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Special Article - Thyroid Hormones

Nongenomic Actions of Thyroid Hormones: Cellular Aspects in the Cardiovascular System

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Thyroid Hormones

Triiodothyronin (T3) and Thyroxine (T4), act on almost every cell and organ with intense effects on the cardiovascular system. The heart is a major target organ for thyroid hormones action, and marked changes occur in cardiac function in patients with hypothyroidism or hyperthyroidism. Although T4 is the major secretion product of thyroid, T3 is responsible for most of the biological effects ascribed to thyroid hormones, including the negative-feedback system over the Thyrotropin-Releasing Hormone (TRH) and Thyroid-Stimulating Hormone (TSH) secretion by the hypothalamus and pituitary, respectively. Among the different tissues, T3 has pivotal effects on the cardiovascular system, acting as an important regulator of cardiovascular hemodynamic through its direct action on the cardiac myocytes, Vascular Smooth Muscle Cells (VSMCs), and endothelium. The endothelium plays a major role in the regulation of cardiovascular homeostasis through the release of vasoactive compounds such as Nitric Oxide (NO), prostacyclin, and Endothelium-Derived Hyperpolarizing Factor (EDHF) [1,2].

The mechanism of action of Thyroid Hormones (TH) has been described to begin in the cell nucleus and to require participation of specific receptor proteins in the nuclear compartment. Among the different tissues, T3 has pivotal effects on the heart and cardiovascular system, acting as an important regulator of cardiac function and cardiovascular hemodynamics through its direct action on the cardiac myocytes, VSMCs, and endothelium [3]. The increase in cardiac output observed in hyperthyroidism is a result of the combination of the increased cardiac function (inotropic and chronotropic effects) and changes in the cardiovascular hemodynamics (lowered systemic vascular resistance and increased blood volume) suggested that reduced vascular resistance could be secondary to alterations in the vascular control mechanisms that favor vasodilatation [4].

It has been suggested that hyperthyroidism is similar to a hyperadrenergic state; however, no evidence suggests that T3 excess enhances the sensitivity of the heart to adrenergic stimulation [5]. The classic genomic actions which are dependent on interaction with nuclear receptors to modulate cardiac myocytes genes expression. T3 enters the cell membrane in a diffusion way, as described for the steroidal hormones or via specific transport proteins such as an energy-dependent carrier that partially depends on the Na^+ gradient. In the nucleus, T3 interacts with the nuclear Thyroid Receptors (TR). The mechanism of action of TH has been described to start in the cell nucleus and to require participation of specific receptor proteins in the nuclear compartment. Otherwise, there is growing evidence about T(3) and T(4)-triggered nongenomic pathways, resulted from their binding to plasma membrane, cytoplasm, or mitochondrial receptors that leads to a rapidly regulation of cardiac functions. Some actions of TH have been assumed to implicate extranuclear mechanisms in a variety of cells and initiated at the plasma membrane receptor for iodothyronines [6]. Non-genomic actions of T3 in the myocardium are envisaged on membrane ion transporter localized at the plasma membrane and in the vascular endothelium on mechanisms associated with N0 metabolism.

The mechanisms of several of the nongenomic actions of TH are not clearly elucidated. They depend upon cellular signal transduction systems and either novel cell surface receptors for TH or extranuclear thyroid hormone receptor (TRα and TRβ) [7]. A cell surface receptor for iodothyronines has been described on a structural protein of the plasma membrane. This protein is integrin αVβ3, a heterodimer that interacts with a substantial number of proteins of the extracellular matrix [8]. Unlike the nuclear effects, the extranuclear ones may be mediated by signal-transducing pathways such as cAMP and protein kinases. TH affects cellular calcium homeostasis, and this effect is probably due to a nongenomic action. T2 and T3 exert short-term nongenomic effects on intracellular calcium by modulating plasma-membrane and mitochondrial pathways [9]. From the cell surface receptor, the thyroid hormone signal is transduced. There is a T3-specific site in the domain, as well as a site at which both T4 and T3 may act). The T3-specific site activates PI3K, T4 being unable to activate PI3K. The consequences of this action of T3 include transcription of the Hypoxia-Inducible Factor-1α (HIF1-α) gene and activation of plasma membrane Na-K-ATPase and its insertion in the plasma membrane [10].

Thyroid disease is quite common. Current estimates suggest that it affects as many as 9% to 15% of the adult female population and a smaller percentage of adult males. Mechanisms linking high and high-normal thyroid function to increased cardiovascular risk remain unclear. Vascular function is markedly affected by thyroid hormones that produce changes in vascular reactivity and endothelial function. Endothelial dysfunction resulting from a reduction in NO availability

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and Low-Density Lipoprotein (LDL) oxidation are common events in cardiovascular disease. Thyroid dysfunction is a frequent condition that confers an increased risk for cardiovascular complications. It may be envisaged that T3 treatment induces increased production of NO, which is associated with activation of the PI3K/Akt signalling pathway, increased NO synthases isoforms, resulting in a significant decrease of Myosin Light Chain (MLC) phosphorylation levels and decreased vascular response to contractile stimuli. The results of recent studies are of potential clinical relevance in this domain.

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