INVITED REVIEW

Vascular and renal function in experimental thyroid disorders

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Abstract

This review focuses on the effects of thyroid hormones in vascular and renal systems. Special emphasis is given to the mechanisms by which thyroid hormones affect the regulation of body fluids, vascular resistance and, ultimately, blood pressure. Vascular function is markedly affected by thyroid hormones that produce changes in vascular reactivity and endothelial function in hyper- and hypothyroidism. The hypothyroid state is accompanied by a marked decrease in sensitivity to vasoconstrictors, especially to sympathetic agonists, alteration that may play a role in the reduced blood pressure of hypothyroid rats, as well as in the preventive effects of hypothyroidism on experimental hypertension. Moreover, in hypothyroid rats, the endothelium-dependent and nitric oxide donors vasodilation is reduced. Conversely, the vessels from hyperthyroid rats showed an increased endothelium-dependent responsiveness that may be secondary to the shear-stress induced by the hyperdynamic circulation, and that may contribute to the reduced vascular resistance characteristic of this disease. Thyroid hormones also have important effects in the kidney, affecting renal growth, renal haemodynamics, and salt and water metabolism. In hyperthyroidism, there is a resetting of the pressure-natriuresis relationship related to hyperactivity of the renin-angiotensin system, which contributes to the arterial hypertension associated with this endocrine disease. Moreover, thyroid hormones affect the development and/or maintenance of various forms of arterial hypertension. This review also describes recent advances in our understanding of thyroid hormone action on nitric oxide and oxidative stress in the regulation of cardiovascular and renal function and in the long-term control of blood pressure.

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Haemodynamic changes

Thyroid disease states have been recognised for more than a century (1). Thyroid disorders are common endocrine disorders in humans and animals (2). Variations from the euthyroid status affect virtually all physiological systems but the effects on the cardiovascular system are particularly pronounced. Thyroid disorders are accompanied by important changes in haemodynamics (3–5) (Table 1). Disturbances in the regulation of systemic arterial blood pressure are seen in both hypo- and hyperthyroid states in man and animals (3–5). Usually, the pathophysiological changes of hyperthyroidism will be the opposite to those occurring in hypothyroidism. Thus, hyperthyroidism shows a hyperdynamic circulation with increased cardiac output, heart rate, pulse pressure and blood pressure and decreased vascular peripheral resistance, whereas the hypothyroid state is associated with low cardiac output, heart rate, pulse pressure and blood pressure and elevated vascular peripheral resistance (3–5).

In addition, hyperthyroidism accelerates (6), while hypothyroidism prevents and reverses, some models of experimental hypertension (6, 7). Hyperthyroidism is also associated with an increase in blood volume, and the converse occurs with hypothyroidism (8, 9). Erythropoiesis and serum levels of erythropoietin change directly with changes in serum levels of thyroxine (T₄).

One of the earliest cardiovascular responses to thyroid hormone (TH) administration is a decrease in peripheral vascular resistance (3–5). This has been observed in both hypothyroid patients and in euthyroid animals after acute thyroid hormone administration. Hyperthyroidism may be associated with up to a 50 percent decline in systemic vascular resistance (SVR) (9, 10). Reduced vascular resistance could be secondary to an increased vascularity and/or to alterations in the vascular control mechanisms that favour a greater vasodilation. Hyperthyroidism has been found to be associated with a greater number of capillary vessels in the muscles of humans (11) and rats (12). Increased capillary density may be accompanied by
an increase in the number of resistance arterial vessels, which could reduce vascular resistance. Also, the local release of vasodilators in peripheral tissues as a consequence of the elevated tissue metabolism associated with hyperthyroidism could cause dilatation of the resistance vessels (13, 14). An alternative hypothesis involves the ability of thyroid hormone to directly reduce arteriolar smooth muscle tone in conductance and resistance vessels (15, 16). In animals, beta-adrenergic blockade has been shown to reverse the triiodothyronine (T3)-mediated drop in systemic vascular resistances and to blunt the increase in cardiac output (17). Moreover, since this increase in blood flow could be partially abolished by atropine, it suggests also a cholinergic-mediated vasodilatory response in hyperthyroidism.

**Vascular function**

**Vasoconstrictors**

Alterations in vascular responsiveness to various vasoconstrictors have been found in hyper- and hypothyroid animals. However, no consensus has been reached concerning the vasoconstrictor response in either hyper- or hypothyroidism. Different authors, utilising different vascular smooth muscle preparations, have found that the response to vasoconstrictors can be reduced, unchanged or enhanced in both thyroid disorders.

These discrepancies may be due to the different experimental approaches used, involving the vascular preparation, duration of the disease, the use of anaesthesia, or the statistical analysis used (18). In addition, some of these studies were undertaken before it was known that the endothelium could modify the action of contractile agonists (19), thus the endothelium may have been damaged in earlier studies.

Intact hypothyroid rats showed a decreased response to norepinephrine with normal responsiveness to angiotensin II (AII) (20). In hindquarter preparations, vascular reactivity to AII in hypothyroid rats showed a raised or normal response depending on the statistical analysis used (18). Also, the renal vascular response to AII was normal in isolated rat kidneys from hypothyroid rats (21).

Vascular responsiveness to phenylephrine (PHE) and other α1-adrenoceptor agonists was found to be decreased in several preparations from hypothyroid animals (22–25) (Fig. 1), although, a normal response has also been observed in the mesenteric vasculature (26, 27). The inhibitory effect of hypothyroidism on PHE-induced contraction was restored by thyroxine replacement therapy (25), suggesting that the actions of antithyroid drugs are dependent on the induction of the hypothyroid state and are not due to a direct action of the drug or to other unrelated factors.

