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Review

Anthocyanins in cardioprotection: A path through mitochondria

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ABSTRACT

Constantly growing experimental data from *in vitro, in vivo* and epidemiological studies show the great potential of anthocyanin-containing fruit and berry extracts or pure individual anthocyanins as cardioprotective food components or pharmacological compounds. In general it is regarded that the cardioprotective activity of anthocyanins is related to their antioxidant properties. However there are recent reports that certain anthocyanins may protect the heart against ischemia/reperfusion-induced injury by activating signal transduction pathways and sustaining mitochondrial functions instead of acting solely as antioxidants. In this review, we summarize the proposed mechanisms of direct or indirect actions of anthocyanins within cardiac cells with the special emphasis on recently discovered their pharmacological effects on mitochondria in cardioprotection: reduction of cytosolic cytochrome c preventing apoptosis and sustainment of electron transfer between NADH dehydrogenase and cytochrome c supporting oxidative phosphorylation in ischemia-damaged mitochondria.

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Abbreviations: Akt, serine/threonine specific protein kinase B; Cy, cyanidin; Cy3G, cyanidin 3-O-glucoside; Dp, delphinidin; Dp3G, delphinidin 3-O-glucoside; eNOS, endothelial NO synthase; ERK1/2, extracellular-signal-regulated protein kinase 1 and 2; GSK3β, glycogen synthase kinase 3 beta; JAK, Janus kinase; Mv, malvidin; Mv3G, malvidin 3-O-glucoside; Pg, pelargonidin; Pg3G, pelargonidin 3-O-glucoside; PKC, protein kinase C; PKG, protein kinase G; PI3K, phosphatidylinositol 3-kinase; Pim-1, Pim-1 proto-oncogene serine/threonine protein kinase; Pn, peonidin; Pn3G, peonidin 3-O-glucoside; Pt, petunidin; Pt3G, petunidin 3-O-glucoside; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription.

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1. Introduction

It is widely accepted that diets rich in fruits and vegetables provide beneficial effects on human health. Most of these effects are thought to be related to flavonoids—polyphenolic compounds of coloured fruits, berries and vegetables, which may act as strong antioxidants and prevent inflammatory reactions leading to various chronic diseases. Chronic inflammation is considered as one of the main factors in development of cardiovascular pathologies such as hypertension, atherosclerosis, endothelial dysfuncion leading to heart ischemia, myocardial infarction and heart failure. Therefore search for new pharmacological means, particularly from natural sources, for controlling such processes is of great value, and it is not surprising that antioxidant and antiinflammatory functions of flavonoids are widely investigated. However in recent years accumulated evidence showed that cardioprotective mechanisms triggered by various flavonoids may extend far beyond antioxidant actions of these conpounds (see reviews Refs. [1–7]). Some of such effects, like modulation of intracellular signaling pathways, have been also attributed to anthocyanins and their derivatives (*i.e.*, chemically different substances from other subgroups of flavonoids) which may affect regulation of cellular metabolism and survival under pathological conditions including ischemia/reperfusion. Thus, in this short review we will discuss recent experimental findings on effects of anthocyanins in protection against ischemic heart damage with particular emphasis on three important effects on mitochondria regulating cell death and survival during myocardial ischemia/reperfusion: (1) anthocyanins serving as substrates for Complex I of electron transfer system, (2) anthocyanins as mild uncouplers of oxidative phosphorylation, and (3) anthocyanins in reduction of cytosolic cytochrome c.

