

# THYROID TODAY<sup>®</sup>

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## THYROID HORMONES AND THE $\beta$ -ADRENERGIC RECEPTOR-ADENYLATE CYCLASE SYSTEM

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There has long been interest in the interrelationships among thyroid hormones, catecholamines, and the  $\beta$ -adrenergic receptor-adenylate cyclase system, because many of the symptoms of hyperthyroidism, such as tachycardia, increased thermogenesis, sweating, tremor, and increased cardiac output, are all suggestive of excessive catecholamine stimulation.<sup>1</sup> Conversely, the symptoms and signs of hypothyroidism, such as bradycardia, are compatible with reduced catecholamine stimulation. A large body of evidence gathered in the 1970s clearly documents that plasma catecholamine levels are not altered in a direction that would account for the changes seen in hyperthyroidism and hypothyroidism.<sup>2</sup> Thus, plasma norepinephrine levels are either low or normal in patients with hyperthyroidism and are usually elevated in patients with hypothyroidism.<sup>3</sup> In addition, alterations in thyroid hormone levels have little effect on plasma epinephrine concentrations. These data suggest that alterations in the concentrations of circulat-

ing catecholamines are not responsible for the symptoms of either hyperthyroidism or hypothyroidism. There is also currently no evidence that thyroxine ( $T_4$ ) or triiodothyronine ( $T_3$ ) interacts directly with adrenergic receptors to stimulate adenylylase activity and hence produce a physiologic effect.

$\beta$ -Adrenergic antagonists such as propranolol have long been known to ameliorate the symptoms of hyperthyroidism, although  $\beta$ -blockers do not appear to alter the biosynthesis, release, or peripheral metabolism of thyroid hormones. These facts, along with the finding of no appropriate change in catecholamine levels, suggested to many investigators that alterations in sensitivity of various end organs to catecholamines might be responsible for the pathophysiologic changes seen in hyperthyroidism and hypothyroidism. The obvious locus for this alteration in sensitivity is the  $\beta$ -adrenergic receptor-adenylate cyclase system.

In the last ten years, a variety of pharmacological and biochemical techniques have been developed that have permitted the detailed investigation of the  $\beta$ -adrenergic receptor-adenylate cyclase system at the molecular level. In this essay, we delineate how altered thyroid hormone levels produce changes in the various protein components of this system and how these changes may explain the pathophysiology of several disease processes.

### HORMONE - SENSITIVE ADENYLATE CYCLASE

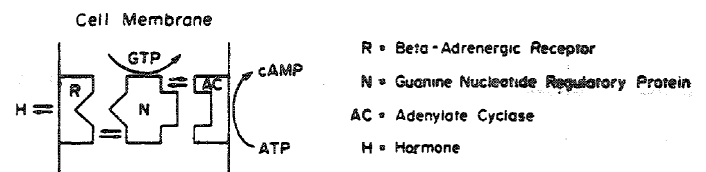


Figure 1. Schematic model of the hormone-sensitive adenylylase system.

## Hyperthyroidism

A general principle that has emerged is that hyperthyroidism is often associated with an increase in the number of  $\beta$ -adrenergic receptors and, possibly, agonist affinity for the receptor. There are exceptions to this generalization, however, which make it necessary to consider tissue-specific effects as well as the experimental animal or human model involved. The exact mechanism responsible for thyroid hormone regulation of receptor number or N protein such as enhanced or decreased protein synthesis or degradation remains unknown.

The most frequently used organ for studies of hyperthyroidism has been the rat heart in animals receiving exogenous  $T_3$  or  $T_4$ . There is almost universal agreement that with this experimental model of hyperthyroidism the number of  $\beta$ -adrenergic receptors in the heart increases. Williams et al<sup>8</sup> were the first to report this and they found a doubling of the number of  $\beta$ -adrenergic receptors without changes in the affinity of the membrane-bound  $\beta$ -adrenergic receptors for [<sup>3</sup>H]dihydroalprenolol. More recent data have suggested that, in addition to the increases in  $\beta$ -adrenergic receptor number, there is an apparent twofold increase in the affinity of  $\beta$ -adrenergic receptors for agonists as manifested by a leftward-shifted agonist competition curve.<sup>9</sup> This shift presumably reflects an improved coupling of the receptor with the enzyme adenylate cyclase that should increase the sensitivity of the heart to catecholamines.

