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News & views

Neuroscience

A metabolic link between cannabis and behaviour

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An active component of cannabis has been shown to disrupt the delicate metabolic balance between neurons and non-neuronal cells called astrocytes, altering social behaviour in mice.

There is a general consensus that higher brain functions, and so, ultimately, behaviour, are controlled by dynamic communication at the synapses that connect neurons. Decades of psychopharmacology studies have validated this view, because most psychoactive drugs seem to exert their effects on mood and behaviour by interfering with the function of chemicals called neurotransmitters at synapses[1]. This mechanism is proposed to mediate behavioural responses to compounds called cannabinoids[1], which are the active ingredient of marijuana. But writing in *Nature*, Jimenez-Blasco *et al.*[2] report a different mechanism of action for the cannabinoid tetrahydrocannabinol (THC) that involves the metabolism of lactate molecules in non-neuronal cells called astrocytes. This discovery cautions against an oversimplistic view of the mechanisms that underlie behaviour.

The role of lactate in brain metabolism is well established[3]. Organelles called mitochondria are the primary subcellular site for the production of energy-carrying ATP molecules. But some ATP is generated in the cytoplasm through a process called glycolysis – this pathway also produces lactate, along with the molecule pyruvate. Mitochondria, in turn, process pyruvate through two cascades of biochemical reactions: the tricarboxylic acid cycle and the oxidative phosphorylation (OXPHOS) chain. The OXPHOS chain consumes oxygen to produce more ATP, with molecules called reactive oxygen species (ROS) created as by-products.

The relative production of ATP and ROS varies between cells and in different physiological conditions. For example, astrocytes robustly produce ROS and tend to rely on glycolysis for energy production, releasing lactate to be used by neurons as an energy source[3,4] (Fig. 1a). By contrast, neurons rely on more-efficient OXPHOS for ATP production, but mostly use lactate released by astrocytes, which neurons convert to pyruvate that then feeds into the tricarboxylic acid cycle and the OXPHOS chain. Perhaps the first hint that this well-oiled metabolic coupling between astrocytes and neurons might be disrupted by THC came from the observation[5] that cannabinoid receptor proteins are present not only on neuronal membranes, but also on mitochondrial membranes – particularly in astrocytes, as reported by Jimenez-Blasco and colleagues.

Jimenez-Blasco *et al.* show that THC acts on one such receptor, mitochondrial cannabinoid receptor 1 ($mtCB_1$). Activation of $mtCB_1$ is known to cause a decrease in oxygen consumption[6] – an indisputable sign of a decrease in cellular metabolism. The authors confirmed this observation in astrocytes, and showed that $mtCB_1$ activation by THC in these cells disrupts the activity of a protein complex called mitochondrial complex I (CI), which is the first component of the OXPHOS chain[4]. Specifically, activation of $mtCB_1$ prevents phosphorylation of a subunit of CI called NDUFS4.

