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REVIEW

Plasma membrane redox enzymes: new therapeutic targets for neurodegenerative diseases

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Abstract Mitochondrial dysfunction caused by oxidative stress appears at early stages of aging and age-related diseases. Plasma membrane redox enzymes act in a compensatory manner to decrease oxidative stress and supply reductive capacity to ensure cell survival. Plasma membrane redox enzymes transfer electrons from NAD(P)H to oxidized ubiquinone and α-tocopherol, resulting in inhibition of further oxidative damage. Plasma membrane redox enzymes and their partners are affected by aging, leading to progression of neurodegenerative disease pathogenesis. Up-regulating plasma membrane redox enzymes via calorie restriction and phytochemicals make cells more resistant to oxidative damage under stress conditions by maintaining redox homeostasis and improving mitochondrial function. Investigation into plasma membrane redox enzymes can provide mechanistic details underlying the relationships between plasma membrane redox enzymes and mitochondrial complexes and provide a good therapeutic target for prevention and delay of neurodegenerative disorders.

Keywords Mitochondrial dysfunction · Neurodegenerative diseases · Oxidative stress · Plasma membrane redox enzymes

Introduction

Neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) are considered age-related diseases since their incidence is correlated with age. During the aging process, cellular and physiological functions in neurons are inevitably attenuated (Miller and Shukitt-Hale 2012; Fernandez del Rio et al. 2016). Deterioration is represented by imbalanced redox homeostasis, impaired energy metabolism, and apoptotic cell death (Braidy et al. 2008; Johannesson et al. 2012; Anandhan et al. 2017). In fact, aging is a stochastic, complex, unavoidable, and irreversible degenerative process (Hayflick 2000). Aging can be explained by several, closely connected theories, including the genetic theory (Le Bourg 2014; Wang et al. 2014), the telomere shortening theory (Tumpel and Rudolph 2012; Zhu et al. 2018), the free radical theory (Liochev 2013; Barja 2014; Koltover 2017), and the mitochondrial dysfunction theory (Kong et al. 2014; Faitg et al. 2017; Grimm and Eckert 2017).

Plasma membrane redox enzymes and their partners

Plasma membrane redox enzymes are NADH-dependent enzymes located on the inner surface of the plasma membrane and require an intracellular electron donor (NAD(P)H) and antioxidant molecules (coenzyme Q (CoQ) and α-tocopherol) for electron transport (Hyun et al. 2006a) (Fig. 1). NAD(P)H is a universal electron donor in the cytosol and is produced by glycolysis and in the mitochondria by the citric acid cycle. CoQ is found in micro-organelles including the plasma membrane and mitochondria and is present in three different forms:

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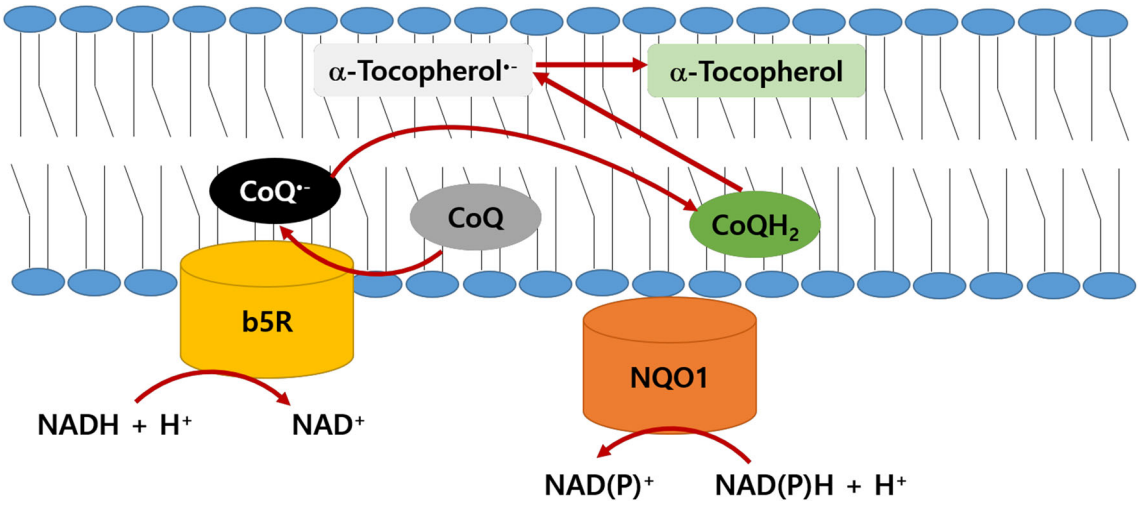

