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Inter-relationship between consequences of mild brain mitochondrial-dysfunction and agents that promote mitochondrial respiration

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Mitochondrial-function is at the nexus of pathways regulating synaptic-plasticity and cellular resilience. The involvement of brain mitochondrial-dysfunction along with increased reactive oxygen species (ROS) levels, accumulating mtDNA mutations and attenuated autophagy are implicated in psychiatric and neurodegenerative diseases. We aimed to model mild mitochondrial-dysfunction assumed to occur in bipolar-disorder (BPD) using exposure of human neuronal cells (SHSY5Y) to rotenone (an inhibitor of mitochondrial-respiration complex-I) and to find out whether ROS scavengers and/or autophagy enhancers can ameliorate neuronal mild mitochondrial-dysfunction. Incubation with an extremely low rotenone dose (10 pM) for 72 and 96 hours did not affect cell viability but induced a dual effect on mitochondrial-respiration. Exposure for 72 hours induced an overshooting several-fold increase in basal, maximal and ATP-linked oxygen-consumption-rate (OCR) but not in non-mitochondrial OCR while exposure for 96 hours significantly decreased all OCR parameters. The autophagy enhancers lithium, trehalose, rapamycin and resveratrol added for the last 24 of the 72 hours exposure to rotenone counteracted rotenone`s effect on OCR parameters. Only lithium added for the last 48 of the 96 hours exposure to rotenone reversed rotenone's effect on OCR parameters. The effect of 10 pM rotenone mimics BPD studies in which neuronal cell death is not discerned despite reproducible reports of mitochondrial-dysfunction. The enhancing effect of the low dose of rotenone on mitochondrial-respiration parameters is interpretable as the cells compensatory response to the very mild mitochondrial-dysfunction. Our regime differs from the rotenone-induced Parkinson's model (10 pM vs. at least 10 nM) by not affecting ROS levels nor cell viability but reducing most OCR parameters following 96 hours of exposure. The effect of lithium reversing rotenone's effect on OCR parameters is compatible with lithium's known positive effects on mitochondrial-function, in general, and oxidative phosphorylation complexes, in particular.

Recent Publications

1. Toker L, et al. (2014) Inositol-related gene knockouts mimic lithium's effect on mitochondrial function. Neuropsychopharmacology 39:319-328.
2. Maurer I C, Schippel P and Volz H P (2009) Lithium-induced enhancement of mitochondrial oxidative phosphorylation in human brain tissue. Bipolar Disord 11:515-522.
3. Clay H B, Sillivan S and Konradi C (2011) Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. Int J Dev Neurosci 29:311-324.
4. Arnold B, et al. (2011) Integrating multiple aspects of mitochondrial dynamics in neurons: age-related differences and dynamic changes in a chronic rotenone model. Neurobiol Dis 41:189-200.
5. Park, et al. (2013) Potential autophagy enhancers protect against fipronil-induced apoptosis in SH-SY5Y cells. Toxicol Lett 223:25-34.

Biography

Odeya Damri is in her last year of PhD in Ben Gurion University. Her research is focusing on psychiatric disorders, in general, and bipolar, in particular. During her MSc she published two articles which focusing on understanding the mechanism of lithium in mice model. With the guidance of the supervisor, the prof. Galila Agam, she attempts to establish a model for manic depression in mice based on mitochondrial minor injury while examining weather ROS scavengers or autophagy enhancers alleviate mitochondrial changes. In addition to that she is teaching biochemistry for the fifth year.

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