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Bioenergetic adaptations to HIV infection. Could modulation of energy substrate utilization improve brain health in people living with HIV-1?

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Abstract

The human brain consumes more energy than any other organ in the body and it relies on an uninterrupted supply of energy in the form of adenosine triphosphate (ATP) to maintain normal cognitive function. This constant supply of energy is made available through an interdependent system of metabolic pathways in neurons, glia and endothelial cells that each have specialized roles in the delivery and metabolism of multiple energetic substrates. Perturbations in brain energy metabolism is associated with a number of different neurodegenerative conditions including impairments in cognition associated with infection by the Human Immunodeficiency Type 1 Virus (HIV-1). Adaptive changes in brain energy metabolism are apparent early following infection, do not fully normalize with the initiation of antiretroviral therapy (ART), and often worsen with length of infection and duration of anti-retroviral therapeutic use. There is now a considerable amount of cumulative evidence that suggests mild forms of cognitive impairments in people living with HIV-1 (PLWH) may be reversible and are associated with specific modifications in brain energy metabolism. In this review we discuss brain energy metabolism with an emphasis on adaptations that occur in response to HIV-1 infection. The potential for interventions that target brain energy metabolism to preserve or restore cognition in PLWH are also discussed.

BRAIN BIOENERGETICS

Delivery and utilization of energy substrates in the brain

The human brain accounts for only 2% of body weight, but uses 20% of the body's resting metabolic capacity, including approximately 20% of the available oxygen and about 25% of the available glucose supply (Allen and Barres, 2009; Attwell and Laughlin, 2001). The brain is dependent on an uninterrupted supply of energy in the form of ATP for the maintenance of its functional and structural integrity (Du et al., 2008). Brain energy production occurs largely through oxidative metabolism, however a growing number of studies have shown evidence that the β -oxidation of fatty acids contributes to cellular energetics (Ebert et al., 2003; Schulz et al., 2015). In the adult brain, the majority of energy consumption (~70%) is related to neuronal signaling with the balance ascribed to essential cellular activities including the turnover of proteins, nucleotides, and lipids (Attwell and Laughlin, 2001). Energy substrates are delivered to the brain from the blood mainly through glucose transporters (GLUTs) and monocarboxylic acid transporters (MCTs). To date, 14 GLUTs have been identified and characterized into three different classes (GLUT I to III) based on sequence similarity and substrate selectivity (Mueckler and Thorens, 2013). GLUTs transport glucose, and other substrates (hexoses or polyols) including fructose, myoinositol, and urate (Joost and Thorens, 2001; McEwen and Reagan, 2004; Mueckler and Thorens, 2013; Thorens and Mueckler, 2009). Glucose delivery and consumption in the mammalian brain is mediated primarily by GLUT1 and GLUT3. GLUT1 is a highly glycosylated 55 kDa protein isoform that is expressed at high concentrations in endothelial cells of the blood-brain barrier (BBB). GLUT3 is a less glycosylated (45 kDa) isoform that is expressed primarily in neurons (Leino et al., 1997; Vannucci et al., 1997). GLUT4, GLUT5 and GLUT8 appear to be expressed in multiple cell types (Joost and Thorens, 2001; McEwen and Reagan, 2004). GLUT5 acts as a fructose transporter in the brain with low affinity for glucose (Shepherd et al., 1992), and is primarily expressed in microglia (Horikoshi et al., 2003; Payne et al., 1997), cerebellar Purkinje cells (Nualart et al., 1999), human blood-brain barrier (Mantych et al., 1993), and pyramidal cells of the hippocampus (Shu et al., 2006). GLUT4 is expressed primarily in neurons of the hippocampus, cortex, cerebellum and hypothalamus (Brant et al., 1993; Leloup et al., 1996; Vannucci et al., 1998). GLUT8 (GLUTX1) is expressed in the brain stem and hypothalamus (Ibberson et al., 2000).

GLUT4 and GLUT8 are sensitive to insulin (Leloup et al., 1996; McEwen and Reagan, 2004). Like GLUTs, insulin receptors are expressed in various brain regions, hippocampus, cerebellum and cerebral cortex, primarily, but not exclusively, in neurons (Doré et al., 1997; Marks et al., 1990; Schulingkamp et al., 2000; Werther et al., 1987). Frequently, insulin receptors exhibit colocalization with GLUT4 (El Messari et al., 1998; McEwen and Reagan, 2004). Indeed, studies have demonstrated that insulin promotes the translocation of intracellular GLUT4 to the plasma membrane in rat hippocampus (Grillo et al., 2009; Livingstone et al., 1995). Studies by Grillo et al., and McNay et al., suggest that insulin-facilitated translocation of GLUT4 may promote memory encoding by enhancing hippocampus neuronal glucose utilization to support increases in neuronal activity that are associated with hippocampal-dependent tasks (Grillo et al., 2009; Pearson-Leary et al., 2018).