Fig. 1 Simplified diagram of PM redox enzymes and electron shuttles involved in electron transfer in the PM. *b5R* cytochrome b5 reductase, $CoQH_2$ reduced form of coenzyme Q, *NQO1* NADH-quinone oxidoreductase

oxidized CoQ, a semi-quinone radical ($CoQ^{\cdot-}$), and reduced CoQ. The reduced form of CoQ (ubiquinol) can scavenge superoxide ($O_2^{\cdot-}$) or lipid radicals alone or in association with α-tocopherol, leading to inhibition of lipid peroxidation propagation and formation of $CoQ^{\cdot-}$ (Crane 2001; Turunen et al. 2004). The semi-quinone radical is converted to ubiquinol by plasma membrane redox enzymes.

Plasma membrane redox enzymes are essentially NADH-dependent enzymes and include cytochrome b5 reductase (b5R) (Marques-da-Silva et al. 2010; Samhan-Arias et al. 2018), NADH-quinone oxidoreductase 1 (NQO1) (Chan et al. 2002; Gray et al. 2011; Ross and Siegel 2017), NADH-ferricyanide reductase (Baker et al. 2004), and NADH-CoQ reductase (Germinario et al. 2000). b5R (EC 1.6.5.5, also called ascorbate free radical reductase) is a 32-kDa FAD-containing monomeric enzyme and is involved in the transfer of one electron from NADH to CoQ in the plasma membrane, forming $CoQ^{\cdot-}$ (Matsuda et al. 2000; Bewley et al. 2001). NQO1 (EC 1.6.99.2, also known as DT-diaphorase) is a 33-kDa homodimeric enzyme with a non-covalently bound FAD (Pey et al. 2016; Ross and Siegel 2017; Chhetri et al. 2018). NQO1 is an important enzyme in the plasma membrane because it does not produce free radicals during electron transport, uses both NADH and NADPH as electron donors, and is induced by oxidative stress. NQO1 is responsible for the transfer of two electrons, resulting in no semi-quinone radicals (Gong et al. 2008; Jaber and Polster 2015). NQO1 is induced through the NF-E2-related factor 2 (Nrf2)-Keap1 pathway (Gan et al. 2013) (Fig. 2). Under normal conditions, Nrf2 is bound to Keap1 and then degraded by the proteasome. However, oxidative stress breaks disulfide bonds in the Nrf2–Keap1 complex, leading to dissociation of Nrf2 (Jaiswal 2000; Nioi and Hayes 2004). Free Nrf2 is translocated into the nucleus and bound to c-Jun. The Nrf2-c-Jun complex can attach to antioxidant response elements and induce detoxifying enzymes, which include NQO1.

Plasma membrane redox enzymes and their functions

The plasma membrane is a very important micro-organelle since it acts as a front line for regulating cellular physiology, such as hormonal and neuronal signaling. It also plays a key role in protection against external oxidative insults (del Castillo-Olivares et al. 2000; Ly and Lawen 2003; Reddy et al. 2017).

Electrons taken from intracellular NAD(P)H by the plasma membrane redox enzymes are transferred to CoQ, leading to neutralization of extracellular oxidative molecules such as ascorbate free radicals (del Castillo-Olivares et al. 2000; Rodriguez-Aguilera et al. 2000; Ly and Lawen 2003; May et al. 2003; Crane et al. 2013; Ross and Siegel 2017) (Fig. 2). CoQ is a crucial electron shuttle in the plasma membrane (Arroyo et al. 2000). The PM redox enzymes protect the plasma membrane from lipid peroxidation by maintaining levels of reduced forms of CoQ and α-tocopherol (Crane et al. 2013; Ross and Siegel 2017). Ubiquinol, a reduced form of CoQ, can protect the mitochondrial function of platelets stored for transfusion ((Merlo Pich et al. 2002), regulate ceramide signaling of apoptotic cell death (Navas et al. 2002; Navas and Manuel Villalba 2004), and enhance mitochondrial function, which results in slowed senescence in senescence-accelerated mice (Tian et al. 2014).

