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A quest to model *in vivo* mild mitochondrial dysfunction in mice

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Despite the high prevalence (~1% of the adult population) of bipolar-disorder its pathophysiology or the mechanism by which effective medications exert their therapeutic effect has not yet been unraveled but data from other groups and ours indicate brain mitochondrial dysfunction in the patients and beneficial effects of mood stabilizers (anti-bipolar drugs) on mitochondrial function. We therefore aim to model mild mitochondrial dysfunction in mice using the oxidative phosphorylation (OxPhos) complex I inhibitor, rotenone, to induce affective-like behavior. Adult ICR mice were treated daily with 0.25, 0.5, 0.75, 1.2 and1.5 mg/kg/day rotenone for four, six and eight weeks following which the mice were subjected to a battery of behavioral tests [open field, elevated plus maze (EPM), sweet-solution (saccharin) preference (SSP), rotarod, forced-swim test (FST) and amphetamine-induced hyperactivity] and neurochemical assays. Chronic administration of all rotenone doses for four weeks did not affect spontaneous activity or time spent in the center of the open field, SSP or behavior in the EPM. 0.5 mg/kg/day for four weeks induced a trend for attenuation of amphetamine-induced hyperactivity. 0.75 mg/kg/day for four or six weeks reduced the immobility time in the FST and protein levels of all mitochondrial respiration complexes except for complex IV in the hippocampus with an inverse effect in the frontal-cortex. As for mitochondrial-respiration – there was a trend for upregulation in the hippocampus and down regulation in the frontal-cortex. Eight weeks of treatment significantly increased the immobility-time and reduced mitochondrial -respiration without affecting protein levels of LC-3II and mitochondrial-respiration complexes. In conclusion, 0.75 mg/kg/day rotenone exhibited dichotomial effect on depressive-like behavior reminiscent of bipolarity. We are currently investigating whether Reactive Oxygen-Species (ROS)-scavengers and/or autophagy enhancers rescue the bipolar-like behavior and neurochemical markers.

Recent Publications

1. Cataldo A M, et al. (2010) Abnormalities in mitochondrial structure in cells from patients with bipolar disorder. Am JPathol 177:575-585.
2. Betarbet R, et al. (2000) Chronic systemic pesticide exposure reproduces features of Parkinson's disease. Nature Neuroscience 3:1301-1306.
3. Fattal O, et al. (2006) Review of the literature on major mental disorders in adult patients with mitochondrial diseases. Psychosomatics 47:1-7.
4. Grover S, et al. (2006) Mania as a first presentation in mitochondrial myopathy. Psych Clin Neurosci 60:774-775.
5. Kato T, et al. (1997) Increased levels of a mitochondrial DNA deletion in the brain of patients with bipolar disorder. Biol Psych 42:871-875.

Biography

Serena Asslih is an MSc student at Ben-Gurion University, Israel. She carries out a behavioral and molecular research project aiming at mimicking mitochondrial dysfunction robustly reported in bipolar disorder under Prof Galila Agam's mentorship. In parallel, to achieve knowledge and practice in the preclinical world, which is her central interest, she took upon herself shift duties in hospital laboratories.

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