Göteborg, 2022

THE NEUROMODULATORY EFFECT OF EXTRACELLULAR IONS IN THE CENTRAL NERVOUS SYSTEM

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, fredagen den 16 september 2022, klockan 13:00

av My Forsberg

Fakultetsopponent:
Professor Fredrik Elinder
Linköpings Universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. Forsberg, M., Seth, H., Björefeldt, A., Lyckenvik T., Andersson, M., Wasling, P., Zetterberg, H., Hanse E., *Ionized calcium in human cerebrospinal fluid and its influence on intrinsic and synaptic excitability of hippocampal pyramidal neurons in the rat*. Journal of Neurochemistry. 2019; 20:121-133.

II. Forsberg, M., Zhou, D., Jalali, S., Seth, H., Björefeldt, A., Hanse E., *Evaluation of mechanisms involved in the calcium-dependent regulation of intrinsic excitability in CA1 pyramidal neurons of rat*. Manuscript

III. Forsberg, M., Olsson, M., Seth, H., Wasling, P., Zetterberg H., Hedner, J., Hanse E., *Ion concentrations in cerebrospinal fluid in wakefulness, sleep and sleep deprivation in healthy humans* Journal of Sleep Research, 2022 Jun; 31(3):e13522

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

Göteborg, 2022

The neuromodulatory effect of extracellular ions in the central nervous system

My Forsberg

Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden, 2022.

Abstract

Neurons are the cells that send and receive signals in the central nervous system. Neuronal signaling is the base for all the complex tasks the human brain is capable of, from the detection of a smell to the composition of a symphony. Neurons are continuously receiving input from the periphery and from other neurons and need to integrate these into their own output. One key factor in this process is the neurons' excitability, how prone they are to be excited over a threshold level for the initiation of a signal. Of fundamental importance for the excitability of a neuron is the concentration of ions in the surrounding environment. This PhD project has studied the effects of shifts in the concentration of extracellular ions on fundamental neuronal behavior such as excitation and synaptic transmission. In the first article, we show that the concentration of biologically active calcium in human cerebrospinal fluid (hCSF) is 1 mM, which is about 85% of the total concentration. Since a concentration of 2 mM calcium, or higher, is traditionally used in *in vitro* electrophysiological research, we then demonstrate the marked differences in intrinsic excitability and synaptic transmission that is caused by using 2 mM calcium as opposed to the physiological concentration. We also demonstrate the critical impact of the extracellular concentration of calcium for the induction of long-term potentiation, further underscoring the importance of carefully considering the extracellular calcium concentration. In the second article, we examine the elusive mechanism behind the inhibitory effect extracellular calcium ions have on neuronal excitability. By excluding mechanisms related to changes of the membrane potential, in intracellular calcium and G protein activation, we conclude that the main mechanism in the concentration range between 1.2-2 mM is neutralization of negatively charged residues in the extracellular part of voltage-gated sodium channels. In the last article, we collected hCSF from healthy volunteers after sleep, sleep deprivation or wakefulness and we show that the concentration of potassium in hCSF varies with the circadian rhythm, indicating a role for extracellular ions in the regulation of the behavioral states of sleep and wakefulness.

Keywords: extracellular ions, excitability, synaptic transmission, sleep, wakefulness

ISBN: 978-91-8009-879-3 (TRYCK) http://hdl.handle.net/2077/71510
ISBN: 978-91-8009-880-9 (PDF)