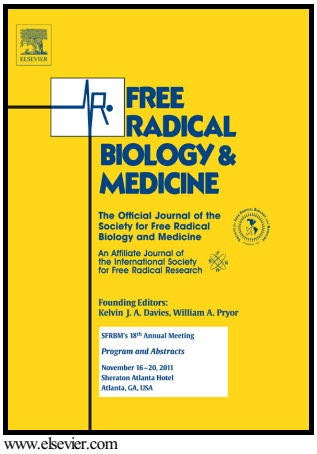
Oxidative stress and neurodegeneration: the possible contribution of quinone reductase 2

Laure-Estelle Cassagnes, Monivan Chhour, Pierre Perio, Jan Sudor, Régis Gayon, Gilles Ferry, Jean A. Boutin, Françoise Nepveu, Karine Reybier



www.elsevier.com

PII: S0891-5849(18)30105-9
DOI: https://doi.org/10.1016/j.freeradbiomed.2018.03.002
Reference: FRB13649

To appear in: *Free Radical Biology and Medicine*

Received date: 12 September 2017
Revised date: 12 January 2018
Accepted date: 2 March 2018

Cite this article as: Laure-Estelle Cassagnes, Monivan Chhour, Pierre Perio, Jan Sudor, Régis Gayon, Gilles Ferry, Jean A. Boutin, Françoise Nepveu and Karine Reybier, Oxidative stress and neurodegeneration: the possible contribution of quinone reductase 2, *Free Radical Biology and Medicine,* https://doi.org/10.1016/j.freeradbiomed.2018.03.002

Oxidative stress and neurodegeneration: the possible contribution of quinone reductase 2

Laure-Estelle Cassagnes[a1], Monivan Chhour[a1], Pierre Perio[a], Jan Sudor[a], Régis Gayon[b], Gilles Ferry[c], Jean A. Boutin[c,], Françoise Nepveu[a], Karine Reybier[a*]

[a] UMR 152 Pharma-Dev, Université de Toulouse, IRD, UPS, 31000 Toulouse France

[b] Vectalys SAS, Canal Biotech 2, 3 rue des satellites, 31400 Toulouse, France

[c] PEX de Biotechnologie, Chimie et Biologie, Institut de Recherches Servier, 125 Chemin de Ronde, 78290 Croissy sur Seine, France

[£] **Present address** : Institut De Recherches Internationales SERVIER, 50 rue Carnot, 92150 Suresnes, France

[*]**Corresponding author**: UMR 152 Pharma-Dev, Université de Toulouse, IRD, UPS, 31000 Toulouse France; karine.reybier-vuattoux@univ-tlse3.fr

Abstract

There is increasing evidence that oxidative stress is involved in the etiology and pathogenesis of neurodegenerative disorders. Overproduction of reactive oxygen species (ROS) is due in part to the reactivity of catecholamines, such as dopamine, adrenaline, and noradrenaline. These molecules are rapidly converted, chemically or enzymatically, into catechol-quinone and then into highly deleterious semiquinone radicals after 1-electron reduction in cells. Notably, the overexpression of dihydronicotinamide riboside:quinone oxidoreductase (QR2) in Chinese hamster ovary (CHO) cells increases the production of ROS, mainly superoxide radicals, when it is exposed to exogenous catechol-quinones (e.g. dopachrome, aminochrome, and adrenochrome). Here we used electron paramagnetic resonance analysis to demonstrate that the phenomenon observed in CHO cells is also seen in human leukemic cells (K562 cells) that naturally express QR2. Moreover, by manipulating the level of QR2 in neuronal cells, including immortalized neuroblast cells and *ex vivo* neurons isolated from QR2 knockout animals, we showed that there is a direct relationship between QR2-mediated quinone reduction and ROS overproduction. Supporting this result, the withdraw of the QR2 co-factor (BNAH) or the addition of the specific QR2 inhibitor S29434 suppressed oxidative stress. Taken together, these data suggest that the overexpression of QR2 in brain cells in the presence of catechol quinones might lead to ROS-induced cell death via the rapid conversion of superoxide radicals into hydrogen peroxide and then into highly reactive hydroxyl radicals. Thus, QR2 may be implicated in the early stages of neurodegenerative disorders.

[1] These authors contributed equally to the work.