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REVIEWS

the underlying dysfunctional lipid metabolism in AD.

The authors tested their hypotheses using two *in vivo* model systems, acute stroke and chemically mediated excitotoxicity. In these cases, consistent with *in vitro* data, LDs accumulate in astrocytes but not in neurons, indicating their transfer. Astrocytes dismantle LDs to fatty acids and then metabolize them through mitochondrially mediated β-oxidation. However, the β-oxidation adversely elevates reactive oxygen species (ROS) [2]. In contrast to neurons, ROS measurement indicated the absence of their accumulation in astrocytes. How do astrocytes handle the deleteriously increased production of ROS? Addressing this intriguing question, transcriptome profiling revealed that astrocytes upregulated oxidative stress-nullifying genes in response to lipid uptake. Notably, these genes were expressed at low levels in neurons, thus explaining their dependence on astrocytes to handle LD-mediated toxicity. However, future studies can explore the precise nature of the exchanged lipid particles that will add laurels to this field. In hyperactive neurons, the vicious cycle of elevated ROS and the accumulation of lipid particles and peroxide adducts could catapult the manifestation of pathophysiological conditions [8,9].

In future, it will be worth investigating the fate of lipid particles formed in different neuronal compartments such as the soma and/or its projections to dissect whether any differences exist in the molecular machineries/mechanisms and kinetics of exocytosis. Also, where precisely are lipid particles released from neurons? Do they prefer any particular domain of the plasma membrane? Understanding the consequences of excitotoxicity for astrocytes *per se* and their implications for neurons could reveal the mechanisms underlying neurodegeneration and neurodevelopmental disorders. Do similar mechanisms for expelling lipid particles exist in cortical neurons or other types? If they are different, this could explain why certain types of neurons are vulnerable in various neurodegenerative conditions. Could blocking neuron–astrocyte lipid transfer *in cellulo* and *in vivo* by genetic or pharmacological means result in neurodegenerative-like phenotypes such as accumulation of ubiquitin-positive aggregates and so on?

To summarize, hyperactive neurons exocytose LDs to evade lipid toxicity. Astrocytes take up these apoE-positive LDs via endocytosis to fuel mitochondria-mediated β-oxidation, and such coupling of lipid metabolism between neurons and astrocytes protects neurons from fatty acid toxicity. The finding of enhanced gene expression to combat increased ROS by astrocytes solves an important piece of the puzzle of how they handle oxidative stress efficiently unlike neurons. At the intracellular level, neurons wield a number of protective mechanisms to overcome accumulating toxic proteins and lipid biochemical intermediates. This study reveals an additional dimension of the intrinsic basic mechanisms of the neuron in how it combats accumulating peroxidized lipid adducts. The crucial function of 'neuronal transfer of lipoprotein particles to astrocytes' as a means to evade toxicity joins the long but important list of metabolic functions arising from neuron–astrocyte harmonization. Despite long years of investigating this harmonization, it continues to surprise us with new angles as we study it.

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Spotlight

Huntington's Disease: Astrocytes Shift to Fatty Acid Metabolism

Bennett Van Houten [1,2,*]

A recent study by Polyzos *et al.* (*Cell Metab.*, 2019) shows that astrocytes in a Huntington disease (HD) mouse model switch from glycolysis to fatty acid oxidation (FAO), causing increased superoxide radical anion production and loss of succinate dehydrogenase (SD) activity. Blocking mitochondria reactive oxygen species (ROS) with an antioxidant compound called XJB-5-151 reversed lipofuscin formation and protected the mice.

Mitochondria not only power essential cellular processes using ATP, but are also the nexus of metabolic flux, helping convert glucose, fatty acids, and amino acids into other precursors essential for life. These organelles couple the metabolism of key intermediates to electron transport and proton movement to establish a robust membrane potential across their inner membrane, driving ATP production. This amazingly clean burning machine turns electron flux and oxygen into water at Complex IV. However, either when working too hard or when forcing a partially broken machine to continue to function, mitochondria can generate an increased flux of superoxide radical anions, a key ROS [1]. It is no wonder then that a large number of human diseases, including neurodegenerative diseases, can be traced to mitochondria dysfunction [2,3].