The decreased sensitivity to PHE exhibited by isolated organs from hypothyroid animals may be explained by a reduction in the number of α1-adrenoceptors present in the vascular smooth muscle or by a change in their coupling efficiency. However, although it has been established that hypothyroidism may modulate the number of α1-adrenoceptors present in cardiac tissue (28), there is currently no direct evidence to suggest that this condition has a similar effect on vascular α1-adrenoceptor density. Moreover, a defective response of the vascular smooth muscle also occurred as a consequence of chronic thyroid deficiency, as indicated by the reduced capacity of KCl or barium chloride to adequately stimulate aortic strips or isolated kidneys, respectively, obtained from hypothyroid rats (21, 24, 29). Moreover, the vasoconstrictor response to ATP in hypothyroid kidneys was also almost absent (29). In summary, most results demonstrate that hypothyroidism is accompanied by a marked decrease in sensitivity to α-adrenergic, purinergic and nonspecific stimulants of vascular smooth muscle in both large arteries and resistance vessels. This alteration in the responsiveness to vasoconstrictors may play a role in the reduced blood pressure of hypothyroid rats, as well as in the preventive effects of hypothyroidism on experimental hypertension.

In hyperthyroidism, there are also many controversial reports with regard to the nature of changes in vasoconstriction. In fact, aortic strips and the isolated and perfused kidney gave divergent results with respect to vascular reactivity to vasoconstrictors (25). Reactivity to the vasoconstrictors was greater in the renal vasculature from hyperthyroid rats than in controls, whereas the aortic strips of these rats were no more reactive than those of controls (Fig. 1).

The data obtained by other laboratories in conductance vessels (aortic strips or rings) from hyperthyroid rats have shown normal (24), increased (30) and decreased (13, 31–33) reactivity to different vasoconstrictors. Reduced α1-adrenoceptor number (31) and lower α1-adrenoceptor-operated calcium channel

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**Table 1** Morphological and haemodynamic variables in experimental thyroid disorders.

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influx of calcium (34) in aortic tissue from hyperthyroid rats have also been reported.

The increased reactivity to vasoconstrictors in the isolated and perfused kidneys from hyperthyroid rats contrasts with the normal response in dog and rat hindlimb vascular beds (18, 35, 36). In mesenteric arteries from hyperthyroid rats both increased (37) and normal (26, 38) $\alpha_1$-adrenoceptor responses were observed, whereas the contraction induced by 5-hydroxytryptamine (5-HT) was increased (37). The contractile response in coronary arteries has also given contradictory results; thus, both an increased reactivity to 5-HT (39) and a normal response to 5-HT, U46619 and methoxamine (40) have been reported.

The data reported indicate that there is no generalised alteration in the response to vasoconstrictors in hyperthyroid rats and that this response is both tissue- and time-dependent. These discrepancies between preparations may also be attributed to inherent functional or regulatory differences between large conduit arteries and arterioles in the different tissues.

**Vasodilators**

In hypothyroid rats, renal sensitivity to endothelium-dependent and nitric oxide (NO) donors vasodilators is significantly reduced (21, 41) (Fig. 1), a finding that contrasts with a normal response in the aorta (41) and in conscious rats (42). Delp et al. (43) found that hypothyroidism is associated with blunted aortic endothelium-dependent vasorelaxation. Takiguchi et al. (27) reported that endothelium-dependent vasodilation in mesenteric vasculature gave divergent results depending on the agonist used, e.g. decreased response to histamine, normal response to acetylcholine (ACh), but no significant changes in the response to papaverine (endothelium-independent agonist). Differences in the preparation used may be the main cause of discrepancies. In hypothyroid rats, a decreased responsiveness to isoprenaline has also been reported in the aorta (31) and the mesenteric vascular bed (27), together with a reduced $\beta$-adrenergic receptor concentration observed in the vasculature of these rats (31). The reduced responsiveness to vaso dilators in the renal vascular bed suggests that this alteration may play a role in the increased total peripheral vascular resistance previously reported in these animals (4, 44).

Conductance (isolated aorta) and resistance (isolated kidney, Fig. 1) vessels from hypertensive hyperthyroid rats showed increased responsiveness to the endothelium-dependent vasodilator ACh (41). This increased endothelium-dependent responsiveness in the preparations from hyperthyroid rats has been confirmed by other laboratories (14, 32, 45) although Lockette et al. (46) observed that the aortae from hyperthyroid rats relaxed less to ACh and that the responses to the calcium ionophore A23187, sodium nitroprusside (SNP), atrial natriuretic factor and 8-Br cGMP were unaltered. Honda et al. (33) showed that T$_4$ treatment for 3 days significantly enhanced ACh- and SNP-induced relaxation in aortic rings from rats and referred to the fact that T$_4$ treatment for a longer period (1–2 weeks) had no significant influence on ACh- and SNP-induced vasorelaxation. The increased endothelium-dependent

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*Figure 1* Response to phenylephrine and to the endothelium-dependent vasodilator acetylcholine (ACh) in isolated kidneys from hypothyroid (methimazole, 0.03%, via drinking water) and hyperthyroid (T$_4$, 75 $\mu$g rat$^{-1}$ day$^{-1}$, s.c.) rats. Data are means±S.E.M. *P < 0.05 compared with controls. RPP, renal perfusion pressure.*
vasodilation usually observed in resistance vessels from hyperthyroid rats may contribute to the reduced vascular resistance characteristic of this disease.

