Neuroprotective role of lactate release from astrocytes in a human *in vitro* model of ischemic stroke

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Abstract: In cerebral ischemic stroke, there is an urgent need to uncover new treatments to protect brain cells from ischemic damage. In the past decades, several neuroprotective strategies have been successfully tested on animal models. Nevertheless, among them only a few have proved to be effective in clinical use. This failure of translation poses doubts on the validity of animal models for the study of human stroke. Recently, Pires Monteiro et al. established a human in vitro model of the cerebral ischemic penumbra consisting of neuronal networks derived from human induced pluripotent stem cells (hiPSCs) cultured on Micro Electrode Arrays (MEAs) and exposed to controlled hypoxic conditions. Using this model, they showed that a treatment strategy based on activation of neuronal activity (i.e. optogenetic stimulation of excitatory neurons) resulted in neuroprotection.

Here, we used the same hiPSCs-based model of the ischemic penumbra to investigate the biological mechanisms underlying the neuroprotective effect mediated by neuronal activation. We hypothesized that optogenetic stimulation of excitatory neurons might maintain or trigger the astrocyte-to-neuron lactate shuttle (ANLS), i.e. lactate release from astrocytes in support of neurons, resulting in neuroprotection. We found that the inhibition of two transporters involved in the ANLS partially impaired the neuroprotective effect mediated by optogenetic stimulation of excitatory neurons. Moreover, the administration of lactate before hypoxia onset and the induction of lactate release from astrocytes during hypoxia showed a neuroprotective effect on cell viability and electrophysiological activity, respectively.

Our results indicate that the ANLS plays a role in neuroprotection and highlight the paramount role of astrocytes in support of neurons in pathological contexts. According to recent literature, our findings suggest that lactate might have a neuroprotective effect in ischemic stroke. Since lactate exerts its effect on multiple therapeutic targets (e.g. glutamate excitotoxicity, oxidative stress, neuronal death) and it could be easily translated into patients, we argue that it represents a valid candidate for neuroprotection, undoubtedly worthy of further investigation.