

REVIEW

The renin–angiotensin system in thyroid disorders and its role in cardiovascular and renal manifestations

Félix Vargas, Isabel Rodríguez-Gómez, Pablo Vargas-Tendero, Eugenio Jimenez¹ and Mercedes Montiel¹

Departamento de Fisiología, Facultad de Medicina, Universidad de Granada, E-18012 Granada, Spain

¹Departamento de Bioquímica y Biología Molecular e Inmunología, Facultad de Medicina, Universidad de Málaga, Boulevard Louis Pasteur 32, 29071 Málaga, Spain

(Correspondence should be addressed to F Vargas; Email: fvargas@ugr.es)

Abstract

Thyroid disorders are among the most common endocrine diseases and affect virtually all physiological systems, with an especially marked impact on cardiovascular and renal systems. This review summarizes the effects of thyroid hormones on the renin–angiotensin system (RAS) and the participation of the RAS in the cardiovascular and renal manifestations of thyroid disorders. Thyroid hormones are important regulators of cardiac and renal mass, vascular function, renal sodium handling, and consequently blood pressure (BP). The RAS acts globally to control cardiovascular and renal functions,

while RAS components act systemically and locally in individual organs. Various authors have implicated the systemic and local RAS in the mediation of functional and structural changes in cardiovascular and renal tissues due to abnormal thyroid hormone levels. This review analyzes the influence of thyroid hormones on RAS components and discusses the role of the RAS in BP, cardiac mass, vascular function, and renal abnormalities in thyroid disorders.

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Thyroid hormones and the renin–angiotensin system

Classically, the renin–angiotensin system (RAS) consists of a cascade of reactions in which angiotensinogen, substrate of the RAS, is cleaved by renin released into the circulation to generate the decapeptide angiotensin I (AI). The peptidyl-dipeptidase angiotensin-converting enzyme (ACE), a membrane-bound metalloprotease primarily present on endothelial cells, converts AI to the octapeptide angiotensin II (AII). AII is the most active known peptide of the RAS and acts on various tissues in the body via selective binding to two major subtypes of G-protein-coupled receptors: AII type 1 (AT₁) and type 2 (AT₂) receptors. The role of the RAS in blood pressure (BP) control is well documented, but it is also involved in the local regulation of numerous functions and can be influenced by different stimuli and hormones, including thyroid hormones.

The RAS is more complex than originally thought, because it operates not only as a circulating endocrine system but also as a local tissue system (Dzau & Herrmann 1982) that has been identified in most organs and tissues studied (e.g. heart, blood vessels, kidney, adrenal gland, pancreas, CNS, reproductive system, and fatty tissues). It plays an

important role in the function of these organs and is involved in cell growth, angiogenesis, proliferation, among others. The local RAS appears to be regulated independently from the circulating system in a specific manner according to the cell type and extracellular stimulus, although it can interact with and complement the circulating system. An intracellular RAS was recently reported, characterized by the presence of a complete functionally active RAS within the cell that can synthesize AII in an independent manner (Kumar *et al.* 2007). Hence, the RAS is a paracrine and intracrine system as well as an endocrine system (Fyhrquist & Saijonmaa 2008). Recognition of the important role of intracellular RAS in the cardiovascular system has grown over the past few decades, with observations that the heart, vascular smooth muscle cells (VSMCs), and fibroblasts can intracellularly generate the vasoactive peptide AII.

Thyroid hormones play an important role in BP control but can exert many other effects on the cardiovascular system, and both hypo- and hyperthyroidism can cause cardiovascular dysfunction (Klein & Ojamaa 1995, 2001, Vargas *et al.* 2006, Ichiki 2010). Thyroid hormones are known to increase the response of tissues to the action of the sympathetic system, and this may be a mechanism by which they regulate BP. However, thyroid hormones can also activate the RAS

without involving the sympathetic nervous system (Kobori *et al.* 2001).

Numerous studies have been performed to characterize the physiological role of thyroid hormones in controlling the synthesis and secretion of RAS components (Jiménez *et al.* 1982, Montiel *et al.* 1987, Carneiro-Ramos *et al.* 2006, Diniz *et al.* 2009). Several *in vivo* and *in vitro* studies have reported that thyroid hormones might modulate the RAS and have evidenced a relationship between the thyroid state and RAS components at both plasma and tissue levels (Kumar *et al.* 2008, Barreto-Chaves *et al.* 2010). Thyroid hormones play a major role in the growth and development of various tissues, including the kidney and lung, which are major sites of renin and ACE synthesis; therefore, thyroid hormone deficiency in early developmental stages can have significant effects on RAS components (Chen *et al.* 2005). In this study, we review the effects of a deficit or excess of thyroid hormones on RAS components (Table 1).

Renin

Since the discovery of renin 100 years ago, various tissues have been found to express the renin gene, although the main source of circulating renin production is located in juxtaglomerular kidney cells (Kurtz 2011). Renin is an aspartyl protease that cleaves AI decapeptide from the angiotensinogen molecule, and numerous *in vivo* studies

have demonstrated the influence of thyroid hormones on circulating renin. Experimental hyperthyroidism produces an increase in plasma renin activity (PRA) and plasma renin concentration (PRC), while the induction of hypothyroidism in adult rats reduces PRA and PRC (Hauger-Klevene & Levin 1976, Jiménez *et al.* 1982). However, different results were obtained when hypothyroidism was induced by surgical thyroidectomy in rats in the first day of life, when an increase in renal renin content (Bouhnik *et al.* 1981) and PRC (Jiménez *et al.* 1984) was observed, suggesting the operation of distinct mechanisms according to the age at which the thyroid hormone deficit is produced.

