Creatine kinase and cardiovascular disease

Horjus, D.J.

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Introduction and outline of the thesis

CREATINE KINASE INTERFERING WITH BLOOD PRESSURE AND PLATELET ACTIVATION

In the world around us energy is a 'hot topic'. Energy production, reduction of energy use and consumption of energy are heavily debated. A sustainable balance in our global energy circuit is a top priority on the political agendas. Similarly, also our interior human energy systems have to be balanced to maintain healthy homeostasis. For example, too much platelet activation causes thrombosis, whereas inhibition or insufficient activation of platelets leads to bleeding.
In this thesis the effect on cardiovascular health of creatine kinase (CK), one of the important enzymes in the interior energy circuit, is examined.

CK catalyzes the chemical equilibrium:

creatinephosphate + adenosinediphosphate (ADP) ↔ creatine + adenosinetriphosphate (ATP).

Hereby, CK supports the cellular energy circuit by facilitating energy transportation from the site of production in mitochondria to sites of energy consumption [1]. By rapid generation of ATP, CK plays a key role in maintaining intracellular energy homeostasis while energy demands fluctuate such as in cardiac and vascular muscle cells [1,2]. This function is vital, and an excess or reduced CK activity can be harmful. For example, a too strong vascular contractility may lead to hypertension [3], whereas too little contractility can lead to fainting [4]. CK is present in many tissues of the body, with the highest activity levels in skeletal muscle, brain, heart and smooth muscle cells [1,5]. The CK activity as can be measured in the blood is the result of the release of cytosolic CK from mainly skeletal muscles, being transported to the bloodstream by lymph drainage [3,6]. In the bloodstream CK can inhibit platelet aggregation by scavenging ADP, a potent platelet activator [7]. Consequently, an intravascular high CK activity may lead to bleeding, but might also protect against thrombotic disease [7].
The last 15 years, cardiovascular disease has remained one of the leading causes of mortality [8]. By studying the effect of CK on cardiovascular disease, we approach this major health problem by providing new insights in its pathophysiology and shed light on potential treatment targets. First, we examine both the effect of the intracellular CK activity and thus its pure energy generating form on blood pressure [1,3]. Secondly, we study its 'side effect' on blood platelets when intracellular CK leaks into the bloodstream [1,7].

CREATINE KINASE AND BLOOD PRESSURE

Hypertension is one of the major risk factors of cardiovascular disease, and therefore its pathophysiology and management are extensively studied [9–11]. The observation of ethnic differences in hypertension is the basis of the first two parts of this thesis [12], i.e.

CK and blood pressure, and CK and hypertensive disorders in pregnancy. A landmark study found that the ethnic differences in blood pressure could be explained by the difference in CK activity between ethnic groups [3]. On the one hand, a low CK activity is associated with syncope, a condition frequently caused by a sudden drop of blood pressure [4]. On the other hand, high CK activity was found to be associated with hypertension in multiple cohorts of the general population [3,13]. Smaller *ex vivo* studies support these associations, showing that inhibition of CK reduces the contractility of small arteries, which may lead to a lowering in blood pressure [14,15]. These findings indicate that the level of CK activity is vital for a healthy balance between relaxation and constriction of the vasculature. First, this thesis provides new insights into whether the CK system may be a possible target for hypertension treatment. Secondly, we investigate the association between CK and blood pressure in specific stadia of a womans' life; namely blood pressure during pregnancy and postpartum, and hypertensive disorders in pregnancy.

CREATINE KINASE AND HEMOSTASIS

The third topic of this thesis concerns the effect of plasma CK activity on platelet aggregation and secondary hemostasis. Already in 1985, removal of ADP by an excess concentration of creatine phosphate/CK was shown to completely inhibit platelet aggregation [16], which revealed the central role of ADP in the activation of platelets. The discovery of the wide range of plasma CK activity in the general population raised the question whether CK within the physiological activity range may also affect platelet activation by scavenging ADP [17]. If true, this would be of clinical relevance because high plasma CK activity may attenuate risk of bleeding as well as of thrombosis. Herewith, the hypothesis for the third part of this thesis was born. We study the effect of plasma CK activity in the physiological range on hemostasis both in vitro and in a large population cohort. Additionally, we discuss the synergistic effect of plasma CK activity with agents with antiplatelet properties.

OUTLINE OF THE THESIS

The central theme of this thesis is the role of CK in cardiovascular disease with focus on blood pressure and platelet aggregation.

Part I describes the studies in which intervention in the CK system was used to evaluate its effect on blood pressure and cardiovascular disease. **Chapter 2** provides an overview of the available literature on the CK substrate creatine, and its analogues, administered by different routes and schemes, to assess its effect on hypertension and cardiovascular disease. Subsequently, in the clinical trial described in **Chapter 3 and 4,** we study the effect of the creatine analogue beta-guanidinopropionic acid on blood pressure in healthy men.

Hereby, we analyze whether intervening into the CK system may be beneficial and assess this substance for its eligibility as a potential antihypertensive drug.
In part II we study the role of CK in blood pressure during and after pregnancy, and in hypertensive pregnancy disorders. First, the association between CK activity and blood pressure during pregnancy is described in **Chapter 5**. Secondly, this chapter debates whether CK activity might play a role in hypertensive pregnancy disorders. Thereafter, **Chapter 6** addresses the hypothesis that high CK may cause a lifelong increased risk of hypertension. In **Chapter 6** we therefore assess whether the susceptibility to hypertension later in life in women with a history of early-onset preeclampsia may be mediated by high CK activity.
In part III the influence of CK on platelet aggregation is investigated. The effect of plasma CK in a physiological activity range on platelet aggregation, discussed in **Chapter 7**, is the starting point for chapters 8 and 9. **Chapter 8** addresses the synergistic platelet inhibiting effect of plasma CK activity with dabigatran and its clinical implications. Additionally, **Chapter 9** provides the results of a sub study of a large community-based study assessing the association between plasma CK activity and D-dimer level, as a marker for fibrin formation and thrombin generation . Given the supportive role of platelets in the secondary hemostasis, high plasma CK activity could indirectly influence the secondary hemostasis by inhibiting platelet activation.
Finally, **Chapter 10** provides a summary and discusses the key findings of this thesis.

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