Thyroid Hormone and Adrenergic Signaling in the Heart

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ABSTRACT

Thyroid hormone action has profound consequences for the heart, ranging from atrial fibrillation to hemodynamic collapse. It has long been known that the cardiovascular signs and symptoms seen in thyrotoxicosis resemble those seen in states of catecholamine excess. However, measured concentrations of serum catecholamines in patients with thyrotoxicosis are typically normal or even low, suggesting an increase in the adrenergic responsiveness of the thyrotoxic heart. In spite of several decades of work, the question of whether thyroid hormone increases cardiac adrenergic responsiveness is still controversial. In this brief review, we consider the reasons underlying this controversy, focusing on the complexity of the adrenergic signaling cascade. **(Arq Bras Endocrinol Metab 2004;48/1:171-175).**

Keywords: Heart; Thyroid; Thyrotoxicosis; Hyperthyroidism; Adrenergic system

RESUMO

O Hormônio Tireoideano e a Sinalização Adrenérgica no Coração.
A ação do hormônio tireoideano tem consequências profundas no sistema cardiovascular, as quais variam desde fibrilação atrial ao colapso hemodinâmico. Há muito sabe-se que os sinais e sintomas cardiovasculares detectados na tireotoxicose assemelham-se aos observados em estados hiper-adrenérgicos. Entretanto, as concentrações séricas de catecolaminas em pacientes com tireotoxicose são tipicamente normais ou mesmo baixas, sugerindo um aumento na responsividade adrenérgica no coração tireotóxico. A despeito de várias décadas de trabalho, a questão sobre se o hormônio tireoideano aumenta a responsividade adrenérgica é ainda controversa. Nesta revisão, nós consideramos os motivos que alimentam esta controvérsia, focalizando na complexidade da cascata de sinalização adrenérgica. **(Arq Bras Endocrinol Metab 2004;48/1:171-175).**

Descritores: Coração; Tireóide; Tireotoxicose; Hipertireoidismo; Sistema adrenérgico

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IT IS WELL KNOWN BY CLINICIANS and researchers that thyroid hormone action has profound consequences for the heart. The pathologic implications of the thyroid-cardiac relationship range from atrial fibrillation in subclinical thyrotoxicosis all the way to hemodynamic collapse and death when severe thyrotoxicosis is superimposed on primary heart disease (1). For practical purposes, the severity of thyroid hormone excess is largely determined at the bedside by the extent of tachycardia, heart rhythm disturbances, and/or systolic hypertension, manifestations that appear early and figure prominently in the course of thyrotoxicosis (2,3).

Several decades ago, it was observed that the cardiovascular signs and symptoms seen in thyrotoxicosis resemble those seen in states of catecholamine excess. However, measured concentrations of serum cate-

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cholamines in patients with thyrotoxicosis are typically normal or even low (4). To explain these observations, it was hypothesized that adrenergic responsiveness is increased in the hearts of patients with thyrotoxicosis (2,5). While studies documenting the effectiveness of β-adrenergic blockade in ameliorating the cardiac symptoms of thyrotoxicosis have lent credence to this hypothesis (6,7), the experimental data accumulated over the past few decades have been mixed. In this review, we briefly discuss the mechanisms by which thyroid hormone action and adrenergic signaling may influence one another, and consider reasons why the data regarding thyroid-adrenergic synergy in the heart has led to controversy rather than consensus.

Thyroid Hormone / β-Adrenergic Synergism

There is no question that increased β-adrenergic tone can cause alterations in the thyroid status of some tissues. For example, in the brown adipose tissue of small mammals, adaptive thermogenesis depends both on cold-induced adrenergic stimulation of uncoupling-protein-1, which promotes heat generation by uncoupling oxidative phosphorylation from ATP synthesis, and on adrenergic stimulation of the type 2 iodothyronine deiodinase (D_2), which promotes tissue-specific thyrotoxicosis via conversion of thyroxine to 3,5,3'-triiodothyronine (8). In this case, the cAMP-responsivesness of D_2 provides a mechansim by which catecholamine excess can directly cause tissue-specific thyroid hormone excess, a pre-requisite for optimal heat generation (9). Because D_2 is also expressed in the human heart (10), β-adrenergic-mediated increases in thyroid status may also occur in this tissue.

How a primary increase in the thyroid status of a tissue such as the heart causes an increase in β-adrenergic responsiveness is less clear. The mechanism of this form of thyroid-adrenergic synergism would presumably involve thyroid hormone-induced inceases in the expression or function of stimulatory elements of the β-adrenergic cascade, and / or decreases in the inhibitory elements. Thus, to evaulate the effects of thyroid hormone on the β-adrenergic cascade, it would be necessary to first understand the biology of the various signaling elements. This understanding has greatly evolved in recent years, but is still far from complete (reviewed in 11-14).

