Oxidative stress, metabolomics profiling, and mechanism of local anesthetic induced cell death in yeast

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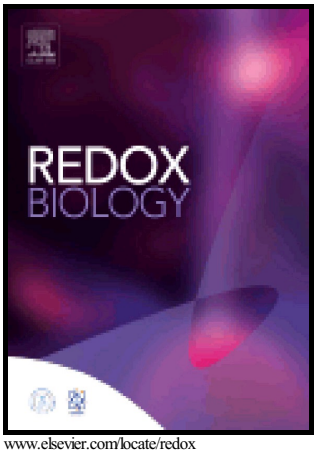

www.elsevier.com/locate/redox

PII: S2213-2317(16)30355-X
DOI: http://dx.doi.org/10.1016/j.redox.2017.01.025
Reference: REDOX569

To appear in: *Redox Biology*

Received date: 22 November 2016
Revised date: 17 January 2017
Accepted date: 19 January 2017

Cite this article as: Cory H.T. Boone, Ryan A. Grove, Dana Adamcova, Javier Seravalli and Jiri Adamec, Oxidative stress, metabolomics profiling, and mechanism of local anesthetic induced cell death in yeast, *Redox Biology*, http://dx.doi.org/10.1016/j.redox.2017.01.025

Oxidative stress, metabolomics profiling, and mechanism of local anesthetic induced cell death in yeast

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Abstract

The World Health Organization designated lidocaine as an essential medicine in healthcare, greatly increasing the probability of human exposure. It has been associated with the ROS generation and neurotoxicity. Physiological and metabolomic alterations, and genetics leading to the clinically observed adverse effects have not been temporally characterized. To study alterations that may lead to these undesirable effects, *Saccharomyces cerevisiae* grown on aerobic carbon sources to stationary phase was assessed over 6 hours. Exposure of an LC_{50} dose of lidocaine, increased mitochondrial depolarization and ROS/RNS generation assessed using JC-1, ROS/RNS specific probes, and FACS. Intracellular calcium also increased, assessed by ICP-MS. Measurement of the relative ATP and ADP concentrations indicates an initial 3-fold depletion of ATP suggesting an alteration in the ATP:ADP ratio. At the 6 hour time point the lidocaine exposed population contained ATP concentrations roughly 85% that of the (-) control suggesting the surviving population adapted its metabolic pathways to, at least partially restore cellular bioenergetics. Metabolite analysis indicates an increase of intermediates in the pentose phosphate pathway, the preparatory phase of glycolysis, and NADPH. Oxidative stress produced by lidocaine exposure targets aconitase causing a decrease in its activity. A decrease