In vitro studies indicated that thyroid hormones influence the synthesis and secretion of renin by juxtaglomerular cells. Ichihara *et al.* (1998) found that triiodothyronine (T₃) administration increases renin secretion, renin content, and renin mRNA in rat juxtaglomerular cell cultures. Various authors observed this direct action in cardiac tissue from hyperthyroid rats and reported that thyroid hormones directly stimulate renin mRNA and the promoter activity of the human renin gene via thyroid hormone regulating element-dependent mechanisms (Gilbert *et al.* 1994, Kobori *et al.* 1997a,b, 2001). These actions of thyroid hormones on renin secretion and renin mRNA are direct and not mediated by changes in sympathetic nervous system activity (Kobori *et al.* 1997a,b). However, the above studies do not rule out the possibility that RAS activity modifications in thyroid

Table 1 Plasma and local renin–angiotensin compounds in thyroid hormone excess or deficit

Compound	Hyperthyroidism	Hypothyroidism
Plasma		
Angiotensinogen	↑ (Dzau & Herrmann 1982, Marchant <i>et al.</i> 1993); ↓ (Jiménez <i>et al.</i> 1982)	↓ (Bouhnik <i>et al.</i> 1981, Jiménez <i>et al.</i> 1982, Katz 2003)
Renin	↑ (Hauger-Klevene & Levin 1976, Jiménez <i>et al.</i> 1982, Santos & Ferreira 2007)	↑ (Jiménez <i>et al.</i> 1984); ↓ (Hauger-Klevene & Levin 1976, Jiménez <i>et al.</i> 1982)
Angiotensin-converting enzyme	↑ (Phillips <i>et al.</i> 1993)	↓ (Montiel <i>et al.</i> 1987, Jiménez <i>et al.</i> 1990)
Angiotensin II	↑ (Marchant <i>et al.</i> 1993, Garcia del Río <i>et al.</i> 1997, Kobori <i>et al.</i> 1997a,b)	↓ (Marchant <i>et al.</i> 1993, Kobori <i>et al.</i> 1997a,b)
New RAS components	–	–
Heart		
Renin	↑ (Kobori <i>et al.</i> 1997a,b)	–
Angiotensin II	↑ (Kobori <i>et al.</i> 1997a,b, 1999, Diniz <i>et al.</i> 2007)	= (Carneiro-Ramos <i>et al.</i> 2007)
AT ₁ R	→ (Carneiro-Ramos <i>et al.</i> 2010); ↓ (Marchant <i>et al.</i> 1993)	= (Marchant <i>et al.</i> 1993); ↑ (Carneiro-Ramos <i>et al.</i> 2007)
AT ₂ R	↑ (Marchant <i>et al.</i> 1993, Carneiro-Ramos <i>et al.</i> 2010)	↑ (Marchant <i>et al.</i> 1993, Carneiro-Ramos <i>et al.</i> 2007)
Kidney		
Renin	↑ (Bouhnik <i>et al.</i> 1981, Kobori <i>et al.</i> 1997a,b, Klein & Ojamaa 2001)	↓ (Kobori <i>et al.</i> 1997a,b)
Angiotensin II	↑ (Klein & Ojamaa 2001)	–
AT ₁ R	–	↓ (Chen <i>et al.</i> 2005)
AT ₂ R	–	↑ (Chen <i>et al.</i> 2005)
Vessels		
Renin	–	–
Angiotensin II	–	–
AT ₁ R	↓ (Fukuyama <i>et al.</i> 2003)	–
AT ₂ R	↑ (Barreto-Chaves <i>et al.</i> 2010)	–

F, Forward; R, reverse.

disorders *in vivo* may be in part mediated by changes in β -adrenergic activity. In fact, an increased number of β -adrenergic receptors were found in the renal cortex in experimental hyperthyroidism (Haro *et al.* 1992), and PRA is enhanced by β -adrenergic stimulation (Churchill *et al.* 1983) and reduced by β -adrenergic inhibition (Atlas *et al.* 1977).

Angiotensinogen

Thyroid hormones play an important role in angiotensinogen synthesis and consumption. The stage of life at which there is a deficit in thyroid hormone influences the synthesis and release of angiotensinogen in this situation, as is the case for other RAS components.