Tse et al<sup>10</sup> have further assessed the  $\beta$ -adrenergic receptor-adenylate cyclase system in the rat heart model. They found that with hyperthyroidism there is an increased number of  $\beta$ -adrenergic receptors, an increased sensitivity and maximal stimulation of adenylate cyclase activity by isoproterenol, a decreased cAMP phosphodiesterase activity, and an increased sensitivity to isoproterenol-induced contraction in ventricular muscle strips. All of these findings are compatible with an increased sensitivity of the heart to catecholamines and help explain the tachycardia and increased force of contraction observed in hyperthyroidism.

An *in vitro* study using rat heart ventricular slices incubated with thyroid hormones has demonstrated that the increase in receptor number results from a two-phase process.<sup>11</sup> The first phase is relatively rapid (one to two hours) and is not dependent on new protein synthesis. A second phase occurs over a longer period of time (~15 hours) and is blocked by protein synthesis inhibitors such as cycloheximide. Thus, we postulate that thyroid hormones can increase  $\beta$ -adrenergic receptors by first permitting already synthesized receptors to be expressed on the cell surface and secondarily by promoting the synthesis of new  $\beta$ -adrenergic receptors by transcription and translation. All of these data suggest that in the heart, hyperthyroidism modulates multiple steps in the transmembrane signaling process, all of which tend to increase the sensitivity of the heart to catecholamines.

The only available tissue model for  $\beta$ -adrenergic receptors in clinical hyperthyroidism has been the circulating mononuclear cell. Conflicting results have been reported.<sup>12-15</sup> Two studies have reported that there are no alterations in  $\beta$ -adrenergic receptor number or in the accumulation of cAMP in response to isoproterenol.<sup>12,13</sup> One possible explanation for the inability of the investigators to find a difference might be that in these studies normal individuals served as controls, rather than the

patients themselves, following appropriate therapy. This is important to recognize because there has been marked variability in the number of  $\beta$ -adrenergic receptors reported on lymphocytes in different individuals. In contrast, two different studies have reported increases in the number of  $\beta$ -adrenergic receptors and an increased sensitivity of adenylate cyclase to isoproterenol stimulation in lymphocytes of patients either given exogenous thyroid hormone or in patients with spontaneous hyperthyroidism. In these studies, the patients served as their own controls, either following therapy for hyperthyroidism or in a double-blind placebo vs  $T_3$  protocol.<sup>14,15</sup> The latter studies suggest that the paradigm observed in the rat heart might well be applicable to the human situation. Further work will be required in the human lymphocyte system to corroborate these findings as well as to assess whether alterations in the coupling mechanism (agonist affinity) or changes in the N protein itself occur in hyperthyroidism.

The liver appears to be an exception in that hyperthyroidism is associated with a decreased number of  $\beta$ -adrenergic receptors in hepatocytes. This decrease is associated with an apparent decrease in the affinity of the receptor for antagonist radioligands.<sup>16,17</sup> In addition, the ability of  $\beta$ -agonists to stimulate adenylate cyclase is decreased and this cannot be corrected with phosphodiesterase inhibitors. These changes in  $\beta$ -adrenergic receptor function appear to be representative of a more generalized hyporesponsiveness in the liver in hyperthyroidism since the abilities of glucagon, guanine nucleotides, and sodium fluoride to activate adenylate cyclase are all reduced.<sup>16,17</sup> Since the quantity of the N protein as assessed by the technique of [<sup>32</sup>P] adenosine diphosphate (ADP) ribosylation is unaltered under these conditions, there may be a decrease in the activity of the catalytic unit of adenylate cyclase itself or in the functionality but not in the quantity of the N protein.<sup>16,17</sup> These findings point out that each individual tissue may respond quite differently to the same alteration in thyroid hormone levels.

