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New Interfaces of Thyroid Hormone Actions With Blood Coagulation and Thrombosis

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Abstract

Substantial clinical evidence indicates hyperthyroidism enhances coagulation and increases the risk of thrombosis. In vitro and clinical evidence implicate multiple mechanisms for this risk. Genomic actions of thyroid hormone as 3,5,3′-triiodo-L-thyronine (T_3) via a nuclear thyroid hormone receptor have been implicated, but recent evidence shows that nongenomic mechanisms initiated at the receptor for L-thyroxine (T_4) on platelet integrin αvβ3 are prothrombotic. The T_4-initiated mechanisms involve platelet activation and, in addition, cellular production of cytokines and chemokines such as CX3CL1 with procoagulatory activities. These procoagulant actions of T_4 are particulary of note because within cells T4 is not seen to be functional, but to be only a prohormone for T_3. Finally, it is also possible that thyroid hormone stimulates platelet-endothelial cell interaction involved in local thrombus generation. In this brief review, we survey mechanisms by which thyroid hormone is involved in coagulation and platelet functions. It is suggested that the threshold should be lowered for considering the possibility that clinically significant clotting may complicate hyperthyroidism. The value of routine measurement of partial thromboplastin time or circulating D-dimer in patients with hyperthyroid or in patients treated with thyrotropin-suppressing dosage of T_4 requires clinical testing.

Keywords

platelet aggregation, hyperthyroidism, L-thyroxine (T_4), cancer, integrin αvβ3

Introduction

Substantial clinical evidence indicates that the complex process of blood coagulation is modulated by thyroid hormone and that the risk of pathologic coagulation is appreciable in hyperthyroidism including in uncommon sites such as cerebral venous thrombosis.[1-9] Research findings disclosed in the past 5 years document some of the coagulation factors whose levels are altered in the setting of elevated circulating thyroid hormone levels (Table 1).[2,7,12] However, the mechanisms of action of thyroid hormone on coagulation appear to be more complex than we have appreciated. An impression that the actions of the hormone on coagulation are wholly genomic in mechanism[16] and mediated by an important nuclear thyroid hormone receptor (TR), TRβ, has overlooked the nongenomic contributions of thyroid hormone to platelet activation and to coagulation-relevant cytokine-chemokine expression, as we discuss below. Endothelial dysfunction may also participate in pathologic coagulation and thyroid hormone can nongenomically affect the behavior of endothelial cells.[17,18]

Although a strong consensus exists that clinical hyperthyroidism and excess thyroid hormone promote pathologic coagulation, it should also be noted that an association has been reported of subclinical hypothyroidism with a prothrombotic coagulation factor profile that can be normalized with L-thyroxine (T_4).[19] Others have reported that selected coagulation factors may be increased in the blood of subclinical patients with hypothyroid.[15] These observations need to be reconciled with the very dominant impression that it is overactivity of the thyroid gland that confers a risk of pathologic clotting.

Observations and Pathophysiology

Thyroid Hormone and Platelet Function

We have reported that physiological concentrations of L-thyroxine (T_4) activate human platelets resulting in

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Table 1. Circulating Procoagulant Factors Increased in Hyperthyroidism.

Factors	References
FVIII	2,7
FXIIIB chain	10
FIX	2,7,10
FXI	10
SERPIN A5[a]	10,11
VWF	2,7,12,13
Fibrinogen	2,7,13,14
PAI-1	8,12
TAFI	15

Abbreviations: PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin-activated fibrinolytic inhibitor; VWF, von Willebrand factor.
[a]Activated protein C inhibitor.

adenosine triphosphate release (degranulation) and aggregation.[20] The hormonal action is initiated nongenomically at integrin αvβ3, a structural protein expressed by platelets that contains receptor for thyroid hormone. Interestingly, the critical intracellular form of T_4, 3,5,3′-triiodo-L-thyronine (T_3), although derived from T_4, does not activate platelets. These observations raise the possibility that high circulating levels of T_4 may support pathologic platelet aggregation and contribute to the increased risk of coagulation imposed clinically by hyperthyroidism.[2,4-6] In addition, chemokines such as CX3CL1 whose production at the level of gene transcription is regulated from αvβ3 by thyroid hormone analogues[21] may induce platelet aggregation and adherence in a clinical setting associated with pathologic clotting.[22]