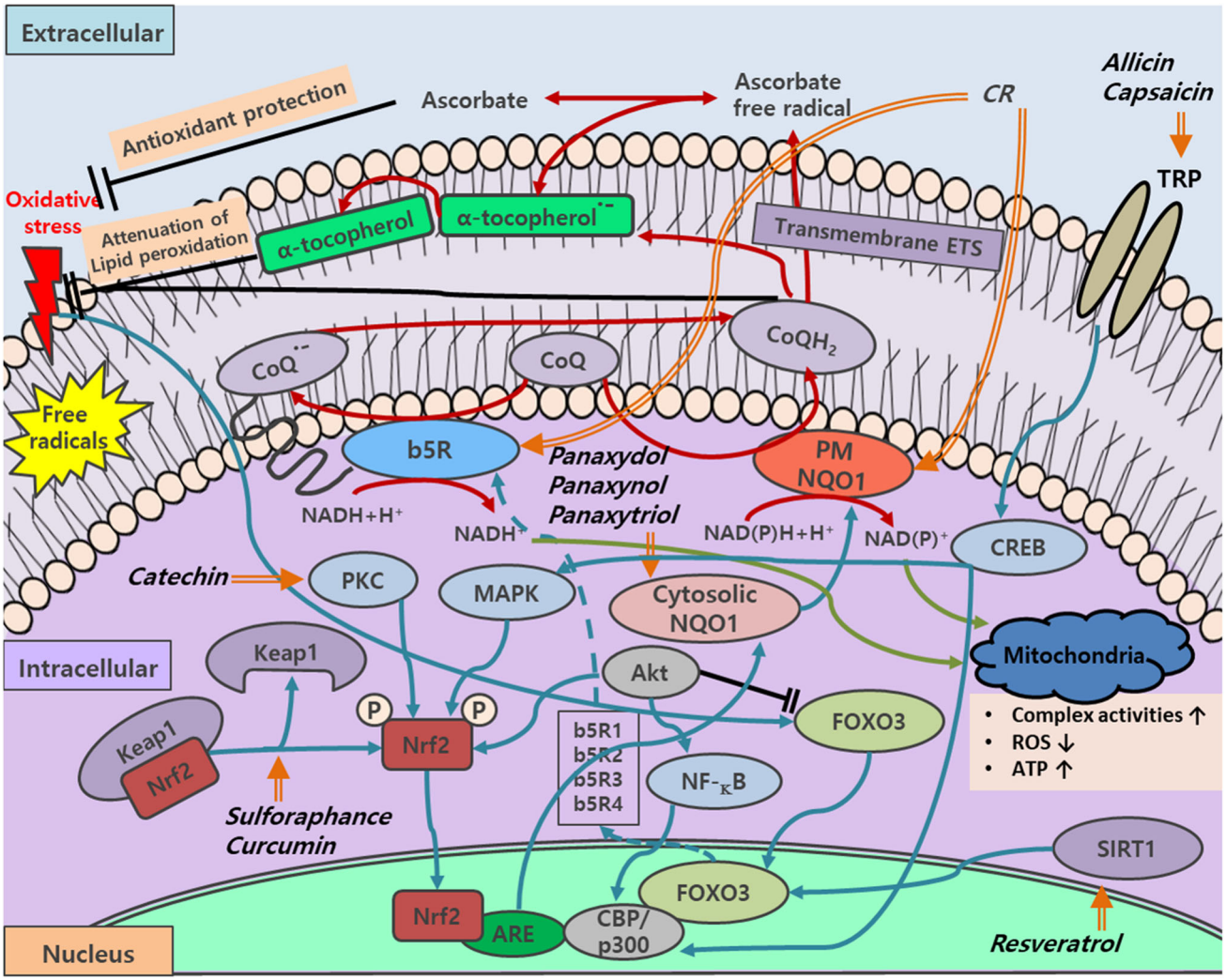

Fig. 2 Neuroprotective mechanisms induced by PM redox enzymes. Electron flows are shown in red, and neuroprotective roles of CR and phytochemicals are marked with orange arrows. *ARE* antioxidant response element, *b5R* cytochrome b5 reductase, *$CoQH_2$* reduced form of coenzyme Q, *CR* calorie restriction, *CREB* cAMP response element, *ETS* electron transport system, *FOXO3* Forkhead box family of transcription factors, *NQO1* NADH-quinone oxidoreductase, *Nrf2* NF-E2-related factor 2, *PKC* protein kinase C

Free radicals, oxidative damage, and mitochondrial dysfunction

ATP is essential for cell survival. However, free radicals (e.g. $O_2^{\cdot-}$) are generated primarily in the mitochondrial when ATP is being produced by oxidative phosphorylation. Free radicals leaked from the electron transport chain can attack biomolecules, such as DNA, lipids, and proteins, resulting in production of abnormal proteins and impairment of many biochemical and physiological functions (Ahsan 2013; Gebicki 2016; Valko et al. 2016). In particular, the mitochondria are more sensitive to oxidative stress because mitochondrial DNA is less tightly packed, and their DNA repair systems and levels of antioxidant capacity are lower than those in the cytosol (Liu et al. 2009). Decreased glutathione peroxidase and lower level of glutathione are identified in damaged mitochondria (Monteiro et al. 2004; Dannenmann et al. 2015; Hardeland 2017).

