) support the importance of blood flow in maintaining normal or even increased rates of glucose uptake in muscle tissue in the hyperthyroid state, despite the defects in the intracellular pathways of insulin-stimulated glucose disposal. To compensate for the resistance of glucose metabolism to insulin, peripheral tissues may increase the sensitivity of glucose utilization to insulin-like growth factor 1 [15].

**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 triiodothyronine for 10 days, by incubating the muscles with 2-deoxyglucose, a glucose analog which 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 [10].

After a 10-day treatment of the rats with triiodothyronine, 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/l. 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. This effect may be caused, at least in part, by less inhibition of hexokinase by glucose 6-phosphate or by the direct effect of insulin on the enzyme [10]. In addition, the effects of insulin on the rate of glucose phosphorylation in muscle under hyperthyroid conditions may be facilitated by an increase in the activity of hexokinase [10].
**Glycogen Synthesis**

Administration of triiodothyronine to rats for 2 days (mild hyperthyroidism) or for 5 (hyperthyroidism of medium severity) or 10 days (severe hyperthyroidism), at 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 [10, 16].

These results agree with findings in healthy subjects rendered hyperthyroid after administration of triiodothyronine for 2 weeks, or in patients with hyperthyroidism; rates of glycogen synthesis were measured with indirect calorimetry during a hyperinsulinemic euglycemic clamp or by the arteriovenous difference technique across the forearm muscles after an oral glucose tolerance test. In these studies, the sensitivity of glycogen synthesis to insulin in muscle was also found to be decreased in the hyperthyroid state [11].

**Glycolysis and Glucose Oxidation**

The decrease in insulin-stimulated rates of glycogen synthesis in muscle in hyperthyroidism redirects glucose residues toward glycolysis and lactate formation [10, 11, 16]. Indeed, the sensitivity of lactate formation to insulin was markedly increased in skeletal muscle isolated from rats made hyperthyroid [16].

In addition to this, an increase in the rate of glycogenolysis may also facilitate lactate formation in muscle in hyperthyroidism. The mechanisms of this effect were examined in the soleus muscle isolated from rats treated with triiodothyronine for 5 days and incubated in the presence of various concentrations of isoprenaline and insulin [17]. In this muscle preparation, hyperthyroidism increased the rates of lactate formation and suppressed those of glycogen synthesis in response to isoprenaline, even in the presence of physiological or supraphysiological concentrations of insulin. Hyperthyroidism had no effect on the number or affinity of β-adrenoreceptors, or β-adrenoreceptor-stimulated or forskolin-stimulated adenylate cyclase activity in the muscle membranes. These results suggest that the increase in lactate formation and its subsequent increase in plasma are due, at least in part, to an increased responsiveness of glycogenolysis to β-adrenergic stimulation in skeletal muscle caused by postreceptor defects [17].

In the soleus muscle isolated from rats made hyperthyroid, an increase in insulin from physiological (10 or 100 mU/l) to maximal levels (1,000 mU/l) did not change the content of glucose 6-phosphate, although the rate of glucose phosphorylation and the flux through glycolysis were both increased [9]. These results suggest that, 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 [10]. 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.