**Endothelial function**

It is well known that the endothelium can modulate vascular smooth muscle tone via the synthesis and release of several endothelium-derived relaxing factors (47). NO and the endothelium-derived hyperpolarising factor (EDHF) are the main mediators of endothelium-dependent renal vasodilatation (48); the former seems to play a major role in large conducting arteries and EDHF appears to be of primary importance in resistance vessels (49, 50). NO synthesis is inhibited, among others, by the analogue Nω-nitro-L-arginine methyl ester (L-NAME) (51). EDHF is an unidentified diffusible substance that relaxes vascular smooth muscle through hyperpolarisation via opening of potassium channels (52, 53). Tetraethylammonium (TEA) and high potassium concentrations have been used to inhibit EDHF activity (54).

The endothelium has been postulated to serve as a pressure and flow sensor; both pressure and flow trigger the release of endothelium-derived relaxing factors (55). In this respect, endothelial denudation augmented the responsiveness to vasoconstrictors in the isolated kidney (56, 57) and increased responsiveness was also produced by the administration of L-NAME or TEA (57), indicating that NO and EDHF modulate the response to vasoconstrictors in the isolated perfused kidney. An impaired release of endothelial mediators of vasodilation plays an important role in the genesis of the functional vascular abnormalities that appear in hypertension, atherosclerosis or diabetes.

Studies using cultured endothelial cells exposed to increased shear stress (58–60) and blood vessels after a period of chronically increased blood flow (61), have shown increased endothelium-dependent vasodilatation, increased nitric oxide synthase (NOS) activity, and/or increased NOS expression. In fact, shear stress regulates the expression of NOS (62) and a shear stress response element has been described in the promoter sequence of the NOS gene (63). It is therefore possible that the increased cardiac output of hyperthyroidism (44) leads to increased NOS activity via a chronic increase in shear stress on the endothelium. In agreement with this notion, an upregulation of constitutive NOS has been reported in the aorta of other diseases that course with hyperdynamic circulation, such as liver cirrhosis (64) and iron-deficiency anaemia (65). Conversely, hypothyroidism, with reduced cardiac output, is associated with blunted endothelium-dependent vaso-relaxation (21, 41, 43) and reduced aortic NOS activity (66).

Preparations from hypothyroid rats show an attenuated responsiveness to vasoconstrictors and especially to the α1-adrenergic agonist, PHE (21, 24, 25). It was suggested that an enhanced NO production by the endothelium plays a role in the hyporesponsiveness to PHE in hypothyroid rats (25). In contrast, our group found that the attenuated renal pressor responsiveness to PHE in the hypothyroid state is not related to an increased activity of endothelium-derived relaxing factors, NO or EDHF (21). Moreover, we found no biochemical (66) or functional (41) evidence of such increased NO activity in hypothyroidism. Propylthiouracil (PTU)-induced hypothyroidism has been shown to cause marked downregulation of NOS gene expression in the rat hypothalamus, an effect which was reversed by dietary supplementation with thyroxine. In addition, hypothyroidism is able to prevent the hypertension induced by a high dose of an NO inhibitor (67), in which an increased pressor responsiveness to vasoconstrictors plays an essential role (68), suggesting that hypothyroidism may reduce the responsiveness to vasoconstrictors even in the absence of NO. Evidence was also provided of abnormalities in EDHF release or K⁺ channels in hypothyroid preparations, given that the dose–response curve to vasoconstrictors was not increased by TEA administration (21). This abnormality in K⁺ channels together with the reduced reactivity to NO may be compensatory responses to the defective contractile system in the vascular smooth muscle of hypothyroid rats.

Hyperthyroidism in rats increases the responsiveness of resistance vessels to the endothelium-dependent vasodilator, acetylcholine (32, 41). McAllister et al. (32) observed that contractile responses to norepinephrine (NE) are reduced in the hyperthyroid state in the presence of functional endothelium, whereas vascular rings denuded of endothelium from euthyroid and hyperthyroid rats did not exhibit significantly different contractile responses to NE. These findings suggest that reduced contractile responses to NE in endothelium-intact vessels are primarily due to endothelial adaptations induced by hyperthyroidism. Similar findings were obtained by Scivoletto and colleagues (13) in rat aortic rings. More recently, Büssemaker et al. (14) determined the effects of acute and chronic hyperthyroidism in vivo on the differential contribution of NO and EDHF to endothelium-dependent relaxation in renal artery rings and observed that endothelium-dependent relaxation was enhanced 36 h and 8 weeks after T₃ treatment. Thirty-six hours after T₃ application, relaxation mediated by EDHF and by NO was significantly enhanced. After 8 weeks of T₃ administration, EDHF-mediated relaxation was impaired, whereas NO-mediated relaxation remained enhanced and the expression of the endothelial NOS was markedly up-regulated in the aorta. Moreover, these authors also reported that the smooth muscle cells of renal arteries from rats treated with T₃ for 8 weeks were significantly hyperpolarised with respect to controls, a phenomenon that may also be secondary to a chronic elevation in shear stress, as this factor is known to stimulate the expression of potassium channels in endothelial cells (69). In this sense, thyroid hormones
NOS activity is upregulated in tissues primarily related to blood pressure control in hyperthyroid rats (66). The mechanism responsible for the enhancement of NOS activity in hyperthyroid rats is not known and various factors may participate alone or in combination. This could be due to a direct effect of thyroid hormones: thus, stimulation of NOS activity via a nongenomic signal generation (10 to 30 s) has been observed in synaptosomes prepared from adult cerebral cortex after addition of T3 (72); NOS activity can also be elevated in response to the high arterial pressure of these animals (73), or to the increased release of vasoactive substances such as All (74) or endothelin (75), which increase NO production and are increased in hyperthyroid rats (76, 77). Finally, the shear stress mechanism induced by the hyperdynamic circulation of these animals can also be involved, as reported above.

