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Review

The role of secretory phospholipases as therapeutic targets for the treatment of myocardial ischemia reperfusion injury

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ABSTRACT

Myocardial reperfusion injury is a consequence of restoration of blood flow post ischemia. It is a complex process involving an acute inflammatory response activated by cytokines, chemokines, growth factors, and mediated by free radicals, calcium overload leading to mitochondrial dysfunction. Secretory phospholipases (sPLA2) are a group of pro-inflammatory molecules associated with diseases such as atherosclerosis, which increase the risk of reperfusion injury. This acute response leads to breakdown of phospholipids such as cardiolipin, found in the mitochondrial inner membrane, leading to disruption of energy producing enzymes of the electron transport chain. Thus the activation of secretory phospholipases has a direct link to the vascular occlusion and arrhythmia observed in myocardial reperfusion injury. Therapeutic agents targeting sPLA2 are under human trials and many are in the preclinical phase. This article reviews the pathological effects of various groups of secretory phospholipases (I, II, V and X) implicated in myocardial ischemia reperfusion injury and the phospholipase inhibitors under development. Considering the fact that human trials in this class of drugs is limited, sPLA2 as a potential target for drug development is emphasized.

Contents

1. Introduction

Cardiovascular diseases (CVD) are the most common cause of death worldwide, both in men and women. CVD includes a group of disorders such as coronary heart disease (also called ischemic heart disease), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein

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thrombosis and pulmonary embolism, all of which lead to myocardial dysfunction. The functioning of the heart depends on the blood flow, which carries oxygen and nutrients for its normal function, but when the blood vessels are narrowed or blocked (in case of atherosclerosis or thrombosis), the heart experiences a state of ischemic shock that may develop into myocardial infarction. After acute ischemic episode observed in patients with ST elevation, timely reperfusion is essential to recover the viable myocardium, based on which ischemic injury is classified as reversible and irreversible injury [1]. While the former manifests as arrhythmia/stunning due to free radical release and calcium overload, it is self-terminating, but the later form of injury occurring due to microvascular occlusion or late reperfusion additionally leads to hyper contracture and mitochondrial dysfunction which is lethal and no therapy exists. Interestingly, the reversibility of this cardiac ischemic injury is not only dependent on the duration (<min/sec) of ischemia but also on the risk factors (diabetes, hypertension) associated with the myocardium. Timely reperfusion of the ischemic heart is the major treatment modality to control ischemic damage, however this process itself can induce cardiomyocyte death termed as reperfusion/revascularization injury [2]. Reperfusion injury induces a spectrum of dysfunctions to myocardium, vasculature and electrophysiology that clinically manifests as arrhythmias and myocardial stunning. At the molecular level, several triggering molecules have been identified, arising from the cardiomyocytes, endothelial cells, and inflammatory cells, which activate the small cytosolic signaling proteins that finally converge on sub cellular structures such as mitochondria [3] and the nucleus [4,5]. A number of studies have indicated that there is an increased activity of phospholipase during ischemia reperfusion [6] and the inhibition of these phospholipases can impart cardio protection to reperfusion injury [7,8]. However, the involvement of the distinct phospholipase subtypes in the pathophysiology of reperfusion injury is not completely explored. The rising number of clinical trials with phospholipase inhibitors in recent times, emphasizes their importance as therapeutic targets, despite facing failures. In the present article, we discuss the research carried out on the specific sub-types of secretory phospholipases ($sPLA_2$) as a potential therapeutic targets for the treatment of myocardial ischemia reperfusion injury.

2. Management of myocardial ischemia reperfusion injury

The ischemic heart experiences nutrient deprivation, and lack of oxygen resulting in metabolic acidosis, hyperkalemia and Ca^{2+} overload leading to a rise in the level of reactive oxygen species (ROS) [9,10]. The pathogenesis of reperfusion injury being multifactorial, the major biochemical alterations that arise from myocardial ischemia reperfusion injury and lead to membrane damage are i) accumulation of metabolic products such as lactic acid [11] and hypoxanthine [12] ii) activation of membrane destructive phospholipases [13] iii) formation of oxygen free radicals [14] iv) infiltration of leukotriene activated neutrophils [15] v) increased circulating catecholamine's [16] vi) cytosolic calcium overload and vii) altered glucose metabolism.

