Functional imaging of astrocyte activity

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Astrocytes have become known to play a central role in various neuroinflammatory diseases. The evaluation of astrocyte activity using functional imaging is becoming more important. Glucose metabolism or oxygen metabolism in the brain can be assessed using the established clinical imaging methods of F-18 fluorodeoxyglucose positron emission tomography (PET) and O-15 PET, respectively. However, until recently, the highly specific evaluation of metabolic activity in astrocytes has never been applied clinically. Since acetate is selectively taken up and metabolized by astrocytes, its usefulness as a tracer for measuring astrocyte activity has been proposed in basic research. In a human study, the activation of astrocytes associated with neuronal activation has been evaluated *in vivo* using 1-C-11 acetate PET (Wyss et al., 2009). Astrocytes supply lactate as an energy source to neurons through monocarboxylate transporters (MCTs) and receive and metabolize neurotransmitter glutamate from neurons. The tricarboxylic acid (TCA) cycle in astrocytes provides energy to convert glutamate released from neurons into glutamine as well as newly generating glutamine for neurons. 1-C-11 acetate is selectively taken up by astrocytes mainly by MCT, especially MCT1 and MCT2, and is metabolized by the TCA cycle via acetyl-CoA. Half of the label derived from 1-C-11 acetate is washed out as CO_2 in the second round of the TCA cycle in astrocytes, and most of the remaining label is metabolized to glutamate. Considering the short half-life of C-11, metabolites in neurons derived from labeled glutamate, which had been transformed from glutamine passed from the astrocytes, is negligible (Wyss et al., 2009). Therefore, the CO_2 washout rate is an index that quantitatively represents the metabolic activity of astrocytes, and the index can be imaged using quantitative PET as the efflux rate of the tracer. Moreover, the tracer accumulation is considered to reflect mainly the labeled glutamine/glutamate pool derived from 1-C-11 acetate. Therefore, 1-C-11 acetate PET can be used to evaluate the central part of astrocyte energy metabolism (**Figure 1**).

Although PET tracers including 18-kDa translocator protein ligands and monoamine oxidase B ligands or MRI sequences for tracking glial cell activity have been developed, 1-C-11 acetate PET is the only functional imaging method that can estimate astrocyte metabolism at the moment.

1-C-11 acetate PET for multiple sclerosis: Multiple sclerosis (MS) is a demyelinating neuroinflammatory disease with various neurological symptoms. Recently, reactive astrocytes have been shown to play a pivotal role in the pathology of MS. Activated astrocytes are thought to become proinflammatory in response to cytokines and to cause neurodegeneration in MS (Yilmaz et al., 2019). We compared 1-C-11 acetate accumulation between patients with multiple sclerosis and normal controls using static PET. As a result, an elevated accumulation of the label in the whole brain in MS patients was clarified (Takata et al., 2014). The production and metabolism of glutamine and glutamate are thought to be promoted by an increase in astrocyte activity.

We quantitatively evaluated astrocyte metabolic activity in patients with multiple sclerosis using 1-C-11 acetate and compared it with the activity in healthy controls (Kato et al., 2020). As a result, the diffuse hypermetabolism of acetate was observed in a wide area of the brain in MS patients. The distribution of this hypermetabolic area was remarkable, especially in the region along the neuronal tract, and was independent of the distribution of lesions on MRI. In diffusion tensor imaging, a significant decrease in fractional anisotropy in the area along the neuronal tract was found in the MS patients, although the decrease in fractional anisotropy was not significantly associated with acetate hypermetabolism. Astrocyte activation may represent a change that leads to subsequent demyelination or myelin repair, while fractional anisotropy appears to be associated with axonal damage. 1-C-11 acetate PET is a useful functional imaging method for assessing the disease state and understanding the pathology of MS though astrocyte activity.

Treatment of multiple sclerosis and astrocyte activity: Activated astrocytes have been identified as the target cells for various MS treatments. Methylprednisolone sodium succinate is an immunosuppressant that is often used to treat multiple sclerosis. Reactive A1 astrocytes are stimulated by interleukin-1α (IL-1α), tumor necrosis factor-α (TNF-α), and complement component 1, q subcomponent produced by microglia. Activated A1 astrocytes damage neurons and oligodendrocytes via cytotoxic cytokines. Methylprednisolone sodium succinate is thought to prevent the activation of astrocytes by suppressing these proinflammatory cytokines IL-1s and TNF-a (Cheng et al., 2016).

Interferon β (IFN-β1b and IFN-β1a) is an effective treatment for MS. Treatment with IFN-β1b and IFN-β1a improves neurological symptoms and restores the level of the myelin protein in the brains of patients with MS. It was clarified that IFN-β1b and IFN-β1a decrease the levels of inflammatory cytokines (IL-6, IL-1β, TNF-α, and IFN-γ) and suppress the activities of astrocytes and microglia (Lubina-Dabrowska et al., 2017).

The T helper 1 cell response triggered by IFN-γ and the astrocytes that are activated by this response are strongly related to MS pathology. Fingolimod (FTY720), an immunosuppressant, is used as a therapeutic agent for MS. FTY720 has been shown to attenuate the astrocyte MHC class II expression activated by IFN-γ in a dose-dependent manner by enhancing β2 adrenergic receptor signaling (Trkov Bobnar et al., 2019).