Plasma angiotensinogen levels in adult rats were not altered by propylthiouracil-induced hypothyroidism (Jiménez *et al.* 1982), but reduced levels were observed in thyroidectomized animals during early stages of development (Bouhnik *et al.* 1981, Jiménez *et al.* 1982, Marchant *et al.* 1993). The decrease in plasma levels in thyroidectomized rats is partially restored by thyroid hormone treatment (Dzau & Herrmann 1982) and may reflect a reduced synthesis in the liver, given that the liver content and release of angiotensinogen are both lower in thyroidectomized animals (Clauser *et al.* 1983, Jiménez *et al.* 1984). However, contradictory results were reported for plasma angiotensinogen concentrations in adult hyperthyroid rats (Dzau & Herrmann 1982, Jiménez *et al.* 1982, Marchant *et al.* 1993), and no significant changes were observed in hyperthyroid dogs (Sernia *et al.* 1993). Discrepancies among studies may be due to the different durations and dosages of the thyroid hormone treatments used to induce hyperthyroidism. Furthermore, changes in plasma angiotensinogen concentrations reflect the balance between its synthesis in the liver and its consumption by PRA. Ruiz *et al.* (1987) found an increase in angiotensinogen synthesis and release in primary cultures of hepatocytes after T_3 and thyroxine (T_4) administration; therefore, the decrease reported by Jiménez *et al.* (1982) in hyperthyroid rat plasma may be attributable to the increased angiotensin consumption by circulating renin in these animals.

Although the angiotensinogen molecule is primarily synthesized and released in the liver, angiotensinogen mRNA has been found in various tissues, including the brain and kidneys, while thyroid hormones have been shown to induce angiotensinogen gene expression at the transcriptional level (Chan *et al.* 1992, Hong-Brown & Deschepper 1992).

Angiotensin-converting enzyme

ACE is a key enzyme of the RAS and is directly involved in forming AII, the bioactive peptide of this system, by removing the C-terminal histidyl-leucine residue from AI. ACE is mainly located in the pulmonary vascular endothelium but has also been found in kidney, liver, brain, and cardiovascular tissues, among others.

ACE activity is influenced by thyroid dysfunction at both circulating and tissue levels. Reduced serum and liver ACE concentrations were reported in neonatal rats with hypothyroidism induced by maternal administration of the anti-thyroid drug methimazole and in adult rats treated with propylthiouracil. Conversely, hyperthyroid rats and patients showed an increase in serum ACE concentrations that was positively correlated with thyroid hormone levels (Montiel *et al.* 1987, Reiners *et al.* 1988, Jiménez *et al.* 1990).

ACE transcription regulation is tissue-dependent. ACE activity and expression were increased in the kidney of T_3 - or T_4 -treated rats (Michel *et al.* 1994, Carneiro-Ramos *et al.* 2006) but reduced in the heart and aorta of T_4 -treated rats (Carneiro-Ramos *et al.* 2006), although some authors reported higher ACE activity in the heart of T_3 -treated rats (Michel *et al.* 1994). In another study, thyroid hormones were found to induce ACE synthesis in endothelial cells (Dasarathy *et al.* 1990).

AII and AII receptors

AII, the main peptide of the RAS, exerts its action by interacting with two types of receptors, AT_1 and AT_2 . The AT_1 receptor is a G-protein-coupled receptor widely expressed in numerous tissues. It mediates most actions of AII (e.g. fluid and electrolyte control and cell growth remodeling and differentiation) and is the main receptor involved in cardiovascular diseases, among many others. The AT_2 receptor subtype appears to have contrary effects to those of the AT_1 receptor, although this depends on the tissue in which they are expressed.

AII levels largely depend on the systemic or tissue levels of renin and angiotensinogen. An increase or deficit in thyroid hormone changes renin and angiotensinogen levels and consequently affects AII levels. The rise in PRA and plasma angiotensinogen observed in hyperthyroidism is associated with increased plasma AII levels, which are reduced in hypothyroidism (Marchant *et al.* 1993, Kobori *et al.* 1997a,b). However, the action of thyroid hormones on angiotensin receptors is tissue-dependent. AII receptors in atrium, thoracic aortic, and liver tissues were increased in experimental hyperthyroidism in dogs (Sernia *et al.* 1993), similar to the findings by Marchant *et al.* (1993) in hyperthyroid rats, in which AII receptors were increased in the heart, liver, and kidneys but reduced in the adrenal gland. However, when the latter study characterized the receptors in the heart by pharmacological inhibitors, they found that AT_2 -subtype density was markedly increased in both hyper- and hypothyroidism, whereas AT_1 -subtype density was decreased in hyperthyroidism and unchanged in hypothyroidism (Marchant *et al.* 1993).

In thyroidectomized fetal sheep, AT_1 RNA expression was decreased in the kidneys and lungs, whereas AT_2 mRNA expression was increased in the kidneys (Chen *et al.* 2005). A decrease in AT_1 receptors was also observed after T_3

administration to cultures of VSMCs and rat aorta and may result from a downregulation of the AT₁ receptor due to the local generation of higher AII values. The mechanism by which thyroid hormones modulate AT₁ receptor operates at transcriptional and post-transcriptional levels (Fukuyama *et al.* 2003).

New RAS components

The past decade has seen the discovery of several new RAS components. The recently described ACE2–Ang-(1–7)–Mas system is mainly expressed in the kidneys, heart, and blood vessels and can counteract the effects of AII by Mas receptor and AT₁ heterodimerization, especially at the cardiovascular level (Santos & Ferreira 2007). The (pro)renin receptor that binds to and activates renin in tissues was also recently discovered (Vargas *et al.* 2009) and, although its functional significance has not been fully elucidated, it can amplify local effects of the RAS. Moreover, activation of the intrarenal RAS by the metabolic receptor GPR91 for succinate, closely associated with oxidative stress, has a hormone-like signaling function in the distal nephron–collecting duct system, which is the major source of (pro)renin in diabetes (Peti-Peterdi 2010) and AII-dependent hypertension (Prieto–Carrasqueo *et al.* 2009). Thyroid hormones can also be expected to have some regulatory effects on these components, although we were unable to trace reports on this specific issue.

