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

Table 1 Morphological and haemodynamic variables in experimental thyroid disorders.

	Hyperthyroidism	Hypothyroidism
Morphological variables		
Body weight	↓	↓
Thyroid weight	↓	↑
Ventricular weight	↑	↓
Kidney weight	↑	↓
Ventricular/body weight	↑	↓
Kidney/body weight	↑	↓
Left ventricle/right ventricle	→	Not measured
Haemodynamic variables		
Blood pressure	↑	↓
Blood volume	↑	↓
Cardiac output	↑	↓
Total peripheral resistance	↓	↑
Heart rate	↑	↓
Pulse pressure	↑	↓

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 (T_3)-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 α_1 -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 α_1 -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 α_1 -adrenoceptors present in cardiac tissue (28), there is currently no direct evidence to suggest that this condition has a similar effect on vascular α_1 -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 α_1 -adrenoceptor number (31) and lower α_1 -adrenoceptor-operated calcium channel

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 , $75 \mu\text{g} \cdot \text{rat}^{-1} \cdot \text{day}^{-1}$, s.c.) rats. Data are means $\pm$ S.E.M. * $P < 0.05$ compared with controls. RPP, renal perfusion pressure.

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) α_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 β -adrenergic receptor concentration observed in the vasculature of these rats (31). The reduced responsiveness to vasodilators 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

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 N^ω-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 vasodilation, 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 vasorelaxation (21, 41, 43) and reduced aortic NOS activity (66).

Preparations from hypothyroid rats show an attenuated responsiveness to vasoconstrictors and especially to the α 1-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

increase the expression of the voltage-dependent K^+ Kv1.5 (70) and other proteins involved in the regulation of membrane potential (71).

Nitric oxide synthase activity in thyroid disorders

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 T_3 (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 AII (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 hypothyroidism and is inversely correlated with serum T_3 , whereas in neural tissues hypothyroidism is associated with a reduced NOS activity (79).

The increased NOS activity in the cardiovascular and renal tissues of hyperthyroid rats is in agreement with the data reported in other tissues. A study using quantitative *in situ* hybridisation histochemistry with a specific oligodeoxynucleotide probe showed that T_3 -induced hyperthyroidism more than doubled the prevalence of NOS gene transcript in the paraventricular (PVN) and supraoptic (SON) nuclei, whereas hypothyroidism produced a highly significant reduction in NOS gene transcripts in the PVN and SON (79). Fernandez *et al.* (80) demonstrated that hyperthyroidism leads to a significant and reversible enhancement in rat liver NOS activity. Hypothalamic nitric oxide synthase gene expression is regulated by thyroid hormones, and up-regulation of NOS gene transcripts induced by the osmotic stimulus of chronic salt loading was markedly attenuated by PTU-induced hypothyroidism.

Nitric oxide synthases 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).

It was reported that T_4 -treated rats became hypertensive after partial NOS inhibition with a dose of 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 T_4 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 T_3 does not regulate iNOS activity in mesangial cells, renal tubular epithelial cells, or macrophages, and that the effects of T_3 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.

Figure 2 Time course of systolic blood pressure measured by the tail-cuff method by direct recording (femoral artery) in conscious rats. Thyroxine (T_4 , $50 \mu\text{g} \cdot \text{rat}^{-1} \cdot \text{day}^{-1}$, s.c.), AG (aminoguanidine, $50 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, via drinking water), 7NI (7-nitroindazole; $30 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, via drinking water). Data are means $\pm$ S.E.M. * $P < 0.05$ compared with controls.

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 3 Pressure-natriuresis relationship in control, hypothyroid (methimazole, 0.03%, via drinking water) and hyperthyroid (T_4 , $75 \mu\text{g} \cdot \text{rat}^{-1} \cdot \text{day}^{-1}$, s.c.) rats. Data are means $\pm$ S.E.M. Horizontal bars represent the S.E.M. of renal perfusion pressure values. * $P < 0.05$ compared with value at lowest pressure.

hyperthyroid rats in order to achieve the same rate of sodium excretion as in a normal animal. These observations are consistent with findings in other models of experimental hypertension (107).

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 hyperthyroidism. 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 T_3 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 T_4 -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 hypothyroid 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, T_3 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 (T_4 , $75 \mu\text{g}\cdot\text{rat}^{-1}\cdot\text{day}^{-1}$, s.c.) rats treated with captopril (CAPT; $30 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$, via drinking water). Values are means $\pm$ S.E.M. * $P < 0.05$ compared with controls, + $P < 0.01$ compared with T_4 -treated rats.

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). Glutathione peroxidase (GPX) and glutathione 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 F_{2α} 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

Figure 5 Mechanisms of action proposed for the thyroid depressing factor (TDF).

by thyrotrophin (174). The normal T_3 and T_4 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

Thyroxine 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

Figure 6 Effects of excess T_4 ($100 \mu\text{g} \cdot \text{rat}^{-1} \cdot \text{day}^{-1}$, s.c.) and deficiency (radiothyroidectomised with $800 \mu\text{Ci } ^{131}\text{I}$, TD) of thyroid hormones on the development of DOCA-salt hypertension in rats. Systolic blood pressure was measured by the tail-cuff method. Data are means $\pm$ S.E.M. * $P < 0.05$ compared with controls.

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). T_3 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, T_3 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 T_3 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 T_3 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 T_3 through a reduction in the need for conventional inotropic drugs (191). Additionally, in the rat postinfarction model of heart failure, treatment with T_4 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 T_3 to brain-dead organ donors was among the first clinical applications of T_3 therapy in which the drug was targetted 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 T_3 after cardiopulmonary bypass improves ventricular performance without oxygen wasting (195). Treatment of children with T_3 after cardiopulmonary bypass operations raises T_3 plasma concentration and improves myocardial function especially in patients with low cardiac output. Furthermore, T_3 reduces the need for postoperative intensive care (194). Patients undergoing coronary artery bypass

treated with T_3 showed a higher cardiac index than the placebo group and the inotropic requirements were also lower in the T_3 -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

hyperthyroidism 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 T_3 in cardiovascular diseases benefiting from its inotropic, vasodilator and cholesterol-lowering activities, using T_3 analogues with selective properties.

