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Original Research Article

Effects of thyroid hormone status on metabolic pathways of arachidonic acid in mice and humans: A targeted metabolomic approach

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ABSTRACT

Symptoms of cardiovascular diseases are frequently found in patients with hypothyroidism and hyperthyroidism. However, it is unknown whether arachidonic acid metabolites, the potent mediators in cardiovascular system, are involved in cardiovascular disorders caused by hyperthyroidism and hypothyroidism.

To answer this question, serum levels of arachidonic acid metabolites in human subjects with hypothyroidism, hyperthyroidism and mice with hypothyroidism or thyroid hormone treatment were determined by a mass spectrometry-based method. Over ten arachidonic acid metabolites belonging to three catalytic pathways: cyclooxygenases, lipoxygenases, and cytochrome P450, were quantified simultaneously and displayed characteristic profiles under different thyroid hormone status. The level of 20-hydroxyeicosatetraenoic acid, a cytochrome P450 metabolite, was positively correlated with thyroid hormone level and possibly contributed to the elevated blood pressured in hyperthyroidism. The increased prostanoid (PG) I_2 and decreased PGE_2 levels in hypothyroid patients might serve to alleviate atherosclerosis associated with dyslipidemia. The elevated level of thromboxane (TX) A_2, as indicated by TXB_2, in hyperthyroid patients and mice treated with thyroid hormone might bring about pulmonary hypertension frequently found in hyperthyroid patients.

In conclusion, our prospective study revealed that arachidonic acid metabolites were differentially affected by thyroid hormone status. Certain metabolites may be involved in cardiovascular disorders associated with thyroid diseases.

Abbreviations: COX, cyclooxygenase; CYP450, cytochrome P450; 11d-TXB_2, 11-dehydro-TXB_2; 15d-PGJ_2, 15-deoxy-delta-12,14-prostaglandin J_2; DHET, dihydroxyeicosatrienoic acid; EET, epoxyeicosatrienoic acid; HETE, hydroxyeicosatetraenoic acid; HDL, high-density lipoprotein; HODE, hydroxyoctadecadienoic acid; 6-keto-$PGF_{1\alpha}$, 6-keto-prostaglandin $F_{1\alpha}$; LC–MS, liquid chromatography–mass spectrometry; LTB_4, leukotrienes B_4; LDL, low-density lipoprotein; LOX, lipoxygenase; MMI, methimazole; NT-proBNP, N-terminal of the prohormone brain natriuretic peptide; PGD_2, prostaglandin D_2; PGE_2, prostaglandin E_2; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$; PGFM, 13,14-dihydro-15-keto-$PGF_{2\alpha}$; PGI_2,prostacyclin I_2; PGIM, 2,3-dinor-6-keto-$PGF_{1\alpha}$; PLA_2, phospholipase A_2; SPE, solid phase extraction; TH, thyroid hormone; T4, thyroxine; T3, triiodothyronine; TSH, thyroid-stimulating hormone; TXA_2, thromboxane A_2; TXB_2, thromboxane B_2.

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Introduction

Thyroid hormone (TH), such as thyroxine (T4) and triiodothyronine (T3), potently affects the heart and vascular system [1]. A classic negative feedback loop mediated by the hypothalamic–pituitary–thyroid axis maintains the physiological inverse relationship between TH and thyroid-stimulating hormone (TSH) [2]. Overt hyperthyroidism refers to the situation when patients are found to have an abnormally low TSH level and a high T4 or T3 level. In contrast, patient with overt hypothyroidism shows an elevated TSH level accompanied by a low free T4 level [3]. Subclinical thyroid dysfunction refers to the situation when serum TSH levels are outside the normal reference range while peripheral T4 and T3 levels are normal [4]. Thyroid dysfunction is a common disorder in the general population [5–7]. Certain signs and symptoms of cardiovascular diseases are frequently found in patients diagnosed with either hypothyroidism or hyperthyroidism. An increased incidence of cardiovascular diseases and coronary atherosclerosis occurs in patients with overt hypothyroidism according to human observational studies [8]. On the other hand, hyperthyroidism induces a hyperdynamic cardiovascular state, which is associated with a faster heart rate, enhanced left ventricular systolic and diastolic function. Systolic hypertension and pulmonary hypertension are two symptoms frequently associated with hyperthyroidism [9,10]. THs affect the cardiovascular systems in multiple ways: for example, THs affect the myocardium and influence the sympathetic nervous system, both of which directly increase cardiac contractility; also, TH can increase peripheral oxygen consumption and substrate requirements, which causes a secondary increase in cardiac contractility [11]. Since THs are potent hormones affecting a wide range of physiological process, more roles of THs in regulating cardiovascular system remain to be uncovered.