In fact, altered mitochondrial function occurs at early stages of neurodegenerative disease pathogenesis, as has been shown through decreased antioxidant defense and increased oxidative damage (Mawrin et al. 2004; Reddy and Reddy 2011; Wen et al. 2011; Moran et al. 2012). Accumulation of mutations in the mitochondrial DNA (Maruszak et al. 2006; (Keogh and Chinnery 2015) can alter mitochondrial complexes, resulting in reduced mitochondrial complex I activity in AD, PD, and amyotrophic lateral sclerosis (ALS) (Ghiasi et al. 2012; Onyango et al. 2017), dysfunctional complex II and IV activity in ALS (Menzies et al. 2002), and defective complex III activity in aged hearts (Lesnefsky et al. 2001). Alterations in

mitochondrial activity can induce ATP depletion, secondarily affecting other biochemical processes.

Compensatory mechanisms in response to mitochondrial dysfunction and oxidative damage

Under energy shortage conditions like mitochondrial dysfunction or intense muscle activity, cells can produce more ATP using alternative systems via lactate fermentation coupled to stimulated glycolysis. Interestingly, cells can survive without functional mitochondria when they are cultured in the presence of pyruvate and uridine. Mitochondria-deficient cells, also called ρ^0 cells, can survive using enhanced glycolytic ATP production coupled to electron transport in the plasma membrane (Piechota et al. 2006; Schubert et al. 2015). Lower production of reactive oxygen species (ROS) and higher activity of the plasma membrane redox enzymes are shown in ρ^0 cells than in the parental cells (Hyun et al. 2007).

Plasma membrane redox enzymes exist in all types of eukaryotic cells (Villalba and Navas 2000; Crane et al. 2013). Plasma membrane redox enzyme activity is also enhanced in human patients with diminished mitochondrial function, which is a representative parameter in insulin-dependent diabetes mellitus (Lenaz et al. 2002). Plasma membrane redox enzymes can protect neuronal cells from oxidative stress-induced apoptosis through maintenance of redox homeostasis when supplemented with ubiquinol (a reduced form of CoQ) in aged and AD brains (Rodriguez-Aguilera et al. 2000; Villalba and Navas 2000). Plasma membrane redox enzymes may be involved in extending the life-span in yeast and mammals by elevating the NAD^+/NADH ratio and stimulating mammalian Sir2 (SIRT1) (Merker et al. 2002; Cohen et al. 2004).

Down-regulation of plasma membrane redox enzymes and neurodegeneration

Alterations in plasma membrane redox enzyme activity and other associated components have been identified in aged tissues and neurodegenerative diseases. Levels of lipid peroxidation and protein nitration are elevated in hepatocytes isolated from aged rats (Oberley et al. 2008; Grossini et al. 2015). Plasma membrane fluidity in rats is related to a decrease in the docosahexaenoic acid/arachidonic acid ratio and changes in composition of other phospholipids (Hashimoto et al. 2001; Moghadam et al. 2013). α-Tocopherol contents are reduced in lymphocytes from non-insulin-dependent diabetes mellitus (NIDDM) patients, suggesting that NIDDM progression could be linked to altered electron transfer by plasma membrane redox enzymes (Yanagawa et al. 2001).

These deteriorations are also reported in AD. NQO1 expression in the hippocampal neurons of 3 × transgenic mice harboring presenilin 1 (M146V), a precursor of amyloid protein (Swe), and tau (P301L) transgenes, which lead to amyloid β plaques and neurofibrillary tangles (Oddo et al. 2003), is lower than in age-matched controls (Torres-Lista et al. 2014). SantaCruz et al. had also observed region-specific alterations in NQO1 activity and expression (SantaCruz et al. 2004). In addition, a possible link between NQO1 mutation and AD has been reported. A missense mutation in codon 187 due to a C609T polymorphism in the NQO1 cDNA can reduce level of NQO1 activity in heterozygote populations (Ross et al. 2000; Kiyohara et al. 2005; Kukongviriyapan 2012; Gong et al. 2013; Pey et al. 2016). Higher levels of the C/T and T/T alleles have also been identified in AD patients (Ma et al. 2003), suggesting that low level of the C/C allele may be a risk factor for AD (Bian et al. 2008).