References

- Parry CH. Collections from the unpublished papers of the late Caleb Hilliel Parry. *Diseases of the Heart* 1825 **2** 111–165.
- Feldman EC & Nelson RW. The thyroid gland. In *Canine and Feline Endocrinology and Reproduction*, edn 2, pp 67–185. Eds EC Feldman & RW Nelson. Philadelphia: WB Saunders & Company, 1995.
- Klein I & Ojamaa K. Thyroid hormone and blood pressure regulation. In *Hypertension: Pathophysiology, Diagnosis and Management*, edn 2, pp 2247–2262. Eds JH Laragh & BN Brenner. New York: Raven Press Ltd, 1995.
- Larsen PR, Davis TF & Hay ID. The thyroid gland. In *Williams Textbook of Endocrinology*, edn 6, pp 389–515. Eds JD Wilson, DW Foster, HK Kronenberg & PR Larsen. London: WB Saunders & Company, 1998.
- Klein I & Ojamaa K. Thyroid hormone and the cardiovascular system. *New England Journal of Medicine* 2001 **344** 501–509.
- Vargas F, García del Río C, Luna JD, Haro JM & Osorio C. Studies on thyroid activity in deoxycorticosterone-salt and Goldblatt two-kidney, one-clip hypertensive rats. *Acta Endocrinologica* 1988 **118** 22–30.
- Andrade J, Haro JM, Jódar E, Luna JD & Vargas F. Effects of methimazole on low renal mass hypertension: changes in blood pressure and pressor responsiveness to vasoconstrictors. *Pharmacology* 1992 **44** 315–323.
- Graettinger JS, Muenster JJ, Checchia CS, Grissom RL & Campbell JA. A correlation of clinical and hemodynamic studies in patients with hypothyroidism. *Journal of Clinical Investigation* 1957 **37** 501–510.
- Graettinger JS, Muenster JJ, Silverstone LA & Campbell JA. A correlation of clinical and hemodynamic studies of patients with hyperthyroidism and with congestive heart failure. *Journal of Clinical Investigation* 1959 **40** 1316–1329.
- Anthonisen P, Holst E & Thomsen AA. Determination of cardiac output and other hemodynamic data in patients with hyper- and hypothyroidism, using dye dilution technique. *Scandinavian Journal of Clinical and Laboratory Investigation* 1960 **12** 472–480.
- Celsing F, Blomstrand E, Melichna J, Terrados N, Clausen N, Lins PE & Jansson E. Effect of hyperthyroidism on fibre-type composition, fibre area, glycogen content and enzyme activity in human skeletal muscle. *Clinical Physiology* 1986 **6** 171–181.
- Capo LA & Sillau AH. The effects of hyperthyroidism on capillarity and oxidative capacity in rat soleus and gastrocnemius muscles. *Journal of Physiology* 1983 **342** 1–14.
- Scivoletto R, Fortes ZB & García-Leme J. Thyroid hormones and vascular reactivity: role of the endothelial cell. *European Journal of Pharmacology* 1986 **129** 271–278.
- Büsemaker E, Popp R, Fisslthaler B, Larson CM, Fleming I, Busse R & Brandes RP. Hyperthyroidism enhances endothelium-dependent relaxation in the rat renal artery. *Cardiovascular Research* 2003 **59** 181–188.
- Ishikawa T, Chijiwa T, Hagiwara M, Mamiya S & Hidaka H. Thyroid hormones directly interact with vascular smooth muscle strips. *Molecular Pharmacology* 1989 **35** 760–765.
- Zwaveling J, Pfaffendorf M & van Zwieten PA. The direct effects of thyroid hormones on rat mesenteric resistance arteries. *Fundamental and Clinical Pharmacology* 1997 **11** 41–46.
- Kapitola J & Vilimovská D. Inhibition of the early circulatory effects of triiodothyronine in rats by propranolol. *Physiologia Bohemoslovaca* 1981 **30** 347–351.
- Koehn MA, Schindler WJ & Stanton HC. Thyroid state and vascular reactivity in rats. *Proceedings of the Society for Experimental Biology and Medicine* 1967 **126** 861–864.
- Vanhoutte PM. Endothelium and control of vascular function. *Hypertension* 1989 **13** 658–667.
- Vargas F, Baz MJ, Andrade J, Luna JD & Haro JM. Thyroid state and pressor responsiveness to vasoconstrictors in conscious rats. *Medical Science Research* 1991 **19** 239–241.
- Moreno JM, Wangenstein R, Sainz J, Rodríguez-Gómez I, Chamorro V, Osuna A & Vargas F. Role of endothelium-derived relaxing factors in the renal response to vasoactive agents in hypothyroid rats. *American Journal of Physiology* 2003 **285** E182–E188.
- Brown JM & Pollock D. The effect of thyroidectomy on the sensitivity of the vasculature of rat hindquarters to agonists. *Journal of Physiology* 1980 **307** 77–78.
- Rahmani MA, Cheema IR, Sen S, Peoples B & Riley SR. The effect of hyperthyroidism and hypothyroidism on α_1 - and α_2 -adrenergic responsiveness in rat aortic smooth muscle. *Artery* 1987 **14** 362–383.
- Sabio JM, Rodríguez-Maresca M, Luna JD, García del Río C & Vargas F. Vascular reactivity to vasoconstrictors in aorta and renal vasculature from hyperthyroid and hypothyroid rats. *Pharmacology* 1994 **49** 257–264.
- Grieve DJ, Fletcher S, Pitsillides AA, Botham KM & Elliott J. Effects of oral propylthiouracil treatment on nitric oxide production in rat aorta. *British Journal of Pharmacology* 1999 **127** 1–8.
- Ishac EJM & Pennefather JN. The influence of the thyroid state upon responses to noradrenaline and phentolamine in perfused mesenteric arterioles from the rat. *Journal of Pharmacy and Pharmacology* 1983 **35** 466–468.
- Takiguchi Y, Satoh N, Hashimoto H & Nakashima M. Changes in vascular reactivity in experimental diabetic rats: comparison with hypothyroid rats. *Blood Vessels* 1988 **25** 250–260.
- Zwaveling J, Batink HD, De Jong J, Winkler-Prins EA, Pfaffendorf M & Van Zwieten PA. Thyroid hormone modulates inotropic responses, α -adrenoceptor density and catecholamine concentrations in the rat heart. *Naunyn-Schmiedeberg's Archives of Pharmacology* 1996 **354** 755–764.
- Vargas F, Osuna A & Fernández-Rivas A. Renal vascular reactivity to ATP in hyper- and hypothyroid rats. *Experientia* 1996 **52** 225–229.
- Field FP, Janis RA & Triggle DJ. Relationship between aortic reactivity and blood pressure of renal hypertensive, hyperthyroid, and hypothyroid rats. *Canadian Journal of Physiology* 1973 **51** 344–353.
- Gunasekera RD & Kuriyama H. The influence of thyroid states upon responses of the rat aorta to catecholamines. *British Journal of Pharmacology* 1990 **99** 541–547.
- McAllister RM, Grossenburg VD, Delp MD & Laughlin MH. Effects of hyperthyroidism on vascular contractile and relaxation responses. *American Journal of Physiology* 1998 **274** E946–E953.
- Honda H, Iwata T, Mochizuki T & Kogo H. Changes in vascular reactivity induced by acute hyperthyroidism in isolated rat aorta. *General Pharmacology* 2000 **34** 429–434.
- Stratton DB & Morrow RJ. Calcium mobilization and sensitivity in intact and triton skinned aorta from thyropathologic rats. *Life Science* 1991 **48** 2207–2214.
- Zsótér T, Tom H & Chappel C. Effect of thyroid hormones on vascular response. *Journal of Laboratory and Clinical Medicine* 1964 **64** 433–441.
- Van der Schoot JB & Moran NC. An experimental evaluation of the reputed influence of thyroxine on the cardiovascular effects of the catecholamines. *Journal of Pharmacology and Experimental Therapeutics* 1965 **149** 336–345.
- Grassby PF & McNeill JH. Hyperthyroidism induces supersensitivity to biogenic amines in rat vascular tissue via a pre- and