Arachidonic acid, a ubiquitous membrane constituent, can be hydrolyzed from membrane phospholipids by phospholipase A_2 (PLA_2) and subsequently metabolized by multiple enzymes including cyclooxygenases (COX), lipoxygenases (LOX), and cytochrome P450 (CYP450) into various eicosanoids (Fig. 1). The sequential actions of COX and specific prostanoid synthases produce prostaglandin PGD_2, PGE_2, PGF_2, prostacyclin (PGI_2), and thromboxane A_2 (TXA_2). Lipoxygenases (LOXs) are responsible for the production of leukotrienes, 5-, 12-, and 15-hydroxyeicosatetraenoic acids (HETEs). Epoxygenases and ω-hydroxylases, two enzymes belonging to P450 monoxygenases, give rise to epoxyeicosatrienoic acids (EETs) and 20-HETEs, respectively. Some of the eicosanoids are active mediators regulating the cardiovascular function under physiological and pathological conditions. In the cardiovascular system, prostanoids have been shown to modulate platelet aggregation, vasorelaxation and vasoconstriction, inflammatory response and leukocyte infiltration [12]. PGI_2 and TXA_2 possess opposite effects in the pathogenesis of atherosclerosis [13]. The disturbed PGI_2/TXA_2 balance may eventually lead to vascular diseases like thrombosis and atherosclerosis. Moreover, emerging evidence shows that EETs and HETEs are critical players in blood pressure regulation [14–16]. It remains to be defined whether abnormal eicosanoid levels may contribute to the pathogenesis of cardiovascular disorders related to thyroid dysfunction.

Table 1
Characteristics of study subjects.

	Eu	Hypo	Hyper
Number (M/F)	14 (5/9)	12 (7/5)	11 (6/5)
Age (yr)	28 ± 1	32 ± 2	29 ± 2
TSH (mU/L)	1.82 ± 0.17	97.43 ± 1.80*	<0.005
Free T4 (pmol/L)	15.92 ± 0.52	2.125 ± 0.37*	84.30 ± 5.89*
Free T3 (pmol/L)	4.471 ± 0.11	1.100 ± 0.15*	35.97 ± 3.36*

Data are mean ± SEM. Eu, euthyroid; hypo, hypothyroid; hyper, hyperthyroid.
* Indicates $P < 0.05$ compared with euthyroid group.

Thyroid dysfunction can cause lipid abnormalities that contribute to the increased risk of endothelial dysfunction, hypertension and coronary heart disease [11]. However, it remains unclear that whether TH can affect the cardiovascular system through the influence of eicosanoids. The purpose of the present study was to uncover the relationships between serum eicosanoids and thyroid dysfunction. Here we profiled major eicosanoids derived from COX, LOX, and CYP450 mediated metabolic pathways in serum obtained from patients with hyperthyroidism and hypothyroidism and in euthyroid controls by the state-of-the-art liquid chromatography–mass spectrometry (LC–MS). To exam if TH status is responsible for the altered eicosanoid levels, we also determined the levels of serum eicoasnoids in mice with drug-induced hypothyroidism and T3-treatment. In this study, we identified several arachidonic acid metabolites that were altered in human with hypothyroidism or hyperthyroidism and in mouse under different thyroid status. Our study provided not only novel insights into

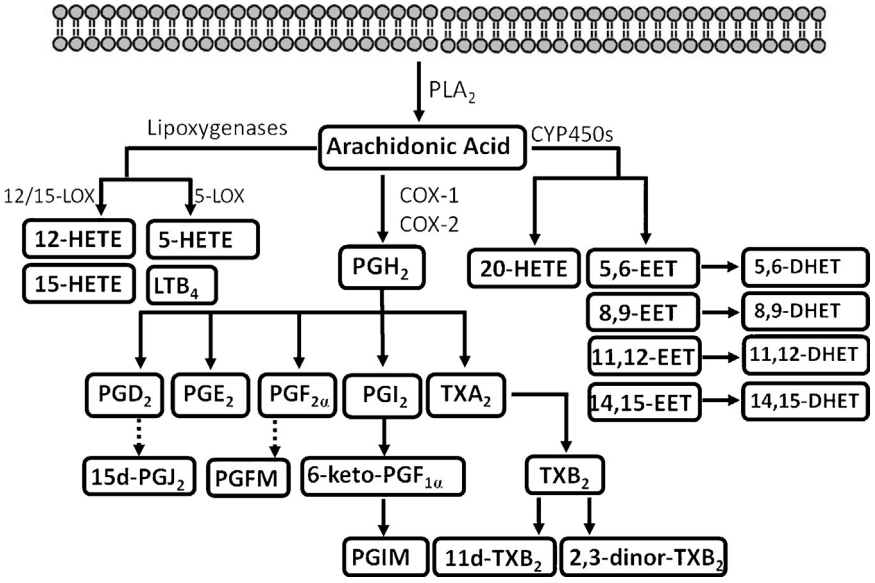

Fig. 1. Cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 monooxygenase (CYP450) metabolic pathways of arachidonic acid.