Alternative energetic substrates

While glucose is considered to be the primary energetic substrate in the adult brain (Cremer, 1982; Sokoloff, 1981), alternative substrates are also used under certain circumstances such as prolonged fasting, diabetes, and during the neonatal and preweaning periods. During the prenatal and suckling periods, brain metabolism is largely dependent on the consumption of ketone bodies (KBs) (Nehlig and Pereira de Vasconcelos, 1993; Pellerin et al., 1998) and lactate can serve as the primary energy substrate during the presuckling period (Dombrowski et al., 1989; Fernández and Medina, 1986). Additionally, during the preweaning period, β -hydroxybutyrate and acetoacetate KBs derived from the hepatic oxidation of maternal milk fat serve as important energy substrates for brain (Hawkins et al., 1971). The transport of these alternative substrates is largely regulated by monocarboxylate transporters (MCTs). MCTs are SLC16 gene family members that are involved in numerous metabolic pathways with some tissue specific expression of individual family members. The primary MCT isoforms that are found in the brain include MCT1 that is expressed in endothelial cells of the blood brain barrier with some expression in astrocytes, and MCT2 that is primarily expressed in neurons (Oldendorf, 1973; Simpson et al., 2007). MCT 1-4 are known to transport monocarboxylic acids such as lactate, pyruvate, ketone bodies, β -hydroxybutyrate and acetoacetate (Halestrap and Price, 1999; Poole and Halestrap, 1993). Rodent studies have shown that MCT expression is increased during brain development consistent with a pivotal role for alternative energetic substrates in early brain development (Pellerin et al., 1998).

KBs are also precursors for the synthesis of lipids (mainly cholesterol) and amino acids (Morris, 2005; Nehlig, 2004). In addition to KBs, under conditions of hypoglycemia, glycogen and amino acids (glutamate, etc.) can also be used as alternative energy substrates to meet energy requirements (Hevor, 1994; Wender et al., 2000). This ability to use multiple types of substrates for energy production ensures that the brain has an uninterrupted supply of ATP when its primary energy source is depleted or otherwise unavailable during fetal development, or as the result of disease activity.

Energy reserves

Glycogen is the primary yet small, energy reserve in brain and it is found predominantly in astrocytes (Cataldo and Broadwell, 1986) and in some motor and embryonic neurons (Cataldo and Broadwell, 1986; Inoue et al., 1988; McKenna, 2007; Saez et al., 2014; Vaughn and Grieshaber, 1972). Glycogen stores in astrocytes serve as a source of lactate to neurons through glycogenolysis in astrocytes followed by lactate transport to neurons (DiNuzzo et al., 2011; Machler et al., 2016; Wender et al., 2000), or converted to pyruvate in the cytosol by lactate dehydrogenase (LDH), which enters mitochondrion tricarboxylic acid cycle (TCA) (Sickmann et al., 2005) for oxidative phosphorylation to produce energy. However, the limited size of glycogen stores and its compartmentalization limits the ability to fully support the brain's energy requirements. The β -oxidation of fatty acids can produce large amounts of ATP, albeit at a slower rate compared with glycolysis. For example, the metabolism of palmitate yields 129 molecules of ATP, compared with glycolysis with a net yield of 2 molecules of ATP. The β -oxidation of fatty acids occurs largely in mitochondria; long chain fatty acids are also metabolized in peroxisomes. The role of fatty acid (FA)

oxidation in the brain is still a matter of debate. Although it was widely accepted that neuronal mitochondria in adult brain do not oxidize FAs (Sch et al., 2016), few studies are challenging the dogma of FAs metabolism in the brain. A study conducted in *Drosophila* demonstrated that the adult brain is able to catabolize FAs and release KBs (Schulz et al., 2015), and a study in rodents showed that octanoate oxidation contributes to total brain oxidative energy production (Ebert et al., 2003).

Cell specific metabolic capabilities of neurons and glia

Energy metabolism in neurons and glial cells is highly interconnected so that these cells metabolize energetic substrates in an integrated fashion (Allaman et al., 2011). There are a number of key enzymes in energy metabolism that show cell type specific expression in the brain such as pyruvate carboxylase and glutamine synthetase that are selectively localized in astrocytes, whereas, neuron specific enolase, glutamic acid decarboxylase, phosphate-activated glutaminase and malic enzyme are distributed in neurons (Martinez-Hernandez et al., 1977; Sweatt et al., 2004; Yu et al., 1983). In glia, glutamine synthetase is highly expressed in cytosol while pyruvate carboxylase is expressed in mitochondria. In neurons, specific enolase and glutamic acid decarboxylase are enriched in cytosol whereas phosphate-activated glutaminase and malic enzyme are enriched in mitochondria (Hertz et al., 2007; McKenna, 2007). This cell-specific localization of enzymes and transporters necessitates the intercellular trafficking of metabolites between neurons and glia to maintain a readily available source of energy for synaptic transmission.

Energy metabolism in astrocytes

Astrocytes are situated to be primary regulators of energy metabolism in the brain. They form a tripartite synapse with pre- and post-synaptic specifications of neurons where they can actively sense the level of synaptic activity, and thereby regulate the energy requirements of neurons in real time (Bak, 2017; Prebil et al., 2011). They also have intimate interactions with vascular endothelium and can regulate nutrient and energy substrate delivery into the brain parenchyma (Magistretti and Allaman, 2015). Glucose enters into astrocytes through the 45 kDa isoform of GLUT1, and is phosphorylated by type I hexokinase (HK) (Balmaceda-Aguilera et al., 2012) to produce glucose-6-phosphate. In astrocytes, most of the type I hexokinase is associated with mitochondria (Lynch et al., 1991), and the relative activity of hexokinase bound to mitochondria is far greater than the activity of cytosolic hexokinase (John et al., 2011). Glucose-6-phosphate is a prominent energetic intermediate that can be further processed by three main metabolic pathways. 1) *Glycolysis*: Glucose-6-phosphate can be processed in the cytoplasm through glycolysis, producing two molecules each of pyruvate, ATP and NADH molecules. Pyruvate can be either converted to lactate by LDH in cytosol or it can enter mitochondria where it is oxidatively metabolized through the TCA cycle. During high levels of neuronal activity, the glycolytic pathway becomes engaged to produce lactate in order to support neuronal energy production. During high levels of neuronal activity, the uptake of oxygen is relatively low compared to the increases in blood flow and glucose uptake. This disparity triggers anaerobic metabolic pathways for energy production in neurons, and promotes the transport of lactate from glia through MCTs to afford neurons an energetic substrate to be used in oxidative phosphorylation to meet energy demands (Bouzier-Sore et al., 2006; Ogawa et al., 1993; Pellerin and Magistretti, 1994). 2).

