PERSPECTIVE

Sigma-1 receptor and neuroprotection: current outlook and potential therapeutic effects

Oxidative stress plays a major role in neurodegenerative disease since central nervous system is particularly vulnerable to reactive oxygen species (ROS) due to several reasons: high consumption of O_2; high production of ROS and nitrosative species, which originate from specific neurochemical reactions (*e.g.*, dopamine oxidation); high deposition of metal ions in the brain with aging leading to Fenton's reactions; high abundance of lipids which are particularly sensitive to oxidation. Therefore, we evaluated several pharmacological strategies directed at investigating the role of various antioxidants to prevent or treating neurodegenerative disorders in various experimental models (Caccamo et al., 2004; Campisi et al., 2004). However, despite several studies performed both *in vitro* and *in vivo* have shown promising results, none of them appear to be of great clinical significance. One possible explanation for such pharmacological profile of antioxidants may be dependent on the complex biochemical cascade underlying neuronal injury. In fact, oxidative stress represents just one of several mechanisms triggered by the pathogenic noxa and it may occur also as a late mechanism of injury. Therefore, several other strategies have been developed in order to obtain a broad range of effects, including the antioxidant effect, and which may also impact on early mechanisms underlying neuronal degeneration. Among such pharmacological strategies possessing pleiotropic effects, sigma receptors seem to play a major role.

Sigma receptors were initially proposed as a subtype of opioid receptors and are classified into two subtypes, σ_1 and σ_2 (Quirion et al., 1992). Sigma-1 receptor is considered to be involved in aging and various diseases, such as schizophrenia, depression, Alzheimer's disease and ischemia. Confirmed σ_1 receptor ligand functions are neuroprotective, anti-amnestic and antidepressant (Maurice et al., 2001). Recently, Schmidt et al. (2016) elegantly reported crystal structures of the human σ_1 receptor in complex with two chemically divergent ligands, PD144418 and 4-IBP. In particular these authors showed that the structures revealed a trimeric architecture with a single transmembrane domain in each protomer. Some studies suggested that σ_1 receptors are involved in modulating the synthesis and release of dopamine (Booth and Baldessarini, 1991). Finally, σ_1 receptor has been shown to act as a molecular chaperone at the mitochondrion-associated endoplasmic reticulum (ER) membrane where it regulates calcium signaling between the two organelles (Hayashi and Su, 2007).

Sigma-1 receptor activity modulates intracellular calcium mobilization *via* interacting with inositol triphosphate receptors (IP3R), L-type voltage-dependent calcium channels and N-methyl-D-aspartate (NMDA) receptors (**Figure 1**).