A second aspect of platelet function to examine in the context of the thyroid hormone-coagulation interface is the interaction of platelets and endothelial cells. This interaction is, of course, an essential step in arterial thrombus formation. It has been reported that human-activated platelets can induce endothelial cell activation[23] and as noted above, we have shown that T_4 activates platelets. The activation of endothelial cells by platelets is achieved at least in part by the interaction of an endothelial cell protein, platelet endothelial cell adhesion molecule-1 (PECAM-1; CD31) with the extracellular domain of integrin αvβ3.[24] PECAM-1 is relevant to intercellular junctions and has other functions. It is found on the surfaces of both platelets and endothelial cells. The extracellular domain of integrin αvβ3 contains the cell surface receptor for thyroid hormone that accounts for a number of nongenomic actions of the hormone within the endothelial cell and at the cell surface. Via the αvβ3 receptor, thyroid hormone can regulate the functions of proteins adjacent to the integrin[17] including the vascular endothelial growth factor receptor and cell surface receptors for other vascular growth factors.[25]

Schlenker and coworkers reported that CD31-positive adult rat brain blood vessels increase in amount in thyroidectomized, hypothyroid animals after treatment with T_4 as compared to the untreated hypothyroid animals, to levels similar to those found in euthyroid animals.[26] In the Schlenker model of angiogenesis, thyroid hormone had a beneficial effect on platelet endothelial interactions resulting in improved angiogenesis. It is unclear whether the effect of T_4 in this setting is due to an increase in the amount of CD31 (PECAM-1) generated or to an increase in the binding of αvβ3 with PECAM-1 that enhances endothelial-platelet interaction. Given these alternatives, the possibility is raised that excess amounts of thyroid hormone may contribute to the risk of excess platelet-endothelial cell adherence via its actions on integrin αvβ3 and is another factor to consider in the genesis of clinically significant increase in coagulability in hyperthyroidism. However, the actions of thyroid hormone on *PECAM-1* gene expression in blood vessels are inconsistent.[27,28]

Increased platelet function has been demonstrated in patients with overt hyperthyroidism by the use of the platelet function analysis screening assay (PFA100), which uses membranes coated with collagen or epinephrine to measure the time that blood flowing across the membranes will form an occluding plug of platelets, the so-called closure time. Although the assay is usually used to detect prolonged closure times indicating platelet dysfunction, Homoncik et al found significantly shorter closure times in a large group of patients with overt hyperthyroidism as compared to euthyroid controls. When T_4 levels fell to normal after treatment, the patients' closure times increased to the normal level. The authors attributed the increased platelet function in hyperthyroidism to increased levels of von Willebrand factor (VWF) and the latter fell to normal after treatment.[29] Similar findings of shortened PFA100 closure times and increased VWF were reported by Horacek et al in patients made mildly hyperthyroid with levothyroxine treatment for thyroid cancer.[12] Increased production of VWF has been shown to represent a genomic effect of T_3 in cultured endothelial cells along with endothelin and fibronectin.[30] In view of the increased platelet aggregation response to T_4 in the absence of excess VWF in the study by Mousa et al noted above,[20] membrane effects of T_4 could also be a factor in the increased platelet closure times found in patients with hyperthyroid.

Coagulation Factors in the Plasma Proteome That Are Affected by Thyroid Hormone

Engelmann et al[11] and Pietzner and coworkers[10] reported changes in the coagulation factors in the plasma proteome in a cohort of 16 healthy men made hyperthyroid by oral T_4 for 8 weeks. The coagulation proteins that showed the most significant increases and correlation with the rise in serum-free T_4 included factors FXIII B subunit, FIX, an inhibitor of activated protein C, SERPIN A5, and α2 antiplasmin (Table 1). These increases and the negative correlation of plasminogen, the fibrinolytic precursor, are consistent with a prothrombotic and hypofibrinolytic state. The increases in FXI, FV, and prothrombin were less strongly correlated with T_4 levels. There was no correlation with FVII, FX, VWF, or fibrinogen.