The major β-adrenergic receptors (β-AR) expressed in the heart are β-AR1 and β-AR2 (15), both coupling to G_s, the adenylyl-cyclase-coupled heterotrimeric stimulatory G-protein, which in turn activaties the classical cAMP / protein kinase A (PKA) pathway (12). However, while the β1-AR activates only the stimulatory pathway, the β2-AR also activates the adenylyl cyclase inhibitory G_i-protein (12) with an efficacy similar to that of carbachol, an M2 muscarinic agonist that activates the major adenylyl cyclase inhibitory pathway in the heart (16). The affinity of β2-AR for the stimulatory or inhibitory G proteins was shown to be determined by PKA-mediated phosphorylation. The PKA-phosphorylated form has lower affinity for G_s protein and enhanced affinity for G_i protein (17). The consequences of the crosstalk originated between G_s and G_i proteins activated by this dual coupling of β-AR2 are not fully understood (12). Its physiological role is probably to adjust β-adrenergic responsiveness, a fine-tuning of the regulation of the pawthay that may play an important role in the normal cardiac function. Furthermore, the concurrent activation of these oposite pathways generates some independent signals that enhance receptor specificity. For instance, studies in "pure" β1 or β2-AR background where the "pure" receptor was expressed in cultured cells from β1 and β2-AR double-knockout mice showed that stimulation of the "pure" β1-AR induces apoptosis while stimulation of the "pure" β2-AR activates concurrent proapoptotic and antiapoptotic signals resulting in cell survival rather than cell death, as is the case for "pure" β1-AR stimulation (18).

Additional complexity exists downstream at each level of the cascade, with multiple isoforms for both G_s and for G_i, as well as for adenylate cyclase itself - adenylate cyclase isoforms 5 and 6 predominate in the heart but may not be expressed on the same cell types (19). Furthermore, β-adrenergic signaling is a highly dynamic process, with downstream kinases (GRKs / BARKs) regulating the functional status of β-ARs in a feedback manner (11), and RGS (regulator of g-protein signaling) proteins performing similar modulatory functions at the level of G-protein signaling (11). Finally, crosstalk between β-adrenergic elements and other G-protein-coupled receptor pathways (alpha adrenergic, muscarinic, etc.) can further modify the output of β-AR signaling. This great complexity in the biology of the β-adrenergic signaling cascade must be kept in mind when considering the data regarding thyroid hormone effects on β-adrenergic responsiveness in the heart.

Studies of Thyrotoxicosis and β-Adrenergic Signaling in the Heart

The majority of studies in this area have focused on the effects of thyroid hormone treatment on β-AR number. Most of them have found that the β-AR number is increased in the hearts of rats following treatment with thyroid hormone, and some of these also reported

increased adenylate cyclase activity (5,20). One study of baboons treated with thyroid hormone also found increased β-AR number (21). In another study the authors found a temporary increase in β-AR binding capacty in rat ventricle membranes isolated from thyrotoxic rats. The binding returned to normal levels after one month of T_4 treatment (22). Only a minority of studies have found no change in β-AR in response to thyroid hormone treatment (23). The potential for differential regulation of β-AR1 and β-AR2 by thyrotoxicosis has been studied using cultured ventricular myocytes, with thyroid hormone treatment preferentially increasing the expression of β-AR1 (24). The same group subsequently demonstrated that β-AR1 may be regulated by T_3 at the transcriptional level (25), one of the few instances where formal thyroid-hormone responsiveness of an adrenergic signaling gene has been documented. While these and other classical studies are often cited as support for intrinsic adrenergic hyperresponsiveness of the myocardium in hyperthyroidism, due to increases in β-AR number, more recent results from transgenic mice with overexpression of β-adrenergic receptors showed that despite the 2 to 400-fold overexpression of the receptor, there was no proportional increase in the binding sites or in the receptor-stimulated cAMP production (26,27), suggesting that alterations in other components downstream in the cascade may be necessary for the increased adrenergic responsiveness during thyrotoxicosis.

The ratios of β-AR to G_s protein to adenylyl cyclase in cardiac myocytes are about 1:200:3 (28), suggesting that G proteins are probably not limiting in β-adrenergic signaling in the heart and that the major factors that could influence cAMP generation in the cardiac myocyte would be either changes in the β-AR or in adenylyl cyclase. At least one study found that thyroid hormone treatment increases cardiac G_s and decreases cardiac G_i in immature ventricular myocytes of rats (23). The changes in G proteins induced by thyrotoxicosis in immature rat myocardium, however, were normalized by the time the rats reached adulthood. cAMP production in response to catecholamines was not measured in these studies. A second study of ventricular membranes harvested from rats following thyroid hormone treatment showed no increase in G_s protein or adenylate cyclase activity (29), although Zwaveling and cols (22) found that the density of Gs proteins were increased in hearts from thyrotoxic rats, without significant changes in adenylyl cyclase in response to isoprenaline or forskolin.

