Modeling cortical spreading depression induced by the hyperactivity of interneurons

Mathieu Desroches[1], Olivier Faugeras[1], Martin Krupa*[2], and Massimo Mantegazza*[3]

[1]Inria Sophia Antipolis Méditerranée – MathNeuro team – 2004 route des Lucioles BP93 06902 Sophia Antipolis cedex, France

[2]University College Cork – Department of Applied Mathematics Cork, Irlande

[3]Institut de Pharmacologie Moléculaire et Cellulaire (IPMC) – Physiopathologie moléculaire – 660 Route des Lucioles SOPHIA ANTIPOLIS 06560 VALBONNE, France

Résumé

Cortical spreading depression (CSD) is a wave of transient intense neuronal firing leading to a long lasting depolarization block of neuronal activity. It is a proposed pathological mechanism of migraine with aura. Some molecular/cellular mechanisms of migraine with aura and of CSD have been identified studying a rare mendelian form: familial hemiplegic migraine (FHM). FHM type 1 & 2 are caused by mutations of the CaV2.1 Ca2+ channel and the glial Na+/K+ pump, respectively, leading to facilitation of CSD in mouse models mainly because of increased glutamatergic transmission/extracellular glutamate build-up. FHM type 3 mutations of the SCN1A gene, coding for the voltage gated sodium channel NaV1.1, cause gain of function of the channel and hyperexcitability of GABAergic interneurons. This leads to the counterintuitive hypothesis that intense firing of interneurons can cause CSD ignition. To test this hypothesis in silico, we developed a computational model of an E-I pair (a pyramidal cell and an interneuron), in which the coupling between the cells in not just synaptic, but takes into account also the effects of the accumulation of extracellular potassium caused by the activity of the neurons and of the synapses. In the context of this model, we show that the intense firing of the interneuron can lead to CSD. We have investigated the effect of various biophysical parameters on the transition to CSD, including the levels of glutamate or GABA, frequency of the interneuron firing and the efficacy of the KCC2 co-transporter. The key element for CSD ignition in our model was the frequency of interneuron firing and the related accumulation of extracellular potassium, which induced a depolarization block of the pyramidal cell. Our model can be used to study other types of activities in microcircuits and of couplings between excitatory and inhibitory neurons.

*Intervenant