One such neurodegenerative disease is HD, a devastating illness caused by a recessive triplet repeat expansion of a glutamine residue in the huntingtin protein encoded by *HTT* [4]. Early symptoms, which typically appear between the ages of 30 and 60 years, include mood swings, depression, and awkwardness in movement. Disease progression leads to loss of striatum function in the brain, resulting in stumbling and falls, dropping items, and forgetfulness. Final stages of this terminal disease include weight loss, overall weakness, and difficulty eating, breathing, and swallowing [4]. Sadly, there is no known cure and, despite several good mouse models, the molecular etiology of the disease is not well understood. In a recent study, McMurray and colleagues harnessed the power of several innovative and complementary technologies to understand metabolic flux and to dissect out the early events contributing to HD [5]. Remarkably, they found that the villains of HD are not neurons, but astrocytes. These cells comprise 80–90% of cells in the striatum and produce key growth factors and metabolites to nourish neurons.

Besides ATP, another important mitochondrial cofactor involved in several enzymatic transactions is NADH. This key metabolite, through its oxidation to NAD^+, drives electron transport from Complex I (also known as NADH dehydrogenase) to an electron carrier (coenzyme C10) and simultaneously facilitates the movement of four protons from the matrix of the mitochondria across the inner membrane, helping to generate the proton gradient that drives ATP production. By using brain slices from the affected striatal region (STR) of HD mice or a control region, the cerebellum (CBL), unaffected by the disease, McMurray's team used a specialized microscopic technique, fluorescence lifetime imaging microscopy (FLIM), to directly visualize the bound and free state of NADH inside living cells. This tool, first developed during the 1990s by Johnson and colleagues [6], has seen a renaissance in recent years, leading to unprecedented views of bioenergetics in living tissue [7].

Using FLIM, McMurray and colleagues followed NADH status in mouse brain slices expressing wild-type or mutant huntingtin protein (mhtt). At just 20 weeks of age, the mice expressing the mutant protein displayed an important switch from the bound to free form of NADH, suggesting that there was a higher fraction of available NADH for biochemical processes. An independent measure of NADH and NAD+ levels in the STR and CBL regions of mhtt mice indicated that the two regions had lower levels of both, and the NADH/NAD+ ratio in the STR region was significantly higher in the STR of mhtt compared with CBL and control animals.

To understand what might be driving these differences, the team turned to another innovative technology that measures the rates of oxygen consumption and extracellular acidification in living cells, surrogate makers for oxidative phosphorylation and glycolysis, respectively. Neither neuronal synaptosomes nor astrocytes showed any differences in either parameter. However, using a permeabilized cell system, the authors observed a loss of Complex II (SD) activity in the astrocytes of STR of mhtt-expressing mice, but not in age-matched control animals. 3D-stochastic optical reconstruction microscopy (3D-STORM) imaging, enzymatic measurements, and western blot analysis confirmed a decrease in SD protein expression and activity in the STR astrocytes of mhtt mice. Altered mitochondrial electron transport is often associated with a release of electrons to oxygen to form superoxide radical anions (Figure 1). Using a mitochondrial-specific fluorescent marker of superoxide production, astrocytes from mhtt mice had a higher flux of superoxide production. What might cause the observed loss in SD activity and increase in ROS production in these young mhtt-expressing mice?