At least four isoforms of adenylyl cyclase (IV,V,VI and VII) are expressed in the heart. These are differentially regulated by Gs and Gi proteins, calcium, PKA, PKC and other cellular components, raising the possibility of selective regulation, which in turn could account for changes in signal transduction and the intensity of the physiological effects. Some studies with transgenic mice have shown that overexpression of type V (30) or type VI (28) adenylyl cyclase isoforms were correlated with proportional increase in the β-adrenergic-stimulated accumulation of cAMP in myocytes. A correlation between thyroid status and adenylyl cyclase activity has been shown in the heart (20,23) as well as brown fat (31) and brain (32), supporting the idea that thyroid hormone could regulate β-adrenergic effects, at least in part, through adenylyl cyclase expression and / or activity. However, only one study to date has examined the expression of adenylyl cyclase V and VI in thyrotoxicosis, finding that T_4 injected rats had no increase in myocardial AC-V or AC-VI mRNA when compared to the euthyroid rats (19). Membranes isolated from treated rats were reported to have a 35% decrease in forskolin-stimulated but not isoproteronol stimulated cAMP production, suggesting that β-AR stimulation by isoproterenol was not affected by the treatment. On the other hand, in another study using isolated hearts from thyrotoxic rats, the inotropic response as measured by the rise in venticular pressure was increased in response to isoprenaline (a non selective β-agonist) but unchanged in response to forskolin (22), suggesting an effect linked to receptor activation.

Sources of Dissonance in the Existing Data

One can point to several factors contributing to the controversy as to whether β-adrenergic responsivess is increased in the thyrotoxic heart. One obvious factor is the method of induction of thyrotoxicosis in experimental animal models. There is considerable controversy about the suitability of the acute induction of thyrotoxicosis in animals models used to predict the changes of chronic thyrotoxicosis which occur in human disease. Most such experiments involve the use of pharmacologic doses of thyroid hormone in rats in which the acute negative caloric balance leads to muscle wasting and significant weight loss. For example, injection of 20µg of thyroxine per day into a 175g rat is more than 10 times the normal daily replacement dose (~1µg / 100g / day for rats), a dose large enough to lead to negative caloric balance and catabolism. This contrasts to the situation with typical human thyrotoxicosis, where the T_4 levels are only 3-4 times the daily replacement dose (33). Another factor is the use of secondary endpoints such as contractility as a guage of adrenergic responsivess rather than

measuring stimulated adenylate cyclase activity or cAMP accumulation. It is now clear that thyroid hormone directly regulates contractile elements such as SERCA and phospholamban (34,35), making these inappropriate surrogates for cAMP generation. A third factor is that most of the intact animal studies were not designed to distinguish between the direct effects of thyroid hormone on the heart, which are mediated by binding of thyroid hormone to its nuclear receptors in cardiac myocytes, and the indirect cardiac effects that may occur in respons to changes in hemodynamic loading conditions engendered by the effects of thyroid hormone on the systemic vasculature and other non-cardiac tissues. Both the direct and indirect effects of thyroid hormone treatment in euthyroid animals may trigger compensatory responses, for example an increase in parasympathetic tone to decrease sympathetic stimulation, which could obscure the analysis of β-adrenergic signaling in cardiac tissue. This is one reason why the results of some whole animal studies significantly differ from cell culture studies. To date, only the heterotopically transplanted unloaded rat heart model and the D_2-transgenic heart model have attempted to address this issue (36,37). Most animal models of thyrotoxicosis use rodents which, contrary to the human situation, do not express D_2 in their hearts. The presence of D_2 is probably the reason why the human heart is so sensitive to small, sometimes even undetectable, changes in serum thyroid hormones levels (37). Thus, the response of rodent hearts to thyroid hormones does not mirror the human response.

CONCLUSIONS

The debate over the effect of thyroid hormone on β-adrenergic signaling has been argued for nearly half a century. However, definitive studies on the subject taking into account the proper dose and duration of thyroid hormone treatment, looking at the proper molecular endpoints, and controlling for indirect effects of thyroid hormone on the heart and compensatory systemic effects, have yet to been performed. As our understanding of β-adrenergic signaling and these experimental issues has greatly improved, one can hope that this question can finally be put to rest.

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