Title: Dissecting genomic and non-genomic effects of Thyroid Hormones in aortic vasodilation

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Basic science

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It is well known that thyroid hormones (THs) are required for cardiovascular functions. This is evident in hypo- and hyperthyroid patients, who suffer from cardiovascular problems. However, the molecular mechanisms how THs impact the cardiovascular system remain incompletely understood, especially when considering the individual contributions of genomic and non-genomic signaling pathways. In this study, we dissected how THs alter the contractility of blood vessels.

To test the direct and immediate effects of THs on the vasocontractility of blood vessels, we dissected short pieces of aorta from mice and mounted them *ex vivo* into a wire-myograph. This device measures the force generated by the contraction of the vessel. The contractile response of dissected aortas was analyzed following a short stimulation with different doses of the biological active thyroid hormone T3 (3,3',5'-triiodothyronine). When the vessels were contracted by the adrenergic agonist phenylephrine in the absence of THs (0 nM T3), lower vasoconstriction was observed as compared to the euthyroid condition (1nM T3). Interestingly, mildly and severely elevated levels of T3 (10 and 100 nM) also caused reduced vasoconstriction at higher levels of phenylephrine. These results indicate that there is an inversed U-shape curve with maximal constrictive capacity at euthyroid condition. To test for unspecific side-effects of T3 based on its hydrophobic molecular structure, its biologically inactive isoform rT3 was used in the same experimental setup, resulting in no changes in vasocontractility at 100nM.

To uncover the molecular pathways through which T3 exerts these short-term effects on vasocontractility, we performed Western Blot analyses to test for ERK, AKT and AMPK phosphorylation in aortas stimulated with T3, rT3, or control. Only AKT signaling was significantly different after T3 stimulation. The results show that T3 can rapidly change vasocontractility, likely involving the non-genomic AKT signaling pathway.

In addition to the non-genomic action, we also tested for possible genomic actions of THs on vasocontractility, treating mice with water containing 1mg/L T4 or control. After four days of treatment, the animals were sacrificed, and their abdominal aortas were dissected for RNA microarray analysis. The results showed several alterations in gene expression, including 10 genes directly related to vasocontractility and blood pressure regulation.

Taken together, our findings demonstrate that genomic and non-genomic actions of TH contribute to the regulation of vascular tone, providing a molecular framework for the understanding of blood pressure regulation and cardiovascular alterations in thyroid disorders.