NOS activity in the tissues from the hypothyroid rats shows a heterogeneous pattern, which is difficult to reconcile with a common explanation or hypothesis, but it may be the result of changes in the expression of the different isoforms of NOS or even related to changes in NOS activity of subcellular fractions. In fact, it has recently been reported (78) that liver and skeletal muscle mitochondrial NOS is increased in hyperthyroid animals (Fig. 2). Cirrhosis of the liver would indicate that the inducible isoform is activated to the inhibition of NO production (94). These results indicate that this important pressor effect is related to the inhibition of NO production (94). These results would indicate that the inducible isoform is activated in hyperthyroid animals (Fig. 2). Cirrhosis of the liver is also associated with hyperdynamic circulation and these rats also show an increased pressor responsiveness to L-NAME, a non-specific NOS inhibitor that did not modify BP in control rats. These observations indicate that the increased pressor responsiveness to L-NAME in hyperthyroid rats may be secondary to an augmented production of NO, which may have an important homeostatic role in these animals. The hypertension that results from the chronic administration of T4 plus the subpressor dose of L-NAME is severely attenuated by losartan administration, indicating that the renin-angiotensin system (RAS) plays an important role in this type of hypertension (93).

AG increased blood pressure in the hyperthyroid rats at doses that had no pressor effect in the control animals. The elevated plasma levels of nitrates + nitrites (an index of NO production) in the hyperthyroid animals decreased with the administration of the drug, indicating that this important pressor effect is related to the inhibition of NO production (94). These results would indicate that the inducible isoform is activated in hyperthyroid animals (Fig. 2). Cirrhosis of the liver is also associated with hyperdynamic circulation and these rats also show an increased pressor responsiveness to iNOS blockade (89). Hence, these observations indicate that iNOS is activated in rats with hyperdynamic circulation. However: it has been shown that T3 does not regulate iNOS activity in mesangial cells, renal tubular epithelial cells, or macrophages, and that the effects of T3 on renal cell growth are not mediated by inducible increases in NO synthesis (95).

Interestingly, it was observed that the administration of the nNOS inhibitor, 7-NI, suppressed or attenuated the increases in blood pressure, heart rate and pulse pressure produced by increasing doses of thyroxine in rats (Fig. 2), having no effects in control rats (authors’ unpublished observations). Therefore, these results suggest that nNOS may participate in developing the characteristic manifestations of hyperdynamic circulation in hyperthyroid rats, probably due to a central mechanism. However, the specific mechanisms by which 7-NI administration suppresses the manifestations of the hyperdynamic circulation of hyperthyroid rats warrant further investigation.

Nitric oxide syntheses and hyperthyroidism

Nitric oxide is known to play a major role in the regulation of vascular tone (81) and renal sodium excretion (82, 83) and, consequently, of arterial blood pressure (BP) (84). Thus, both the acute and the chronic administration of NOS inhibitors increases systemic arterial BP (85, 86). Nitric oxide can be generated by the activity of neuronal (nNOS), inducible (iNOS), and endothelial (eNOS) nitric oxide synthase. These NOS isoforms are all widely distributed in organs related to blood pressure control and are present in the normal rat kidney (87), thus they have been implicated in the regulation of sodium excretion and blood pressure. Aminoguanidine (AG) is a selective iNOS inhibitor in vitro (88) and in vivo (89, 90) and 7-nitroindazole (7NI) produced relatively selective inhibition of nNOS over eNOS (91) and decreased the protein expression of nNOS in the aorta (92).
Renal function

Renal growth and renal sodium handling

It is well known that hypothyroidism decreases and hyperthyroidism increases the kidney-to-body weight ratio. The mechanism is not fully understood but the participation of the renin-angiotensin system has been proposed. Thus, Kobori et al. (96) observed that losartan caused regression of thyroxine-induced renal hypertrophy. However, it has also been reported that the chronic administration of captopril (97) or losartan (93) did not modify renal hypertrophy in hyperthyroid rats.

Thyroid disorders have important effects on renal function and salt and water metabolism (98–100). Hypothyroidism induced by thyroidectomy or chemical means results in an increased diuresis and natriuresis under basal conditions (98–100), after saline expansion (101, 102) or sodium restriction (101). This tendency to lose sodium has been suggested to represent a mechanism by which hypothyroidism prevents experimental arterial hypertension and it has even been suggested that it could predispose to shock (99). However, it was not confirmed later in hypothyroid methimazole-treated rats under the conditions described above (99, 103, 104). Moreover, absolute and fractional excretion of water and sodium of hypothyroid rats was found to be normal in a study of pressure-diuresis-natriuresis (105), which demonstrates that the hypothyroidism induced by methimazole cannot be considered a sodium-losing syndrome. The discrepancy in the results may be due to the different protocols used, with changes in such fundamental factors as duration of hypothyroidism, the use of anaesthetic (98) and the use of loads of the same volume as in control rats (106) without taking into account the reduced body weight of hypothyroid rats.

