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Relation between diabetes mellitus, thyroid hormones and caffeine

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ABSTRACT

Diabetes mellitus (DM) has an important relation with thyroid hormones (TH) dysfunctions, and if analyzed accurately, may contribute to the diagnosis of clinical conditions such as hyperglycemia and insulin resistance (IR). Relevant studies are being made about the role of TH in mediating metabolic actions related to DM, acting in many glands and energetic subtracts regulator tissues. Some issues, such as the action of TH over the ionic regulation in the cells, altering actions in different paths; its role over the negative feedback by downregulations upon insulin action, but provoking an increase in β pancreatic cells proliferations, point out important directions to research. The mechanisms of action related to thyroid hormones and the insulinotropic action form a counterbalance, and if an imbalance occur (hyperthyroidism or hypothyroidism) it may be noted the presence of DM or IR. The interactions between TH, DM and caffeine are unknown aspects in the literature, which need a better attention and the development of experimental clinic studies to elucidate their mechanisms and clinical applications.

INTRODUCTION

Thyroid hormones (TH) regulate essential metabolic process to a normal growth and development, they also regulate the organism metabolism, correlating the body weight and the expenditure of energy (Knudsen *et al.,* 2005; Fox *et al.,* 2008; Iwen *et al.,* 2013; Gnocchi *et al.,* 2016). The complex system of negative feedback involving the thyroid glands, synthesizes and secretes in blood circulation the hormones thyroxine (T_4) and triiodothyronine (T_3) related to pituitary gland, that produces the thyroid-stimulation hormone (TSH or thyrotropin). This hormone stimulates the synthesis of TH in the thyroid gland, being the secretion of TSH inhibited by the increase of TH. Hormonal concentrations of T_3 and T_4 are determined by thyrotropin-releasing hormone (TRH), produced in the hypothalamus in the paraventricular nucleus, which stimulates the liberations of TSH of pituitary gland. TRH is inhibited by TH (Filiers, 2009; Ortiga-Carvalho *et al.,* 2016). Hyperthyroidism, excess of TH, triggers a hypermetabolic state characterized by the increase of released energy at rest, weight loss, reduction in cholesterol levels and increase of lipolysis and gluconeogenesis (Motomura *et al.,* 1998; Brent, 2008; Da Poian and Castanho, 2015). Conversely, hypothyroidism characterizes the reduction of energy liberation, weight gain, increase of cholesterol levels, reduction of lipolysis and gluconeogenesis (Brent, 2012). A chain of adrenergic innervations in thyroid gland stimulates the control of activation and liberation of TH, influencing the response of TSH stimulation (Sundler *et al.,* 1989). Catecholamine (cortisol, adrenaline) increase the conversion of T_4 to T_3 through the specific activity of deubiquitinase enzyme that acts over the activity of up regulators of deubiquitin 2 protein, enhancing the levels of T_3 in the thyroid cellular nucleus (Gereben *et al.,* 2008). This synergism between TS and sympathetic nervous system (SNS) may be involved in alteration of energy storage or liberation (Ribeiro *et al.,* 2001).

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The influence of TH over the metabolic pathway that controls energy emerge through the balance of energy storage and liberation (Cheng *et al.*, 2010; Liu et a., 2010; Iwen *et al.*, 2013) maintaining the endocrine regulators with actions over the brain, white and brown adipose tissue, skeletal muscle, liver and pancreas. The focus of TH over the energetic action, and over the regulation of lipids and carbohydrates metabolic pathways, describes the influence of these hormones over pathological conditions such as diabetes mellitus (DM).

TH triggers the raise of fatty acids in plasma in hyperthyroidism conditions. The reduction of intracellular levels of fatty acids are associated with the hepatic sensibility through modulation of substrate capitation by insulin and lipid oxidation (Chavez e Summers, 2010).

Thyroid hormones over insulin and glucose metabolism

TH are crucial to glucose homeostasis (Wennlund *et al.*, 1986; Kim *et al.*, 2002), and in contrast, insulin is the first hormone responsible for the glucose control, that leads us to suppose that there may be a relation in the effect of T_3 and insulin, determining lipid and glucose metabolic pathways (Lambardiari *et al*, 2011). Recent studies indicate that euthyroid individuals may have fluctuations in the concentrations of TH in plasma, correlating to changes in the insulin secretion and sensibility (Ortega *et al.*, 2008; Roos *et al.*, 2007). Lambardiari *et al*, (2011) evaluated euthyroid subjects in early stage of DM type 2 (DMT2), investigating the association of TH levels with the sensibility of glucose by the insulin metabolism, and it was detected that the levels of T_3 and T_4 were reduced in the individuals with DMT2 compared with the control group.