The RAS in low-T₃ syndrome and subclinical thyroid disorders

Changes in thyroid function parameters are observed in starvation and fasting, cardiac disease (Kozdag *et al.* 2005, Pingitore *et al.* 2005), renal disease (Lim *et al.* 1980, Zoccali *et al.* 2005), renal transplantation (Hekmat *et al.* 2010), ageing (Tognini *et al.* 2010), and increased saline intake (Cruz *et al.* 2011), leading to low-T₃ syndrome (also known as non-thyroidal illness syndrome or euthyroid sick syndrome). This syndrome is characterized by low circulating T₃ levels and normal or decreased T₄ levels and, usually, by normal thyroid stimulating hormone (TSH) levels. It remains controversial whether a reduction in T₃ during critical illness represents an adaptive change to reduce catabolism. Conversely, the low T₃ levels could contribute to the severity of illness (Warner & Beckett 2010, Economidou *et al.* 2011). Several factors have been implicated in low-T₃ syndrome, including: increased T₃ receptor expression, which may be responsible for maintaining euthyroidism in the face of reduced circulating thyroid hormone levels (Williams *et al.* 1989); reduced enzyme activity of 5′-monodeiodinase, responsible for converting T₄ to T₃ in peripheral tissues (Mebis & Van den Berghe 2011); reduced plasma selenium concentration, a shared cofactor with antioxidant enzymes and deiodinases (Van Lente & Daher 1992); increased cytokine levels

(Hermus *et al.* 1992, Boelen *et al.* 1995); and increased levels of Triac (T₃ analog) and/or Tetrac (T₄ analog), which may feedback to the pituitary/hypothalamus region and cause a secondary hypothyroidism (Carlin & Carlin 1993). Low-T₃ syndrome is also a strong prognostic predictor of death in patients with heart disease, giving additional information to the conventional clinical and functional cardiac parameters (Iervasi *et al.* 2003, Kozdag *et al.* 2005, Pingitore *et al.* 2005).

The few studies to address RAS activity in low-T₃ syndrome were performed under different conditions and yielded contradictory results. Thus, Gottardis *et al.* (1992) performed a prospective study on the effect of decreased serum T₃ levels on atrial natriuretic peptide, aldosterone, AII, renin, and antidiuretic hormone in organ donors before organ harvesting. They observed secondary T₃ hypothyroidism and a marked PRA elevation in these patients but no significant change in ADH or aldosterone, indicating a dissociation of the renin–angiotensin–aldosterone mechanism in brain-dead patients. Emdin *et al.* (2004) also reported that PRA and aldosterone levels were significantly higher in heart failure patients than in healthy subjects and showed a significant linear increase from controls through to patients with severe heart failure, while T₃ and FT₃ levels were significantly decreased in heart failure patients. However, subsequent studies reported normal PRA and aldosterone values in heart failure patients (Pingitore *et al.* 2008, Fontana *et al.* 2012), and Pingitore *et al.* (2008) found a significant decrease in plasma aldosterone but no change in PRA after T₃ infusion.

Subclinical hypo- and hyperthyroidism are defined as normal serum-free T₄ and T₃ levels associated with elevated or subnormal serum TSH levels, respectively, with scant symptoms or signs of thyroid dysfunction. Subclinical hypothyroidism is relatively prevalent in the general population, especially among women and the elderly, and both subclinical thyroid dysfunctions are associated with detrimental effects on the cardiovascular system (Romaldini *et al.* 2004, Duggal *et al.* 2007, Donangelo & Braunstein 2011). Subclinical hypothyroidism is characterized by decreased cardiac contractility; increased peripheral vascular resistance; abnormal lipid metabolism; cardiac dysfunction; diastolic hypertension, which confers an elevated risk of atherosclerosis; and ischemic heart disease (Mikhail *et al.* 2008, Ochs *et al.* 2008, Ashizawa *et al.* 2010, Razvi *et al.* 2010, Cai *et al.* 2011). For its part, subclinical hyperthyroidism is associated with atrial fibrillation, increased cardiac contractility and left ventricular mass, and diastolic and systolic dysfunction, and these patients are almost threefold more likely to suffer atrial fibrillation (Romaldini *et al.* 2004, Duggal *et al.* 2007, Donangelo & Braunstein 2011). Only one study has analyzed RAS activity in these subclinical thyroid disorders, finding no differences in PRA or plasma aldosterone between patients with subclinical hypothyroidism and normal individuals (Sahún *et al.* 2001). Further research is required to develop knowledge on RAS activity in these thyroid conditions.

Role of the RAS in cardiovascular and renal abnormalities

Blood pressure

Abnormalities in BP control are observed in both hypo- and hyperthyroid states in humans and animals (Klein & Ojamaa 1995, 2001, Larsen *et al.* 1998). Pathophysiological changes in hyperthyroidism are usually the opposite of those in hypothyroidism. Thus, hyperthyroidism is characterized by a hyperdynamic circulation and elevated BP, whereas hypothyroidism is associated with a reduced cardiac output and reduced BP (Klein & Ojamaa 1995, 2001, Larsen *et al.* 1998), and some experimental models of hypertension have been accelerated by hyperthyroidism (Vargas *et al.* 1988) and prevented or reversed by hypothyroidism (Vargas *et al.* 1988, Andrade *et al.* 1992).