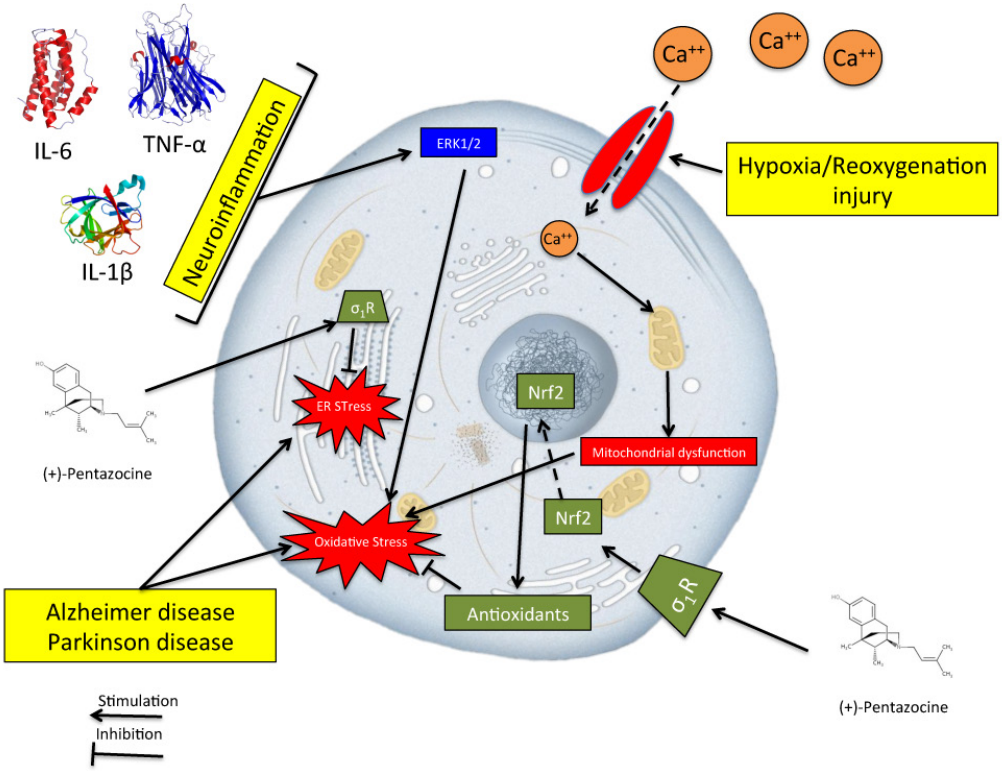

Figure 1 Schematic representation of pleiotropic protective effects of σ_1 receptor.
Molecular protective effects include so far antioxidant effect *via* ERK1/2 pathway, chaperone effect and Nrf2 activation. ERK1/2: Extracellular signal-regulated kinase 1/2; IL-6: interleukin-6; IL-1β: interleukin-1β; Nrf2: nuclear factor E2-related factor-2; TNF-α: tumor necrosis factor-α.

Sigma-1 receptor ligands show neuroprotective effects against cerebral ischemia. For example, intravenous administration of 4-phenyl-1-(4-phenylbutyl) piperidine attenuates infarction volume in rat cortex and striatum following middle cerebral artery occlusion (MCAO) by preventing ischemia-evoked nitric oxide production (Harukuni et al., 2000). Treatment with a different σ_1 receptor ligand, PRE-084, also reduces MCAO-induced infarct volume and prevents neurological deficits by inhibiting pro-inflammatory cytokines and enhancing anti-inflammatory cytokines (Allahtavakoli and Jarrott, 2011). Finally, σ_1 receptor has been shown to mediate antioxidant and anti-inflammatory effects. In particular, Wu et al. (2015) showed that SKF83959, a potent allosteric modulator of σ_1 receptor, significantly suppressed the expression/release of the pro-inflammatory mediators, such as tumor necrosis factor-α, interleukin-1β, inducible nitric oxide synthase, and inhibited the generation of reactive oxygen species (**Figure 1**). Furthermore, they showed that the protective effects of SKF83959 were abolished by concomitant treatment with selective σ_1 receptor antagonists (BD1047 or BD1063). Furthermore, Pal et al. (2012) showed that σ_1 receptor knockout mice exhibited higher levels of oxidative stress. Several molecular mechanisms underlying such antioxidant and anti-inflammatory effects. In particular, σ_1 receptor regulates the activation of antioxidant responsive element (ARE). ARE promoters are under transcriptional control of the transcription factor NF-E2-related factor 2 (Nrf2) which indicates that the sigma-1 receptor is capable of signaling through this transcriptional pathway in an as yet unknown mechanism. To this regard, previous studies showed that (+)-pentazocine, a sigma-1 receptor agonist, leads to the increase of two important Nrf2 targets: NAD(P)H quinone oxidoreductase 1 (NQO1) and superoxide dismutase 1 (SOD1). Consistently with these evidences, our recent report (Heiss et al., 2016) suggests that (+)-pentazocine restores cell viability and inhibits apoptosis in microglia cells *via* extracellular signal-regulated kinase 1/2 (ERK1/2) pathway in a model of hypoxia/reoxygenation.

Conclusions and future directions: Taken all together, the above mentioned studies suggest that sigma-1 receptor is a suitable target for pharmacological strategies for neuroprotection since they possess pleiotropic protective effects: chaperone activity reducing ER stress; inhibition of cell signaling cascade triggering the inflammatory response; activation of ARE and activating antioxidant and anti-inflammatory enzymes. Given the intracellular localization of sigma-1, this molecular target may be exploited to selectively deliver additional molecules to further potentiate the effect of sigma-1 agonists. Such new class of compounds, defined as bi-functional sigma-1 ligands, has been already available in our laboratories and we are looking forward to test their biological and pharmacological properties under various experimental conditions.

Giovanni Li Volti*, Paolo Murabito

Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy (Li Volti G)
Azienda Ospedaliera Universitaria Policlinico "G. Rodolico", University of Catania, Catania, Italy (Murabito P)

***Correspondence to:** *Giovanni Li Volti, M.D., Ph.D., livolti@unict.it.*
***Accepted:** 2016-08-09*
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