Levels of other plasma membrane components, sphingomyelin and cholesterol, are also altered in the aged and in AD (Cutler et al. 2004). CoQ in the mitochondria from different tissues are decreased by up to 50% in aged patients and people with AD (Mariani et al. 1991; Ernster and Dallner 1995). Total α-tocopherol level in serum is significantly lower in AD patients than in age-matched people (Bourdel-Marchasson et al. 2001; Polidori and Mecocci 2002). Levels of oxidized forms of α-tocopherol are increased in patients with AD and vascular dementia (Tohgi et al. 1994). In addition, impaired plasma membrane redox enzymes and decreased levels of CoQ and α-tocopherol are found in the hippocampus and cortex of 3 × transgenic mice (Hyun et al. 2010).

These studies have demonstrated that impairment of lipids and electron shuttles in the plasma membrane can be biomarkers of aging and neurodegenerative disorders and suggest that their composition can be restored with activated plasma membrane redox enzymes.

Up-regulation of plasma membrane redox enzymes and neuroprotection

The previously described findings suggest that the aging process can be delayed if activity of the plasma membrane redox enzymes is up-regulated. Up-regulated plasma membrane redox enzymes can cause a higher NAD^+/NADH ratio (Merker et al. 2002), which is also induced by calorie restriction (Cohen et al. 2004). In fact, calorie restriction is known as the only reliable method for extending life-span in mammalian models (Spindler 2001; Heilbronn and Ravussin 2003; Guarente and Picard 2005).

Table 1 Phytochemicals involved in neuroprotection

Phytochemical	Target pathway	Inducible protein	References
Sulforaphane	Nrf2-ARE	NQO1	Kraft et al. (2004)
Curcumin	Nrf2-ARE	NQO1	Balogun et al. (2003)
Allicin	Mitochondria	UCP	Oi et al. 1999)
	Ion channel	TRP	Macpherson et al. 2005)
	Nrf2-ARE	NQO1	Chen et al. (2004)
Panaxydol	Nrf2-ARE	NQO1	Lee et al. (2009)
Panaxynol			
Panaxytriol			
Catechin	PKC/Nrf2-ARE	NQO1	Mandel et al. (2005)
Resveratrol	SIRT1	NF-$_K$B	Araki et al. (2004)
	FOXO3	GADD45	Kobayashi et al. 2005)
	MAPK/CREB	ERK/p38	Das et al. (2006)
	Nrf2-ARE	HO-1/GST	Chen et al. (2005)
Hypericin	Apoptosis	Bcl-2	Vantieghem et al. (2002)
Capsaicin	Ion channel	TRP	Macpherson et al. (2005)
Celastrol	HSF1	Hsp70/Hsp90	Westerheide et al. (2004)
Uwhanchungshimwon	Apoptosis	Bcl2/Bcl-xL/BMP7	Song et al. (2001)
Ondamtanggagambang	Nrf2-ARE	HO-1	Kim et al. (2006)

ARE antioxidant response element, *Bcl-2* B cell lymphoma 2, *Bcl-Xl* B-cell lymphoma-extra large, *BMP7* bone morphogenetic protein 7, *ERK* extracellular-signal regulated kinase, *CREB* cAMP response element, *FOXO* Forkhead box family of transcription factor 3, *GADD45* growth arrest and DNA damage 45, *GST* glutathione S-transferase, *HO-1* heme oxygenase 1, *HSF1* heat-shock factor 1, *MAPK* mitogen-activating protein kinase, *NF-$_K$B* nuclear factor kappa light chain enhancer of activated B cells, *Nrf2* NF-E2-related factor 2, *PKC* protein kinase C, *UCP* uncoupling protein

Calorie restriction is involved in mitochondrial biogenesis and regulation of mitochondrial membrane fluidity (Lambert et al. 2004; Lopez-Lluch et al. 2006). Calorie restriction diminishes ROS production in the mitochondria by decreasing free protons and increasing uncoupling protein levels (Agarwal et al. 2005; Bevilacqua et al. 2005; Hagopian et al. 2005). As a result, calorie restriction can reduce oxidative damage and increase antioxidant capacity.