- postjunctional mechanism. *Journal of Pharmacology and Experimental Therapeutics* 1988 **244** 1027–1035.
- 38 Zwaveling J, Winkler Prins EA, Maas MAW, Pfaffendorf M & van Zwieten PA. The influence of hyperthyroidism on pharmacological induced contractions of isolated resistance arteries. *European Journal of Pharmacology* 1996 **300** 91–97.
  - 39 Miyazawa K, Hashimoto H & Nakashima M. Altered responsiveness of coronary arteries in hyperthyroid rats. *Archives Internationales de Pharmacodynamie et the Therapie* 1989 **297** 120–132.
  - 40 Zwaveling J, Pfaffendorf M & van Zwieten PA. The influence of hyperthyroidism on vasoconstrictor and vasodilator responses in isolated coronary and renal resistance arteries. *Pharmacology* 1997 **55** 117–125.
  - 41 Vargas F, Fernández-Rivas A, García-Estañ J & García del Río C. Endothelium-dependent and endothelium-independent vasodilation in hyperthyroid and hypothyroid rats. *Pharmacology* 1995 **51** 308–314.
  - 42 Vargas F, Montes R, Sabio JM & García-Estañ J. Role of nitric oxide in the systemic circulation of conscious hyper- and hypothyroid rats. *General Pharmacology* 1994 **25** 887–891.
  - 43 Delp MD, McAllister RM & Laughlin MH. Exercise training alters aortic vascular reactivity in hypothyroid rats. *American Journal of Physiology* 1995 **268** H1428–H1435.
  - 44 Klein I. Thyroid hormone and the cardiovascular system. *American Journal of Medicine* 1990 **88** 631–637.
  - 45 Iwata T & Honda H. Acute hyperthyroidism alters adrenoceptor- and muscarinic receptor-mediated responses in isolated rat renal and femoral arteries. *European Journal of Pharmacology* 2004 **493** 191–199.
  - 46 Lockette W, Otsuka Y & Hirt E. The endothelium and cyclic guanosine monophosphate in hyperthyroid induced hypertension. *Agents and Actions Supplements* 1987 **22** 125–132.
  - 47 Furchgott RF & Vanhoutte PM. Endothelium-derived relaxing and contracting factors. *FASEB Journal* 1989 **3** 2007–2018.
  - 48 Vargas F, Sabio JM & Luna JD. Contribution of endothelium-derived relaxing factors to acetylcholine-induced vasodilatation in the rat kidney. *Cardiovascular Research* 1994 **28** 1373–1377.
  - 49 Garland CJ, Plane F, Kemp BK & Cocks TM. Endothelium-dependent hyperpolarization: a role in the control of vascular tone. *Trends in Pharmacological Sciences* 1995 **16** 23–30.
  - 50 Campbell WB & Gauthier KM. What is new in endothelium-derived hyperpolarizing factors? *Current Opinion in Nephrology and Hypertension* 2002 **11** 177–183.
  - 51 Ishii K, Chang B, Kerwin JF Jr, Huang ZJ & Murad F. N^ω-Nitro-L-arginine. A potent inhibitor of endothelium-derived relaxing factor formation. *European Journal of Pharmacology* 1990 **176** 219–223.
  - 52 Brayden JE, Quayle JM, Standen NB & Nelson MT. Role of potassium channels in the vascular response to endogenous and pharmacological vasodilators. *Blood Vessels* 1991 **28** 147–153.
  - 53 Vanhoutte PM. Other endothelium-derived vasoactive factors. *Circulation* 1993 **87** (Suppl V) V9–V17.
  - 54 Adeagbo ASO & Triggle CR. Varying extracellular [K⁺]: a functional approach to separating EDHF- and EDNO-related mechanisms in perfused rat mesenteric arterial bed. *Journal of Cardiovascular Pharmacology* 1993 **21** 423–429.
  - 55 Rubanyi GM, Freay AD, Kauser K, Johns A & Harder DR. Mechanoreception by the endothelium: mediators and mechanisms of pressure- and flow-induced vascular responses. *Blood Vessels* 1990 **27** 246–257.
  - 56 Ercan ZS, Soydan AS & Türker RZ. Possible involvement of endothelium in the responses of various vasoactive agents in rabbit isolated perfused kidney. *General Pharmacology* 1990 **21** 205–209.
  - 57 Vargas F & Osuna A. Modulatory role of endothelium-derived relaxing factors on the response to vasoconstrictors and flow-pressure curve in the isolated perfused rat kidney. *Journal of Vascular Research* 1996 **33** 119–123.
  - 58 Noris M, Morigi M, Donadelli R, Aiello S, Foppolo M, Todeschini M, Orisio S, Remuzzi G & Remuzzi A. Nitric oxide synthesis by cultured endothelial cells is modulated by flow conditions. *Circulation Research* 1995 **76** 536–543.
  - 59 Ranjan V, Xiao Z & Diamond SL. Constitutive NOS expression in cultured endothelial cells is elevated by fluid shear stress. *American Journal of Physiology* 1995 **269** H550–H555.
  - 60 Uematsu M, Ohara Y, Navas JP, Nishida K, Murphy TJ, Alexander RW, Nerem RM & Harrison DG. Regulation of endothelial cells nitric oxide synthase mRNA expression by shear stress. *American Journal of Physiology* 1995 **269** C1371–C1378.
  - 61 Nodaud S, Philippe M, Arnal J, Michel B & Soubrier F. Sustained aortic endothelial nitric oxide synthase expression *in vivo* in a model of chronic high blood flow. *Circulation Research* 1996 **79** 857–863.
  - 62 Xiao Z, Zhang Z & Diamond SL. Shear stress induction of the endothelial nitric oxide synthase gene is calcium dependent but not calcium-activated. *Journal of Cellular Physiology* 1997 **171** 205–211.
  - 63 Marsden PA, Heng HH, Scherer SW, Hall AV, Shi XM, Tsui LC & Schappert KT. Structure and chromosomal localization of the human constitutive endothelial nitric oxide synthase gene. *Journal of Biological Chemistry* 1993 **268** 17478–17488.
  - 64 Martin PY, Xu DL, Niederberger M, Weigert A, Tsai P, St John J, Gines P & Schrier RW. Upregulation of endothelial constitutive NOS: a major role in the increased NO production in cirrhotic rats. *American Journal of Physiology* 1996 **270** F494–F499.
  - 65 Ni Z, Morcos S & Vaziri ND. Up-regulation of renal and vascular nitric oxide synthase in iron-deficiency anemia. *Kidney International* 1997 **52** 195–201.
  - 66 Quesada A, Sainz J, Wangenstein R, Rodriguez-Gomez I, Vargas F & Osuna A. Nitric oxide synthase activity in hyperthyroid and hypothyroid rats. *European Journal of Endocrinology* 2002 **147** 117–122.
  - 67 Vargas F, Fernández-Rivas A & Osuna A. Effects of methimazole in the early and established phases of L-NAME hypertension. *European Journal of Endocrinology* 1996 **135** 506–513.
  - 68 Vargas F, Fernández-Rivas A & Osuna A. Vascular reactivity and flow-pressure curve in isolated perfused kidneys from L-NAME hypertensive rats. *Journal of Hypertension* 1996 **14** 373–379.
  - 69 Hoger JH, Ilyin VI, Forsyth S & Hoger A. Shear stress regulates the endothelial Kir2.1 ion channel. *PNAS* 2002 **99** 7780–7785.
  - 70 Ojamaa K, Sabet A, Kenessey A, Shenoy R & Klein I. Regulation of rat cardiac Kv1.5 gene expression by thyroid hormone is rapid and chamber specific. *Endocrinology* 1999 **140** 3170–3176.
  - 71 Pachuki J, Burmeister LA & Larsen PR. Thyroid hormone regulates hyperpolarization-activated cyclic nucleotide-gated channel (HCN2) mRNA in the rat heart. *Circulation Research* 1999 **85** 498–503.
  - 72 Chakrabarti N & Ray AK. Rise of intrasynaptosomal Ca²⁺ level and activation of nitric oxide synthase in adult rat cerebral cortex pretreated with 3-5-3'-L-triiodothyronine. *Neuropsychopharmacology* 2000 **22** 36–41.
  - 73 Vaziri ND, Zhenmin N & Oveisi F. Upregulation of renal and vascular nitric oxide synthase in young spontaneously hypertensive rats. *Hypertension* 1998 **31** 1248–1254.
  - 74 Hennington BS, Zhang H, Miller MT, Granger JP & Reckelhoff JF. Angiotensin II stimulates synthesis of endothelial nitric oxide synthase. *Hypertension* 1998 **31** 283–288.
  - 75 Hirata Y, Hayakawa H, Suzuki E, Kimura K, Kikuchi K, Nagano T, Hirobe M & Omata M. Direct measurement of endothelium-derived nitric oxide release by stimulation of endothelin receptors in rat kidney and its alterations in salt induced hypertension. *Circulation* 1995 **91** 1229–1235.
  - 76 Marchant C, Brown L & Sernia C. Renin-angiotensin system in thyroid dysfunction in rats. *Journal of Cardiovascular Pharmacology* 1993 **22** 449–455.
  - 77 Singh G, Thompson EB & Gulati A. Altered endothelin 1 concentration in the brain and peripheral regions during thyroid dysfunction. *Pharmacology* 1994 **49** 184–191.