The RAS plays an important role in regulating cardiovascular and renal functions (Guyton 1980) and consequently in regulating BP. As reported above, hypothyroidism is associated with low PRA (Hauger-Klevane *et al.* 1977, Bouhnik *et al.* 1981), whereas hyperthyroidism is accompanied by RAS hyperactivity (Ganong 1982, Jiménez *et al.* 1982, Marchant *et al.* 1993). Hence, PRA and plasma angiotensinogen, AII, and aldosterone levels are directly related to plasma thyroid hormone concentrations (Ganong 1982, Jiménez *et al.* 1982, Marchant *et al.* 1993). Acute RAS blockade markedly decreases arterial pressure and improves renal hemodynamics in hypertensive hyperthyroid rats (García-Estañ *et al.* 1995), and the long-term administration of captopril prevents T₄-induced hypertension (García del Río *et al.* 1997), indicating an important role for the RAS in the elevated BP of hyperthyroidism.

Increased BP in the hyperthyroid state has been considered a model of cardiogenic hypertension (Klein 1990, Klein & Ojamaa 1995, Larsen *et al.* 1998), in which the elevated BP is largely maintained by increased cardiac output secondary to elevated stroke volume and higher heart rate. However, hyperthyroid rats treated with captopril showed normal BP with elevated heart rate and probably higher cardiac output (García del Río *et al.* 1997), indicating the importance of the RAS and that the increased cardiac output is not the main factor responsible for hypertension in hyperthyroidism.

T₄ accelerates the course of Goldblatt 2K-1C hypertension (typical renin-dependent model), while production of a hypothyroid state simultaneously with its experimental induction prevents this hypertension (Vargas *et al.* 1988). These data suggest that thyroid hormones modulate the pressor effect of the RAS. However, the suppression of thyroid hormone levels does not reverse 2K-1C hypertension in its established phase (Vargas *et al.* 1992). The discrepant effects of hypothyroidism in established hypertension have not been explained, although they may involve irreversible morphological changes in the vascular wall (Folkow 1990).

Cardiac mass

Mechanisms underlying cardiac hypertrophy secondary to elevated thyroid hormone levels include a direct hormonal effect on the heart and indirect effects related to adrenergic nervous system stimulation and left ventricular loading conditions (Klein 1988, 2003, Morgan & Baker 1991). Besides increasing cardiac work by raising the systolic BP and heart rate, thyroid hormones upregulate the gene expression of atrial natriuretic factor (ANF), a major marker of cardiomyocyte hypertrophy, in isolated cardiomyocytes (Eppenberger-Eberhardt *et al.* 1997) and regulate the transcription of various genes related to myocyte contractile machinery after binding to nuclear receptors (Brent *et al.* 1991).

Several authors have described a close relationship between thyroid hormone levels and the RAS in the development of cardiac hypertrophy in hyperthyroidism (Kobori *et al.* 1997*a,b*, 1999, Hu *et al.* 2003, Carneiro-Ramos *et al.* 2006, 2007, Diniz *et al.* 2007, 2009). Kobori *et al.* (1997*a,b*, 1999) demonstrated that cardiac renin, renin mRNA, and AII levels are all increased in thyroxin-treated rats in a manner independent of the sympathetic nervous system and circulating RAS, and that these increases contribute to the development of cardiac hypertrophy (Kobori *et al.* 1997*a,b*). Moreover, thyroxin-induced cardiac hypertrophy is reduced by blockade of the AT₁ receptor with losartan (Kobori *et al.* 1997*a,b*, 1999, Hu *et al.* 2003), independently of sympathetic activation (Kobori *et al.* 1997*a,b*). However, the ACE inhibitor captopril, which is clinically effective at reducing cardiac hypertrophy in essential arterial hypertension (Dunn *et al.* 1984), inhibited circulating RAS and reduced BP but failed to prevent cardiac hypertrophy in T₄-treated hyperthyroid rats (Bedotto *et al.* 1989, García del Río *et al.* 1997). These discrepancies may be explained by differences in pharmacological effects between ACE inhibitors and AII receptor antagonists, given that ACE-independent AII synthesis has been reported in the heart (Urata *et al.* 1990, Phillips *et al.* 1993); therefore, chronic administration of an ACE inhibitor may not completely inhibit cardiac AII synthesis. However, positive effects on thyroid-induced cardiac hypertrophy have also been obtained with ACE inhibitors (Hu *et al.* 2003), while negative effects have been found with losartan (Rodríguez-Gómez *et al.* 2003). Consistent with the negative outcomes reported with losartan, AII exerts a direct growth effect on neonatal cardiac cells but does not promote growth responses in adult cardiomyocytes (Sadoshima & Izumo 1993, Wada *et al.* 1996).