Components in the plasma membrane can also be up-regulated by calorie restriction. Plasma membrane redox enzyme activity was enhanced by calorie restriction, whereas this activity significantly decreased in the livers and brains from ad libitum-fed mice (De Cabo et al. 2004; Hyun et al. 2006b). Plasma membrane lipids are protected from lipid peroxidation by calorie restriction (Hyun et al. 2006b). Overexpressed NQO1 or b5R also made neuronal cells more resistant to oxidative/nitrative stress, but cells with down-regulated redox enzymes were more vulnerable to insults (Hyun et al. 2012; Hyun and Lee 2015). These findings suggest an important role of plasma membrane redox enzymes in maintaining normal brain function.

Plasma membrane redox enzymes, improvement of mitochondrial function, and neuroprotection

Mitochondrial dysfunction causes energy shortage, resulting in alterations in biochemical cascades. As stated earlier, energy shortage problems can be solved, in part, by enhanced glycolysis linked to fermentation and by activated plasma membrane redox enzymes (for example, in ρ^0 cells). The possibility of improving mitochondrial function by overexpressing NQO1 or b5R has been reported. Transfected NQO1 or b5R can induce enhanced mitochondrial complex activity with lower ROS production and higher ATP generation, possibly due to more efficient electron transport in mitochondrial complexes (Hyun et al. 2012; Hyun and Lee 2015). Improved mitochondrial function, decreased oxidative damage, and modest lifespan extension were also found in transgenic mice overexpressing b5R (Martin-Montalvo et al. 2016). These mice showed reduced levels of liver cancer following treatment with diethylnitrosamine and lower levels of inflammatory parameters.

Similar effects can be induced in cells cultured in the presence of sulforaphane and curcumin, which break disulfide bonds between Nrf2–Keap1, and result in expression of several detoxifying enzymes, including NQO1 and heme oxygenase 1 (HO-1) (Turpaev 2013),

(Fig. 2; Table 1). Sulforaphane is an isothiocyanate present in broccoli sprouts and can activate Nrf2, which translocates to the nucleus, binds to an antioxidant response element (ARE), and induces detoxifying enzymes, for instance NQO1 (Yanaka et al. 2005). Retina cells cultured with sulforaphane are more resistant to UV-induced photooxidative damage (Gao and Talalay 2004; Tanito et al. 2005). Curcumin is a phenolic component enriched in curry (Joe et al. 2004), and following dietary supplement containing curcumin, transient ischemic damage was lower in gerbils (Wang et al. 2005). Similarly, a transgenic AD mouse model (APPSw Tg2576) fed curcumin showed reduced amyloid β (Aβ) level, lower oxidative damage, and less inflammation due to protective mechanisms that include HO-1 and p38 MAP kinase (Lim et al. 2001). Moreover, organosulfur compounds found in garlic and onions can protect neurons in several ways. Allium and allicin enhance the level of an uncoupling protein (UCP), leading to protection of hippocampal neurons from Aβ and tunicamycin (Oi et al. 1999). Allicin and other phytochemicals can activate transient receptor potential ion channels in the plasma membrane, resulting in attenuation of stress (Macpherson et al. 2005). Organosulfur products can also induce cellular stress responses through stimulation of the Nrf2-ARE pathway (Chen et al. 2004). Panaxydol, panaxynol, and panaxytriol, which are found in lipid-soluble ginseng extracts, induce NQO1 expression (Lee et al. 2009). Overexpressed NQO1 protected cells from toxic components in lipid-soluble ginseng extracts (Kim et al. 2016). Other neurohormetic phytochemicals can also contribute to protection of cells against a variety of toxic insults via activation of various cell survival mechanisms (Table 1).

Conclusion

By supporting survival mechanisms through increased NAD^+/NADH ratios and decreased oxidative stress, plasma membrane redox enzymes can protect neurons during mitochondrial dysfunction due to aging or from a neurodegenerative disorder. Down-regulated plasma membrane redox enzymes are one cause of neurodegenerative disease, which up-regulated plasma membrane redox enzymes can delay. Taken together, these findings indicate that mitochondrial dysfunction should be an early target for aging therapy and could be solved by enhancing plasma membrane enzymes. In addition, plasma membrane redox enzymes may play a central role in maintaining redox homeostasis and energy metabolism through regulation of the SIRT gene in the nucleus and mitochondrial energetics (Fig. 2). Animals overexpressing plasma membrane redox enzymes or phytochemicals that induce plasma membrane redox enzymes may be good model systems for investigating AD pathogenesis. PM redox enzymes may be good therapeutic targets for delaying aging and neurodegenerative disease.

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Compliance with ethical standards

Conflict of interest The author has no conflicts of interest to declare.

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