Pentose phosphate pathway: Glucose-6-phosphate can be processed through the pentose phosphate pathway in the neuronal cytosol leading to the production of NADPH and ribose 5-phosphate; NADPH is required for lipid and steroid biosynthesis. A small number of studies have demonstrated that the pentose phosphate pathway is more active in several disease conditions such as Alzheimer's (Allaman et al., 2010), and traumatic brain injury (TBI); (Dusick et al., 2007). Indeed, the pentose phosphate pathway protects neurons from oxidative and nitrative stress (Bolanos and Almeida, 2010). A small number of *in vitro* studies have provided evidence that the pentose phosphate pathway is preferred in astrocytes under conditions of oxidative stress (Gelman et al., 2018; Stincone et al., 2015). However, the energy yield from this pathway is less than one-tenth compared with glycolysis (Brekke et al., 2012; Kreft et al., 2012). 3). *Glycogenesis:* Glucose-6-phosphate is stored in the form of glycogen in astrocytes by glycogen synthase. Glycogen can be rapidly mobilized as an emergency energy substrate when cerebral glucose supply is suddenly depleted, or is unstable in certain conditions such as hypoglycemia and aglycemia (Obel et al., 2012; Wender et al., 2000).

Energy metabolism in neurons

Glucose enters neurons through GLUT3 transporters (Maher et al., 1991). Glucokinase (GK) in neurons plays a role as a glucose sensing enzyme, it allows the brain to regularly monitor glucose levels to control peripheral metabolic functions involved in energy and glucose homeostasis (De Backer et al., 2016; Dunn-Meynell et al., 2002). Glucose not only serves as an energy substrate but also acts as a signaling molecule in glucose-sensitive neurons; so-called glucose-excited (GE) and glucose-inhibited (GI) neurons (Dunn-Meynell et al., 2002; Wang et al., 2004). Both GE and GI neurons are present in hypothalamus or brainstem which are glucose-sensing brain regions (Kang et al., 2004; Thorens, 2012). Neurons have extremely high energy requirements that require a sustained high rate of oxidative metabolism compared with glial cells that have lower energy requirements (Bouzier-Sore et al., 2006; Lebon et al., 2002). To meet these energy requirements, neurons efficiently use lactate as an energy substrate (Bouzier et al., 2000; Serres et al., 2005). Glycolytically-derived pyruvate is converted to lactate by lactate dehydrogenase in astrocytes, and readily exported by the mono-carboxylate transporters MCT1 (Bröer et al., 1997; Pierre and Pellerin, 2005), and MCT4 (Tekköt et al., 2005). Extracellular lactate is taken up by neurons through the MCT2 transporter. In neurons, lactate can be used as an energy substrate following its conversion to pyruvate by lactate dehydrogenase 1 (Bélanger et al., 2011). Pyruvate enters into the mitochondrial TCA cycle for oxidative phosphorylation (Aubert and Costalat, 2005; Barros and Weber, 2018). The glycolytic rate in neurons is slow compared to astrocytes due to lack of 6-phosphofructose-2-kinase/fructose-2,6-bisphosphatase-3 (Bélanger et al., 2011). Glycolytic and pentose phosphate pathways must be maintained in balance in order to meet the energy requirements of neurons. The use of lactate as an oxidative substrate provides high amounts of ATP, bypasses the glycolytic pathway, and spares glucose for the pentose phosphate pathway (Bolaños et al., 2010; Bélanger et al., 2011). The direct oxidation of glutamate via a partial tricarboxylic acid (TCA) cycle can also provide energy to neurons during normal metabolism (Hertz et al., 2007; McKenna et al., 1996), and for use when neurotransmitter synthesis requirements are high (McKenna, 2007) and glucose levels are low (Sonnewald and McKenna, 2002).

Glutamate role in astrocytes and neurons (Glutamate-Glutamine Cycle)

Glutamate plays a key role in linking carbohydrate and amino acid metabolism through the TCA cycle, as well as regulating nitrogen trafficking and ammonia homeostasis in the brain. Glutamate released from neurons as a synaptic transmitter is transported into astrocytes primarily through glia-enriched glutamate transporters (excitatory amino acid transporters) EAAT1 and EAAT2 (Danbolt, 2001). This glutamate is then either converted to glutamine by the astrocyte-specific glutamine synthetase (Derouiche, 2003) or to α -ketoglutaric acid by glutamate dehydrogenase when glutamate concentrations exceed the capacity of glutamine synthase (McKenna et al., 1996; McKenna et al., 2000; Yu et al., 1982). Alpha-ketoglutaric acid in astrocytes largely enters into the TCA cycle for oxidative metabolism in mitochondria (Yu et al., 1982; Yudkoff et al., 1994). This suggests that elevated glutamate may also be used by astrocytes as an energy source via a partial TCA cycle, and as a primary energy substrate via glycogen synthesis (Prebil et al., 2011). Glutamine can be transferred to neurons and converted back to glutamate by deamination that is catalyzed by phosphate-activated glutaminase. Neurons lack the enzyme pyruvate carboxylase (Yu et al., 1983), and hence depend on glia for the *de novo* synthesis of glutamate (Danbolt, 2001; Hertz and Zielke, 2004). Glutamine also serves as the main precursor for gamma amino butyric acid (GABA), (Sonnewald et al., 1993), and some of the GABA released by neurons is taken up and metabolized by astrocytes. The maintenance of GABAergic neurotransmission also relies on anaplerosis (replacing TCA cycle intermediates that have been extracted for biosynthesis) (Schousboe et al., 2013).