RAS components are known to act locally and under differential regulation (Bader 2002). There is substantial evidence that most of the AII in cardiac tissue derives from the myocardial synthesis of AI rather than from the systemic circulation (Katz 2003). The intracellular synthesis of AII is evidenced by the presence of AII in cardiomyocytes (Dostal *et al.* 1992) and by the release of AII into the medium in cardiomyocyte cultures (Sadoshima & Izumo 1993). Besides

its well-documented hemodynamic impact, circulating and locally generated AII also stimulates cardiomyocyte growth and fibrosis in the adult myocardium and modulates cardiac hypertrophy (Morgan & Baker 1991, Fischer & Hilfiker-Kleiner 2007).

Thyroid hormones activate growth in cardiomyocytes *in vitro* and *in vivo* (Kuzman *et al.* 2005, Kenessey & Ojamaa 2006). The RAS is activated in hyperthyroidism and is probably involved in the development of cardiac hypertrophy, given that AII acts as a myocyte growth factor (Baker & Aceto 1990, Fischer & Hilfiker-Kleiner 2007) and the AT₁ receptor behaves as a mediator of AII-induced cardiac hypertrophy (Sadoshima & Izumo 1993). However, Carneiro-Ramos *et al.* (2010) observed no change in cardiac AT₁ receptor expression in hyperthyroidism-induced cardiac hypertrophy. The same study found that AT₂ receptor expression is increased in thyroid hormone-induced cardiac hypertrophy and that the AT₂ receptor is involved in the development of thyroid hormone-induced cardiac hypertrophy *in vivo* and *in vitro*. Although the effects of the AT₂ receptor are generally opposite to those of the AT₁ receptor, several studies have reported that both receptors are expressed in some tissues (Booz 2004). For instance, AT₁ and AT₂ receptors share, at least in part, a common signaling pathway in cardiac tissue (Mifune *et al.* 2000, Ichihara *et al.* 2001), which may explain the similar effects observed after their stimulation.

Recent studies suggested that thyroid hormone also acts via a non-genomic mechanism by binding to plasma cytoplasmic membrane receptors that are able to activate signaling pathways (Davis *et al.* 2005). In this context, acute experiments showed that local AI and AII levels and AT₁ receptor expression are rapidly increased by T₃ treatment, and that AT₁ receptor silencing and blockade totally prevents T₃-induced cardiomyocyte hypertrophy (Diniz *et al.* 2009).

Other studies focused on the intracellular transduction mechanisms underlying the rapid effects of T₃ on cultured cardiomyocytes. T₃ was found to produce a fast increase in phosphoinositide-3-kinase activity with a consequent activation of its downstream effectors, as one of the mechanisms by which thyroid hormone regulates physiological cardiac growth (Kenessey & Ojamaa 2006). Diniz *et al.* (2009) also found that PI3K mediates the rapid activation by T₃ of the Akt/GSK3- β /mTOR signaling pathway in cardiomyocyte cultures, reporting that PI3K inhibition completely blocks activation of this T₃-promoted signaling pathway.

AII receptors were also shown to participate in the thyroid hormone induction of cardiac TGF- β 1 in cardiac hypertrophy (Diniz *et al.* 2007). Hyperthyroid animals were found to have elevated cardiac AII levels that interact with AT₁ and AT₂ receptors and increase cardiac TGF- β 1 mRNA and protein levels, thereby directly or indirectly promoting thyroid hormone-induced cardiac hypertrophy. These authors also reported that cardiac AII levels are not changed in hypothyroid animals.

Another study found that hypothyroid rats have increased cardiac AT₁ and AT₂ receptors that are not accompanied by

All changes, confirming these results in primary cultures of cardiomyocytes to rule out possible hemodynamic influences (Carneiro-Ramos *et al.* 2007). The authors suggested that thyroid hormone deprivation increases AT₁ and AT₂ receptor expression as a compensatory response. ANF expression, the index of cardiac hypertrophy, was lower in hypothyroid rats than in control animals.

Vascular function

T₃ produces arterial relaxation and reduces systemic vascular resistance, resulting in an increased cardiac output (Vargas *et al.* 2006). Vascular RAS may participate, at least in part, in the vascular effects of thyroid hormones. Fukuyama *et al.* (2003) demonstrated that T₃ downregulates AT₁ receptor mRNA expression at both transcriptional and post-transcriptional levels in cultured VSMCs and rat aorta. The binding assay showed a decrease in AT₁ receptor density with no alteration of the affinity to AII. Downregulation of the AT₁ receptor attenuates the biological function of AII, reducing the AII-induced [Ca²⁺]_i response. The AT₁ receptor is downregulated after several hours of T₃-stimulation, indicating that the suppression is a genomic effect of T₃. Because a 10 min incubation with T₃ does not affect the calcium response, it is unlikely that T₃ directly inhibits calcium response to AII. Therefore, genomic effects of T₃ in downregulating the AT₁ receptor may be involved in reducing vascular resistance in the hyperthyroid state. It is possible that T₃ may indirectly inhibit vascular AT₁ receptor effects via nitric oxide (NO) production (Rodríguez-Gómez *et al.* 2003) in addition to directly downregulating the AT₁ receptor. However, NO would not participate in modulating AT₁ expression after T₃ administration, because L-NAME, an inhibitor of NO synthase, has no effect on T₃-induced AT₁ receptor downregulation in VSMCs (Fukuyama *et al.* 2003). Moreover, Barreto-Chaves *et al.* (2010) showed that T₃ upregulates the AT₂ receptor in the aorta of hyperthyroid rats and in VSMC cultures treated with pharmacological doses, suggesting that enhanced AT₂ receptor expression may also participate in the vasodilation observed in hyperthyroidism.