- 78 Carreras MC, Peralta JG, Converso DP, Finocchietto PV, Rebagliatti I, Zaninovich AA & Poderoso JJ. Modulation of liver mitochondrial NOS is implicated in thyroid-dependent regulation of O₂ uptake. *American Journal of Physiology* 2001 **281** H2282–H2288.
- 79 Ueta Y, Levy A, Chowdrey HS & Lightman SL. Hypothalamic nitric oxide synthase gene expression is regulated by thyroid hormones. *Endocrinology* 1995 **136** 4182–4187.
- 80 Fernandez V, Cornejo P, Tapia G & Videla LA. Influence of hyperthyroidism on the activity of liver nitric oxide synthase in the rat. *Nitric Oxide* 1997 **1** 463–468.
- 81 Gardiner SM, Compton AM, Bennett T, Palmer RMJ & Moncada S. Control of regional blood flow by endothelium-derived nitric oxide. *Hypertension* 1990 **15** 486–492.
- 82 Romero JC, Lahera V, Salom MG & Biondi ML. Role of the endothelium-dependent relaxing factor nitric oxide on renal function. *Journal of the American Society of Nephrology* 1992 **2** 1371–1387.
- 83 Cowley AW, Mattson DL, Lu S & Roman RJ. The renal medulla and hypertension. *Hypertension* 1995 **25** 663–673.
- 84 Moncada S, Palmer RMJ & Higgs EA. Nitric oxide: physiology, pathophysiology and pharmacology. *Pharmacological Reviews* 1991 **43** 109–142.
- 85 Fernández-Rivas A, García-Estañ J & Vargas F. Effects of chronic increased salt intake on nitric oxide synthesis inhibition-induced hypertension. *Journal of Hypertension* 1995 **13** 123–128.
- 86 Zatz R & Baylis C. Chronic nitric oxide inhibition model six years on. *Hypertension* 1998 **32** 958–964.
- 87 Thorup C & Persson AEG. Nitric oxide and renal blood pressure regulation. *Current Opinion in Nephrology and Hypertension* 1998 **7** 197–202.
- 88 Griffiths MJD, Messent M, MacAllister RJ & Evans TW. Aminoguanidine selectively inhibits inducible nitric oxide synthase. *British Journal of Pharmacology* 1993 **110** 963–968.
- 89 Ortiz MC, Fortepiani LA, Martínez C, Atucha NM & García-Estañ J. Renal and pressor effects of aminoguanidine in cirrhotic rats with ascites. *Journal of the American Society of Nephrology* 1996 **7** 2694–2699.
- 90 Mattson DL, Maeda CY, Bachman TD & Cowley AW Jr. Inducible nitric oxide synthase and blood pressure. *Hypertension* 1998 **31** 15–20.
- 91 Moore PK, Wallace P, Gaffen Z, Hart SL & Babbedge RC. Characterization of the novel nitric oxide synthase inhibitor 7-nitro indazole and related indazoles: antinociceptive and cardiovascular effects. *British Journal of Pharmacology* 1993 **110** 219–224.
- 92 Xu L, Carter EP, Ohara M, Martin PY, Rogachev B, Morris K, Cadnapaphornchai M, Knotek M & Schrier RW. Neuronal nitric oxide synthase and systemic vasodilation in rats with cirrhosis. *American Journal of Physiology* 2000 **279** F1110–F1115.
- 93 Rodríguez-Gómez I, Sainz J, Wangenstein R, Moreno JM, Duarte J, Osuna A & Vargas F. Increased pressor sensitivity to chronic nitric oxide deficiency in hyperthyroid rats. *Hypertension* 2003 **42** 220–225.
- 94 Rodríguez-Gómez I, Wangenstein R, Moreno JM, Chamorro V, Osuna A & Vargas F. Effects of chronic inhibition of inducible nitric oxide synthase in hyperthyroid rats. *American Journal of Physiology* 2005 **288** E1252–E1257.
- 95 Trachtman H, Jacques C, Citron J & Futterweit S. Effect of triiodothyronine on nitric oxide production in mesangial cells and renal tubular epithelial cells. *Research Communications in Molecular Pathology and Pharmacology* 1996 **93** 69–78.
- 96 Kobori H, Ichihara A, Miyashita Y, Hayashi M & Saruta T. Mechanism of hyperthyroidism-induced renal hypertrophy. *Journal of Endocrinology* 1997 **136** 9–14.
- 97 García del Río C, Moreno MRR, Osuna A, Luna JD, García-Estañ J & Vargas F. Role of the renin-angiotensin system in the development of thyroxine-induced hypertension. *European Journal of Endocrinology* 1997 **136** 656–660.
- 98 Michael UF, Barenberg RL, Chavez R, Vaamonde CA & Paper S. Renal handling of sodium and water in the hypothyroid rat. *Journal of Clinical Investigation* 1972 **51** 1405–1412.