Brain energetics and cognitive function

Cognitive function decreases with advancing age including declines in temporal, parietal, and cerebral cortex glucose utilization that are most prominent in the frontal cortex (Pantano et al., 1984; Shen et al., 2012; Steffener et al., 2013). Although the factors contributing to these age-related declines in cognitive function are not entirely understood, decreases in cerebrovascular circulation are thought to contribute to reductions in the delivery of energetic substrates to brain parenchyma and to the removal of toxic metabolic byproducts (Hoyer, 1982b; Mattson and Arumugam, 2018; van Es et al., 2010). This hypoperfusion is accompanied by decreased expression of glucose transporters and enzymes involved in glycolysis and oxidative phosphorylation (Ding et al., 2013; Horwood and Davies, 1994; Hoyer, 1982a; Kalaria and Harik, 1989; Rapoport et al., 1996). Since neuronal activity accounts for ~70% of energy utilization in brain, these cells are most vulnerable to damage from hypometabolism. Synaptic transmission requires a great deal of energy to produce, package and release neurotransmitter, and neuronal depolarization/repolarization is regulated by rapid changes in ionic gradients that rely on energy-dependent ion pumps (Attwell and Laughlin, 2001; Burnashev et al., 1995; De Jong et al., 1997; Helmchen et al., 1997; Sheng et al., 1998). A hypometabolic state results in the loss of synapses that are insufficiently metabolically supported. The resultant perturbation of neural circuits is thought to be the biological basis of cognitive slowing associated with normal aging (Kapogiannis and Mattson, 2011; Leal and Yassa, 2013; Schliebs and Arendt, 2011).

The importance of energy availability to cognitive function is further supported in experimental settings. In rodents, bilateral hippocampal injection of glycogenolysis

inhibitors such as 1, 4-dideoxy-1, 4-imino-D-arabinitol (DAB) or isofagomine significantly impaired long-term memory. Memory impairment was prevented when lactate was co-injected with DAB (Suzuki et al., 2011). The importance of lactate transport in long term memory formation was tested by knocking down lactate transporters MCT1, MCT2 or MCT4 (individual or in combination) using bilateral injections of oligodeoxynucleotides (ODNs) into rat hippocampus. Reductions in MCT1, MCT2 or MCT4 expression resulted in long term memory loss tested 24 h after administration, and the impairment was sustained for at-least 6 days. Memory impairments were rescued by lactate injection in MCT4 knockout, but not in MCT2 knock out mice. Further, injection of lactate or glucose failed to rescue long term memory impairment in rats with depletion of MCT2, suggest that lactate transport through MCT2 may be crucial for long-term memory formation (Suzuki et al., 2011). These data were supported by an independent study that compared brain glucose utilization in aged (22 to 24 months) compared to young rats (3 months) with performance in water maze, motor coordination, open field activity, and somatosensory reactivity (Gage et al., 1984). In the water maze test, aged rats exhibited poorer performance when compared to the young animals in distance swam, platform crossings, and escape latency suggestive of age-associated impairments in the acquisition of spatial learning. Likewise, aged animals showed decreased activity behavior in the open field tests compared with their younger counterparts. There were no significant differences in motor coordination on the rotarod test, and the total integrated response in the somatosensory reactivity test were not different between old and young animals. To correlate these findings with the age-related cerebral metabolic rate, they measured local cerebral glucose utilization by using [^{14}C]-2-deoxy-D-glucose and autoradiography (Sokoloff et al., 1977); glucose utilization was significantly reduced in regions of septohippocampal and the prefrontal cortex of aged animals. These observations demonstrate that reduced cerebral glucose utilization was correlated with spatial memory impairment measured in the water maze, but did not correlate with performance in motor and somatosensory tests(Gage et al., 1984).

Similar relationships between regional deficits in brain glucose utilization have been found in human studies. In a voxel-based morphometric study, Nishi (Nishi et al., 2010) and colleagues examined the correlation between glucose hypometabolism and neuropsychological performance in patients with mild cognitive impairment (MCI). They measured performance on verbal and visual delayed recall and executive function tasks in 30 patients with MCI and 15 healthy controls aged 61 to 76; patients with MCI exhibited significantly worse performance in all three tasks as well as significant reductions in brain glucose uptake measured by ^{18}F -fluorodeoxyglucose (FDG)-position emission tomography (PET). Reduced FDG uptake in bilateral posterior cingulate cortex correlated with deficits in visual delayed recall, while FDG uptake in the right middle frontal gyrus and right superior frontal gyrus correlated with impairments in two-relational reasoning of the Raven's colored progressive matrices (RCPM). Reduced FDG uptake in the right medial temporal cortex, right prefrontal cortex and left superior parietal cortex was associated with worse verbal recall (Nishi et al., 2010). Together these findings suggest that efficient brain energy utilization is critical for several aspects of memory formation.

