Abstract Information

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Title of the Symposium :	The rising Star symposium: IBRO Neuroimmunology Schools in Africa Alumni Research and Progress
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Thematic Area :	Neuroimmunology, Neuroinflammation, and Neuroinfection
Title :	CBD Effect on Neuroinflammation-Induced Metabolic Changes in Astrocytes: Focus on Cannabinoid Receptor Type 1

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Abstract : Neuroinflammation is implicated in various neurodegenerative disorders. During neuroinflammation, immune cells like microglia and macrophages release cytokines that cause neurotoxicity and neuronal death. These cytokines also affect astrocytes, the main glial cells of the brain; astroctytes thereby altering their metabolic function. Astrocytes release lactate, which in turn is used by neurons to fuel their mitochondrial metabolism. However, this metabolic coupling can become defective during neuroinflammation. In this context, the present work aimed to explore: (i) the impact of lipopolysaccharides (LPS)-induced neuroinflammation on the lactate and ATP dynamics of astrocytes, (ii) the potential rescuing effect of cannabidiol (CBD) treatment on the neuroinflammation-mediated metabolic failure, and (iii) the involvement of Cannabinoid type 1 Receptors (CB1R), on the LPS and CBD effects. These objectives were studied in cortical glia-neuron co-cultures derived from wild-type mice, CB1R-Knockout mice, and DN22-mice (lacking CB1 receptor expression on mitochondria). To study the lactate and ATP dynamics, state-of-the-art genetically encoded fluorescent biosensors for lactate and ATP were expressed in astrocyte via a viral approach, and their activity was imaged in real-time with fluorescent microscopy. In parallel to this, immunofluorescence analyses of GFAP, STAT3, p-STAT3, and GAP43 levels were performed as proxy markers of neuroinflammation. Astrocyte were treated with Vehicles, LPS, CBD, or

LPS + CBD for 24 hours before experiments. Our results showed that LPS treatment induced an increase in intracellular lactate that was reversed in CB1R-KO astrocytes, where lactate production significantly decreased following LPS exposure. Interestingly, CBD significantly rescued the metabolic abnormalities induced by LPS, which required CB1 receptor expression. LPS treatment also sensitizes astrocytes to mitochondrial inhibition and increases the depletion of ATP by Complex IV inhibition in CB1R-WT astrocytes. Our immunofluorescence assays showed that GFAP, STAT3, p-STAT3, and GAP43 levels were significantly upregulated in astrocytes following LPS exposure, while CBD treatment was able to revert this LPS-mediated effect.

Our data is consistent with a rewiring of astrocyte metabolism induced by inflammatory conditions,and propose CB1R as key controller of the CBD-mediated effects on the metabolic activity of astrocytes. This suggests a promising strategy for downregulating neuroinflammation and consequently diminishing negative neurological outcomes.