European Journal of Pharmacology 802 (2017) 44–51

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Regulation of autophagy by some natural products as a potential therapeutic strategy for cardiovascular disorders

Mahmoud Hashemzaei[a], Reza Entezari Heravi[b], Ramin Rezaee[c], Ali Roohbakhsh[d], Gholamreza Karimi[d,*]

[a] Department of Pharmacodynamics and Toxicology, School of Pharmacy, Zabol University of Medical Sciences, Zabol, Iran
[b] Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Zabol University of Medical Sciences, Zabol, Iran
[c] Department of Physiology and Pharmacology, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran
[d] Pharmaceutical Research Center, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

ARTICLE INFO

Keywords:
Autophagy
Cardiovascular diseases
Resveratrol
Berberine
Curcumin

ABSTRACT

Autophagy is a lysosomal degradation process through which long-lived and misfolded proteins and organelles are sequestered, degraded by lysosomes, and recycled. Autophagy is an essential part of cardiomyocyte homeostasis and increases the survival of cells following cellular stress and starvation. Recent studies made clear that dysregulation of autophagy in the cardiovascular system leads to heart hypertrophy and failure. In this manner, autophagy seems to be an attractive target in the new treatment of cardiovascular diseases. Although limited activation of autophagy is generally considered to be cardioprotective, excessive autophagy leads to cell death and cardiac atrophy. Natural products such as resveratrol, berberine, and curcumin that are present in our diet, can trigger autophagy via canonical (Beclin-1-dependent) and non-canonical (Beclin-1-independent) pathways. The autophagy-modifying capacity of these compounds should be taken into consideration for designing novel therapeutic agents. This review focuses on the role of autophagy in the cardioprotective effects of these compounds.

1. Introduction

Natural products like resveratrol (RES), berberine (BER), and curcumin (CUR) are present in our diet and famous for their neuroprotective, anticancer, and cardioprotective effects (Hashemzaei et al., 2016; Hosseinzadeh et al., 2011). Since these compounds have antioxidant, anti-inflammatory, and autophagy-modulating activities, application of them may be useful in cardiovascular diseases. RES, a polyphenol that is found in the skin of black grapes, has strong antioxidant, neuroprotective, and anticancer effects (Albani et al., 2010; Hashemzaei et al., 2016). BER, an isoquinoline alkaloid, is found in many plants including *Berberis vulgaris*. It has diverse pharmacological effects including anti-microbial, antinociceptive, and cholesterol-lowering properties (Hassani et al., 2016; Imenshahidi et al., 2014). Curcumin (CUR) is a diarylheptanoid compound found in turmeric (Fig. 1).

Autophagy is a physiological life-sustaining process. It is considered as an evolutionarily and genetically-controlled pathway that is always active in the cells at a basal level (Hamasaki et al., 2013). It is predominantly a pro-survival mechanism that is activated during nutrient deprivation, restriction of energy, lack of oxygen, absence of growth factors, and cellular stress (Roohbakhsh et al., 2016a, 2016b). During autophagy, misfolded proteins and damaged organelles undergo a recycling process. Therefore, they are sequestered in vesicles and degraded upon fusion with lysosomal compartments (Nishida et al., 2009). The capability of all organs including heart tissue to adapt to nutrient–deprivation results in the maintenance of cellular energy homeostasis (De Meyer and Martinet, 2009).

2. Autophagic pathways

Autophagy is a complex multi-process, which is also called programmed cell death type 2. It starts with autophagosome formation from sequestration of damaged organelles and long-lived misfolded proteins that are engulfed in double-membrane vesicles (Inguscio et al., 2012). Then, these vesicles fuse with lysosomes to form autophagolysosomes resulting in degradation of the contents of the vesicles (Inguscio et al., 2012). There are three main types of autophagy namely, macroautophagy, microautophagy, and chaperone-mediated autophagy (Fig. 2) (Table 1).

* Corresponding author.
E-mail address: KarimiG@mums.ac.ir (G. Karimi).

http://dx.doi.org/10.1016/j.ejphar.2017.02.038
Received 13 September 2016; Received in revised form 22 February 2017; Accepted 22 February 2017
Available online 24 February 2017
0014-2999/

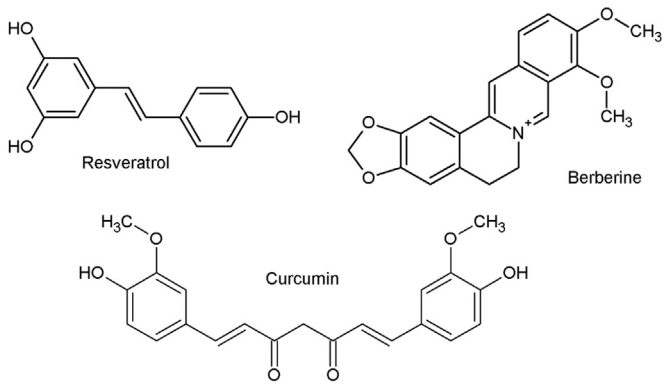

Fig. 1. Chemical structure of resveratrol, berberine, and curcumin.