BRAIN BIOENERGETICS IN PEOPLE LIVING WITH HIV-1

Cognition

Prior to the advent of antiretroviral therapy (ART), cognitive impairment in PLWH was typically progressive and the onset of frank dementia was an indicator of impending death (Heaton et al., 2011; Mora-Peris et al., 2016; Nabha et al., 2013). With ART, PLWH have the potential to live near normal life spans, notwithstanding preexisting comorbid conditions or complications that develop over time. Functional cognitive impairments in PLWH on ART are less frequent and less severe (Nyongesa et al., 2018; Sacktor et al., 2001); current estimates suggest that 15-20% of PLWH exhibit functional cognitive impairment that impacts activities of daily living (Heaton et al., 2010; Robertson et al., 2007; Woods et al., 2009). An additional 25-30% are reported to have a milder form of cognitive impairment that does not impact activities of daily living (Goodkin et al., 2001; Woods et al., 2009), although these individuals are more likely to progress to symptomatic cognitive impairment (Grant et al., 2014). Cognitive impairments in PLWH often occur in conjunction with advanced immunosuppression (or are associated with previous immune compromise) (Anand et al., 2010; Pharmacokinetic and Clinical Observations in People Over fifty et al., 2018; Watkins and Treisman, 2015), but can also occur independently of other symptoms of HIV-1 infection, and in some individuals may be the only manifestation of infection (Navia and Price, 1987). While the exact mechanisms by which HIV infection leads to cognitive impairments are still poorly understood, there is considerable evidence that disturbances in CNS energy metabolism, in conjunction with persistent CNS inflammation, drives neurological dysfunction. Modifying ART regimens in PLWH can partially (although sometimes only temporarily) reverse cognitive impairment in some individuals (Altair Study et al., 2010; Chawla et al., 2018; Underwood and Winston, 2016), suggesting that viral products or immune/inflammatory dysfunction may be important in mediating neurological decline. These data also suggest that functional impairment rather than irreversible cell death may underlie cognitive impairment in this population (Dougherty et al., 2002; Gendelman et al., 1998; Gisslen et al., 1998; Nath and Sacktor, 2006; Portegies, 1995; Tozzi, 2003).

Brain energy utilization

Cognitive impairments in PLWH are often associated with ongoing neurological damage including persistent glial infection, brain volume loss, inflammation, synaptodendritic damage and disruptions in white matter integrity (Cardenas et al., 2009; Churchill et al., 2006; Kraft-Terry et al., 2009; McMurtry et al., 2008). These neuropathological changes coincide with shifts in brain energy utilization that appear early in the course of cognitive impairment and become progressively dysregulated over time. In ART-treated individuals with undetectable plasma viral loads there are varying degrees of reduced glucose uptake in the mesial frontal gyrus (Andersen et al., 2010), and evidence for small but consistent age-related reductions of glucose uptake in the anterior cingulate cortex (Towgood et al., 2013). Using serial MRS imaging, progressive abnormalities were identified in choline, N-acetylaspartate, glutamate and glutamine containing compounds in multiple brain regions of HIV-infected subjects on stable cART (Ernst et al., 2010; Gongvatana et al., 2013). In particular, neurocognitive decline appears to be specifically associated with reduced glutamate and glutamine-containing compounds in multiple brain regions including frontal

white and grey matter, basal ganglia, and parietal grey matter, and correlate with deficits in executive function, motor and psychomotor speed, attention, and working memory (Ernst et al., 2010; Gongvatana et al., 2013; Meyerhoff et al., 1996; Mohamed et al., 2010).

Brain adaptations to HIV-infection appear to occur at very early time points following infection by HIV. Studies conducted in acutely HIV-infected individuals have demonstrated lower choline (Cho), glutamate-glutamine (Glx) and choline/creatine (Cho/Cr) ratios in the frontal cortex, increased myoinositol (MI) and myoinositol/creatine (MI/Cr) ratios, with trends towards lower Glx concentrations in the basal ganglia (Lentz et al., 2011). They followed these subjects with repeated imaging and found that many of these metabolic changes were sustained. At approximately 2 months following infection, increases in Cho, Cho/Cr ratios, and choline/n-acetylaspartate (Cho/NAA) were observed in frontal gray matter, with the Cho and Cho/Cr ratios sustained above baseline levels for at-least 6 months following HIV infection (Lentz et al., 2011). In white matter, Cho/Cr and Cho/NAA levels were elevated 2 months following HIV infection and were sustained for 6 months. Regional increases in Cho and Cho containing compounds are thought to be indicative of increased plasma membrane lipid metabolism resulting from glial activation, suggesting that a brain inflammatory response occurs at very early time points following HIV-infection (Lentz et al., 2011). Indeed, altered levels of cerebral metabolites have been observed in independent studies at very early time points following infection (Cassol et al., 2014; Peterson et al., 2014; Young et al., 2014). In the basal ganglia, glutamate/glutamine (Glx) levels were increased compared to baseline levels, and 2-month levels (Ernst et al., 2010). Elevations in MI are thought to be indicative of microglial activation, consistent with an early microglial response following infection. Lentz et al., demonstrated a correlation between the numbers of circulating CD16+ monocytes and brain NAA and Cho levels (Lentz et al., 2011), suggesting that this apparent microglial and astrocytes activation may be the result of HIV-infected monocytes trafficking into brain parenchyma at very early time points following HIV infection (Gongvatana et al., 2013).

