Prolactin and vascular disease; a first cautious assessment
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Citation for published version (APA):

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Chapter 1

General introduction and outline.

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Several hormonal disturbances are associated with atherosclerotic vascular disease and thrombosis.

Coronary artery disease, which is the consequence of atherosclerosis, is still the leading cause of death worldwide, and with an estimated mortality rate of seven million per year, it represents 30% of all global deaths [1]. Additionally, venous thromboembolism is a commonly encountered and potentially lethal disease, which recurs frequently and causes serious long-term complications. The incidence rate of venous thromboembolism may exceed 1 per 1000 in the general population [2]. There is still an ongoing need to improve understanding of the pathogenesis of both atherosclerotic vascular disease and venous thromboembolism in order to develop additional therapies. Of interest, the association between several endocrine disorders and cardiovascular disease has been acknowledged for many decades. Both an extreme excess or deficiency as well as subclinical variation in thyroid, steroid and somatotropic hormones increase the occurrence of atherosclerotic vascular disease and consequently cardiovascular mortality and may also affect the occurrence of venous thrombosis [3,4]. The studies presented in this thesis focus on the potential of prolactin to influence vascular disease, a still largely unexplored area.

What do we know about prolactin in relation to vascular disease?

Prolactin was discovered in the 1930s as a hormone that stimulates milk synthesis by the breasts and is produced in the anterior pituitary by lactotrophic cells. These cells produce prolactin in response to stimuli such as estrogen and thyrotropin-releasing hormone, whereas dopamine has an inhibitory effect on prolactin secretion [5]. Interestingly, the last two decades several in vitro and mouse studies, including mice deficient for prolactin or for its receptor, have indicated that prolactin, besides its well-recognized function for lactation, may play a role in several other (patho)physiological processes, such as regulation of the immune response [6]. For the larger part, it is unclear how these findings apply to humans. Indeed prolactin can be of relevance both in men and women, since systemic prolactin levels do not differ much between men and non-pregnant or non-lactating women [7].

Prolactin may modulate cellular pathways in atherosclerotic and thrombotic vascular disease.

Atherosclerotic plaque formation starts with monocytes attaching to endothelial cells of the arterial vessel wall that express cell adhesion molecules upon activation by oxidized low density cholesterol (LDL) and inflammatory cytokines [8]. In vitro data indicate that prolactin has the ability to stimulate adhesion of monocytes to endothelium [9]. Prolactin has also been shown to stimulate smooth muscle cell proliferation [10], which suggests that prolactin might stimulate intima media thickening, an important process in atherosclerotic plaque formation. Disruption of atherosclerotic plaques leads to thrombus formation and arterial occlusion. Blood platelets are key components in thrombus formation [11], however, data on a possible relationship between prolactin and platelet function are inconclusive [12;13]. Nonetheless, prolactin enhances prothrombin synthesis in rat liver microsomes and maximizes the effect of estrogen on hemostatic parameters in ovariectomized and hypophysectomized rats [14,15].

The overall process of fibrinolysis seems not to be affected by prolactin [16]. Against this background, we postulate that prolactin could have the ability to modulate atherosclerotic plaque formation, the events after rupture of the plaque, and the clotting process, by directly influencing local cellular processes.

Prolactin may modulate conventional cardiovascular risk factors

When lactotrophic cells undergo neoplastic transformation, they will give rise to a prolactinoma, a prolactin-secreting pituitary adenoma. Of interest, clinical studies indicate that prolactinoma patients display metabolic disturbances, which are in accordance with the criteria of the metabolic syndrome. Indeed, having the metabolic syndrome may contribute to atherosclerotic plaque formation, since it is predictive of cardiovascular disease and mortality [17,18]. In fact, prolactinoma patients have high hsCRP levels and elevated insulin resistance indexes [19-22]. Additionally, flow-mediated dilation (FMD) is lower in these patients, indicating endothelial dysfunction [22]. Some studies report that prolactinoma patients display hypercholesterolemia, low HDL-cholesterol and hypertriglyceridemia [19,20,23]. Other studies, however, show no association between prolactin and lipid profile [21,22]. Despite these suggestive findings, no studies on cardiovascular mortality in relation to prolactin levels have been conducted.

OUTLINE OF THE THESIS

Taken together, at the start of our quest, previous studies suggested that prolactin may have the potential to contribute to cardiovascular disease, either through direct modulation of local cellular processes within atherosclerotic plaques or thrombi, or through influencing conventional cardiovascular metabolic risk factors.

Additionally, angiogenesis is one of the processes that may either support or interfere with vascular homeostasis, depending on the underlying process. Some observations indicated that intact prolactin could promote new vessel formation in vivo [24,25]. Whether these effects result from a direct effect of prolactin on endothelial cells is unclear. Therefore, we decided to explore this issue. This thesis consists of two parts, Part I includes clinical studies in which we aimed to evaluate associations between prolactin and coronary artery disease, venous thrombosis or atherothrombotic parameters and this part contains a hypothesis-generating review. Part II involves fundamental research; here we explore the effect of prolactin on mechanisms involved in atherosclerotic vascular disease or angiogenesis.

Part I: Prolactin and coronary artery disease, venous thrombosis or atherothrombotic parameters.

In chapter 2 we investigate whether prolactin levels can predict the occurrence of coronary artery disease. Next, in chapter 3 we explore how prolactin is related to hsCRP in patients with myocardial
Hyperprolactinemia of pregnancy is not associated with increased in vivo endothelial function, insulin sensitivity and inflammatory markers in Part II: The effect of prolactin on mechanisms involved in atherosclerotic vascular disease or angiogenesis.

In chapter 9 we investigate the effect of prolactin on platelet function in vitro. In chapter 8 we study whether the prolactin receptor is expressed locally within atherosclerotic plaques. Additionally, in chapter 9 we describe the effect of high prolactin levels on atherosclerotic plaque formation in mice. In chapter 10, the role of prolactin in angiogenesis is investigated.

REFERENCES