Life Sciences 135 (2015) 68–76

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Flavonoids and mitochondrial pharmacology: A new paradigm for cardioprotection

Lara Testai [1]

Department of Pharmacy, University of Pisa, via Bonanno, 6-56100 Pisa, Italy
Interdepartmental Center of Nutraceutical Research and Food for Healthy "Nutrafood", Università di Pisa, via del Borghetto, 80-56124 Pisa, Italy

ARTICLE INFO

Article history:
Received 15 December 2014
Received in revised form 24 March 2015
Accepted 25 April 2015
Available online 23 May 2015

Keywords:
Flavonoids
Cardioprotection
Mitochondrial pharmacology
Mitochondrial target

ABSTRACT

Acute myocardial ischemia is one of the major causes of illness and of deaths in Western society; therefore the definition of the signaling pathways involved in the cardioprotection represents a challenging goal in order to discover novel pharmacological approaches. In this regard, a number of epidemiologic studies demonstrate a relationship between intake of flavonoid-rich foods and reduction of cardiovascular risk factors and mortality. Moreover, numerous experimental studies have examined flavonoid-induced cardioprotective effects on several animal models of myocardial ischemia/reperfusion. As concerns the mechanisms of action, although the antioxidant effect of flavonoids has been long thought to be a crucial factor accounting for cardioprotection, mitochondrial pathways (ion channels, protein kinases, etc.) are presently emerging as specific pharmacological targets more relevantly involved in the anti-ischemic effects of some flavonoids.
Since these pharmacodynamic features seem to be poorly considered, this review examines the mitochondrial role in the cardioprotective mechanisms of some members of this phytochemical class, by describing the biological pathways and reporting an overview of the most important experimental evidence in this field.

Contents

E-mail address: lara.testai@farm.unipi.it.
[1] Mailing address: via Bonanno, 6-56100 Pisa, Italy.

http://dx.doi.org/10.1016/j.lfs.2015.04.017
0024-3205/

1. Introduction

1.1. Myocardial ischemia and cardioprotective strategies

Acute myocardial ischemia is one of the major causes of illness in Western society and despite the recent advances in therapy, it is still responsible for a number of deaths. Indeed, the reduced coronary blood supply leads to cell death and loss of cardiomyocyte population, resulting in serious and often irreversible consequences on myocardial functionality [1]. The myocardial cell death during an ischemic episode is mainly caused by necrosis, due to the irreversible opening of the mitochondrial permeability transition pore (mPTP) [2]. The most effective strategy to reduce ischemic damage is an early reperfusion, but paradoxically the reperfusion in itself is responsible for additional damage, due to apoptotic cell death; indeed, the global myocardial damage is referred to as ischemia–reperfusion (I/R) injury [3].

The beginning of the reperfusion is associated with a burst of reactive oxygen species (ROS) production, probably formed by complex I and complex III of the respiratory chain [4]. The mitochondrial proteins are particularly susceptible to ROS-induced damage: ROS have direct effects on the respiration and play a critical role in the opening of the mPTP [5–8].

mPTP is a high conductance mega-channel, anchored between the mitochondrial outer and inner membrane. When it is assembled, it allows the connection between the cytoplasm and mitochondrial matrix, and during ischemia it is closed, because of an acidic cytosolic pH [9,10]. Indeed the rapid energization of mitochondria at reperfusion leads to electrogenic uptake of Ca^{2+}, previously accumulated into the cytosol during ischemia. This factor, together with the rise of ROS production and the recovery of neutral pH, promotes the opening of mPTP [11,12]. As a consequence of mPTP opening, all small molecular weight solutes (<1.4 kDa) equilibrate across the inner membrane; in contrast, the largest molecules (i.e. proteins) remain entrapped in the matrix, exerting an osmotic pressure that leads to the uptake of water and matrix swelling. Although the unfolding of the cristae allows the matrix to expand without rupture of the inner membrane, the outer one breaks and leads to the release of pro-apoptotic proteins, confined in the inter-membrane space, such as cytochrome c [13–15]. There is an increasing evidence that time of mPTP opening is closely correlated with the extent of I/R damage; indeed, inhibitors of the pore opening (such as cyclosporine A) protect the heart from I/R injury. On the other hand, many strategies, aimed at inhibiting mPTP opening, represent challenging potential approaches to contain extension of myocardial damage; these phenomena are called ischemic pre-conditioning (IPreC) and ischemic post-conditioning (IPostC) [16].