- 99 Bradley SE, Stephan F, Coelho JB & Reville P. The thyroid and the kidney. *Kidney International* 1974 **6** 346–365.
- 100 Emmanuel DS, Lindheimer MD & Katz IA. Mechanism of impaired water excretion in the hypothyroid rat. *Journal of Clinical Investigation* 1974 **54** 926–934.
- 101 Taylor RE & Fregly MJ. Renal response of propylthiouracil-treated rats to injected mineralocorticoids. *Endocrinology* 1964 **75** 33–41.
- 102 Holmes EW & DiScala V. Studies on the exaggerated natriuretic response to a saline infusion in the hypothyroid rat. *Journal of Clinical Investigation* 1970 **49** 1224–1236.
- 103 Vargas F, Baz MJ, Luna JD, Andrade J, Jodar E & Haro JM. Urinary excretion of digoxin-like immunoreactive factor and arginine-vasopressin in hyper- and hypothyroid rats. *Clinical Science* 1991 **81** 471–476.
- 104 Katz IA & Lindheimer MD. Renal sodium- and potassium-activated adenosine triphosphatase and sodium reabsorption. *Journal of Clinical Investigation* 1973 **53** 796–804.
- 105 Vargas F, Atucha N, Sabio JM, Quesada T & García-Estañ J. Pressure-diuresis-natriuresis response in hyper- and hypothyroid rats. *Clinical Science* 1994 **87** 323–328.
- 106 Stephan F, Jahn H & Reville P. Etude comparative de la concentration, de la composition et du débit des urines du rat normal et du rat hypothyroïdien soumis à des épreuves aiguës de surcharge isotonique. *Journal de Physiologie* 1964 **56** 233–258.
- 107 Guyton AC. *Arterial Pressure and Hypertension*. Philadelphia: WB Saunders, 1980.
- 108 Ford RV, Owens JC, Curd GW, Moyer SH & Spurr CL. Kidney function in various thyroid states. *Journal of Clinical Endocrinology* 1961 **21** 548–553.
- 109 Cutler RE, Glatte H & Dowling JT. Effect of hyperthyroidism on the renal concentrating mechanism in humans. *Journal of Clinical Endocrinology* 1967 **27** 453–460.
- 110 Fregly MJ, Brimhall RL & Galindo OJ. Effect of the antithyroid drug propylthiouracil on the sodium balance of rats. *Endocrinology* 1962 **71** 693–700.
- 111 García-Estañ J, Atucha N, Quesada T & Vargas F. Involvement of the renin-angiotensin system in the reduced pressure-natriuresis response of hyperthyroid rats. *American Journal of Physiology* 1995 **268** E897–E901.
- 112 Moreno JM, Rodríguez-Gómez I, Wangenstein R, Osuna A, Bueno P & Vargas F. Cardiac and renal antioxidant enzymes and effects of tempol in hyperthyroid rats. *American Journal of Physiology* 2005 **289** E776–E783.
- 113 Weetman AP, Tomlinson K, Amos N, Lazarus JH, Hall R & McGregor AM. Proteinuria in autoimmune thyroid disease. *Acta Endocrinologica* 1985 **109** 341–347.
- 114 Tanwani LK, Lohano V, Broadstone VL & Mokshagundam SP. Minimal change nephropathy and Graves' disease: report of a case and review of the literature. *Endocrine Practice* 2002 **8** 40–43.
- 115 Levey GS. Catecholamine sensitivity, thyroid hormone and the heart. *American Journal of Medicine* 1971 **50** 413–420.
- 116 Bilezikian JP & Loeb JN. The influence of hyperthyroidism and hypothyroidism on α - and β -adrenergic receptor systems and adrenergic responsiveness. *Endocrine Reviews* 1983 **4** 378–396.
- 117 Polikar R, Kennedy B, Ziegler M, O'Connor T, Smith J & Nicod P. Plasma norepinephrine kinetics, dopamine- β -hydroxylase and chromogranin A in hypothyroid patients before and following replacement therapy. *Journal of Clinical Endocrinology and Metabolism* 1990 **70** 277–281.
- 118 Harrison TS, Siegel JH, Wilson WS & Weber WJ. Adrenergic reactivity in hyperthyroidism. *Archives of Surgery* 1967 **94** 396–402.
- 119 Landsberg L. Catecholamines and hyperthyroidism. *Clinics in Endocrinology and Metabolism* 1977 **6** 697–718.
- 120 Nielsen HV, Hasselstrom K, Feldt-Rasmussen U, Mehlsen J, Siersbaek-Nielsen K, Friis T, Haunso S & Trap-Jensen J. Increased sympathetic tone in forearm subcutaneous tissue in primary hypothyroidism. *Clinical Physiology* 1987 **7** 297–302.

