Thyroid hormones (THs) exert marked effects on cardiac function that result from direct effects of the hormones on the cardiac myocyte as well as effects on the peripheral vasculature. The latter effect is best demonstrated by the characteristically high systemic vascular resistance (SVR) observed in patients (and experimental animals) with hypothyroidism, which is rapidly reversed with TH treatment. Hyperthyroidism produces a marked decrease in SVR, which in turn facilitates an increase in cardiac output and augments peripheral blood flow characteristic of this disease state.

Over 85% of the TH synthesized and released from the thyroid gland is in the form of tetraiodothyronine (thyroxine, T4). Conversion of T4 to the biologically active form of the hormone, triiodothyronine (T3), occurs by 5' monodeiodination (type I 5' deiodinase) primarily in the liver and kidney and, to a smaller extent, by type II 5' deiodinase activity in the pituitary and brain. In most tissues, the mechanism of TH biological action occurs by the entry of T3 into the cell by facilitated transport and the binding of T3 to specific nuclear T3 receptors (TRs), which regulate transcription of target genes. In the heart, these genes include contractile proteins (myosin heavy chains) as well as calcium transport/regulatory proteins (sarcoplasmic reticulum calcium–activated ATPase, phospholamban). Nuclear TRs, which belong to the steroid superfamily of transcription factors, bind T3 with much greater affinity than T4 and can either positively or negatively regulate transcriptional activity, depending on the presence or absence of T3 and a T3-responsive DNA element. Thus, the inotropic effect of TH on the cardiac myocyte is primarily determined by its ability to alter cellular phenotype. In addition, nongenomic actions of T3 have been identified, in which T3 regulates the ion flux of plasma membrane ion channels that in turn determine membrane potential, depolarization characteristics, and contractile activity.

The cardiovascular hemodynamic effects of TH cannot be explained solely by the positive inotropic and lusitropic effects of T3 on the heart. As previously studied, the fall in SVR promotes and facilitates the increase in cardiac output of both the normal and the pathological failing heart. This has been clearly demonstrated in patients receiving short-term T3 infusion after cardiac surgery and in patients with advanced congestive heart failure, in whom the rise in cardiac index was linked to the fall in SVR. In experimental animals and human studies, T3 was shown to enhance ventriculoarterial coupling and augment left ventricular work with a lower increment in left ventricular oxygen consumption compared with that resulting from inotropic agents. Given these observations, the mechanism by which TH promotes a fall in vascular resistance gains clinical significance.

Studies using vascular smooth muscle (VSM) cells isolated from rat aorta and cultured on a deformable matrix demonstrated that exposure to T3 caused these cells to relax rapidly, suggesting a nongenomic mechanism of action. This effect was selective for T3 and was not mediated by cAMP or nitric oxide. Hormone-binding studies using VSM cell plasma membrane showed that T3 bound with an \( \approx 100 \)-fold greater affinity than T4. While both T3 and T4 caused relaxation of preconstricted isolated skeletal muscle resistance arterioles within 20 minutes after exposure to hormone, T3 was more effective at all concentrations studied (10\(^{-7}\) to 10\(^{-10}\) mol/L). This difference between the vasodilatory effectiveness of T3 and T4 on VSM may be resolved by the observations of Mizuma et al, who have shown in this issue of Circulation Research the presence of an iodothyronine deiodinase in human VSM cells. They report that this deiodinase activity is characteristic of a type II enzyme (brain and pituitary), such that the enzymatic activity is regulated by T4, whereas its expression is transcriptionally regulated by cAMP and T3. The presence of this enzyme in human vascular cells suggests that VSM cells are physiological targets for the action of TH, and that VSM can convert T4 to the active hormone T3 to promote cellular activity.

The identification of four thyroid hormone receptor mRNA isoforms in both human aortic and coronary VSM confirms previous reports of TR mRNAs in rat primary VSM cells and points to a classic genomic action of T3 in these cells. This implies that in addition to the nongenomic effects of T3 on vascular tone, T3 may determine VSM contractility by regulating its phenotype through classic nuclear transcription mechanisms. However, as acknowledged by Mizuma et al, the target genes for T3 action in the VSM cell remain unknown. It is interesting to speculate that T3 target genes in VSM cells may be similar to those previously described in the cardiac myocyte, which include the sarcoplasmic reticulum Ca\(^{2+}\)-activated ATPase, phospholamban (PLB), and plasma-membrane ion channels, such as voltage-gated Kv1.5 and Kv4.2, Na\(^{+}\)-Ca\(^{2+}\) exchanger, and Na\(^{+}\)-K\(^{-}\)-ATPase. The role of T3 in regulating protein phosphorylation of these...
calcium channels/transporters may additionally modulate VSM contractility by changes in SR and sarcoulemmal ion flux. 18,19

Studies using genetic ablation of the PLB gene showed alterations in aortic smooth muscle cell contractility, suggesting a possible molecular mechanism by which TH regulates SVR. 20 If PLB expression in VSM is negatively regulated by T₃, as it is in the cardiac myocyte, 17 then TH could promote cell relaxation in a manner similar to the lusitropic effect characteristic of the myocardium. 3 Furthermore, TH acting through either increased cAMP-dependent protein kinase or calcium-calmodulin–dependent protein kinase activity to increase PLB phosphorylation in VSM, as has been reported in the heart, may provide a mechanism by which T₃ regulates cellular relaxation. 18,19,21

The presence of type II 5’ monodeiodinase in VSM additionally raises the question of how this system may function in the disease states of atherosclerosis and hypertension. Although a recent study 22 has shown accelerated atherosclerotic disease in patients with even mild hypothyroidism, the long-held association between hypothyroidism and hypercholesterolemia probably underlies much of this pathology. The finding that as many as 25% of hypothyroid patients have diastolic hypertension with an increased SVR points to a possible molecular mechanism by which TH regulates alterations in aortic smooth muscle cell contractility, suggesting a possible molecular mechanism by which TH regulates SVR. 20 If PLB expression in VSM is negatively regulated by T₃, as it is in the cardiac myocyte, 17 then TH could promote cell relaxation in a manner similar to the lusitropic effect characteristic of the myocardium. 3 Furthermore, TH acting through either increased cAMP-dependent protein kinase or calcium-calmodulin–dependent protein kinase activity to increase PLB phosphorylation in VSM, as has been reported in the heart, may provide a mechanism by which T₃ regulates cellular relaxation. 18,19,21

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Drawing from the study by Mizuma et al 15 and using methodology recently reported by Pachucki et al, 23 who overexpressed the type II deiodinase in the cardiac myocyte, it may be possible to target TH to the VSM. This approach may allow increased conversion of T₄ to T₃ in the VSM cell, thereby increasing the cellular action of the hormone and providing a novel mechanism for regulating SVR and blood pressure. Recent reports have studied the ability of TH analogues to lower plasma lipids without concomitant changes in cardiovascular hemodynamics. 24 Conversely, with the evidence that VSM is a target for TH action, a TH analogue that acts selectively at the VSM cell to promote vasodilatation may serve as a novel class of antihypertensive agents.

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References


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