Neuropsychopharmacology www.nature.com/npp

HOT TOPICS

Serotonin minting new mitochondria in cortical neurons: implications for psychopathology

Sashaina E. Fanibunda[1,2] and Vidita A. Vaidya[1]

Neuropsychopharmacology (2021) 46:259–260; https://doi.org/10.1038/s41386-020-00824-3

Serotonin, a phylogenetically ancient molecule that predates the evolution of the nervous system, was likely co-opted to function as a neurotransmitter. Serotonin retains "pre-nervous" trophic-factor actions influencing development and growth, while exerting pleiotropic neurotransmitter effects on diverse brain functions and behavior [1]. Serotonin is speculated to exert antioxidant-like actions [1]; however, its influence on the energy producing organelle, mitochondria, and on a neuron's stress buffering capacity remains poorly understood.

Mitochondrial function is essential to fulfill substantial neuronal metabolic demands, maintain excitability, and facilitate synaptic transmission. Mitochondria serve as key signaling platforms, coupling metabolic status to mitochondrial dynamics, biogenesis and function, and influence neuronal metabolism, intracellular signaling, and synaptic plasticity [2]. Mitochondrial biogenesis is an adaptive mechanism that responds to cellular energetic demands and oxidative insults, and can promote neuronal viability. We hypothesized that serotonin in keeping with its putative trophic and antioxidant-like actions, may serve as an upstream modulator of mitochondria in neurons and thus influence stress buffering.

Our study demonstrates that serotonin, via the serotonin$_{2A}$ receptor, enhances mitochondrial biogenesis in rodent cortical neurons, increases mitochondrial function, respiratory capacity, and ATP generation [3]. These intriguing effects arise via recruitment of master modulators of mitochondrial biogenesis, the sirtuin SIRT1, and the transcriptional coactivator PGC-1α, that are strongly implicated in metabolic control and longevity. Serotonin infusion or chemogenetic activation of endogenous serotonin release increased neocortical mitochondrial mass and function. The serotonin-mediated increase in respiration and ATP production is not simply a consequence of greater mitochondrial mass, but also reflects improved OxPhos efficiency per mitochondrion. Our study identifies the serotonin$_{2A}$ receptor-SIRT1-PGC-1α axis as a putative target to enhance neuronal mitochondrial function. The influence of serotonin on mitochondria likely extends beyond neurons, as serotonin$_{1F}$ and serotonin$_{2A/2C}$ receptors enhance renal mitochondrial biogenesis [4], and serotonin$_{2B}$ receptors modulate cardiomyocyte mitochondrial structure/function [5].

Serotonin reduces cellular reactive oxygen species (ROS), upregulates ROS scavenging enzymes, and profoundly enhances neuronal survival of cortical neurons challenged with oxidative and excitotoxic stress. The prosurvival effects of serotonin are mediated via the serotonin$_{2A}$ receptor and require SIRT1 [3]. This link between serotonin, bioenergetics, and neuronal survival provides a new framework for how serotonin signaling impacts stress responses, both at a cellular and organismal level. Our study motivates further investigation to address the contribution of mitochondrial modulation to the effects of serotonin on mood regulation, neuroplasticity, and senescence.

Mitochondria have recently emerged as important targets to consider both from the perspective of pathogenesis and treatment of psychiatric disorders [6]. Mitochondria contribute to the buffering of stress-associated allostatic load, and mitochondrial dysfunction can hamper stress-adaptation and enhance risk for psychopathology [2]. Mounting evidence suggests that selective serotonin reuptake inhibitors (SSRIs) can impact mitochondrial function; however, these effects vary based on the SSRI utilized, motivating a systematic examination of the influence of SSRIs on mitochondrial biogenesis, dynamics, and function. Our findings uncover a pathway linking serotonin, via the metabolism and longevity-associated sirtuin, SIRT1, to neuronal survival and the amelioration of mitochondrial dysfunction, with important implications for both neurodegenerative and neuropsychiatric diseases.

FUNDING AND DISCLOSURE

This work was funded by the Tata Institute of Fundamental Research, Department of Atomic Energy, Government of India, under project no. RTI4003. The authors declare no competing interests.

ACKNOWLEDGEMENTS

The authors would like to thank all the co-authors on our study Fanibunda et al. [3], Sukrita Deb, Dr Babukrishna Maniyadath, Praachi Tiwari, Utkarsha Ghai, Dr Samir Gupta, Dr Dwight Figueiredo, Dr Noelia Weisstaub, Dr Jay A. Gingrich, Dr Ashok D. B. Vaidya, and Dr Ullas Kolthur-Seetharam.

AUTHOR CONTRIBUTIONS

SEF and VAV wrote the short review.

ADDITIONAL INFORMATION

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

REFERENCES

1. Azmitia EC. Serotonin and brain: evolution, neuroplasticity, and homeostasis. Int Rev Neurobiol. 2007;77:31–56.

[1]Department of Biological Sciences, Tata Institute of Fundamental Research, Mumbai 400005, India and [2]Medical Research Centre, Kasturba Health Society, Mumbai 400056, India
Correspondence: Vidita A. Vaidya (vvaidya@tifr.res.in)

Published online: 26 August 2020

2. Morava E, Kozicz T. Mitochondria and the economy of stress (mal)adaptation. Neurosci Biobehav Rev. 2013;37:668–80.
3. Fanibunda SE, Deb S, Maniyadath B, Tiwari P, Ghai U, Gupta S, et al. Serotonin regulates mitochondrial biogenesis and function in rodent cortical neurons via the 5-HT_{2A} receptor and SIRT1-PGC-1α axis. Proc Natl Acad Sci USA. 2019;116:11028–37.
4. Harmon JL, Wills LP, McOmish CE, Demireva EY, Gingrich JA, Beeson CC, et al. 5-HT2 receptor regulation of mitochondrial genes: unexpected pharmacological effects of agonists and antagonists. J Pharm Exp Ther. 2016;357:1–9.
5. Nebigil CG, Etienne N, Messaddeq N, Maroteaux L. Serotonin is a novel survival factor of cardiomyocytes: mitochondria as a target of 5-HT2B receptor signaling. FASEB J. 2003;17:1373–5.
6. Filiou MD, Sandi C. Anxiety and brain mitochondria: a bidirectional crosstalk. Trends Neurosci. 2019;42:573–88.