- 121 Fagius J, Westermark K & Karlsson A. Baroreflex-governed sympathetic outflow to muscle vasculature is increased in hypothyroidism. *Clinical Endocrinology* 1990 **33** 177–185.
- 122 Williams LT, Lefkowitz RJ, Watanabe AM, Hathaway DR & Besch HR Jr. Thyroid hormone regulation of β -adrenergic receptor number. *Journal of Biological Chemistry* 1977 **252** 2787–2789.
- 123 Haro JM, Sabio JM & Vargas F. Renal and cardiac β -adrenoceptors in thyroxine-treated rats. *Journal of Endocrinological Investigation* 1992 **15** 605–608.
- 124 Bilezikian JP & Loeb JN. Mechanisms of altered β -adrenergic responsiveness in the hyperthyroid and hypothyroid turkey erythrocyte. *Life Science* 1982 **30** 663–674.
- 125 Klein I. Thyroxine-induced cardiac hypertrophy: time course of development and inhibition by propranolol. *Endocrinology* 1988 **123** 203–210.
- 126 Levey GS & Klein I. Catecholamine-thyroid hormone interactions and the cardiovascular manifestations of hyperthyroidism. *American Journal of Medicine* 1990 **88** 642–646.
- 127 Dratman MB, Goldman M, Crutchfield FL & Gordon JT. Nervous system role of iodocompounds in blood pressure regulation. *Life Science* 1982 **30** 611–622.
- 128 Foley CM, McAllister RM & Hasser EM. Thyroid status influences baroreflex function and autonomic contributions to arterial pressure and heart rate. *American Journal of Physiology* 2001 **280** H2061–H2068.
- 129 Hauger-Klevene JH, De Vito E & Fasciolo JC. The effect of thyroid hormone and renin production and release by rat kidney slices. *Acta Physiologica et Pharmacologica Latinoamericana* 1977 **27** 37–43.
- 130 Bouhnik J, Galen FX, Brown H & Zavaleta J. The renin-angiotensin system in thyroidectomized rats. *Endocrinology* 1981 **108** 647–650.
- 131 Ganong WF. Thyroid hormones and renin secretion. *Life Science* 1982 **30** 577–584.
- 132 Jiménez E, Montiel M, Narváez JA & Morel M. Effects of hyper- and hypothyroidism on the basal levels of angiotensin I and kinetic parameters of renin angiotensin system in male rats. *Revista Española de Fisiología* 1982 **38** 149–154.
- 133 Churchill PC, Churchill MC & McDonald FD. Evidence that β -adrenoceptor activation mediates isoproterenol-stimulated renin secretion in the rat. *Endocrinology* 1983 **113** 687–692.
- 134 Atlas SA, Sealey JE, Larag JH & Moon C. Plasma renin and 'prorenin' in essential hypertension during sodium depletion, beta-blockade and reduced arterial pressure. *Lancet* 1977 **2** 785–789.
- 135 Arnaout MA, Awidi AS, El-Najdawi AM, Khateeb MS & Ajlouni KM. Arginine-vasopressin and endothelium-associated proteins in thyroid disease. *Acta Endocrinologica* 1992 **126** 399–403.
- 136 Ali M, Rougon-Rapuzzi G & Clos J. Response of the hypothalamo-neurohypophyseal axis (AVP system) and the kidney to salt load in young propylthiouracil-treated rats. *Hormone and Metabolic Research* 1985 **17** 502–506.
- 137 Kim JK, Summer SN & Schrier RW. Cellular action of arginine vasopressin in the isolated renal tubules of hypothyroid rats. *American Journal of Physiology* 1987 **253** F104–F110.
- 138 Letizia C, Centanni M, Cesareo R, De Ciocchis A, Cerci S, Scuro L, Fumarola A, D'Ambrosio C & Scavo D. Increased plasma levels of endothelin-1 in patients with hyperthyroidism. *Metabolism* 1995 **44** 1239–1242.
- 139 Lam H-C, Wang J-P, Lee J-K, Ho L-T, Han T-M, Lu C-C, Chiang H-T, Cheng D-L & Bloom SR. The lung contents of endothelin are altered by thyroid hormone status in the rat. *Regulatory Peptides* 1993 **49** 33–39.
- 140 Rebello S, Thompson EB & Gulati A. Endothelin mechanism is altered in thyroid states in the rat. *European Journal of Pharmacology* 1993 **237** 9–16.
- 141 Lam HC, Lee JK, Lai KH & Chiang HT. Plasma endothelin levels are unaltered by thyroid hormone status in humans. *Cardiovascular Pharmacology* 2000 **36** (Suppl 1) S382–S385.
- 142 McAllister RM, Luther KL & Pfeifer P. Thyroid status and response to endothelin-1 in rat arterial vessels. *American Journal of Physiology* 2000 **279** E252–E258.