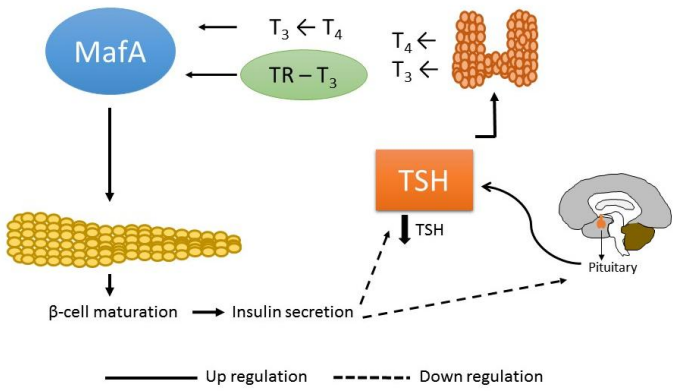

Fig. 1: Role of insulin in control of thyroid hormones through hypothalamic-pituitary axis.

In pancreas, receptors of TH are important for a normal development of the islets. *MAF* gene encode transcription factors, and the expression of *MafA* isotype has as its main objective to regulate the growth, proliferation and development of β pancreatic cells (Aramata *et al.*, 2007). It is suggested that TH may physiologically regulate the expressions of *MafA*, increasing its expressions and directing insulin secretion maturation, regulated by glucose, in β pancreatic cells of neonate mice; whereas the inhibition of thyroid hormones' synthesis prevents or delays the maturation of these systems, and TH administration results in a precocious development of the tissue (Aguayo-Mazzucato *et al.*, 2013) (Figure 1). *In vitro*, T_3 has not altered the insulin secretion stimulated by glucose and may play an important role in the maturation of β cells of neonate mice (Aguayo-Mazzucato *et al.*, 2013), demonstrating to be relevant to insulin homeostasis.

TH inhibit the insulin liberation stimulated by glucose, associated with SNS actions, triggering an increase in glucose utilization and oxidation in islets, describing then, an action of downregulation (Mullur *et al.*, 2014). This stimulus occurs due to the adrenergic action over thyroid gland, enhancing the liberation and conversion of TH and causing a consequent rise in glucose levels.

In contrast, the treatment with T_3 prevents the damage and maintainx the structure, size and consistence of β cells of streptozotocin-induced diabetic animal models (Verga *et al.*, 2011), propitiating an increase of insulin liberation (Figure 1). The treatment with T_3 prevented hyperinsulinemia, but not the hyperglycemia, in obese animals (Torrance *et al.*, 1997). Therefore, TH act in the maturation and development of β cells, albeit controlling the insulin clearance due to a synergic stimulation with SNS, maintaining the glucose homeostasis (Moog *et al.*, 2015).

Is has been stablished that in hyperthyroidism condition a stimulation of gluconeogenesis occurs, as well as a reduction of it in hypothyroidism (Comte *et al.*, 1990). The treatment with T_4 increases alanine transportation to the hepatocytes, enhancing gluconeogenesis by alanine conversion to glucose (Singh *et al.*, 1978). Moreover, the treatment with T_3 demonstrated to increase genes that regulate glycogenolysis and gluconeogenesis in liver (Feng *et al.*, 2000; Gnocchi *et al.*, 2016).

Relation between diabetes and thyroid hormones

Insulin resistance (IR) and the function of β cells are inversely correlated to TH stimulation, explained by the antagonist effects of TH over insulin along the TSH enhancement. The increase of serum TSH usually demonstrates a reduction in TH levels by negative feedback mechanism, as well as the increase in TH levels decreases the effects of insulin in tissues (Chen *et al.*, 2010; Nishanth *et al.*, 2016).

TH act directly in the insulin secretion (Figure 1). In the hypothyroidism condition there is an increase of insulin secretion stimulated by glucose in the β cells, and the opposite occurs in the hyperthyroidism condition, reducing the secretion of insulin stimulated by glucose (Stanick *et al.*, 2005; Mitrou *et al.*, 2010). Furthermore, an increase in insulin clearance occurs also during thyrotoxicosis disorder (Stanick *et al.*, 2005). The deregulation of TH may affect the glucose homeostasis, acting over the reduction of the mitochondrial activity, what shows a link between the described action of TH and DM (Crunkhorn e Patti, 2008), however this relation is still unknown.