Brain gene expression profiling studies have provided additional evidence for widespread perturbations in brain energy metabolism in PLWH who have cognitive impairment (Borjabad et al., 2011). In this study there were at least 41 gene expression changes in PLWH who had cognitive impairment compared to PLWH with normal cognition. These included genes involved with ATP/ADP glutamine, glutamate, and glutamine metabolism, glycolysis, mitochondrial function, and insulin signaling (Borjabad et al., 2011). These findings are further supported by a study from our group showing that accumulations of specific TCA cycle and glycolytic intermediates were associated with temporal changes in cognitive status (Dickens et al., 2015). In particular, elevated citrate and acetate with decreased creatine was associated with worsening cognitive status (predictive accuracy of 92%, sensitivity of 88%, and 96% specificity), while elevated glutamine and glucose with decreased *myo*-inositol, β -glucose, and creatinine were associated with improvements in cognitive status (predictive accuracy of 92%, sensitivity of 100% and specificity of 84% (Dickens et al., 2015). Untargeted cerebral spinal fluid (CSF) metabolomic analyses of young PLWH found that a number of metabolites were altered in PLWH on ART compared to HIV-negative controls (Cassol et al., 2014). These included metabolites linked to biosynthetic pathways such as the production of neurotransmitters (glutamate, N-

acetylaspartate), mitochondrial function (3-dehydrocarnitine, succinate and malate), glial activation (myo-inositol), oxidative stress, ketone bodies (betahydroxybutyric acid, 1,2-propanediol), and metabolic waste products (1,2 propanediol, p-cresol sulfate, phenylacetyl glutamine, etc.). A second targeted plasma metabolomic analysis found a large number of energetic intermediates dysregulated in PLWH including 40 acylcarnitines, 19 biogenic amines, and hexoses (Scarpelini et al., 2016). The severe deregulation in acylcarnitine metabolism in plasma suggests widespread mitochondrial dysfunction in PLWH.

Providing alternative fuels for the brain

In aggregate, these findings suggest that adaptations in brain energy metabolism may be central to the pathogenesis of cognitive impairment in PLWH, and that interventions designed to preserve cellular bioenergetics could protect CNS function in this population. In particular, these studies suggest that promoting anaerobic metabolism in brain could protect PLWH from cognitive impairment. As described above, ketone bodies can be used by brain as a fuel source and astrocyte glycogen stores can be converted to lactate that is shuttled to neurons in times of high energy demand or when glucose becomes depleted. The question then becomes, how can we safely promote anaerobic metabolism in the brain of PLWH? Exercising to exhaustion can produce ketone bodies and lactate that enter into brain (van Hall et al., 2009). However, the intensity of exercise required to produce enough lactate and ketone bodies to drive anaerobic metabolism in brain is prohibitive for many PLWH. A ketogenic diet can force the use of alternate energy substrates by limiting the types of fuel available (Barañano and Hartman, 2008). Ketogenic diets or modified Atkins diets are becoming increasingly popular for a variety of reasons, but medically this high-fat diet is best known for its ability to successfully reverse status epilepticus (Barborka, 1928; Kverneland et al., 2015; Ma et al., 2007) and may delay the genesis of various types of epilepsy (Coppola et al., 2002; Lefevre and Aronson, 2000), (Henderson et al., 2006; Neal et al., 2008). Experimental evidence from rodents has demonstrated that ketone bodies produced from the consistent ingestion of a ketogenic diet can serve as alternative energy substrates for the brain as evidenced by increases in the numbers of mitochondria and a higher phosphocreatine to creatine ratio (Bough et al., 2006). Additional evidence from our group has shown in tissue culture experiments that ketone body treatments can protect neurons from HIV-1 Tat-induced cellular stress by reducing levels of intracellular calcium, reducing reactive oxygen species, restoring mitochondrial membrane potential, and increasing bioenergetic efficiency (Hui et al., 2012). Dietary supplementation of creatine can increase levels of cellular ATP through the creatine-phosphocreatine shuttle (Bessman and Carpenter, 1985; Burke et al., 2003), and we have previously shown that creatine supplementation protects against HIV-1 Tat-induced neuronal death by preventing mitochondrial hypopolarization, preserving cellular ATP levels, and preventing opening of the mitochondrial permeability transition pore (Stevens et al., 2014). These data suggest that providing the brain with alternative energy substrates (alternative to glucose), may protect the brain. Another possibility is the use of intranasally delivered insulin to push energy metabolism towards alternative fuels. A bolus delivery of insulin to brain parenchyma presumably would stimulate insulin receptors and promote the cellular uptake and utilization of glucose. This depletion of available glucose would require a shift in energy substrate

utilization to alternate fuels. There are in addition numerous beneficial effects of insulin for CNS protection.

