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INTRINSIC ACTIVITY

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MEETING ABSTRACT

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Effects of selective 5-HT$_{2A}$ agonists and antagonists on cell metabolism and mitochondrial function in neonatal primary astrocytes

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Background: The 5-HT$_{2A}$ receptor is one of the most widely spread G protein-coupled receptors in the central nervous system. It is also expressed in a number of cells in peripheral tissues. It is involved in regulation of such diverse functions as smooth muscle contraction, platelet aggregation, arousal and mood. The effects of its activation have mostly been studied on neurons. Recently, its important role in other cells have been discovered. Importantly, serotonin has been shown to regulate mitochondrial biogenesis via 5-HT$_{2A}$ receptors. Our aim was to study similar effects on neonatal astrocytes, which express 5-HT$_{2A}$ receptors.

Methods: We examined the effect of the selective 5-HT$_{2A}$ agonist 2,5-dimethoxy-4-iodoamphetamine (DOI), serotonin (5-HT) as a nonselective agonist of serotonin receptors, and the selective 5-HT$_{2A}$ antagonist ketanserin on cell viability and cellular metabolism of primary neonatal astrocyte cell cultures. We administered different concentrations of 5-HT (0.1–10 µM), DOI (0.1–10 µM), ketanserin (5–50 µM), as well as combination of serotonin and DOI with ketanserin for 48 hours before determining the energy phenotype. To characterize the energy phenotype of astrocytes, we measured oxygen consumption rate and extracellular acidification rate using Agilent Seahorse. To assess the mitochondrial function in more detail, we calculated basal respiration, maximal respiration, proton leak, spare respiratory capacity and coupling efficiency.

Results: We observed no effect of serotonin and DOI (5-HT$_{2A}$ agonists) on cell viability in all studied concentrations, whereas ketanserin (a 5-HT$_{2A}$ antagonist) decreased cell viability at high concentrations. We discovered that DOI increased basal respiration of neonatal astrocytes, while 5-HT had no effect.

Discussion: In light of recent discoveries of the importance of astrocytes in neuroprotection and their ability to transfer functional mitochondria [1] we hypothesize that some of the postulated neuroprotective effects of 5-HT$_{2A}$ receptor agonists are a consequence of an increased mitochondrial biomass in supportive tissue astrocytes. Our results show a change in cellular metabolism of astrocytes when selective 5-HT$_{2A}$ receptor ligands are applied. Indeed, the oxygen consumption rate increased at all studied concentrations of selective 5-HT$_{2A}$ agonists. In conclusion, further studies are warranted to confirm that observed changes in astrocyte energy phenotypes are specific 5-HT$_{2A}$-receptor-mediated effects.

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Keywords: 5-HT$_{2A}$ receptors – astrocytes – energy metabolism – mitochondria – serotonin

Reference

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