Seizures and Amyloid-β induce similar changes in neuronal network metabolic parameters in mouse hippocampal slices.

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Abstract.

Major risk factors for neurodegenerative diseases share brain hypometabolism as one common outcome. In turn, many neurodegenerative pathologies result in brain hypometabolism; both epilepsy and Alzheimer's disease are characterised by disruptions in glucose metabolism. However, the causative link between energy shortage and neuronal pathologies in these diseases has remained elusive. Using real-time brain slice recordings of energy metabolism parameter (NAD(P)H, FAD, pO2 and extracellular glucose) transients in response to network activation, we found that induced epileptic seizures and amyloid-beta peptide both result in similar and long-lasting disruptions of neuronal energy metabolism, suggesting a common path of action. In addition, we found that in both cases, subsequent addition of pyruvate, the principal mitochondrial fuel possessing multiple neuroprotective properties, completely normalised the disputed energy state. Our data supports the hypothesis that energy metabolism deficiency underlies the initiation of neurodegenerative diseases.

Major risk factors for acquired epilepsy (traumatic brain injury, stroke, viral infection, status epilepticus (Waldbaum and Patel, 2010; Pitkanen et al., 2015) all share hypometabolic brain state as the common outcome; in turn, epileptic patients’ also exhibit brain hypometabolism, seen as reduced glucose utilization in FDG-PET analysis (Goffin et al., 2008). To examine whether epileptic activity impairs
metabolism and induces changes in network function, we measured synaptic stimulation-induced (10Hz, 10s) metabolic (oxygen, NAD(P)H, FAD and extracellular glucose) parameter transients in hippocampal slices before and after a few seizures (which resulted in massive glucose/oxygen consumption and oxidative stress) induced by 1s, 100Hz synaptic stimulation in the presence of 4-AP. All measurements were done in absence of aberrant activity: 4-AP was washed out completely and the slices were allowed to stabilize (20-30min) prior to post-seizure recordings.

Metabolic dysfunction induced by ILEs was demonstrated by a strongly decreased NAD(P)H overshoot as well as a decreased FAD undershoot (Fig. 1A). We reported previously that the NAD(P)H overshoot is associated mainly with cytosolic glycolysis(Ivanov et al., 2014) whereas the initial dip reflects the oxidative metabolism activity. Thus, taken together with the seizure-induced decrease in glucose consumption (Fig. 1A) these data suggest a reduced activity of cytosolic glycolysis following the seizures. Mitochondrial oxidative metabolism seemed to remain unaltered as the NAD(P)H/FAD oxidation phases and oxygen consumption were similar prior to and following seizures (Fig. 1A).

After seizures and 4-AP washout, glucose consumption induced by SC stimulation decreased significantly compared to control, pre-4-AP, levels (Fig. 1C). This effect was long-lasting, as glucose transients did not reveal any trend towards recovery following 4-AP washout for at least 100 minutes. Interestingly, the glucose consumption in response to SC stimulation, reduced following seizures, was significantly normalized to near-control levels by subsequent addition of 5mM pyruvate (Fig. 1C).

Decreased cerebral glucose consumption is also an early and well-established biomarker of AD (Costantini et al., 2008; Cunnane et al., 2011; Chen and Zhong, 2013). This pathology is likely a major contributor to brain hypometabolism. However, the mechanism(s) underlying this phenomenon is yet unclear. We measured the same as above metabolic parameters in hippocampal slices before and after 1-hour Aβ1-42 application.
Similar to the seizure effects, Aβ_{1-42} induced a strong decrease in both NAD(P)H overshoot and FAD undershoot while not affecting oxidative phases of the transient responses (Fig. 1B). The Aβ_{1-42} application also resulted in a strong reduction in stimulation-induced glucose transients, which were not affected by insulin but normalized close to the control levels by the subsequent application of pyruvate (Fig. 1D).

Therefore, these results reveal an interesting similarity in the effects of seizures and Aβ_{1-42} on hippocampal cell’s metabolism. We suggest that the oxidative stress created by both seizures and Aβ_{1-42} is a trigger of observed changes and presumably is one initiation factor for both acquired epilepsy and sporadic AD.

References


Figure legend.

Beta-amyloid and seizures disrupt neuronal energy metabolism in a similar manner. A: Stimulation-induced transients in metabolic parameters in slices before (black) and following induced seizures (red). B: Stimulation-induced transients in metabolic parameters parameters in slices before (black) and following beta-Amyloid wash-in (red). C: Stimulation-induced glucose uptake example traces, amplitude and integral means in slices in control (black), following seizures (red) and after subsequent
addition of pyruvate (blue). D: C: Stimulation-induced glucose uptake example traces, amplitude and integral means in slices in control (black), following beta-amyloid application (red) and after subsequent addition of pyruvate (blue) or insulin (green).