A reduction in the ability to concentrate urine has also been reported in hypothyroid rats (98, 102). However, other studies showed that the concentrating ability was not impaired in methimazole-treated rats (103) whereas hyperthyroid rats showed an increased concentrating capacity after water deprivation (103).

While the effects of hypothyroidism on renal function have been studied extensively, there is less information concerning the effect of hyperthyroidism, in which a tendency towards sodium retention is seen. Thus, absolute and fractional sodium excretion was decreased in hyperthyroid rats under normal conditions (104), and a reduced natriuresis after isotonic and hypertonic saline loads has also been observed in hyperthyroid rats (103). Moreover, hyperthyroid rats, with clear arterial hypertension, show a shift in the acute pressure-diuretic-natriuretic response towards higher pressures (Fig. 3). This shift was due to both a decrease in the filtered load of sodium and an increase in tubular sodium reabsorption (105). The consequence of these changes in the pressure-natriuresis relationship is that blood pressure would have to be elevated in

Figure 2 Time course of systolic blood pressure measured by the tail-cuff method by direct recording (femoral artery) in conscious rats. Thyroxine (T4, 50 μg.rat−1.day−1, s.c.), AG (aminoguanidine, 50 mg.kg−1.day−1, via drinking water), 7NI (7-nitroindazole; 30 mg.kg−1.day−1, via drinking water). Data are means ± S.E.M. *P < 0.05 compared with controls.

Figure 3 Pressure-natriuresis relationship in control, hypothyroid (methimazole, 0.03%, via drinking water) and hyperthyroid (T4, 75 μg.rat−1.day−1, s.c.) rats. Data are means ± S.E.M. Horizontal bars represent the S.E.M. of renal perfusion pressure values. *P < 0.05 compared with value at lowest pressure.
Renal blood flow (RBF) and glomerular filtration rate (GFR)

Contradictory findings for RBF and GFR have been reported in hyperthyroid patients (108, 109) and in hypothyroid humans and rats (98, 100, 101). These differences may be due to the fact that RBF and GFR, in some studies, were not normalised by kidney weight, especially as hyper- and hypothyroid rats have larger and smaller kidneys respectively than controls. In this regard, Fregly et al. (110) noted that when RBF and GFR are related to kidney size, the ratios are the same as those for intact controls. However, several reports indicate that creatinine clearance in conscious rats, normalised per kidney weight, is decreased by thyroxine administration (93, 94, 105, 111, 112), in a dose- and time-related manner.

Proteinuria

Several studies have shown that hyperthyroid rats have increased proteinuria, which is consistent with the presence of proteinuria in patients with Graves’ disease (113). This alteration is unrelated to blood pressure, since antihypertensive therapy was ineffective in reducing proteinuria (93, 112). Proteinuria seems also to be unrelated to the activity of the renin-angiotensin system (93) or oxidative stress (112). These observations suggest that proteinuria in the hyperthyroid state may be produced by a direct action of thyroid hormones, increasing the permeability of the glomerular barrier. In this context, Tanwani et al. (114) reported a possible association between thyrotoxic patients and a nephrotic syndrome attributable to a minimal changes nephropathy, a clinical entity defined by selective proteinuria that occurs in the absence of lesions in the glomerular capillary wall. The only detectable abnormalities involve the epithelial visceral cells with effacement of foot processes.

The sympathetic function in thyroid disorders

The cardiovascular manifestations of hyperthyroidism are suggestive of an increased sympathetic activity (115). These include tachycardia, widened pulse pressure, hyperdynamic circulation, and an increased cardiac output (4, 44). It has been suggested that adrenal or free nerve ending catecholamine production and release is increased in hyperthyroidism and decreased in hypothyroidism (115–117). But assessments of sympathetic activity suggest that sympathetic outflow is either unchanged or reduced (118, 119) in hypothyroidism. In contrast, whereas clinical features of hypothyroidism are consistent with reduced sympathetic function, the measurement of several variables indicate that sympathetic activity is elevated in hypothyroidism (120, 121).

In an attempt to solve this apparent discrepancy, direct measurements of myocardial (122, 123) and renal (123) content of beta-adrenergic receptors in hyperthyroid rats were performed. The membranes from hyperthyroid hearts and kidneys contain a significantly greater number of beta-adrenergic binding sites when compared with euthyroid animals (122, 123). These data suggest that the increase in beta-adrenergic activity might arise from a direct thyroid hormone-mediated increase in adrenergic receptor number via the process of ‘upregulation’. Other reports found no change in the beta-adrenergic receptor number in experimental hyperthyroidism (117, 124). In animals, beta-adrenergic blockade with propranolol has been shown to reverse the T3-mediated drop in SVR (17) and to blunt the increase in cardiac output. Klein et al. (125) have reported that chronic propranolol treatment blocks the T4-induced increase in heart rate, heart work, and cardiac hypertrophy associated with experimental hyperthyroidism.

At present, the apparent hyperadrenergic cardiovascular system of hyperthyroidism does not appear to result solely from the effects of adrenergic stimulation. It has been suggested that these changes are the result of a combination of the effects of both thyroid hormone and catecholamines upon the heart and the peripheral circulation (126). Since there exists chemical structure similarities between thyroid hormone and catecholamines, Dratman et al. (127) have postulated a central nervous system role for iodocompounds as neurotransmitters stemming from their ability to enhance heart rate when administered intrathecally.