The systemic response to AII in hyper- and hypothyroid rats was found to be similar to that in controls (Vargas *et al.* 1991). Vascular reactivity to AII in hindquarter preparations from hypothyroid rats is elevated or normal according to the statistical analysis used (Koehn *et al.* 1967). However, the systemic response to AII (and to norepinephrine and vasopressin) is markedly reduced in low-renal mass hypertensive rats treated with methimazole, which prevents and reverses the hypertension (Andrade *et al.* 1992).

The renal vascular response to AII is normal in the isolated perfused kidneys from hypothyroid rats and is not influenced by the blocking of endothelial relaxing factors or by endothelium removal (Moreno *et al.* 2003). AII has been reported to stimulate NO production in numerous preparations (Millat *et al.* 1999). The NO inhibitor L-NAME enhances the dose-response curve to AII in control kidneys,

indicating that NO counteracts the pressor effect of AII in the isolated perfused rat kidney. However, the AII dose–response curve is not modified by L-NAME in hypothyroid preparations, suggesting a reduction of AII-induced NO release in the hypothyroid kidney. This finding is consistent with observations that hypothyroid kidneys are less responsive to acetylcholine (Vargas *et al.* 1995), an endothelium-dependent vasodilator that triggers the release of NO (Furchgott & Vanhoutte 1989). The normal response to AII in hypothyroid kidneys may also be attributable to a decrease in counter-regulation by NO, as indicated by the reduced response to sodium nitroprusside (Ignarro *et al.* 1981). However, additional studies are required to determine the cause of this abnormal AII–NO interaction in the vasculature of the hypothyroid kidney.

Vascular reactivity to vasoconstrictors is modulated by K⁺ channels. Thus, K⁺ channel openers inhibit AII-induced vasoconstriction (McLeod & Piper 1992), while tetraethylammonium (TEA), a K⁺ channel blocker, induces a dose-dependent increase in vascular sensitivity to AII (Sabineau & Marthan 1993). TEA administration does not significantly modify the pressor response to AII in hypothyroid rat kidneys (Moreno *et al.* 2003), possibly because of a lower generation of endothelium-derived hyperpolarization factor in response to vasoconstrictors or, alternatively, a larger number of closed K⁺ channels in compensation for the defective contractile system in the vascular smooth muscle of hypothyroid rats (Sabio *et al.* 1994). To date, only this last study has investigated the action of hypothyroidism on vascular K⁺ channels, and further research is warranted to elucidate the mechanism responsible for these effects.

Various authors have demonstrated that AII plays a critical role in atherosclerotic vascular disease (Strawn *et al.* 2000, Lonn *et al.* 2001), and several reports have examined the relationship between atherosclerosis and thyroid function (Barth *et al.* 1987, Lev-Ran 1994, Ichiki 2010). For example, a study on the relationship between atherosclerosis and thyroid function in patients with stable angina showed an exacerbated progression of coronary atherosclerosis in patients with lower serum T₃ levels (Barth *et al.* 1987). These findings suggest that thyroid hormones may be protective against atherosclerosis and that the T₃-induced downregulation of the AT₁ receptor reported above (Fukuyama *et al.* 2003) may participate in this effect.

Renal hypertrophy

Thyroid disorders produce morphological and functional changes in the mammalian kidney (Bradley *et al.* 1974). The kidney-to-body weight ratio is decreased by hypothyroidism and increased by hyperthyroidism (Stephan *et al.* 1982, García del Río *et al.* 1997, Vargas *et al.* 2006), while hypothyroidism impairs renal compensatory hypertrophy in rats (Stephan *et al.* 1982, Andrade *et al.* 1992). Bradley *et al.* (1974) reported that T₄-induced renal hypertrophy *in vivo* is associated with a rise in the mitotic index, and Stephan *et al.* (1982) found an

increase in DNA content. The mechanism is not fully understood, but participation of the RAS has been proposed, because AII is known to have potent cell proliferation effects in several tissues *in vitro* (Gill *et al.* 1977) and *in vivo* (Casellas *et al.* 1997). Kobori *et al.* (1998) observed that T₄ produces renal hypertrophy in rats, with an increase in renal renin mRNA expression and in renal renin and AII levels. They also reported that thyroid hormone-induced renal hypertrophy is reduced by losartan but not by nicardipine, with a decrease in renal AII levels, suggesting a possible role for intrarenal RAS in the renal hypertrophy of hyperthyroidism. However, renal hypertrophy in hyperthyroid rats is not modified by chronic captopril (García del Río *et al.* 1997) or losartan (Rodríguez-Gómez *et al.* 2003) treatment. The reasons for these discrepancies are not clear.