These plasma proteome findings differed somewhat for unclear reasons from those of earlier studies using conventional

functional assays of coagulation factors in patients with hyperthyroidism and also healthy individuals treated with T_4. The earlier studies also reported elevations in FIX and FXI but found increases in factor VIII, VWF, and fibrinogen and plasminogen activator inhibitor-1 as well.[2,7,12,15,31] This information is summarized in Table 1. Compared to clots from euthyroid individuals, ultrastructure examination of clots from patients with hyperthyroidism showed much denser fibrin network and increased clot lysis times consistent with hypofibrinolysis.[32]

Procoagulatory Cytokines and Chemokines Affected by Thyroid Hormone

In vitro experiments with human umbilical endothelial cells show that interleukin (IL)-1 stimulation can trigger production of prothrombotic factors ultra large VWF multimers and tissue factor as well as inflammatory cytokines, IL-6 and IL-8, and adhesion molecules.[33] Interleukin-1 gene expression is subject to regulation by thyroid hormone analogues such as tetraiodothyroacetic acid (tetrac) and modified tetrac (Nanotetrac).[34,35] Levels of other cytokines relevant to coagulation and endothelial dysfunction favoring coagulability occur in both subclinical and overt hyperthyroidism.[36] In these clinical settings, increased circulating levels of cytokines IL-6, IL-12, and IL-18 have been described.

As mentioned above, tetrac in its nanoparticulate form as Nanotetrac regulates the transcription of the gene of the chemokine CX3CL1, specifically via the cell surface receptor on integrin αvβ3. Secreted by endothelial cells in response to certain inflammatory factors, CX3CL1 induces increased platelet adherence to collagen,[22] and we now know that release of this cytokine is also regulated by thyroid hormone analogues acting nongenomically at integrin αvβ3.[21] Chemokine CXCL3 production is significantly upregulated in thrombin-stimulated endothelial cells,[37] and this chemokine is also subject to control from αvβ3 by thyroid hormone analogues.[21]

Can Thyroid Hormone Affect Coagulation in Brain?

Rapidly dividing endothelial cells express plasma membrane integrin αvβ3,[38] and nongenomic action of T_4 at the receptor on this integrin supports endothelial cell division[13,17] and endothelial cell migration toward extracellular matrix protein cues.[18] The vasculature of brain tumors, particularly glioblastoma multiforme, is prone to develop clots.[39] These may lead to local necrosis, but also to angiogenesis. T_4 presented by blood hormone transport proteins is taken up by choroid plexus transthyretin (TTR), enabling transport of this hormone into cerebrospinal fluid and brain.[40] T_4 has actions of its own on neurons[25] but is particularly important in the central nervous system as a prohormone for T_3. We have shown that Nanotetrac is readily accumulated by orthotopic glioblastoma xenografts.[41] Therefore, thyroid hormone would be expected to support coagulation in brain and brain neoplasms, but it is not clear how much of a role the hormone plays in intratumoral coagulation.

Is Thyroid Hormone a Factor in Cancer-Associated Thrombosis?

Cancer-associated thrombosis continues to be a focus of extensive study.[42-47] The recent observation of the contribution of the platelet to this association[48] raises the possibility—given the control of platelet function exercised by physiological concentrations of thyroid hormone, as discussed above—that this hormone can contribute to the pathogenesis of the association.

