Medical Xpress

Lactate triggers genes that modify brain activity

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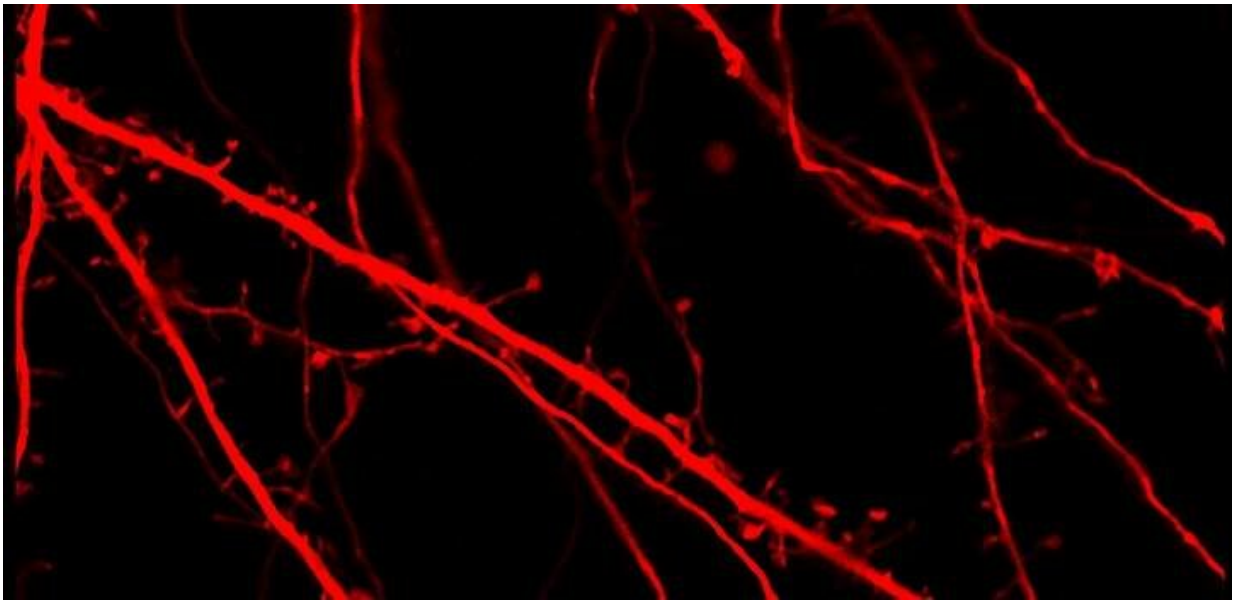

Fluorescently labeled neuronal dendritric ramifications. Credit: KAUST

A genome-wide study led by Dean Pierre Magistretti sheds light on the mechanisms through which lactate regulates long-term memory formation and neuroprotection.

The breakdown of sugar in non-neuronal brain cells, called astrocytes, produces lactate, which gets shuttled to neurons as a source of energy. This lactate not only supports the energy demands of neurons, but also

rapidly and transiently activates multiple genes that modulate neuronal activity and regulate brain function.

Previous studies have shown that lactate stimulates the expression of genes encoding proteins involved in neuronal activity by signaling through N-methyl-D-aspartate (NMDA) receptors. Magistretti's latest study reveals the extent to which lactate modifies gene expression in cortical neurons and also points to the mechanisms through which lactate modulates brain function.

The team's genome-wide analysis of gene transcription revealed that lactate exposure triggers the expression of more than 400 genes, some of which are crucial for modifying brain structure and function in response to internal and external influences, known as neuroplasticity.

"We found that lactate stimulates synaptic activity-dependent genes in the short-term and genes involved in regulating neuronal excitability in the long-term," explains the first author of the paper Michael Margineanu, a KAUST Master's student.

A culture of primary cortical neurons at 11 days in vitro. Credit: KAUST

After only an hour of exposure to lactate, 113 genes were differentially expressed compared with controls. Among them were genes known to mediate the NMDA-receptor-dependent response to neuronal activity and those known to be involved in the mitogen-activated protein kinase (MAPK) signaling pathway that regulates neuronal survival.

Selectively blocking NMDA receptors with the inhibitor MK-801 confirmed that 41 percent of the genes modulated by lactate after one hour were activated in an NMDA-receptor dependent manner.

The study also revealed that nicotinamide adenine dinucleotide (NADH), a by-product of the metabolic processing of lactate to pyruvate, was able to regulate the expression of more than 60 percent of the genes that were modulated by lactate after one hour. NADH is crucial for the production of adenosine triphosphate (ATP), the major energy currency of the cell. This finding highlights the influence of the cells' energy production process on neuronal gene expression and signaling.

In addition to identifying genes that are stimulated in a non-NMDA-receptor dependent manner, the study also revealed upregulation in the expression of genes involved in neuronal excitability after six hours of lactate exposure.

"The genes that we have identified could contribute to the development of novel therapeutic targets for neurodegenerative diseases in which brain energy metabolism is altered, such as Alzheimer's disease," concludes Margineanu.

More information: L-lactate regulates the expression of plasticity and neuroprotection genes in cortical neurons: a transcriptome analysis. *Frontiers in Molecular Neuroscience*. www.frontiersin.org/articles/1 … nmol.2018.00375/full

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