RTG 1830
GERMAN CANADIAN
COMPLEX MEMBRANE PROTEINS
IN CELLULAR DEVELOPMENT AND DISEASE

# P5

## The role of monocarboxylate transporters (MCTs) in the uptake of ketone bodies into neurons and glial cells (Joachim Deitmer / Holger Becker)

Epilepsy is a common neurological disorder affecting approximately 1% of the population worldwide. Even intense afford is put into the development of adequate drugs to treat seizures, more than ¼ of epileptic patients remain poorly controlled by these drugs. On the other hand it is known since decades, that ketone bodies, formed by the body during starvation or a ketogenic diet, protect the brain against these types of intractable or refractory epilepsy. However, the mechanism by which this protection occurs is still poorly understood. Aim of this project is to investigate the role of various isoforms of monocarboxylate transporters (MCTs), which carry lactate, pyruvate and ketone bodies, on neuronal activity. Therefore uptake experiments with radioactively labeled substrate in astrocytic and neuronal cell cultures, as well as parallel patch-clamp recordings and pH measurements in acute slices of cerebellum and hippocampus will be performed. Furthermore, we will employ transgenic mouse models, which are susceptible for epileptic seizures, to determine the effects of modulating the transport of ketone bodies via MCTs on neuronal activity and the onset and incidence of seizures. We will apply various ketone bodies to check the ability of neurons to take up these substrates, and if this causes a change in their excitability. MCT activity will be measured in BCECF-loaded slices of mouse cerebellum by following the acidification induced by substrate/proton co-transport. The rate of acidification is indicative of MCT activity, and fluxes can be calculated after calibration of the signal and determination of the proton buffering power of the cells studied.

Changes in the expression and activity of MCTs brought about by ketone body exposure might affect not only the transport of ketones and neuronal excitability, but also the movement of lactate, which is hypothesized to be exchanged between glial cells and neurons under physiological conditions to help meeting the energy demand of neurons. The acute effects of acetoacetate and β-hydroxybutyrate on lactate uptake will be studied using conventional and multi-photon fluorescence microscopy.

Our results should help to further unravel protective mechanisms of ketone bodies and their transport by MCTs for brain hyperexcitability, and to disclose new therapeutic targets for neurological disorders like epilepsy.