To address this question, the team turned to a third innovative technology involving mass spectrometry network analysis of key metabolic intermediates associated with mitochondrial function. Amazingly, the levels of key amino acids and the tricarboxylic acid cycle (TCA) metabolites malonate and fumarate, products of SD, were lower, whereas levels of several fatty acids and lipids were higher in the striatum of mhtt mice. It would appear that the astrocytes in the mhtt animals have lower glucose utilization and a concomitant increase in FAO to keep pace with their high energy demands. While this short-term use of fatty acids maintains proper ATP levels, the long-term consequence of this metabolic switch may be increased ROS production. SD is sensitive to superoxide anion radical attack due to key FeS centers. To test this hypothesis, the team treated animals with XJB-5-131, a mitochondrially targeted antioxidant compound, developed in the laboratory of Wipf *et al.*, that has previously been shown to mitigate the HD phenotype in

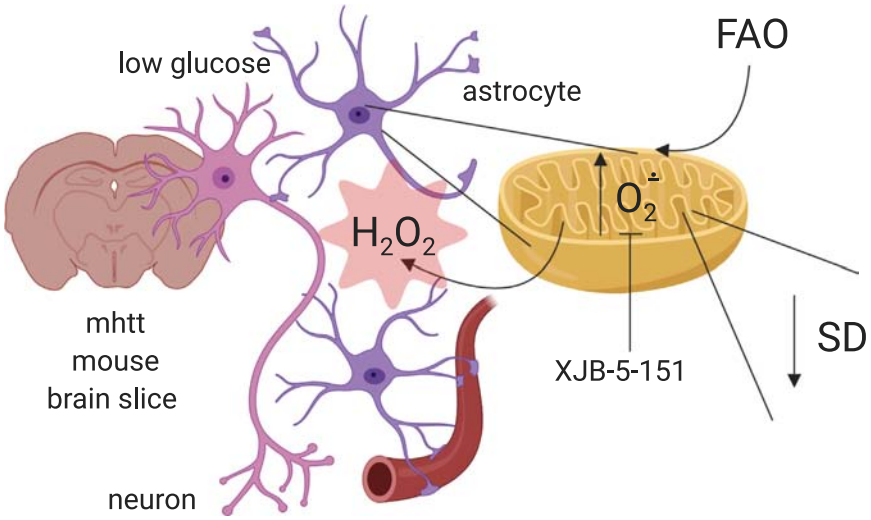

Figure 1. Metabolic Reprogramming in Astrocytes Helps to Drive Huntington's Disease. Low glucose levels in the brains of mutated huntingtin protein (mhtt) mice drive a shift from glycolysis to fatty acid oxidation (FAO) in striatum astrocytes. This increased reliance on FAO, while maintaining proper ATP levels, causes an increase in superoxide radical anion production and conditions of oxidative stress. Superoxide damages FeS centers in succinate dehydrogenase (SD), causing a loss of activity and protein. Hydrogen peroxide (H_2O_2), which is freely diffusible, can cause damage to many macromolecules within astrocytes and in nearby astrocytes. The mitochondrially targeted antioxidant XJB-5-151 can help reverse this phenotype.

mhtt mice [8,9]. XJB-5-131 decreased the dependence of FAO and decreased lipofuscin-rich granules, a product of oxidized fatty lipids and proteins (Figure 1).

The overall significance of this work is that this team found that, early during the course of disease progression in a mouse model of HD, striatum astrocytes undergo a metabolic switch to burn more fatty acids, leading to the regional-specific loss of neurons in this brain region. This increase in FAO causes an increase flux in ROS and subsequent loss of SD activity. This important study raises several key questions. First, does the mouse model faithfully recapitulate early changes in patients with HD and, if so, are their pharmacological approaches to reverse these metabolic changes? Second, how widespread is the ROS damage? Is it confined to the astrocytes or can ROS be released in the form of free diffusible hydrogen peroxide to damage macromolecules, such as DNA, proteins, and lipids, in neurons? Third, does loss of FeS centers in SD cause protein turnover, and subsequent increase in FAO? Does XJB-5-151 help to preserve SD activity? Finally, does this metabolic reprogramming cause alterations in the epigenome? No doubt McMurray and her team are already working on these and other questions and I eagerly await their next installment on the molecular pathophysiology and potential new clinical treatment options to help some 30 000 patients in the USA alone with this devastating disease.

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