Roles for insulin in cognition

Accumulating evidence suggests there are abnormalities of insulin signaling in PLWH (Gutierrez and Balasubramanyam, 2012; Kalra et al., 2011; Pedro et al., 2018). HIV infection itself causes alterations in insulin signaling, lipid distribution, glucose homeostasis, and metabolism with, or without ART (Gutierrez and Balasubramanyam, 2012; Non et al., 2017). Insulin resistance has been described in patients with HIV infection similar to patients with Alzheimer's disease, type II diabetes, and obesity (Arnold et al., 2018; Valcour et al., 2005; Ye, 2013), and ART can additionally impact insulin resistance and metabolic disorders which have also been linked to poorer cognitive function (Idiculla et al., 2011; Leow et al., 2003). We (Kim et al., 2019) used the homeostatic model assessment of insulin resistance (HOMA-IR) to demonstrate higher HOMA-IR levels in PLWH who exhibit declining cognition compared to PLWH who have stably normal cognition; a 10-point increase in insulin levels was associated with 1.44 greater odds of having declining vs normal cognition. Several decades of research have shown that insulin has multiple actions in brain that regulate many of the same neural pathways perturbed by HIV infection including energy metabolism, lipid metabolism, neurotransmitter channel activity, neurite outgrowth, synaptic strength, and inflammatory signaling (Craft and Watson, 2004; Grinspoon et al., 1998; Grinspoon and Bilezikian, 1992; Hardy et al., 2001; Hoyer, 2002a, b; Hughes et al., 2005; Palacios et al., 2006; Sellmeyer and Grunfeld, 1996; Agrawal and Gomez-Pinilla, 2012; Agrawal et al., 2014; Costello et al., 2012; De Felice and Ferreira, 2014; Emmanuel et al., 2013; Gobel and Langemann, 2011; Lee et al., 2011; Needleman and McAllister, 2008; Nelson et al., 2014), suggesting that insulin could protect the CNS in PLWH. The peptide hormone insulin and insulin-like growth factors provide broad neuroprotective actions on multiple cell types by regulating a wide-range of cellular functions associated with neurotrophic and anti-inflammatory responses (Aleman and Torres-Aleman, 2009; Cole and Frautschy, 2007; Heidenreich, 1993; Heidenreich et al., 1983; Jonas et al., 1997) (Aljada et al., 2001; Dandona, 2002; Dandona et al., 2002; Dandona et al., 2001). Insulin receptors are distributed widely throughout the brain including cortical and subcortical structures, and are enriched in the hypothalamus and limbic system including the hippocampus and piriform cortex where they play a vital role in higher cognitive functions such as learning and memory (Havrankova et al., 1981; Havrankova et al., 1978a; Havrankova et al., 1978b; Zhao et al., 1999; Zhao et al., 2004). At the molecular level, insulin and its receptors are thought to regulate learning and memory processes through multiple downstream intracellular cascades including shc, Grb-r/SOS, Ras/Raf, and MEK/MAP kinases as well as PI3K, PKC and Akt (Niswender et al., 2003; Zhao and Alkon, 2001). Insulin has also been shown to modulate the concentrations of multiple neurotransmitters such as acetylcholine and norepinephrine (Campfield and Smith, 1983) can modulate synaptic plasticity, acting as a direct regulator of both synaptic GABAergic (inhibitory) and glutamatergic (excitatory) receptors (van Bussel et al., 2016). Physiology studies have shown that insulin signaling modulates long term potentiation (LTP) induced by NMDA receptor activation (Martín et al., 2011), and regulates the endocytosis of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors,

which is associated with long-term depression (LTD) of excitatory synaptic transmission (Wang, 2008) (Man et al., 2000). In normal laboratory animals and human volunteers, exogenous administration of insulin has been shown to enhance basal cognitive performance. For example, acute intra-cerebroventricular injection of insulin has shown memory enhancement on a passive-avoidance task in rodents. In human volunteers, intravenous insulin administration has shown memory improvement for both story recall and the Stroop interference test (Watson et al., 2009), and improves performance in several standard memory tasks including immediate and delayed word list recall, digit spanning, object location, and mirror tracing craft (Craft et al., 2012; Reger et al., 2008; Shemesh et al., 2012). Insulin has complex and multidimensional effects on neuronal survival, cognition, learning and memory processes.

Evidence supporting the use of intranasal insulin to treat/prevent cognitive impairment in PLWH

Intranasal delivery might have several advantages over oral or injectable insulin modifying drugs to treat neurodegenerative conditions. Intranasal delivery provides a rapid delivery of insulin to the CNS via bulk flow along olfactory and trigeminal perivascular channels, and slower delivery via olfactory bulb axonal transport. This direct delivery results in therapeutically relevant concentrations of insulin in brain without adversely affecting blood insulin or glucose levels. The intranasal-delivery of insulin was recently tested in conventional mice infected with a chimeric HIV (EcoHIV) (He et al., 2014). The EcoHIV infected mice resemble early/chronically HIV-infected asymptomatic individuals whose immune system can suppress but not eliminate virus (elite controllers), as well as in PLWH on effective ART. As in PLWH, despite viral control, EcoHIV infected mice develop neurological disease with many characteristics that are similar to what has been observed in PLWH including a low HIV brain burden, relatively benign brain pathology, with evidence of dendritic and synaptic damage, dysregulation of energy metabolism genes, and learning and memory impairments in behavioral tests (Borjabad et al., 2011; He et al., 2014). In a recent study we found that intranasal insulin treatment of EcoHIV infected mice completely reverses cognitive impairment in infected animals, as measured by performance on a radial arm water maze test (Kim et al., 2019). EcoHIV infected mice showed reductions of MAP2 staining in the CA1 and CA3 regions of the hippocampus compared to controls that coincides with cognitive impairment in these animals. Intranasal insulin treatment restored MAP2 stained dendrites to levels not different from uninfected control mice, suggesting that EcoHIV infection did not cause neuronal loss, but damaged neuronal dendrites in a manner that was reversible by intranasal insulin treatment (Kim et al., 2019). Similar findings were obtained in a feline immunodeficiency model of HIV infection (Maingat et al., 2009; Power, 2018). These data are consistent with studies showing that exogenous insulin administration enhances basal cognitive performance in laboratory rats, in human volunteers, and improves cognitive deficits patients with Alzheimer's disease and type-2 diabetes (Table 1). We also found changes in energy metabolite profiles of EcoHIV infected mice were partially reversed by intranasal insulin therapy (Kim et al., 2019). Together, these findings suggest that insulin delivered directly to brain could protect or restore neural function in PLWH by promoting critical pathways of energy metabolism that are intrinsically protective.