- 143 Kohno M, Murakawa K, Yasunary K, Nishizawa Y, Morii H & Takeda T. Circulating atrial natriuretic peptides in hyperthyroidism and hypothyroidism. *American Journal of Medicine* 1987 **83** 648–652.
- 144 Kohno M, Takaori K, Matsuura T, Murakawa K, Kanayama Y & Takeda T. Atrial natriuretic polypeptide in atria and plasma in experimental hyperthyroidism and hypothyroidism. *Biochemical and Biophysical Research Communications* 1986 **134** 178–183.
- 145 Wong NL, Huang D, Guo NS, Wong EF & Hu DC. Effects of thyroid status on atrial natriuretic peptide release from isolated atria. *American Journal of Physiology* 1989 **256** E64–E67.
- 146 Matsubara H, Hirata Y, Yoshimi H, Takata S, Takagi Y, Iida T, Yamane Y, Umeda Y, Nishikawa M & Inada M. Effects of steroid and thyroid hormones on synthesis of atrial natriuretic peptide by cultures of atrial myocytes of rat. *Biochemical and Biophysical Research Communications* 1987 **145** 336–343.
- 147 Mori Y, Nishikawa M, Matsubara H, Toyoda N, Masaki H, Yonemoto T, Takagi Y & Inada M. Regulation of atrial natriuretic hormone production by triiodothyronine in cultures of rat atrial myocytes. *Acta Endocrinologica* 1991 **125** 694–699.
- 148 Griendling KK, Sorescu D & Ushio-Fukai M. NAD (P)H oxidase: role in cardiovascular biology and disease. *Circulation Research* 2000 **86** 494–501.
- 149 Wilcox CS. Reactive oxygen species: roles in blood pressure and kidney function. *Current Hypertension Reports* 2002 **4** 160–166.
- 150 Schnackenberg CG & Wilcox CS. Two-week administration of Tempol attenuates both hypertension and renal excretion of 8-iso prostaglandin $F_{2\alpha}$. *Hypertension* 1999 **33** 424–428.
- 151 Duarte J, Pérez-Palencia R, Vargas F, Ocete MA, Pérez Vizcaino F, Zarzuelo A & Tamargo J. Antihypertensive effects of the flavonoid quercetin in spontaneously hypertensive rats. *British Journal of Pharmacology* 2001 **133** 117–124.
- 152 Beswick RA, Zhang H, Marabe D, Catravas JD, Hill WD & Webb RC. Long-term antioxidant administration attenuates mineralocorticoid hypertension and renal inflammatory response. *Hypertension* 2001 **37** 781–786.
- 153 Duarte J, Jiménez R, O'Valle F, Galisteo M, Pérez-Palencia R, Vargas F, Pérez-Vizcaino F, Zarzuelo A & Tamargo J. Protective effects of the flavonoid quercetin in chronic nitric oxide-deficient rats. *Journal of Hypertension* 2002 **20** 1843–1854.
- 154 Sainz J, Wangenstein R, Rodríguez-Gómez I, Moreno JM, Chamorro V, Osuna A, Bueno P & Vargas F. Antioxidant enzymes and effects of tempol, a membrane permeable radical scavenger, on the development of NO inhibition induced-hypertension. *American Journal of Hypertension* 2005 **18** 871–877.
- 155 Mitchell JB, Samuni A, Krishna MC, DeGraff WG, Ahn MS, Samuni U & Russo A. Biologically active metal-independent superoxide dismutase mimetics. *Biochemistry* 1990 **29** 2802–2807.
- 156 Zou AP, Li N & Cowley AW Jr. Production and action of superoxide in renal medulla. *Hypertension* 2001 **37** 547–553.
- 157 Mori T & Cowley AW Jr. Renal oxidative stress in medullary thick ascending limbs produced by elevated NaCl and glucose. *Hypertension* 2004 **43** 341–346.
- 158 Gredilla R, Barja G & Lopez-Torres M. Thyroid hormone-induced oxidative damage on lipids, glutathione and DNA in the mouse heart. *Free Radical Research* 2001 **35** 417–425.
- 159 Giavarotti S, Rodrigues L, Rodrigues T, Junqueira VB & Videla LA. Liver microsomal parameters related to oxidative stress and antioxidant systems in hyperthyroid rats subjected to acute lindane treatment. *Free Radical Research* 1998 **29** 35–42.
- 160 Asayama K, Dobashi K, Hayashibe H & Kato K. Effects of β -adrenergic blockers with different ancillary properties on lipid peroxidation in hyperthyroid rat cardiac muscle. *Endocrinologia Japonica* 1989 **36** 687–694.
- 161 Sawant BU, Nadkarni GD, Thakare UR, Joseph LJ & Rajan MG. Changes in lipid peroxidation and free radical scavengers in

