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Title of Project: *Improving glucose energy metabolism in temporal lobe epilepsy*

Summary:
We previously showed that glucose oxidation and the activity of pyruvate dehydrogenase (PDH) are reduced in the chronic stage of the pilocarpine mouse epilepsy model, 3 weeks after status epilepticus (SE). This is expected to result in lower energy levels. Energy shortage destabilises membrane potentials and neuronal signalling, which can contribute to seizure generation and also slow recovery from seizures. We failed to obtain material from human epilepsy surgeries and could not investigate the activities of PDH in people.

The reduced activity of PDH in the epilepsy animal model is likely caused by increased phosphorylation by PDH kinase of the E1α subunit of PDH, which downregulates PDH activity. In this grant we explored to which extent inhibition of this phosphorylation is a possible approach to treat epilepsy. Chronic dichloroacetate (DCA, 50 and 100 mg/kg/day) treatment was tested in acute seizure and the chronic pilocarpine model. We also determined the effects on phosphorylation state, activity and protein levels of PDH in the chronic stage of the pilocarpine model. DCA treatment did not increase latencies to seizures in the acute flurothyl seizure test and was slightly proconvulsant in the 6 Hz test. The latencies to seizures in a second-hit flurothyl test were decreased in “epileptic” SE vs. “healthy“ No SE mice in the chronic stage, but were not restored by DCA. In mice that had experienced pilocarpine-induced SE and were in the chronic “epileptic” stage of the model, PDH activity was reduced by 65% compared to “healthy” No SE mice. This was partially alleviated with DCA treatment. Also, PDH protein levels were decreased by 37% and phosphorylation at Ser^{300} of PDH was increased by 52% in SE mice, but were not significantly changed with DCA. Moreover DCA treatment decreased the amounts of total PDH by 23% in No SE mice, which may explain the proconvulsant effects in the 6 Hz test. The reduction in PDH protein levels during the chronic epileptic stage suggests increased degradation of the protein, which may contribute to the deficient glucose oxidation found in epilepsy. Taken together, DCA did not

have any anti-convulsant effects in the tested models. Future studies utilising other PDH kinase inhibitors are required to determine whether this treatment approach is viable.

At the same time we found that triheptanoin another metabolic treatment improved PDH activity in the chronic epileptic stage of this model and glucose metabolism improved. It is unclear to which extent the anticonvulsant or metabolic effects of triheptanoin are responsible for the improvements. Taken together, improving glucose energy metabolism is still a promising approach to prevent epileptic seizures. Alternatively, auxiliary fuels in addition to glucose may be used, the current research focus of our laboratory.

Resulting publications from this grant:

Durie D, McDonald TS, **Borges K.** (2018) The effect of dichloroacetate in mouse models of epilepsy. Epilepsy Res, 145: 77-81.

McDonald TX, Puchowicz M, **Borges K.** (2018) Impairments in oxidative glucose metabolism and metabolic treatments thereof. Frontiers in Cellular Neuroscience 12. 10.3389/fncel.2018.00274.

McDonald, T., M.P. Hodson, I. Bederman, M. Puchowicz, and K. Borges, *Triheptanoin alters [U-13C6]-glucose incorporation into glycolytic intermediates and increases TCA cycling normalizing the activities of pyruvate dehydrogenase and oxoglutarate dehydrogenase in a chronic epilepsy mouse model.* Journal of Cerebral Blood Flow and Metabolism, 2019. 2019 Mar 19:271678X19837380. doi: 10.1177/0271678X19837380