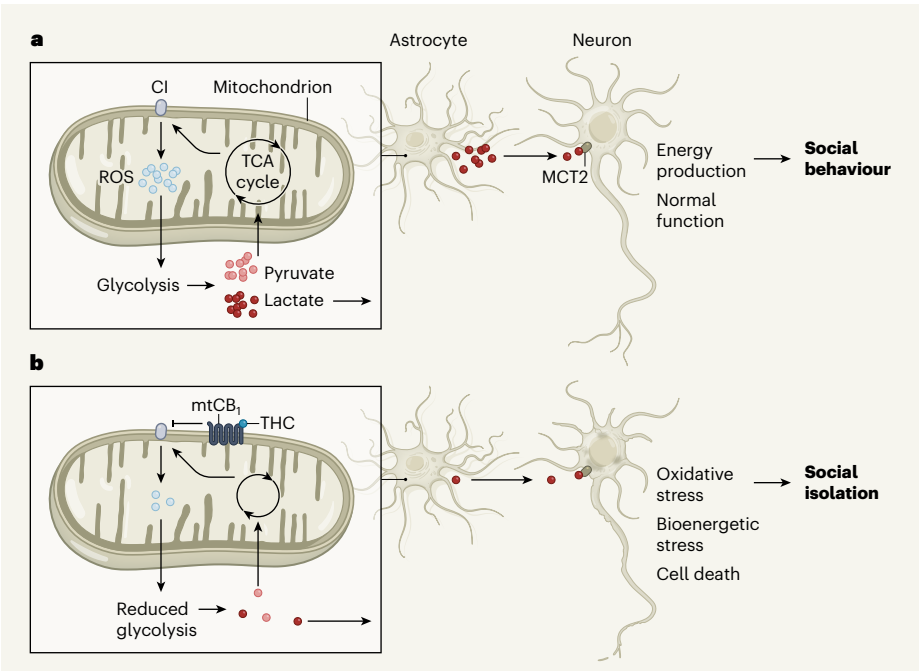

Figure 1 | Disrupting a delicate metabolic balance. a, Cellular energy metabolism in organelles called mitochondria involves a cascade of chemical reactions called the oxidative phosphorylation chain, of which the protein mitochondrial complex I (CI) is a component. CI activity leads to the production of reactive oxygen species (ROS). In turn, ROS promote a metabolic process called glycolysis, in which the molecules pyruvate and lactate are generated from glucose in the cell cytoplasm. Pyruvate is metabolized in mitochondria through the tricarboxylic acid (TCA) cycle, which feeds back into oxidative phosphorylation. Lactate is typically shuttled from astrocyte cells and into neurons by the protein MCT2. Here, lactate is used to generate energy, enabling normal neuronal functions and circuits involved in social behaviour. **b**, Jimenez-Blasco *et al.*[2] report that the compound tetrahydrocannabinol (THC) binds to its receptor (mitochondrial cannabinoid receptor 1; $mtCB_1$) on mitochondrial membranes in astrocytes. $mtCB_1$ disrupts the activity of CI, downregulating this metabolic pathway and so decreasing the amount of lactate that is shuttled to neurons. This causes oxidative and bioenergetic stress in the neurons, as well as neuron death, and results in social isolation in mice.

NDUFS4 promotes the formation of ROS[4]. The ROS formed in the mitochondria of astrocytes signal back to the cell's cytoplasm to stimulate glycolysis and lactate production[7]. In line with these observations, Jimenez-Blasco *et al*. found that stimulation of $mtCB_1$ by THC decreases lactate production in astrocytes by decreasing ROS production (Fig. 1b). The authors went on to validate their results *in vivo*, by downregulating various components of the THC-mediated pathway in the astrocytes of mice.

Next, Jimenez-Blasco and colleagues demonstrated that a THC-mediated decrease in lactate formation by astrocytes has deleterious effects on neurons. The authors grew neurons *in vitro* alongside astrocytes that had previously been exposed to THC. The neurons showed a decrease in electric potential across the mitochondrial membrane and an increase in mitochondrial ROS compared with neurons co-cultured alongside untreated astrocytes, indicating bioenergetic and oxidative stress. Neurons purified from THC-treated mice also had increased mitochondrial ROS levels compared with those from control animals, and showed signs that they were undergoing a type of programmed cell death called apoptosis. All of these negative effects, both *in vitro* and *in vivo*, could be reversed by delivering lactate to the neurons.

The authors found that THC-treated mice exhibited abnormal behaviour in the form of social isolation — the animals spent more time physically separated from others in their cage than did the control mice. The effect could be reversed by administration of lactate. Mice also exhibited social isolation when the group downregulated (in the brain's hippocampus and prefrontal cortex) the expression of a protein called MCT2 that mediates the entry of lactate into neurons. These observations reinforce the role of lactate shuttling between astrocytes and neurons in higher brain functions.

Taken together, Jimenez-Blasco and colleagues' observations highlight the importance of taking a broad view of how complex behaviours are regulated, beyond simple neuron-to-neuron communication. The authors' demonstration that lactate-mediated metabolic coupling between neurons and astrocytes modulates one social behaviour in mice mirrors previous studies, in which the transfer of lactate from astrocytes to neurons was shown to be necessary for synaptic plasticity (changes in the strength of the connections between neurons) and memory consolidation[3,8]. A growing body of work is therefore highlighting astrocytes as key mediators of higher brain functions.

There are several pressing avenues for further research. In particular, it remains to be seen how the effects exerted on neurons by decreased lactate availability evoked social isolation. Because it is clear that other behavioural effects of cannabinoids — such as those on learning and memory — involve standard neuronal signalling[7], the contributions of each mechanism to behaviour should now be teased out. Furthermore, the potential implications of this study for humans, particularly as far as behaviour is concerned, need to be explored.

Jimenez-Blasco and colleagues' work demonstrates how lactate can function as a signalling molecule that affects behaviour. It also highlights the tight coupling between energy metabolism and neuronal signalling in the brain. This exciting link is sure to be much studied in the future.

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