The dual regulation of oxidative stress by sigma1 receptors (σ1R) in physiological or pathological conditions

Nino Gogadze,1,2 Nino Natashvili,2 Elene Zhuravtova,2 Didier Morin,2 Davit Mikeladze2 and Tangui Maurice1

1INSERM U1188, University of Montpellier, P-34051 Montpellier, France. 2The Institute of Chemical Biology, Ilia State University, Tbilisi, 0162, Georgia.

Introduction
Alzheimer’s disease (AD) is one of the most spread forms of dementia in the world. It is suggested that mitochondrial alterations present the appearance of pathological hallmarks of the disease such as accumulation of amyloid β-peptide and hyperphosphorylated tau protein. The sigma, receptor (σ1R) is a cholinergic protein residing at mitochondria associated endoplasmic reticulum (MAM) membranes (Halmes et al. [1]). The σ1R is highly expressed in the central nervous system and its activation by ligands stimulates remodeling and neuroprotection, as observed in several mouse models in vitro and in vivo [2]. The σ1R constitutes a Ca2+ channel and σ1R-mediated Ca2+ influx and mitochondrial ROS production and/or mitochondrial respiration and complex activity using direct application of selective peptide (AP500). The σ1R agonists (PRE-084, DHEAS, ANAVEX1-41, ANAVEX3-71) increased total ROS production in physiological condition but decreased it in pathological conditions. The σ1R agonists (HCAO, progesterone) have no significant effect. The σ1R agonists and antagonist showed no direct effect on respiration, but the agonists enhanced the ROS production triggered by direct application of AP500 on mitochondria. The area under the curve of the effect of the σ1R agonist, markedly increased complex I activity in physiological conditions, while antagonist did not. This effect was blocked by treating cells with GSK-3β. These data reflect the activity of the σ1R. These experiments as a whole showed that σ1R activity result in dual regulation of the mitochondrial oxidative stress status: in basal conditions, the σ1R agonists attenuated the oxidative stress, while in pathological conditions, agonists promoted a marked antioxidant effect.

Figure 1
σ1R agonists (a, b), but not antagonists (c), increased mitochondrial ROS under physiological conditions in mouse forebrain mitochondria. (a) agonist/tangantist studies. (b) dose-response effect of σ1R ligands (a, c) induced increase in mitochondrial ROS in mouse forebrain mitochondria.

Figure 2
σ1R agonists (b, c), but not antagonists (d) attenuate ApoE-induced increase in mitochondrial ROS in mouse forebrain mitochondria.

Figure 3
σ1R ligands failed to markedly impact oxygen consumption (state 3 or OCR) in mouse forebrain extracts.

Figure 4
σ1R ligands attenuated Aβ1-42-induced alteration of respiration in mouse forebrain mitochondria.

Figure 5
σ1R agonist, but not antagonist, increased complex I activity in mouse forebrain mitochondria under physiological conditions.

Figure 6
σ1R ligands failed to affect complex II-IV activity in mouse forebrain mitochondria.

Figure 7
σ1R ligands attenuated Aβ1-42-induced alteration of complex I and IV activities in mouse forebrain mitochondria.

Figure 8
σ1R ligands failed to markedly affect NOS activities (a, b) and ROS activity (c, d) in mouse brain mitochondria (a, c) and homogenates (b, d) under physiological conditions.

Figure 9
Proposed model of interaction between σ1R and the mitochondrial electron transfer chain.

References

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Authors Contributions
Nino Gogadze, Nino Natashvili, Elene Zhuravtova, Didier Morin, Davit Mikeladze and Tangui Maurice.

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