Immunomodulatory treatment with glatiramer acetate has been shown to improve neurovascular damage in experimental autoimmune encephalomyelitis mice. Activated astrocytes change their morphology and consequently reduce connections with the neuronal synapses and blood vessel coverings by end-foot degeneration. Astrocyte morphology is reportedly normalized in experimental autoimmune encephalomyelitis mice treated with glatiramer acetate (Eilam et al., 2018).

Thus, major therapeutic drugs for MS may alter astrocyte activity and prevent neuronal damage. Therefore, it might be possible to evaluate the indications and effects of therapeutic agents for MS objectively by evaluating astrocyte activity using 1-C-11 acetate PET.

Other neurological disorders and astrocyte activity: Astrocyte dysfunction and reduced energy metabolism have been recognized to play important roles in epilepsy. The specific production of 4,5-C-13 glutamine and 1,2-C-13 gamma amino butyric acid from acetate in astrocytes after the administration of 1,2-C-13 acetate is reportedly decreased in the hippocampal formation, in the entorhinal/piriform cortex, and in the neocortex in the kainic acid model of mesial temporal lobe epilepsy. These results suggest a decrease in acetate metabolism in epileptogenic lesions. A decrease in the glutamate-glutamine cycle associated with a reduction in astrocyte energy metabolism in lesions not only

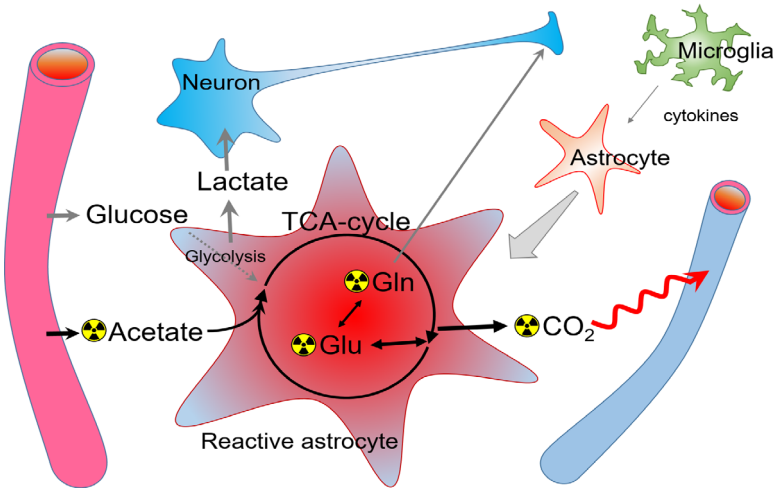

Figure 1 | **Metabolism of 1-C-11 acetate by reactive astrocytes.**
Astrocytes are activated by IL-1s, TNF-α, or complement component 1, q subcomponent released by microglia in the MS brain. 1-C-11 acetate is taken up from the capillary by reactive astrocytes in a selective manner mainly via MCTs. 1-C-11 acetate is metabolized through the TCA cycle in the reactive astrocytes to oxalosuccinate or oxoglutarate and is released as C-11 CO_2 to the capillary during the second round of the TCA cycle. Some of the labels are transformed to and accumulate as a glutamate/glutamine pool, part of which is released to neurons. Here, it is important to note that the label uptake by nerves is relatively small and delayed. Therefore, the release of the label as CO_2 from neurons is further delayed. Gln: Glutamine; Glu: glutamate; IL: Interleukin; MCT: monocarboxylate transporter; MS: multiple sclerosis; TCA: tricarboxylic acid; TNF: tumor necrosis factor.

causes an increase in extracellular glutamate concentration, but also decreases gamma amino butyric acid production (Boison and Steinhauser, 2018).

The balance of amyloid β (Aβ) production and clearance is an important factor in the progression of Alzheimer disease. Astrocytes play a major role in Aβ clearance through the blood brain barrier. This function may be reduced in reactive astrocytes with an altered morphology, resulting in reduced Aβ clearance in the patient's brain. In addition, reactive astrocytes may enhance the activity of β-secretase and γ-secretase and promote Aβ production (Cai et al., 2017).

The main cause of Parkinson's disease (PD) is the loss of dopaminergic neurons. Glutamate excitotoxicity is thought to be a mechanism of PD pathogenesis leading to dopaminergic neuron death, movement disorder, and cognitive dysfunction. In addition, the down-regulation of aquaporin 4 as a result of astrocyte dysfunction has been suggested to initiate and cause the progression of PD pathophysiological disorders (Hindeya Gebreyesus and Gebrehiwot Gebremichael, 2020).

In traumatic brain injury, a number of lines of evidence suggest that reactive astrocytes regulate brain tissue inflammation and neural circuit or synaptic functions associated with neuron damages. Activated astrocytes play a critical role in post-traumatic brain injury synaptic plasticity and neural circuit remodeling, and their function also affects the development of epilepsy (Burda et al., 2016).

Thus, the activity of astrocytes is closely associated with the pathology of many kinds of neuroinflammatory or neurodegenerative diseases. 1-C-11 acetate PET is expected to contribute important information to the diagnosis of diseases and a better understanding of the pathological mechanisms of neurological disorders in terms of the evaluation of astrocyte activity *in vivo*. Particularly in MS, 1-C-11 acetate PET showed that astrocyte activity was widely enhanced not only in lesions with apparent abnormalities observed on MRI, but also in normal-appearing brain regions along the neuronal tracts. In addition, the effect of therapeutic agents for MS could potentially be predicted at an early stage by evaluating the activities of astrocytes.

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