Subclinical Hypothyroidism and Clinical Blood Coagulation

Increased clinical risk of thromboembolism has been incompletely profiled in 2 patient groups with subclinical hypothyroidism.[49,50] This appears to be inconsistent with the body of evidence reviewed above that thyroid hormone positively affects the expression or function of a variety of the components of the coagulation process and is inconsistent with reports of acquired von Willebrand disease in hypothyroidism.[51] However, the principal diagnostic feature of subclinical hypothyroidism is an elevation of circulating pituitary thyrotropin (thyroid-stimulating hormone [TSH]), reflecting the feedback inhibition relationship between circulating thyroid hormone levels and TSH. Serum TSH levels in the range encountered in subclinical hypothyroidism have been independently associated with in vitro thrombogenicity as measured with the Badimon chamber in recent studies of patients with acute coronary syndrome[52] or with clinical deep venous thrombosis.[53] It is not clear what the precise mechanisms for such observations might be, but TSH has been shown to induce endothelial cell dysfunction in association with altered expression of genes for endothelial nitric oxide synthase, prostacyclin (PGI_2), and several other factors,[54] raising the possibility that endothelial cell-platelet interactions could be affecting coagulation in low-grade hypothyroidism. A very limited literature on overt hypothyroidism and coagulation does not support an increased risk of thrombosis in thyroid hypofunction.

Discussion

The classic coagulation factors whose levels may be increased by elevated circulating levels of thyroid hormone are summarized in Table 1. The importance of the contributions of such factors to the increased risk of thrombosis or thromboembolism in patients with hyperthyroidism should be made clear to practitioners.

What we add here to the pathophysiology of thrombotic risk in hyperthyroidism is a panel of other prothrombotic mechanisms now recognized to be active in the setting of increased circulating levels of thyroid hormone. These mechanisms have been disclosed in clinical studies and via in vitro models that have relied on changes in thyroid hormone concentrations

within the range encountered clinically. The mechanisms include enhancement by thyroid hormone of platelet activation, release of procoagulatory cytokines and chemokines, and possible interactions of activated platelets and endothelial cells that may provide a specific basis and early step for intravascular thrombosis. These actions of the hormone appear to be nongenomic in mechanism, that is, they do not depend on primary interactions between T_3 and nuclear receptor (TR) proteins.

Central nervous system thrombosis has been reported as a complication of increased blood levels of thyroid hormone, as noted above. The blood-brain barrier is not an impediment to thyroid hormone access to brain. The hormone has a specific system for accessing brain and spinal fluid that involves binding of T_4 to a choroid plexus protein (TTR) that enables cerebrospinal fluid and brain uptake of the hormone. Such uptake is particularly important to brain development, but has negative aspects, as well, because the hormone is procoagulatory and may be a growth factor for glioblastoma.[55]

The impact of thyroid hormone on the process of coagulation should serve for endocrinologists to lower the threshold of suspicion of coagulopathy in patients with hyperthyroid. Routine measurement in the setting of thyrotoxicosis of coagulation factors is not practiced, but in view of the correlation of thrombosis risk with the degree of elevation of free thyroxine,[2] it would be useful for endocrine organizations to determine systematically whether a policy is indicated for the threshold at which coagulation evaluation is indicated in hyperthyroidism. This may also apply to patients with thyroid carcinoma whose endogenous thyrotropin post-thyroidectomy is under suppression with exogenous T_4 in greater than replacement dosage.[56] Evaluation might initially involve measurement of widely available activated partial thromboplastin time (aPTT) and the D-dimer fibrin degradation product at the time of diagnosis of thyroid disease.

A final issue is the occurrence of apparently idiopathic thrombosis in the patient who is clinically eumetabolic. This is relevant to the patient with cancer population that expresses increased coagulation risk. In such patients, is a serum-free T_4 value found to be in the upper quartile of the normal range a risk factor for the hypercoagulable state? We would propose that this issue needs formal evaluation in a clinical protocol that includes measurement of aPTT, D-dimer, or other indexes of clotting risk.

Conclusions

Recent observations emphasize previously unappreciated mechanisms by which thyroid hormone stimulates the process of coagulation. These mechanisms involve platelets, coagulation factors, cytokines, and endothelial cells. Reemphasis is due on the risk of thrombosis that has been documented in series of patients with hyperthyroid. Topics raised here are whether the possibility of a concomitant hypercoagulable state should be investigated routinely in patients with hyperthyroid and whether borderline elevation of circulating thyroid hormone contributes to thrombosis in euthyroid patients who are hypercoagulable. These topics deserve formal clinical evaluation.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Drs Davis and Mousa hold stock in a small pharmaceutical company, NanoPharmaceuticals LLC, that is developing anticancer drugs, and Dr Davis is Chief Scientific Officer at the company.

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