Evidence from animal models showed 48% increase in lysophospholipids especially ceramide after 30 minutes of ischemia followed by 3 h of reperfusion [17]. This rise is due to the membrane damage caused by endogenous activation of phospholipases that results in the liberation of eicosanoids and initiates subsequent lipid signaling [18]. Yano et al. substantiated these findings using a sPLA2 $V^{-/-}$ mice that showed reduced infarction in myocardial IR injury [19].

The established clinical management for the acute myocardial infarction is coronary revascularization therapy using either thrombolytic therapy or primary percutaneous coronary intervention. These procedures are often encountered with post-surgical complications such as arrhythmia, myocardial stunning, lethal reperfusion induced injury or accelerated necrosis [1]. Even though the timely myocardial revascularization coupled with latest advancements in surgical interventions greatly reduces the mortality and morbidities, about 50 per cent of the damage to heart tissue following myocardial infarction is as a result of lethal reperfusion injury [1]. Despite all efforts, reperfusion injury remains a major problem in the post-operative care of myocardial infracted patients, considering the fact that approximately 1.6 million cardiac reperfusion procedures are performed every year in the cardiac centers and hospitals in the western world, where in most of the cases are readmitted at a later stage due to multiple organ failure [20].

3. Phospholipase and myocardial ischemia reperfusion

Breakdown of myocardial phospholipids in to fatty acids, lysophopholipids and un-esterified arachidonic acid by phospholipase is one of the major events that occur during ischemia reperfusion injury [13]. But the specific type of phospholipase involved in this mechanism is not fully explored. In general, phospholipases are classified based on their structure and function into four families, namely A, B, C and D, based on the ester bond that is cleaved within a phospholipid molecule (Table 1) [21]. In another classification, phospholipases are broadly divided into acyl hydrolases and the phosphodiesterases. Phospholipase A_1 (PLA_1), phospholipase A_2 (PLA_2), phospholipase B (PLB), and lysophospholipase $A_{1/2}$ ($LysoPLA_{1/2}$) constitute the acyl hydrolases, whereas the phosphodiesterases are represented by phospholipase C (PLC) and phospholipase D (PLD).

Among the major types, phospholipase A (PLA) plays a significant role in the pathophysiology of myocardial ischemia reperfusion injury (Fig. 1). The Fig. 2 gives a short overview of the various drugs targeting the phospholipases for treatment of ischemia reperfusion injury. Similarly, in Table 2, we have reviewed the different types of phospholipases targeted in the pre-clinical studies for the treatment of myocardial ischemia reperfusion injury. Among the various types of phospholipases involved in the

Table 1
Categories of Phospholipases.

Major Type of Phospholipase	Sub types	Secondary signaling molecules produced	Cleavage site
Phospholipase A1	Extracellular (PS-PLA1,mPA-PLA1α,mPA-PLA1β,lipases) and intracellular (iPLA1α,iPLA1β,iPLA1γ)	2-lyso phosphatidyl choline, free fatty acid and lysophopsholipid	Sn1 position of acyl ester bond
Phospholipase A2	Secreted PLA2 (Type 1, 2,3), Intracellular cytosolic and Ca^{+2} independent	1-lyso phosphatidyl choline, free fatty acid, Eicosanoids, Platelet activating factor	Sn2 position of acyl ester bond
Phospholipase C	6 subtypes, PLC β, PLCε, PLCγ, PLCδ, PLCη and PLCξ	Diacyl glycerol, Inositol phosphates and phosphatidylcholine	Glycerol 3-OH and Phosphate
Phospholipase D	PLD1 and PLD2	Phosphatidic acid, choline	Phosphodiester bond