Renal sodium handling

Thyroid disorders have a major impact on renal function and on salt and water metabolism. Experimental hypothyroidism increases diuresis and natriuresis under normal conditions and after various stresses, whereas there is a tendency to retain sodium in hyperthyroidism (Vargas *et al.* 2006). A shift in the acute pressure diuresis and natriuresis (PDN) response toward higher pressures was observed in hypertensive hyperthyroid rats, attributable to a lower filtered sodium load and higher tubular sodium resorption (Vargas *et al.* 1994). Because of these changes in the PDN relationship, the BP of hyperthyroid rats must rise to achieve the same sodium excretion rate as in a normal animal. The RAS was found to participate in this phenomenon, given that AII inhibition by captopril significantly improves (without normalizing) the PDN response and renal hemodynamics in hyperthyroid rats but not in controls (García-Estañ *et al.* 1995). AII blockade with losartan also significantly improves renal hemodynamics and excretion in hyperthyroid rats (García-Estañ *et al.* 1995). These results indicate that an increased intrarenal activity of the RAS is partly responsible for the blunted renal PDN mechanism of hyperthyroid rats and consequently for their elevated arterial pressure.

Renal injury and proteinuria

Selective thyroidectomy prevents the deterioration of chronic renal failure in remnant rat kidney (Alfrey 1986) by reducing transcapillary hydraulic pressure (Conger *et al.* 1989). It has been proposed that these protective effects are mediated by inhibition of the intrarenal RAS, given that thyroid hormones activate the intrarenal RAS and increase renal AII, which exerts cell proliferation effects in the kidney. Therefore, thyroidectomy probably inhibits this effect, with a consequent reduction in transcapillary hydraulic pressure.

Several studies have reported increased proteinuria in hyperthyroid rats, consistent with the presence of proteinuria in patients with Graves' disease (Weetman *et al.* 1985). This disorder appears to be unrelated to RAS activity

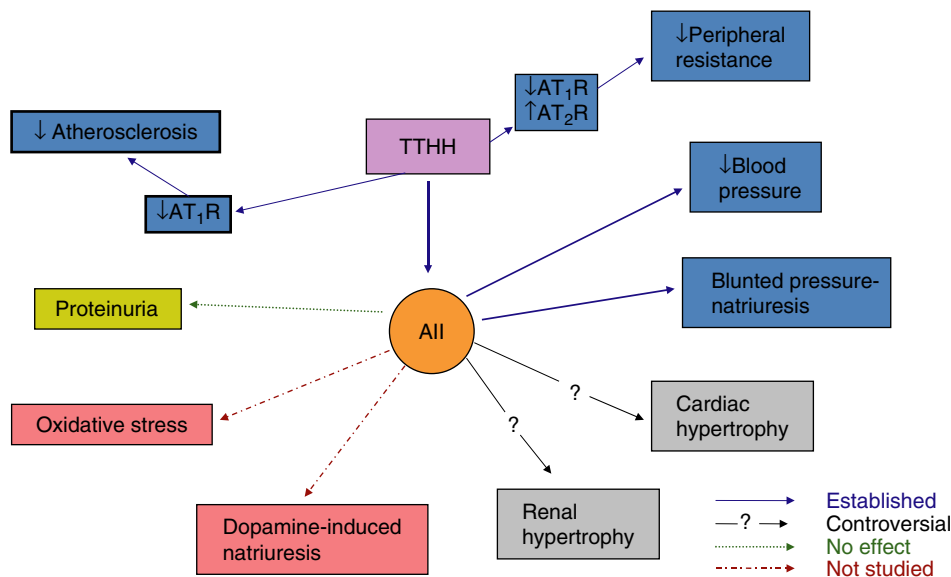


Figure 1 Role of thyroid hormones and the renin–angiotensin system in the cardiovascular and renal manifestations of thyroid hormone excess. The figure summarizes the confirmed and potential participation of All in the effects of thyroid hormones. TTHH, thyroid hormones; All, angiotensin II; AT₁R and AT₂R, angiotensin type 1 and type 2 receptors. A full colour version of this figure is available via <http://dx.doi.org/10.1530/OE-11-0349>.

(Rodríguez-Gómez *et al.* 2003) or BP, given that it is not reduced by antihypertensive therapy (Rodríguez-Gómez *et al.* 2003, Moreno *et al.* 2005). These observations suggest that proteinuria in the hyperthyroid state may be attributable to the direct action of thyroid hormones in increasing the permeability of the glomerular barrier. In this respect, Tanwani *et al.* (2002) also observed proteinuria in patients with Graves' disease.

Renal aminopeptidases regulate intrarenal RAS activity, modulating the degradation of RAS peptides (Segarra *et al.* 2006). Damaged tubular cells release these enzymes into the ultrafiltrate, thereby increasing their activity in urine. Our group recently investigated urinary aminopeptidase activities as early biomarkers of kidney injury, finding that a higher activity of urinary aminopeptidases precedes the increase in proteinuria in hyperthyroid rats (Perez-Abud *et al.* 2011). Moreover, from a diagnostic standpoint, urinary aminopeptidase values may be suitable predictors of renal injury.

Perspectives

This review discusses changes in the RAS induced by thyroid hormones and reports novel insights into the participation of the RAS in the main cardiovascular and renal manifestations of hyper- and hypothyroidism. It is known that the heart and blood vessels can intracellularly generate All, but the effect of thyroid disorders on this process and its significance are poorly understood. Further research is also warranted on the relationship between the RAS and other important factors

related to thyroid disorders (e.g. NO production, oxidative stress, and dopamine-induced natriuresis) and on the role of new RAS activation pathways in the regulation of cardiovascular and renal function and, therefore, in long-term BP control (Fig. 1).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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