- kidney of hypothyroid and hyperthyroid rats. *Indian Journal of Experimental Biology* 2003 **41** 1334–1337.
- 162 Seymen HO, Civelek S, Seven A, Yigit G, Hatemi H & Burak G. Iron supplementation in experimental hyperthyroidism: effects of oxidative stress in skeletal muscle tissue. *Yonsei Medical Journal* 2004 **45** 413–418.
  - 163 Seymen HO, Seven A, Civelek S, Yigit G, Hatemi H & Burak G. Evaluation of antioxidant status in liver tissues: effects of iron supplementation in experimental hyperthyroidism. *Journal of Basic and Clinical Physiology and Pharmacology* 1999 **10** 315–325.
  - 164 Venditti P, Balestrieri M, Di Meo S & De Leo T. Effect of thyroid state on lipid peroxidation, antioxidant defences, and susceptibility to oxidative stress in rat tissues. *Journal of Endocrinology* 1997 **155** 151–157.
  - 165 Sewerynek J, Wiktorska J, Novak D & Lewinski A. Methimazole protection against oxidative stress induced by hyperthyroidism in Graves' disease. *Endocrine Regulation* 2000 **34** 83–89.
  - 166 Kim KM, Paeng KJ, Hahm JR, Kim DR & Chung BC. Elevated urinary 8-isoprostaglandin F_{2α} in females with Graves' hyperthyroidism. *Prostaglandin, Leukotrienes, and Essential Fatty Acids* 2004 **71** 143–147.
  - 167 Kojima A, Takahashi Y & Ohno SI. An elevation of plasma TSH concentration in spontaneously hypertensive rats. *Proceedings of the Society for Experimental Biology and Medicine* 1975 **149** 661–663.
  - 168 Fregly MJ, Kim KJ & Hood CI. Development of hypertension in rats treated with aldosterone-acetate. *Toxicology and Applied Pharmacology* 1969 **15** 229–243.
  - 169 Threatch RM, Fregly MJ & Field FP. Interrelationship among blood pressure, renal function, thyroid activity and renal thyroid depressing factor in renal hypertensive rats. *Pharmacology* 1982 **24** 201–210.
  - 170 Werner SC, Manger WM, Radicevich MW & Storf IV. Excessive thyrotropin concentrations in the circulation of the spontaneously hypertensive rat. *Proceedings of the Society for Experimental Biology and Medicine* 1975 **148** 1013–1017.
  - 171 Wright GL, Knecht E, Badger D, Samueloff S, Toraason M & Dukes-Dobos F. Oxygen consumption in the spontaneously hypertensive rat. *Proceedings of the Society for Experimental Biology and Medicine* 1978 **159** 449–452.
  - 172 MacParland RP & Rapp JP. [Na⁺-K⁺] activated adenosine triphosphatase and hypertension in Dahl salt-sensitive and salt-resistant rats. *Clinical and Experimental Hypertension* 1982 **4** 379–385.
  - 173 Levey HA. Studies on the mechanisms of action of liver extract in inhibiting uptake of ¹³¹I *in vitro* by the rat thyroid gland. *Endocrinology* 1967 **80** 417–422.
  - 174 Fregly MJ & Threatch RM. Renal-thyroid interrelationship in normotensive and hypertensive rats. *Life Science* 1982 **30** 589–599.
  - 175 Lutherer LO, Burns AH, Fregly MJ & Field FP. Inhibitory effect of ultracentrifugal fraction of rat renal homogenate on TSH stimulated ¹³¹I uptake by bovine thyroid slices. *Proceedings of the Society for Experimental Biology and Medicine* 1971 **138** 414–417.
  - 176 Rioux F & Berkowitz BM. Role of the thyroid gland in the development and maintenance of spontaneous hypertension in rats. *Circulation Research* 1977 **40** 306–312.
  - 177 Rodger RL & McNeill JH. Antihypertensive effect of thyroidectomy in SHR: associated changes in heart performance. *American Journal of Physiology* 1986 **250** 600–605.
  - 178 Salgado E. Effect of thyroidectomy on hypertension, nephrosclerosis and cardiac lesions produced by deoxycorticosterone acetate (DCA) treatment in the rat. *Endocrinology* 1954 **55** 112–115.
  - 179 Fregly MJ. Effects of propylthiouracil on development and maintenance of renal hypertension in rats. *American Journal of Physiology* 1958 **194** 149–154.
  - 180 Vargas F, Castillo MA & Haro JM. Methimazole treatment reduces cardiac hypertrophy and mortality without a concomitant reduction in blood pressure in established Goldblatt two kidney-one clip hypertension. *Experientia* 1992 **48** 755–758.
  - 181 Folkow B. Structural factor in primary and secondary hypertension. *Hypertension* 1990 **16** 89–101.
  - 182 Schümann HJ, Borowski E & Gross G. Changes of adrenoceptor-mediated response in the pithed rat during propylthiouracil-induced hypothyroidism. *European Journal of Pharmacology* 1979 **56** 145–152.
  - 183 Rials SJ, Sullivan MM & Hansen JR. Effects of thyroidectomy on blood pressure of DOCA-hypertensive rats. *Federation Proceedings* 1982 **41** 1660.
  - 184 Salter DR, Dyke CM & Wechsler AS. Triiodothyronine (T₃) and cardiovascular therapeutics: a review. *Journal of Cardiac Surgery* 1992 **7** 363–374.
  - 185 Chen W, Lah M, Robinson PJ & Kemp BE. Phosphorylation of phospholamban in aortic smooth muscle cells and heart by calcium/calmodulin dependent protein kinase II. *Cellular Signalling* 1994 **6** 617–630.
  - 186 Klemperer JD, Ojamaa K & Klein I. Thyroid hormone therapy in cardiovascular disease. *Progress in Cardiovascular Diseases* 1996 **38** 329–336.
  - 187 Morkin E, Ladenson P, Goldman S & Adamson C. Thyroid hormone analogs for treatment of hypercholesterolemia and heart failure: past, present and future prospects. *Journal of Molecular and Cellular Cardiology* 2004 **37** 1137–1146.
  - 188 DiPierro FV, Bavaria JE, Lankford EB, Polidori DJ, Acker MA, Streicher JT & Gardner TJ. Triiodothyronine optimizes sheep ventriculo-arterial coupling for work efficiency. *Annals of Thoracic Surgery* 1996 **62** 662–669.
  - 189 Klemperer JD, Zelano J, Helm RE, Berman K, Ojamaa K, Klein I, Isom OW & Krieger K. Triiodothyronine improved left ventricular function without oxygen wasting after global hypothermic ischemia. *Journal of Thoracic and Cardiovascular Surgery* 1995 **109** 157–165.
  - 190 Burman KD. Is triiodothyronine administration beneficial in patients undergoing coronary artery bypass surgery? *Journal of the American Medical Association* 1996 **275** 723–724.
  - 191 Cimochoowski GE, Harostock MD & Foldes PJ. Minimal operative mortality in patients undergoing coronary artery bypass with significant left ventricular dysfunction by maximization of metabolic and mechanical support. *Journal of Thoracic and Cardiovascular Surgery* 1997 **113** 655–666.
  - 192 Morkin E, Pennock GD, Raya TE, Bahl JJ & Goldman S. Development of a thyroid hormone analogue for the treatment of congestive heart failure. *Thyroid* 1996 **6** 521–526.
  - 193 Novitzky D, Cooper DK, Chaffin JS, Greer AE, DeBault LE & Zuhdi N. Improved cardiac allograft function following triiodothyronine therapy to both donor and recipient. *Transplantation* 1990 **49** 311–316.
  - 194 Bettendorf M, Schmidt KG, Grulich-Henn J, Ulmer HE & Heinrich UE. Triiodothyronine treatment in children after cardiac surgery: a double-blind, randomised, placebo-controlled study. *Lancet* 2000 **356** 529–534.
  - 195 Novitzky D, Human PA & Cooper DKC. Inotropic effect of triiodothyronine following myocardial ischemia and cardiopulmonary bypass: an experimental study in pigs. *Annals of Thoracic Surgery* 1988 **45** 50–55.
  - 196 Sirlak M, Yazicioglu L, Inan MB, Eryilmaz S, Tasoz R, Aral A & Ozyurda U. Oral thyroid hormone pre-treatment in left ventricular dysfunction. *European Journal of Cardio-Thoracic Surgery* 2004 **26** 720–725.
  - 197 Mahaffey KW, Raya TE, Pennock GD, Morkin E & Goldman S. Left ventricular performance and remodelling in rabbits after myocardial infarction. *Effects of thyroid hormone analogue. Circulation* 1995 **91** 794–801.
  - 198 Morkin E, Pennock GD, Spooner PH, Bahl JJ & Goldman S. Clinical and experimental studies on the use of 3,5-diiodothyropropionic acid, a thyroid hormone analogue, in heart failure. *Thyroid* 2002 **12** 527–533.

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