Neuromodulation of hippocampal single cell- and network activity by human cerebrospinal fluid

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligt försvaras i hörsal Arvid Carlsson Academicum, Medicinaregatan 3, Göteborg

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Opponent: Ole Paulsen, Professor
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Avhandlingen baseras på följande delarbeten:

I. Bjorefeldt A, Andreasson U, Daborg J, Riebe I, Wasling P, Zetterberg H, Hanse E. **Human cerebrospinal fluid increases the excitability of pyramidal neurons in the *in vitro* brain slice**. J Physiol. 2015; 20: 121-133.

II. Bjorefeldt A, Wasling P, Zetterberg H, Hanse E. **Neuromodulation of fast-spiking and non-fast-spiking hippocampal CA1 interneurons by human cerebrospinal fluid**. Submitted manuscript.

III. Bjorefeldt A, Kurudenkandy R, Hanse E, Fisahn A. **Human cerebrospinal fluid promotes spontaneous gamma oscillations in the hippocampus *in vitro***. In manuscript.

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ABSTRACT

Neuromodulation is a key process determining the function of central neurons. The brain extracellular fluid contains numerous neuromodulatory substances (neuromodulators), but how they collective influence neuronal activity *in vivo* is not known. This thesis work attempts to shed light on this issue by examining the neuromodulatory influence of human cerebrospinal fluid (hCSF) on neurons in rat and mouse hippocampal brain slices, using a matched artificial cerebrospinal fluid (aCSF, devoid of neuromodulators) as control. The methodology comprises intracellular and extracellular recording techniques and, to lesser extent, biochemical and histological procedures. In **paper I** we examine the effect of hCSF on CA1 pyramidal cells. We find that hCSF induces *in vivo*-like properties in these neurons, powerfully boosting spontaneous action potential firing, depolarizing the resting membrane potential and lowering the action potential threshold. **In paper II** we record from GABAergic fast-spiking and non-fast-spiking interneurons in the CA1 hippocampus and show that hCSF excites both types of neurons through mechanisms involving reductions in afterhyperpolarization amplitudes and action potential threshold. Finally, in **paper III**, we show that hCSF induces spontaneous network gamma oscillations in the CA3 stratum pyramidale, via a cholinergic mechanism, and enhances electrical theta resonance in CA1 pyramidal cells through potentiation of two separate voltage-gated conductances. Taken together, the findings in this thesis project suggest that neuromodulators in brain extracellular fluid significantly contribute in shaping neuronal activity *in vivo*.

Keywords: Hippocampus, Neuromodulation, Cerebrospinal fluid

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