A variety of other tissues have been studied in hyperthyroidism and some of these tissue-specific responses are shown in Table 1. These studies all point out that when changes are seen in the  $\beta$ -adrenergic receptor-adenylate cyclase system (with the exception of the liver), the alteration is in a direction that augments the sensitivity of the tissue to catecholamines.

## Hypothyroidism

Hypothyroidism has been induced in animal models by two main approaches: either through thyroidectomy or the administration of propylthiouracil. In general,  $\beta$ -adrenergic receptor number appears to be decreased in many tissues under hypothyroid conditions. The rat heart again has been the most widely studied tissue. There appears to be universal agreement that  $\beta$ -adrenergic receptor number is decreased in rat hearts from hypothyroid animals. Brodde et al<sup>18</sup> found this change to be associated with decreased isoproterenol stimulated contractility and cAMP accumulation with no alteration in calcium-stimulated contractility. This suggested that the alteration induced by lack of thyroid hormone may have exerted a specific effect on the  $\beta$ -adrenergic receptor system. In addition, they found that basal, isoproterenol-stimulated, and sodium fluoride-stimulated adenylate cyclase activity were all significantly lower in membranes derived from hypothyroid ani-

changes seen in the components of the  $\beta$ -adrenergic receptor-adenylate cyclase system in response to the same pathophysiological conditions, ie, increased or decreased thyroid hormone levels. This fact makes it hazardous to propose sweeping generalizations concerning the effect of thyroid hormone levels on the  $\beta$ -adrenergic receptor-adenylate cyclase system, but rather suggests there are complex interrelationships between thyroid hormones and the protein synthesis and degradation pathways and that changes in the  $\beta$ -adrenergic receptor-adenylate cyclase system represent one small aspect of a much larger picture.

The studies presented here do, however, provide a basis for understanding at the molecular level the clinical observation that alterations in circulating thyroid hormone levels do alter

the apparent sensitivity of tissues to circulating and locally released catecholamines. It is clear that alterations in responsiveness to catecholamines may reside at the level of the  $\beta$ -adrenergic receptor itself in some tissues, may reside at postreceptor sites in other tissues, and may reside in multiple loci in still other tissues. Future investigation appears to be needed in two specific areas. First, detailed studies of postreceptor sites such as the N protein (the coupling process) are needed as well as of possible changes in the catalytic unit itself. Second, delineation is required of the underlying processes such as altered protein synthesis, processing, or degradation by which thyroid hormones produce quantitative or qualitative changes in each component of the system. (See H.H. Samuels, THYROID TODAY, Volume II, Number 3, 1979.)

**Table 1**  
Regulation of  $\beta$ -Adrenergic Receptor-Adenylate Cyclase System  
in Hyperthyroidism

Tissue	$\beta$ -Adrenergic Receptor No.	Coupling Process	Adenylate Cyclase Activity
Rat heart	↑	↑	↑
Human mononuclear cell	↑,-	N.D.	↑,-
Rat fat	-	↑	N.D.
Rat lung	-	N.D.	N.D.
Rat brain	-	N.D.	N.D.
Turkey erythrocyte	-	-	↑
Rat liver	↓	N.D.	↓

N.D. = not determined  
- = no change demonstrated

**Table 2**  
Regulation of  $\beta$ -Adrenergic Receptor-Adenylate Cyclase System  
in Hypothyroidism

Tissue	$\beta$ -Adrenergic Receptor No.	Coupling Process	Adenylate Cyclase Activity
Rat heart	↓	-	↓
Rat reticulocyte	↓	↓	↓
Turkey erythrocyte	↓	-	↓
Rat brain	↓	N.D.	N.D.
Rat fat	-	↓	↓
Rat skeletal muscle	↓	N.D.	N.D.
Rat submaxillary gland	↓	N.D.	N.D.
Rat lung	↓	N.D.	N.D.
Rat liver	↑	N.D.	↑

N.D. = not determined  
- = no change demonstrated

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