Thyroid status also influences baroreflex function and autonomic contributions to arterial pressure and heart rate (128). Hypothyroid rats exhibited blunted sympathoexcitatory and tachycardic responses to decreases in blood pressure. In hyperthyroid rats, arterial baroreflex function generally was similar to that in euthyroid rats. Hypothyroid rats exhibited a greater fall in both mean arterial pressure and in heart rate than euthyroid rats after autonomic blockade. The hyperthyroid rats had similar autonomic contributions to resting mean arterial pressure as the euthyroid rats (128).

The renin-angiotensin system

The endocrine system plays an important role in the regulation of the cardiovascular and renal function, and therefore in blood pressure control under normal conditions as well as in thyroid disorders.
The importance of the renin-angiotensin-aldosterone system (RAAS) in the long-term control of arterial pressure and renal function is well established (107). Hypothyroidism is associated with low plasma renin (129, 130). In contrast, hyperthyroidism is accompanied by hyperactivity of the RAAS (76, 131, 132). Thus, plasma renin activity and plasma levels of angiotensinogen, angiotensin II and aldosterone are directly related to plasma levels of thyroid hormones (76, 131, 132). Moreover, it has been shown that T₃ treatment increases angiotensin receptor density in the kidney, liver and both cardiac ventricles (76).

The changes in the activity of the renin-angiotensin system in thyroid disorders may be mediated, in part, by changes in β-adrenergic activity. Thus, it has been reported that in experimental hyperthyroidism the renal cortex has an increased number of β-adrenergic receptors (123) and it is well known that β-adrenergic stimulation enhances (133) and β-adrenergic inhibition reduces (134) plasma renin activity (PRA).

Acute RAS blockade markedly decreases arterial pressure and improves renal haemodynamics and excretion in hypertensive hyperthyroid rats (111), and long-term administration of captopril prevents T₄-induced hypertension (97). These results indicate that the RAS plays an important role in the increased blood pressure and renal alterations of hyperthyroidism (Fig. 4).

Increased blood pressure in the hyperthyroid state has been considered a model of cardiogenic hypertension (3, 4, 44), in which the increased blood pressure is mainly maintained by increased cardiac output secondary to elevated stroke volume and increased heart rate. However, the fact that hyperthyroid rats treated with captopril showed normal blood pressure with increased heart rate (97), and probably increased cardiac output, indicates that the increased cardiac output is not the main factor responsible of hypertension in hyperthyroidism.

Other vasoactive hormones

Arnaout et al. (135) have reported that plasma vasopressin (AVP) levels, which are increased in hyperthyroid and reduced in hypothyroid patients, were normalised after returning to the euthyroid state. In rats, contradictory results have also been observed with respect to plasma AVP levels in hypothyroid rats (136, 137), and no significant differences in total urinary excretion of immunoreactive AVP in control hyper- or hypothyroid rats under normal conditions have been found (103). However, a hyper-responsiveness in hyperthyroid and a hyporesponsiveness in hypothyroid rats to AVP was observed after stimuli such as 24 h water deprivation or a hypertonic saline load (103).

Plasma endothelin (ET) concentration is not changed in the hypothyroid state in human (138) and rats (139, 140), whereas plasma ET levels were found to be elevated in hyperthyroid patients (138) and rats (139, 140), although normal levels of ET have also been reported in plasma from hyper- and hypothyroid patients (141). Moreover, altered ET concentrations in brain and peripheral regions have been found during thyroid dysfunction. Thus, the pituitary showed an increase in ET concentration in hyperthyroid rats when compared with euthyroid ones, while hyperthyroid rats did not show any significant change in ET concentration in the pituitary (77). In peripheral tissues, ET was not altered in the heart and adrenals of hyper- and hypothyroid rats when compared with euthyroid rats (77). Vascular reactivity to ET has been shown to be similar to controls in hyper- and hypothyroid rats (142).

Hyperthyroidism causes an increase in atrial natriuretic peptide (ANP) secretion and a decreased release occurs in hypothyroid humans (143) and rats (144, 145). Moreover, it has been reported that, in cultured rat atrial myocytes, T₃ stimulates both synthesis and release of ANP (146, 147).

**Figure 4** Mean arterial pressure (MAP) and heart rate (HR) measured by direct recording (femoral artery) in conscious control and hyperthyroid (T₄, 75 μg rat⁻¹ day⁻¹, s.c.) rats treated with captopril (CAPT, 30 mg kg⁻¹ day⁻¹, via drinking water). Values are means ± s.e.m. *P < 0.05 compared with controls, +P < 0.01 compared with T₄-treated rats.

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Oxidative stress in hyperthyroidism

There is considerable evidence that oxidative stress from superoxide and other reactive oxygen species (ROS) contributes to the development of cardiovascular diseases, diabetes and renal insufficiency (148, 149). Several studies have implicated oxidative stress in the pathogenesis of arterial hypertension in genetic animal models (150, 151) and in secondary forms of this disease (152–154) in rats. Moreover, tempol (4-hydroxy-2,2,6, 6-tetramethyl piperidinoxyl), a stable metal-independent and cell membrane-permeable low-molecular weight superoxide dismutase (SOD) mimetic (155), and other antioxidants have been shown to decrease BP in spontaneously hypertensive (SH) rats (150, 151), DOCA-salt (152) and nitric oxide inhibition-induced hypertension (154). ROS also play an important role in the pathogenesis of renal diseases, producing vascular, glomerular, tubular and interstitial injury (149). Moreover, it was recently demonstrated that ROS also participates in renal haemodynamics and sodium excretion (156), and that T₃ administration increases intracellular superoxide concentration in isolated medullary thick ascending limbs of Sprague-Dawley rats (157). Thyroxine-treated rats show a significantly decreased SOD activity in renal cortex and left and right ventricles (112). These findings indicate a quantitative deficiency of intracellular SOD in hyperthyroid rats that may produce an increased renal and cardiovascular oxidative stress. In this context, Gredilla et al. (158) reported that chronic administration of T₄ for 5 weeks induced oxidative damage in lipids, glutathione, and DNA in the mouse heart.