Then, IPreC consists of transient brief episodes of I/R (typically of 2–5 min) before a severe prolonged episode of I/R, it was first described in dog hearts [18], and thereafter confirmed in many mammalian species, including humans [19–21].

More recently, Zhao and colleagues defined the IPostC, demonstrating that brief intermittent cycles of coronary re-occlusion (typically 30 s) and reperfusion (30 s) during the first minute of reperfusion after a severe ischemic event, reduce the infarct size by about 40% in canine hearts [22]. As observed for the IPreC, also the IPostC has been confirmed in many mammalian species [23,24].

The definition of the signaling pathways of IPreC and IPostC, paved the way to develop pharmacologic strategies designed to produce cardioprotection with drugs able to trigger the same mitochondrial pathways.

The IPreC, as well as IPostC which recruits analogous signaling pathways, is mediated by numerous endogenous factors, including adenosine [25], acetylcholine [26], bradykinin [27] and opioids [28–33] and gaseous molecules, such as NO [34–36] and H_2S [37].

Moreover, both IPreC and IPostC involve the activation of protein kinase C (PKC), and possibly other kinases. The translocation of PKCε can be considered as an additional mechanism for protection: the phosphorylation of the mPTP components directly inhibits the pore opening [38–40]. Furthermore, a plethora of other kinases are thought to be involved in the protective signaling pathways, such as: phosphoinositide 3-kinase/Akt (PI3K/Akt), mitogen-activated protein kinase (MAPK), caspase, Bcl2/Bax, Janus kinase/Signal Transducer and Activator of Transcription (JAK/STAT) and Protein kinase G (PKG), and cyclic AMP-dependent protein kinase A (PKA) [41–43]. In addition to kinases, several types of potassium channels present in the inner mitochondrial membranes have been suggested to be end-effectors in cardioprotection. Presently, both ATP-sensitive [44] and calcium-activated [45,46] potassium channels have been recognized (Fig. 1).

2. Evidence of cardioprotection by flavonoids

2.1. Epidemiological studies

A number of epidemiological studies demonstrate a relationship between intake of foods containing flavonoids and reduction of cardiovascular disease mortality and its risk factors. One of the first prospective studies demonstrating such a correlation was the Zutphen Elderly Study, published from Hertog and colleagues in 1993 [47]. This study was carried out on a small cohort of 805 men in The Netherlands assuming flavonols and flavones; but from 1976 to today over 20 prospective cohorts, in western countries and in the United States of America, have been performed [48–62].

However, although a number of cohort studies support the correlation between flavonoid intake and a lower risk of mortality associated with cardiovascular diseases, many variability factors emerge, hindering the interpretation of data, such as food composition and variability in flavonoid content [63,64]. A further aspect of variability is the different effects of specific flavonoids, because they are very different in physiochemical properties, bioavailability and bioactivity. In fact, even if almost all flavonoids have antioxidant properties, some of them have specific pharmacodynamic profiles [65].

Black tea consumption, for example, is related to reduction of coronary heart disease and myocardial infarction in epidemiological studies; although there is an evident heterogeneity of effects across countries, perhaps because of differences in the tea dose from country to country [66].

Epidemiological studies on wine consumption suggest a consistent dose–response cardiovascular preventive effect [67], and such evidence is stronger and more homogeneous than that seen with black tea, at least in part because of more accurate intake measurement of wine consumption [68].

2.2. Classification and sources of flavonoids

Flavonoids are a family of phenolic compounds almost ubiquitous in plants. More than 5000 distinct flavonoids have been identified. Chemically, flavonoids consist of a benzopyran heterocycle linked to a benzene ring. They can be divided in different groups depending on the degree of oxidation of the C in position 4, the hydroxylation pattern and the substitution of the C3 position. The main subclasses of flavonoids are six: flavonols, flavones, flavanones, flavan-3ols, anthocyanidins and isoflavones (Fig. 2).

Among these, flavonols are the most widespread in food and the most prominent are quercetin and kaempferol. The richest food sources of flavonols are onions, broccoli, apples and blueberries; red wine and tea also contain significant amounts of flavonols [64,69,70].

Flavones are much less present than flavonols in fruits and vegetables; the most prominent are luteolin and apigenin, specially present in parsley and celery [50].

Flavanones, such as naringenin and hesperetin, are present in high concentrations almost exclusively in citrus fruits. Main sources of