2.1. Macroautophagy

Macroautophagy (called autophagy) is a process during which proteins and organelles are engulfed in a double-membrane vesicle that forms through the elongation and sealing of a *de novo*-generated membrane to form an autophagosome (Hamasaki et al., 2013; Mizushima et al., 2004). Formation of phagophor, a complex of Beclin-1, phosphatidylinositol 3-kinaseVPS34 (VPS34) and VPS15, results in recruitment of autophagy proteins to elongate the membrane (Kihara et al., 2001). During the process of membrane elongation, cargo receptors and adaptors, bind to the proteins that are on the surface of autophagosome to facilitate the engulfment process (Itakura et al., 2012; Moreau et al., 2013). Syntaxin 17, a soluble NSF attachment protein receptor (SNARE), facilitates phagophor attachment to the lysosome and finds other SNARE receptors like LAMP8 that enable fusion between the membranes (Itakura et al., 2012).

There are canonical and non-canonical autophagy signaling pathways (Codogno et al., 2012). In the canonical pathway that occurs in the case of energy restriction, class 3 phosphoinositide-3-kinase, Atg6, and ubiquitin-like conjugation reactions induce autophagosome formation (Codogno et al., 2012; De Meyer and Martinet, 2009). Although the mechanisms of canonical and non-canonical autophagy are different, these two pathways come together in covalent conjugation of Atg8 homologs to phosphatidylethanolamine in the autophagic membranes that are expanded via phagophor. Sequestering occurs in the autophagosome that is delivered to lysosomes for degradation (Codogno et al., 2012; De Meyer and Martinet, 2009).

2.2. Microautophagy

Microautophagy is the direct uptake of cellular constituents that enter lysosomes via direct invagination, protrusion, or septation of the lysosomal limiting membrane. Although the underlying mechanisms of microautophagy are not yet well elucidated but it has been established that it happens in both yeast and mammalian cells (Mijaljica et al., 2011). There are two types of microautophagy namely, selective and nonselective. Nonselective microautophagy can randomly degrade sequestered cargo entered into the lysosomes, whereas selective microautophagy can degrade specific organelles including mitochondria, nucleus, and peroxisomes (Li et al., 2012; Mortimore et al., 1988).

2.3. Chaperone-mediated autophagy

Chaperone-mediated autophagy (CMA) is different from other types of autophagy in terms of mechanisms, types of animals, and cytosolic contents that must be degraded (Dice, 2007). In the CMA that occurs in higher animals rather than yeast, the protein that is supposed to be recognized by the lysosome should constitutively express hspc70s (Bejarano and Cuervo, 2010). This recognizes exposed KFERQ (Lys-Phe-Glu-Arg-Gln) motifs of cytosolic proteins and facilitates their entrance into the lysosomes via the LAMP-2A receptor (Kaushik and Cuervo, 2008; Kiffin et al., 2004). When the cells are under stress, this type of autophagy is started and recycled organelles and proteins are used to produce new ones and prepare energy (Cuervo et al., 1995). CMA and macroautophagy coordinate to allow cells to survive at the time of stress (Orogo and Gustafsson, 2015).

3. Signaling pathways regulating autophagy

Autophagy is crucial for conserving energy in cardiomyocyte

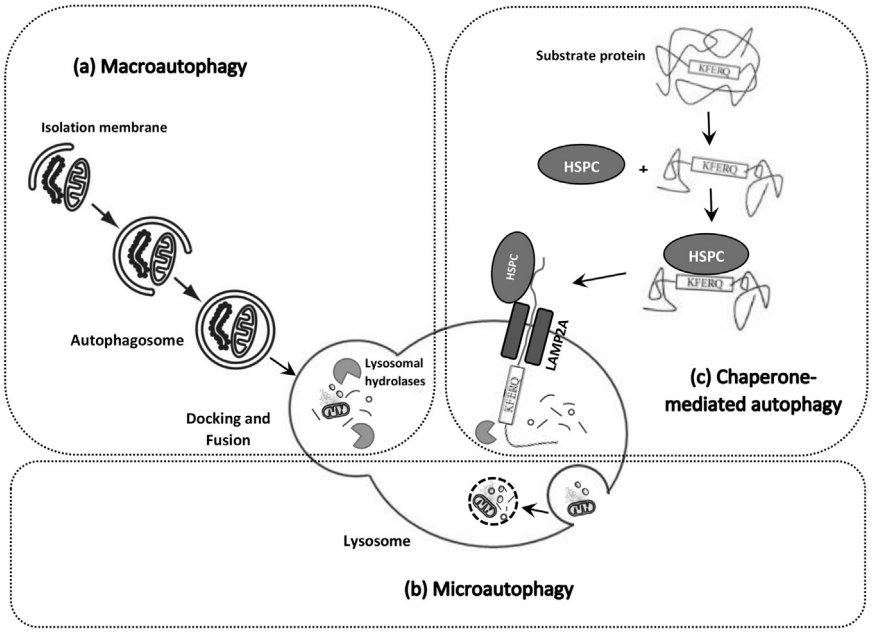

Fig. 2. Autophagy is the natural destructive mechanism for degradation and recycling of cellular components by at least three pathways: (a) Macroautophagy is the main pathway that involves the isolation membrane, formation of double-membrane autophagosome, which subsequently fuses with the lysosome to deliver its content for degradation, (b) Microautophagy occurs by invagination of the lysosomal membrane and then internalized after membrane scission, (c) In chaperone-mediated autophagy (CMA), unfolding of substrate protein allows the heat shock protein complex (HSPC) to bind to the KFERQ sequence of the substrate protein and target it to the lysosome for degradation via a channel formed from LAMP2A.