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COMMENTARY

Astrocyte glucose metabolism highlights the link between cannabis use and social behavior

The central nervous system (CNS) comprises of neurons and non-neuronal glial cells. Astrocytes are the most abundant type of specialized glial cells found in the CNS. Being a key component of the CNS, astrocytes carry out several complex functions associated with behavioral changes, as well as acting as the first responders to all forms of CNS insults[1]. In recent years, significant progress has been made toward elucidating the role of astrocytes in CNS pathologies, and this substantial amount of research has led to the identification of a vast molecular arsenal that is available at the disposal of the astrocytes.

A major function of astrocytes is to capture glucose from the bloodstream to provide energy and allow the necessary neuronal activity to take place. This apparently simple function ensures and allows for cognitive functions to be carried out at an optimal level. Depending on the physiological status, the generation of adenosine triphosphate and reactive oxygen species (ROS) varies among different cell types.

On one hand, astrocytes predominantly rely on glycolysis for energy production and generate lactate from glucose or glycogen as the source in response to neuronal signals. This metabolic process leads to a robust level of ROS production, and the lactate released from the astrocytes is utilized by neurons as an energy source. Neurons, on the other hand, predominantly rely on the more efficient oxidative phosphorylation (OXPHOS) for adenosine triphosphate production. Neurons mostly use lactate that is generated and subsequently released by astrocytes, which is then converted to pyruvate that feeds into the tricarboxylic acid cycle and the OXPHOS chain[2]. In this context, in neurons, the mitochondrial complex I assembles to form mitochondrial supercomplexes and increase OXPHOS efficacy, whereas the majority of astroglial complex I remains free. This results in low OXPHOS activity in glial cells in comparison with neurons. Therefore, astrocytes produce higher levels of mitochondrial reactive oxygen species[3], which, through a cascade of signaling steps, controls the expression of key genes involved in glucose metabolism.

Decades of research in psychopharmacology have established that most psychoactive drugs affect mood and behavior by interfering with the function of various neurotransmitters at synapses. Cannabinoids, which are the active ingredient of marijuana, mediate behavioral responses in a similar manner[4]. Neurons, in contrast, control astrocyte activity by means of receptors – including type 1 cannabinoid receptors (CB_1) – that are expressed in the astrocytes. The psychoactive component of *Cannabis sativa*, and of other (endo)cannabinoids – Δ^9-tetrahydrocannabinol (THC) – mainly targets the cannabinoid receptors that are widely expressed in the brain and regulates behavioral responses[4]. Neurons abundantly express CB_1 receptors and, thereby, control many cannabinoid-induced effects. However, previous studies have shown that CB_1 receptors expressed in the astroglial cells control the communication between astrocytes and neurons at the synaptic and behavioral level[5].

In this current study, Jimenez-Blasco *et al.*[6] report a novel mode of action of THC by unraveling a link between cannabinoid and glucose metabolism in the astrocytes. This study provides a fresh outlook regarding the role and underlying mechanism of cannabinoids in regulating behavioral patterns.

Initially, Jimenez-Blasco *et al.*[6] questioned whether the activation of mitochondrial CB_1 ($mtCB_1$), which are expressed in the astrocytes, on THC exposure has any effect on cellular metabolic homeostasis, and how this effect can modulate behavioral patterns in mice. On confirming that the astrocytes express functional $mtCB_1$ receptors[5], the authors showed that activation of astrocyte $mtCB_1$ in mice alters glucose metabolism and subsequent reduction of lactate production in the brain. The reduction of lactate levels hampered neuronal function and led to a deterioration in social interaction-related behavioral patterns in the animals. These findings indicate that the finely tuned metabolic coupling between astrocytes and neurons might be disrupted on activation of the cannabinoid receptor signaling pathway.

The oxygen consumption rate positively correlates with cellular metabolic homeostasis. Here, the authors observed that $mtCB_1$ activation by THC led to a reduction of oxygen consumption *in vitro*. In addition, mitochondrial complex I activity, the initiating point of the OXPHOS chain, was disrupted on $mtCB_1$ activation. Mechanistically, THC-activated $mtCB_1$ prevents phosphorylation of the complex I subunit, NDUFS4. NDUFS4 has been shown to promote the formation of ROS[3]. Mitochondrial ROS provides a feedback signal to activate the glycolytic pathway and induce lactate production. Accordingly, Jimenez-Blasco *et al.*[6] showed that THC-stimulated $mtCB_1$ hampers lactate production in astrocytes by decreasing ROS production (Figure 1). These results were validated *in vivo*, by attenuation of several mediatory components of the THC pathway in the astrocytes.

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In the basal state, ROS-dependent lactate production in the astrocytes, and utilization of this lactate by the neurons play a critical role in regulating neuronal activity and functions. Thus, to address the effect of reduced lactate formation on neurons, Jimenez-Blasco *et al.*[6] co-cultured neurons with astrocytes pretreated with THC. Detailed analysis of these neurons showed a significant decrease in mitochondrial membrane potential and an increase in mitochondrial ROS formation when compared with the untreated astrocytes, indicative of bioenergetic and oxidative stress. Interestingly, the authors observed that lactate supplementation in these co-cultures protected against cannabinoid-induced neuronal stress. Next, the authors sought to ascertain the relevance of their findings *in vivo*. They observed that THC-treated mice sowed abnormal and reclusive behavior, being socially isolated in nature than the untreated mice. In line with their findings *in vitro*, lactate administration reversed this effect. Finally, to address the effect of lactate at the molecular level, the researchers genetically targeted neuronal monocarboxylate transporter 2, a transporter that facilitates the entry of lactate into neurons. Downregulation of monocarboxylate transporter 2 gene expression in the brain hippocampus and prefrontal cortex in mice led to reduction in social interaction, reinforcing the implication of lactate shuttling between astrocytes and neurons, and its contribution toward higher brain functions (Figure 1).