Conclusions

Through the use and continued development of ART, infection by HIV has been transformed from nearly universal terminal illness to a chronic manageable disease. However, it is important to note that the management of HIV-infection through ART is not a cure, and there are a number of comorbid conditions that cumulatively develop with the length of infection, and time on ART, even in PLWH who exhibit viral suppression (Dickens et al., 2017; Jacob et al., 2017; Lorenc et al., 2014; Nabha et al., 2013). Despite ART, cognitive impairments continue to be a comorbid condition that frequents PLWH (Chawla et al., 2018; Lorenc et al., 2014; Valdez et al., 2016). Encouragingly however, residual cognitive impairments in PLWH on suppressive ART may be the result of reversible neuronal damage (Nabha et al., 2013; Webb et al., 2009) rather than frank cell loss. These findings provide motivation for the continued development of neurotherapeutics and/or interventions that could restore and preserve cognitive function in PLWH. Dietary or pharmacological interventions that push brain anaerobic metabolism may restore cellular functions that are lost with energetic adaptations in brain which occur with HIV infection and ART.

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Figure 1. Energetic adaptations to HIV infection.

Schematic representation of energy metabolism in the **A)** healthy brain and **B)** brains of people living with HIV (PLWH). Enzymes are depicted in purple, metabolic products are black, transporters are green, and known metabolic abnormalities in PLWH are depicted in red. Abbreviations: pyruvate (PYR), N-acetyl aspartate (NAA), glutamate (GLU), glutamine (GLN), oxaloacetate (OAA), alpha-Keto glutarate (α -KG), adenosine diphosphate (ADP), adenosine triphosphate (ATP), phosphocreatine (CrP), creatine (Cr), acetyl-coenzyme A (Ac-CoA) glycolysis (GLY), glutamine synthetase (GS), glutamate dehydrogenase (GDH), aspartate aminotransferase (AT), lactate dehydrogenase (LDH) pyruvate dehydrogenase (PDH), glycogen synthase (GS), phosphate activated glutaminase (PAG), pyruvate carboxylase (PC), pyruvate dehydrogenase (PDH), pyruvate carboxylase (PC), aspartate- N acetyl transferase (ASP-NAT), glutamate transporter (GLUT), monocarboxylate transporter (MCT), excitatory amino acid transporter (EAAT), insulin receptor (IR).

Table 1.
Summary of past and ongoing human intranasal insulin trials.

Adapted from, (Shemesh et al., 2012), (Craft et al., 2012; Fan et al.; Fan et al.; McIntyre et al.; Novak et al., 2013), ([Clinicaltrials.gov](https://clinicaltrials.gov))

REFERENCE	DOSE OF INTRANASAL INSULIN TESTED	PATIENT POPULATION	ASSESSMENT
Benedict, 2004	160 IU (long-term)	Healthy	<ul style="list-style-type: none"> • Word list (immediate recall) • Word list (delayed recall)
Reger, 2006	20 or 40 IU (acute)	Probable AD or MCI vs. healthy	<ul style="list-style-type: none"> • Story recall (immediate + delayed recall) • Word list (immediate + delayed recall)
Benedict, 2007	20 IU Aspart* vs. 20 IU Regular (long term)	Healthy men	<ul style="list-style-type: none"> • Word list (immediate recall) • Word list (delayed recall)
Benedict, 2008	160 IU (acute)	Healthy, normal weight, with no medications	<ul style="list-style-type: none"> • Digit span (immediate recall) • Object location (immediate recall) • Mirror tracing (immediate recall)
Hallschmid, 2008	160 IU (long-term)	Obese men	<ul style="list-style-type: none"> • Word list (delayed recall) • Word list (immediate recall)
Reger, 2008	20 IU (long term)	AD or MCI	<ul style="list-style-type: none"> • Memory score (immediate/ delayed recall ratio) • Voice onset time (immediate/delayed recall ratio)
Reger, 2008	10, 20, 40, 60 IU (acute)	AD or MCI vs. healthy	<ul style="list-style-type: none"> • Story recall (immediate recall or delayed recall) • Word list learning (immediate recall, delayed recall)
Krug, 2010	160 IU (acute)	Healthy postmenopausal women	<ul style="list-style-type: none"> • Digit span (immediate recall) • Object location(immediate recall)
Fan, 2012	140 IU (acute)	schizophrenic	<ul style="list-style-type: none"> • Hopkins Verbal Learning Test (Immediate recall) • Hopkins Verbal Learning Test (Delayed)
Craft, 2012	10 or 20 IU bid	AD or MCI	<ul style="list-style-type: none"> • Verbal Memory Composite
Craft, 2012	20 or 40 IU	AD or MCI	<ul style="list-style-type: none"> • Story recall (delayed recall)
McIntyre, 2012	40 IU (long term)	Euthymic with bipolar disorder	<ul style="list-style-type: none"> • California Verbal Learning Test, second edition • Process Dissociation Task
Burns, 2012	40 IU (acute)	Early AD	<ul style="list-style-type: none"> • fMRI activation • Cognitive battery.

REFERENCE	DOSE OF INTRANASAL INSULIN TESTED	PATIENT POPULATION	ASSESSMENT
Novak, 2013	40 IU (long term)	Diabetic	<ul style="list-style-type: none">• Brief Visuo-spatial Memory Test-Revised• Verbal fluency measures
Fan, 2013	40 IU (long term)	Schizophrenic	<ul style="list-style-type: none">• Cognitive battery.
Craft, 2013	20 IU bid	AD or MCI	<ul style="list-style-type: none">• Cognitive battery.
Haley, 2013	20 IU	AD	<ul style="list-style-type: none">• Cerebral glutamate concentration• Cognitive battery