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4-aminopyride challenge: a tool to study hyperexcitability of neuronal circuits after controlled cortical impact in rats

Epileptogenesis leading to posttraumatic epilepsy (PTE) is a common and debilitating sequala of traumatic brain injury (TBI). After TBI, secondary brain damage induces neuronal hyperexcitability and a lower seizure threshold in the neuronal circuit, leaving susceptibility to the development of epilepsy. Dysregulation of the extracellular space (ECS) size, which directly influences circuit excitability, may contribute to its development.
Our lab has identified fast ECS shrinkages called rapid volume pulsations (RVPs) in chemo-convulsant models of epileptiform activity, including the potassium channel blocker 4-aminopyridine (4-AP). RVPs synchronistically occur with ictal-like and interictal-like activity in-vitro and in-vivo.
Measuring RVPs in a PTE model will provide insight into hyperexcitable neuronal circuits after TBI. Spontaneous epileptiform activity and RVPs have been seen in controlled cortical impact (CCI) model rats, but because it cannot be predicted when they may occur spontaneously, they are impractical to record experimentally. To further investigate RVPs in this model, a method to coax hyperexcitable circuits into reliably producing ictal-like activity is needed.
We have developed a chemo-convulsant challenge determining 4-AP concentration that consistently induces RVPs in brain slices from injured animals, but not slices from naïve animals. 4-AP was tested in increasing concentrations in the range of 1μM to 20μM against uninjured mouse neocortical slices and CCI injured rat neocortical slices. In slices from CCI rats, RVPs coinciding with epileptiform activity were seen with the use of 5μM 4-AP. In slices from naïve mice, the minimum 4-AP concentration required to induce RVPs in the neocortex in was 17.5μM. By manipulating the hyperexcitability of the post-TBI neocortex, we can consistently evoke RVPs that would otherwise not occur. The 4-AP challenge provides a consistent platform to investigate the role of RVPs and the ECS during PTE development.