A reduced catalase (CAT) activity has been reported in the liver (159), heart muscle (160), and whole kidney (161) of hyperthyroid rats. A reduced CAT activity in the left ventricle of hyperthyroid rats has also been shown, whereas it was elevated in the renal cortex and medulla (112). Glutation peroxidase (GPX) and glutation reductase (GR) activities were reduced by T₄ administration except in the renal medulla. A reduction in GPX activity has also been reported in the liver (162), heart (160), and skeletal muscle (163) of T₄-treated rats. On the other hand, Sawant et al. (161) reported increased GPX activity in the kidney of hyperthyroid rats. In general, these findings suggest that oxidative stress in hyperthyroidism may be due to a primary downregulation of antioxidant enzymes. These decreases may determine a reduced O₂⁻ inactivation, as indicated by the increase in 24-h urinary isoprostane F₂α excretion and plasma malonyldialdehyde (MDA) levels in patients and T₄-treated rats (112, 164–166). Moreover, it has been shown that chronic tempol administration attenuates the development of hypertension in hyperthyroid rats (112), in agreement with similar reports in genetic and secondary forms of hypertension (150–154), and reduces plasma MDA and total urinary excretion of F₂ isoprostanes in hypertensive hyperthyroid rats, but not in controls. In summary, the results reported indicate that hyperthyroidism is associated with reduced enzymatic antioxidant activities in renal and cardiac tissues and suggest that oxidative stress participates in T₄-induced hypertension.

The thyroid gland and blood pressure

The thyroid depressing factor

Alterations in thyroid function accompany the development of experimentally induced hypertension. In spontaneously hypertensive rats (167), mineralocorticoid (168) and renal encapsulated hypertensive rats (169), an increase in thyroid gland weight has been reported. A sigmoid relationship was observed between the ratio of thyroid weight to body weight and systolic blood pressure. The thyroid weight ratio increased significantly when systolic blood pressure rose to levels of 160-169 mmHg. Fregly et al. (168) suggest that an unidentified primary factor increases blood pressure to the threshold range without thyroid mediation, but when exceeding the threshold range, thyroid weight increases and may mediate further elevation of blood pressure. Several variables were studied to determine if thyroid weight increases were secondary to hyper- or hypofunction of the gland, with T₃ and T₄ serum levels being the most frequently measured. In spontaneously hypertensive rats, age-dependent variations (170) have been seen and contradictory results in adult rats have been reported (167, 170, 171). A decrease in T₃ and T₄ serum levels in Dahl rats (172) and a reduction in T₃ serum concentrations in encapsulated hypertensive rats (169) were observed. DOCA-salt hypertensive rats had a marked reduction in comparison with their suitable controls, uninephrectomised-salt normotensive rats (6). However, no significant differences were observed in vasculorenal Goldblatt two kidney-one clip (2K-1C) hypertensive rats with respect to sham-operated rats (6). The data obtained in DOCA-salt hypertension indicated that the increase in thyroid weight, previously reported in mineralocorticoid hypertension, could be the result of a hypoactive goitre. Hence, the data do not support the fact that an increase in thyroid function plays a role in the elevated blood pressure of mineralocorticoid hypertension.

Reduced thyroid activity reported in hypertension is believed to be mediated by the action of an unidentified substance referred to as the ‘thyroid-depressing factor’ (TDF) (Fig. 5) by Threutte et al. (169). This substance was found in the liver (173), spleen (174), kidney(175) and plasma (169). TDF is produced and released into the blood at a greater rate in hypertensive rats than in normotensive rats (174). This factor reduces the uptake and binding of ¹³¹I by the thyroid gland and blocks the ¹³¹I uptake stimulated
by thyrotrophin (174). The normal T₃ and T₄ serum levels observed in Goldblatt 2K-1C hypertensive rats suggest that TDF could not be activated in renin-dependent hypertension.

**Thyroid hormones and experimental hypertension**

Thyroglucine accelerates the course of DOCA-salt and Goldblatt 2K-1C hypertension (6), whereas surgical or radiochemical thyroidectomy and antithyroid drugs reduce the high blood pressure in experimental hypertension produced in several different ways, despite differences in the underlying pathophysiological mechanisms. This reduction is observed especially in the early phase of hypertension. Thus, when a hypothyroid state is produced in young SH rats, or simultaneously with the induction of hypertension by experimental means, it is able to prevent genetic- (176, 177), DOCA-salt- (6, 178) (Fig. 6), low renal mass- (7), renal- (179), 2K-1C- (6) and nitric oxide inhibition (L-NAME)-induced (67) hypertension. However, in the established phase, discrepancies have been observed depending on the duration (177) and the aetiology of the model (7, 67, 180) of hypertension. Thus, methimazole markedly reduced blood pressure levels in the low renal mass model (7), whereas it did not reverse 2K-1C (180) or L-NAME (67) hypertension despite a suppression of thyroid hormone levels. Moreover, the reasons for the discrepant effects of hypothyroidism in the established phase of hypertension have not been investigated, although irreversible morphological changes as well as modifications in collagen synthesis or distribution in the vascular wall may be involved (181).