2. Heart ischemia/reperfusion-induced injuries

Heart diseases, such as myocardial infarction or ishemic heart failure, are the major causes of death in the developed countries, and unfortunately the mortality rate from these diseases is still increasing [8,9]. During ischemia, the supply of oxygen and nutrients to the heart is impaired, and mitochondria in cardiomyocytes undergo rapid structural and functional changes: suppression of oxidative phosphorylation mainly due to the inhibition of Complex I of the electron transport system and/or ATP synthase, loss of mitochondrial membrane integrity due to opening of mitochondrial permeability transition pore and release of cytochrome c from mitochondria [10–13] (see Fig. 1). Furthermore, intracellular signaling pathways that promote apoptosis and necrosis are activated [14]. Inhibition of Complex I activity caused by short periods of ischemia usually can be reversed during reperfusion, however protracted ischemic periods cause severe irreversible inhibition of Complex I and subsequent cessation of ATP production by oxidative phosphorylation [15]. One of the earliest irreversible events in ischemic heart damage—the liberation of cytochrome c from mitochondria may lead to cardiomyocyte apoptosis (reviewed in Ref. [16]). Cytochrome c when in cytosol binds to apoptotic protease-activating factor-1. This leads to the formation of apoptosome that

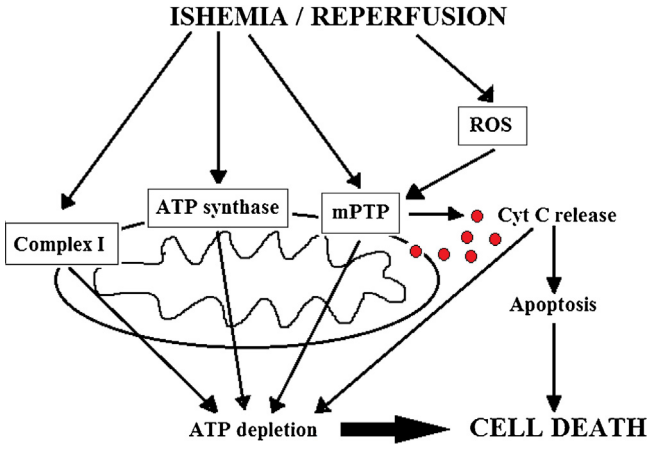

Fig. 1. Scheme of ischemia/reperfusion targets in heart mitochondria leading to cell death. Ischemia/reperfusion in the heart leads to inhibition of Complex I, ATP synthase, opening of mitochondrial permeability transition pore and subsequent release of cytochrome c, ATP depletion, apoptosis and cell death (for more details see text).

activates procaspase-9 and initiates caspase cascade resulting in apoptotic cell death [17,18]. Though the loss of cytochrome c from mitochondria is usually considered as «a point of no return» after which cells become comited to death by apoptosis or necrosis, there is experimental evidence suggesting that the execution phase of apoptosis can be regulated by the redox state of cytochrome c, so that reduced form of cytochrome c has been shown to be less potent in activating caspases than oxidized in cultured cells [19–21] or isolated perfused hearts [22].

Anthocyanins, according to the recently reported *in vitro* and *in vivo* experiments with animals as well as several epidemiological or clinical studies in humans, have been demonstrated to be effective in protection of the heart against ischemia/reperfusion-induced injury and in reduction of mortality related to cardiovascular diseases [23–29]. Putative molecular mechanisms of cardioprotective action of various anthocyanins will be discussed in further sections.

3. Chemical structure and natural sources of anthocyanins

Anthocyanins are polyphenolic water soluble pigments providing the blue, purple and red colour for various parts of plants especially in edible berries [30,31]. To date, more than 600 different anthocyanins have been reported [32] and that number constantly grows. Chemically, anthocyanins are the glycosylated forms of aglycones (anthocyanidins), which are polyhydroxy and polymethoxy derivatives of 2-phenylbenzopyrylium salts (Fig. 2).

There are 30 different anthocyanidins identified and six of them, namely delphinidin (Dp), cyanidin (Cy), malvidin (Mv), pelargonidin (Pg), petunidin (Pt), and peonidin (Pn), comprise aproximately 90% of all anthocyanidin derivatives found in nature [30,31,33]. Interestingly, these six anthocyanidins differ only in the presence of hydroxyl and methoxyl groups in the 3′ and 5′ positions in B ring