The influence of IF over the hypothalamic-pituitary axis has been discussed in the literature, yet, conflicting results are reported, showing a positive association between homeostatic model assessment (HOMA) and TSH, while negative relations between IR and T_4 were found by the same authors, or denied by others (Ambrosi *et al.,* 2010). In DM condition, different investigations show that the serum levels influence in the control of diabetic condition and suggest a relation between the decrease of T_3 production and the worsening of glucose utilization (Schlienger *et al.,* 1982). Furthermore, thyrotoxicosis causes hyperinsulinemia with TH reduction and an increased glucose synthesis, what, by unknown mechanisms, triggers IR (Aguayo-Mazzucato *et al.,* 2013). Thus, the association between the production and the metabolism of carbohydrates was evaluated in diabetic patients, and a reduction in T_3 production was shown, being correlated with a reduction in glucose utilization.

Hypothyroidism reduces the production of liver glucose and may trigger IR by unknown factors (Aguayo-Mazzucato *et al.,* 2013). Ambrosi *et al* (2010) showed an increase in TSH levels in obese patient with IR (1.8±1.0 *vs* 1.6±0.9 µUI/l; p=0.03) and reduction of serum T_4 (13.8±2.3 vs 15.0±2.2 pmol/l; p<0.001), when compared to patients with normal insulin sensibility. Moreover, a positive relation occurred between fasting insulin values (p<0.001, r=0.152) and HOMA (HOMA-IR; p<0.001, r=0.148). The relation between thyroid function, obesity and DMT2 seems to exist, mainly influenced by IR. In Lambardiari *et al*, (2011) study, HOMA-IR was positively associated with T_3 and T_4, suggesting that the levels of TH are positively associated with IR, what may be part of the pathological mechanism to explain the beginning of DMT2 progress.

Hyperthyroidism is being associated with metabolic syndrome and cardiovascular disease components (Ichiki 2010). In euthyroidism, there is a positive relation between T_4 and TSH concentrations and cardio metabolic variables. T_3 hormone is reduced in some situations such as obesity, insulin concentrations, IR, diastolic and systolic pressure and dyslipidemias; however it is favored by hyperglycemia (De Pergola 2010). The risk of IF increases if the individual has reduced concentration of free T_4 (Luna-Vasquez *et al.,* 2014). Moreover, evidences indicate that there is a reduction of T_3 in diabetic subjects (Saunders, 1978).

Ions regulation by thyroid hormones

It is known that T_3 hormone is important for a normal development of skeletal muscle, and a healthy thyroid gland is required to the development of the muscular mass and also to the differentiation of biochemical and contractile characteristics of the muscle (Finkelstein *et al.,* 1991). This hormone has a great impact over the composition of the isoforms properties of myosin and sarcoplasmic reticulum (SR). Hypothyroidism causes some changes in the SR, enducing an enhancement in the transport of Ca^{++} of SR and in the percentage of expressed protein fibers to SR Ca^{++} ATPase enzymes in the skeletal muscles of rats (Li *et al.,* 1996). Thyroid hormone responsive elements were found in genes that codify proteins of myocardial contraction and Ca^{++} homeostasis regulators (Forini *et al.,* 2001). Evidences suggest a reduction of 45% in the Ca^{++} myosine ATPase activity in diabetic animals (Malhotra *et al.,* 1979), similar to the reductions that occurs during hypothyroidism (Dillmann, 1980). In hypertireoidic and diabetic animals a significant reduction of Ca^{++} myosine ATPase activity occurred, however, the administration of 0.3 µg of T_3/100g BW/day normalized the enzyme activity in hypertireoidic animals, but failed again in diabetic animals (Dillmann, 1982).

Hyperthyroidism is related to the enhancement of protein kinase C (PKC), this type of protein is responsible to control the phosphorylation of insulin receptor and consequently the IR, what may be reversible with TH treatment. PKC enzymes are activated by signals; such as rises in the diacylglycerol (DAG) or in calcium ions (Ca^{++}) concentrations. These enzymes play an important role in several signal transduction cascades (Lin *et al*, 2008). The chronic exposition to T_3 triggers a late internal increase of Ca^{++} and an external enhancement of K. Thus, a long exposition of T_3 enhances the time of Na^+ channels inactivation in cardiac myocytes, increasing the Na^+ channels flow in ventricular myocytes and also increasing cellular Ca^{++} harvesting in the myocytes (Wang *et al.,* 2002).