Several haemodynamic, cardiovascular and endocrine changes produced by hypothyroidism may interfere with the development of hypertension: hypothyroidism reduces body weight, heart rate, cardiac output (4, 44) and contractility (177), decreases the response to exogenous mineralocorticoids (102), and diminishes the pressor response to norepinephrine (20, 182). Therefore, a reduced pressor responsiveness to vasoconstrictors may participate in this phenomenon. Thus, the blood pressure response to vasoconstrictors was reduced to values even lower than those observed in control rats in intact low renal mass hypothyroid rats (7). Moreover, a decreased reactivity to vasoconstrictors was also reported in aortic strips from spontaneously hypertensive (168) and...
DOCA-salt (183) thyroidectomised rats. In summary, these observations indicate that the antithyroid treatment interferes with the development of hypertension regardless of its aetiology. However, precise knowledge of the participation of different factors requires further investigations that could permit the establishment of a common pathophysiological mechanism.

**Thyroid hormone as a tool in the therapy of cardiovascular diseases**

The potential therapeutic use of TH is related to its acute effects (184–186). T₃ was shown to enhance ventricle-arterial coupling and augment left ventricular work with a lower increment in left ventricular oxygen consumption (187). Unlike conventional inotropic drugs, which improve cardiac function at the cost of increased oxygen consumption and, thus, decrease efficiency, T₃ may improve cardiac function without additional cost in the myocardial oxygen consumption by decreasing afterload, increasing coronary blood flow, and improving cardiac performance (184, 185, 188). Moreover, TH also improves left ventricular function and calcium handling in pressure overload cardiac hypertrophy (189).

The cardiovascular haemodynamic effects of TH cannot be explained solely by the positive inotropic effects of T₃ on the heart. TH may have modest direct vasodilatory effects(15) that promote a fall in SVR and facilitate the increase in cardiac output of both the normal and the pathological failing heart (44). Administration of T₃ has been proposed to increase cardiac output and to decrease vascular resistance in certain clinical settings when conventional inotropic drugs prove insufficient (190). Patients with poor ventricular function may benefit the most from the use of T₃ through a reduction in the need for conventional inotropic drugs (191). Additionally, in the rat postinfarction model of heart failure, treatment with T₄ produced a positive inotropic response, including an increase in left ventricular contractility and an increase in left ventricular end-diastolic pressure (192).

The administration of T₃ to brain-dead organ donors was among the first clinical applications of T₃ therapy in which the drug was targeted specifically at improving haemodynamic performance and enhancing organ retrieval (193). Serum thyroid hormone concentration declines transiently during critical illness and after surgical procedures (194). In animal models, the use of exogenous T₃ after cardiopulmonary bypass improves ventricular performance without oxygen wasting (195). Treatment of children with T₃ after cardiopulmonary bypass operations raises T₃ plasma concentration and improves myocardial function especially in patients with low cardiac output. Furthermore, T₃ reduces the need for postoperative intensive care (194). Patients undergoing coronary artery bypass treated with T₃ showed a higher cardiac index than the placebo group and the inotropic requirements were also lower in the T₃-treated group (196).

Given these observations, THs have unique actions that make them novel and possible useful agents for the treatment of heart failure. Because of the potential adverse effects of THs, however, there has been interest in developing analogues with fewer undesirable side effects. Beginning in the 1950s, extensive efforts were made to develop TH analogues that could utilise the cholesterol-lowering property in euthyroid individuals without affecting the heart. These efforts culminated in the development of analogues that selectively bind to the beta-type nuclear thyroid hormone receptors, which are responsible for the cholesterol-lowering activity, but without activating the alpha-type receptors present in the heart. Beta-selective compounds may be useful in lowering cholesterol in euthyroid individuals who are intolerant of treatment with statins (186).

Screening of compounds structurally related to levothyroxine identified 3,5,diiodothyropropionic acid (DIPTA) as an analogue with inotropic selectivity and low metabolic activity in hypothyroid rats. DIPTA binds to both alpha and beta-type TH receptors with relatively low affinity. DIPTA is well tolerated and could represent a useful new agent for the treatment of congestive heart failure (186, 197). This compound also lowers cholesterol and may be a useful adjunct to standard heart failure therapy (197). Also, DIPTA was administered alone or in combination with captopril in rat and rabbit postinfarction models of heart failure, and the result was that cardiac output was increased and left ventricular end-diastolic pressure was decreased without a change in heart rate (192, 197, 198). In summary, the ability of THs to increase cardiac performance, to lower systemic vascular resistance together with their cholesterol-lowering properties may provide a novel treatment option for cardiovascular diseases alone or in combination. Moreover, future precise knowledge of the mechanisms of action of THs on the cardiovascular factors referred to above should allow a better use of THs as therapeutic agents.

**Concluding remarks**

In this review we describe the main vascular and renal manifestations of hyper- and hypothyroidism, and discuss the new insights into the mechanisms that participate in these alterations. Thus, the role of the endothelium-derived relaxing factors NO and EDHF in the abnormalities in vascular function, the changes in NOS activity in hyper- and hypothyroidism and the contribution of NOS isoenzymes to the long-term control of blood pressure in the hyperthyroid state have been analysed. Moreover, the participation of oxidative stress in cardiovascular and renal abnormalities in
hypothyroidism have also been analysed. All these observations open new perspectives for the assessment of the cardiovascular and renal abnormalities of thyroid disorders. Finally, we have reviewed the novel therapeutic use of T₃ in cardiovascular diseases benefitting from its inotropic, vasodilator and cholesterol-lowering activities, using T₃ analogues with selective properties.

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