In conclusion, the findings of Jimenez-Blasco *et al.* shed light into how complex behaviors are regulated and finely tuned at the molecular level. Additionally, this fascinating work further strengthens the ever-developing concept of astrocytes as

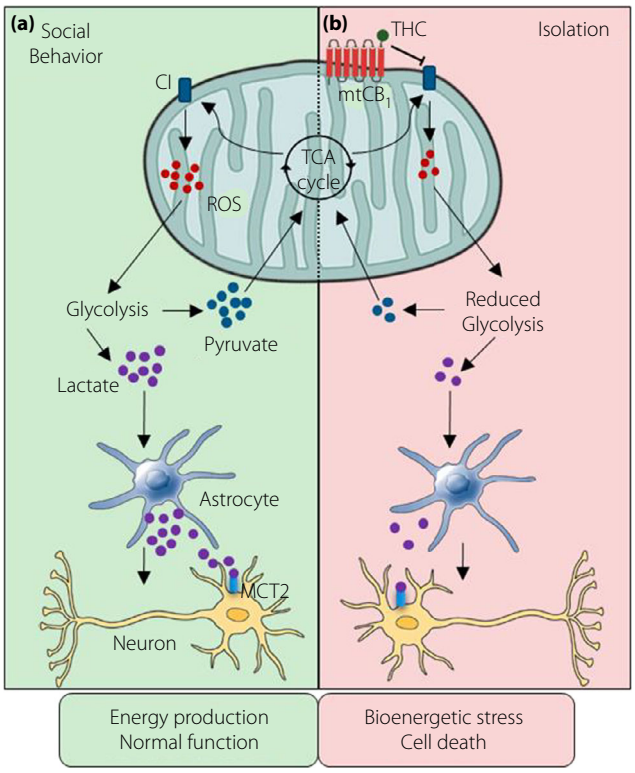

Figure 1 | Addiction disrupts neuronal metabolic balance. (a) Mitochondrial contribution toward the regulation of cellular energy metabolism is mediated by the oxidative phosphorylation chain, mitochondrial complex I (CI), being a key component of this chain. CI activity leads to the production of reactive oxygen species (ROS), which promotes glycolysis and produces pyruvate and lactate as end-products in the cytosol. Pyruvate is metabolized in mitochondria through the tricarboxylic acid cycle, which feeds into the oxidative phosphorylation. Monocarboxylate transporter 2 (MCT2), a neuronal transporter protein, facilitates the entry of lactate from astrocytes to the neurons. Thus, lactate acts as the main source of energy production in the neurons, enabling normal neuronal functions and is a critical metabolite responsible for normal social behavior. (b) In this study, Jimenez-Blasco *et al.*[6] showed that an active component of cannabis, tetrahydrocannabinol (THC), disrupts the balance between neurons and astrocytes to alter social behavior in mice. THC exposure activates its receptor (mitochondrial cannabinoid receptor 1; mtCB1), which is localized on mitochondrial membranes in astrocytes. Activated mtCB1 disrupts oxidative phosphorylation through inhibitory phosphorylation of its key component, CI. This disruption leads to a downregulation of glucose metabolism and reduces lactate availability to the neurons, ultimately causing neuronal stress and cell death. Impaired neuronal function results in abnormal behavior in the form of social isolation in mice.

the critical mediatory cell type in the context of higher brain functions.

Earlier, in 2012 in *Nature Neuroscience*[7] and in 2016 in *Nature*[8], the collaboration between research groups led by Dr Pedro Grandes and Dr Giovanni Marsicano at the University of Bordeaux reported, for the first time, the presence of CB_1 receptors in neuronal mitochondria, the activation of which reduces mitochondrial activity leading to memory loss. However, the key question that remained was how to delineate the functional role of CB_1 receptors located in the astrocyte mitochondria. Therein lies the significance of this current study by Jimenez-Blasco *et al.* in extending our understanding of addiction and social behavior at the molecular level. Their work further highlights how metabolic products, such as lactate, act as a messenger molecule to affect behavioral patterns. This work reinforces the idea of how concertedly energy metabolism and neuronal signaling work in the brain.

At a time when the debate over cannabis is returning to the forefront – with cannabinoids being made accessible as off-the-counter substances for patients in need of palliative treatment, as well as for recreational users – the researchers also believe that this type of work is required to better understand how the body's various cannabinoid receptors interact with the drug, as well as its impact on health in the context of disease susceptibility. More of such research would make it possible to ensure the optimal management of patients who might require this type of therapy. This exciting connection requires in-depth analysis to broaden our understanding of higher brain functions.

DISCLOSURE

The authors declare no conflict of interests.

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