Caffeine and thyroid hormones

Caffeine is an inhibitor of phosphodiesterase, and may influence hormonal secretion or inhibition by the rise of cyclic adenosine monophosphate (cAMP), or indirectly, affecting neurotransmitters and consequently hypothalamic clearance factors (Arnaud, 2011). Caffeine is rapidly absorbed by the gastrointestinal system and reveals plasma concentration peaks between 30 and 60 minutes. Only 1 to 3% of caffeine is excreted without any modification in urine. The metabolic rate of caffeine is variable, with a half-life of 4 to 6 hours (Panchal *et al.,* 2012).

It is known that high doses of caffeine (200 mg/kg) may affect the secretion of several hormones, and in short-term experiments (1week) a reduction in TSH secretion was shown after a daily caffeine intake (Spindel *et al.,* 1983; Spindel and Wurtman, 1984). Bartsch *et al.,* (1996) aimed to elucidate the effect of a sub-chronical consumption of caffeine over thyroid (per 90 days - 104mg/kg/day). This study demonstrated an increase of body weight to the animals that consumed caffeine, however, no alterations occurred in T_3 and T_4 levels, adrenal weight, histopathology of thyroid on the 21st and 90th day. Spindel *et al.,* (1980) showed that caffeine may reduce TSH and GH concentration in a dosage of 50mg/Kg. The reduction of TSH was followed by a T_3 and T_4 reduction after 4h of caffeine administration. In vitro, caffeine did not alter significantly the hormonal secretion of pituitary cells.

The glucose harvesting by β pancreatic cells is performed by an insulin-independent glucose transporter, glucose transporter 2 (GLUT2). GLUT2 transports glucose to cytosol, after the conversion of this molecule and formation of adenosine triphosphate (ATP) occur. The enhancement of ATP block ATP-sensitive potassium channels (KATP channels), increasing intracellular K^+, triggering a depolarization of the membrane and

an input of Ca^{++}, trough voltage-dependent calcium channels (VDCC). The elevation of $[Ca^{++}]_i$ concentration stimulates the secretion of insulin, presumably by the liberation of the molecule storage in the β cells granules (Quesada *et al.*, 2006). It has been reported that caffeine may stimulate insulin secretion trough β pancreatic cells, due to the rise of intracellular Ca^{++} (Park *et al.*, 2009).

In the skeletal muscle, insulin bind to its receptor causing the phosphorylation of the tyrosine of the receptor, resulting in insulin receptor substrates (IRS-1 and 2), IRS1 and 2 mediate the effects of insulin over glucose metabolism, through the activation of phosphatidylinositol (PI)-3 kinase and PKA/AKt and by the increase of GLUT4 and glycogen synthase (GS) (Defronzo, 2010). However, once the insulin receptor is not operating with its hormone, an insulin resistance occurs and the metabolism of glucose does not occur (D'Agostino *et al.*, 2001). Caffeine may increase the expression of GLUT, due to an enhancement of Ca^{++} intracellular and also to the expression of the enzyme activated by AMD (AMPK) (Park *et al.*, 2009; Conde *et al.*, 2012).

Therefore, possibly with the insulinotropic action of caffeine, there is a reduction of TH concentration, triggering a balance in the influx of cellular substrates and perhaps, a greater catalytic action of the energetic substrates, in tissues such as the skeletal muscle and adipose tissue, as well as, a production and liberation of energy by the cell, due to the increased concentration of intracellular Ca^{++} caused by caffeine.

Conclusion and future perspectives

An important progress occurred in the comprehension of TH roles mediating metabolic actions related to DM, acting in several glands and energetic substrates regulator tissues. Some theme, such as the action of TH over the ionic regulation in the cells altering their activity in different paths; as well as, over a negative feedback by downregulation on insulin action, increasing pancreatic β cells, indicate important directions to research. The action mechanisms related to thyroid hormones and insulinotropic action form a counterbalance, in which occurring an imbalance (hyper or hypothyroidism) it may be observed the presence of DM or IR. The interaction between TH, DM and caffeine is still an unknown issue in the literature, that needs better attention and the development of new experimental clinical studies in order to elucidate its mechanisms and clinical application.

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