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Progressive increase in cortical excitability over time after severe traumatic brain injury in rats

Posttraumatic epilepsy (PTE) can occur in up to 40% of patients who sustain a severe traumatic brain injury (TBI). Despite decades of research, there are no therapeutic interventions to prevent PTE. Moreover, in many cases of PTE, seizures cannot be controlled with standard antiseizure medications (ASMs). Early intervention with ASMs may be one strategy to prevent PTE by interdicting the posttraumatic epileptogenic cascade. Using the controlled cortical impact (CCI) injury model in rats, our lab is examining the posttraumatic epileptogenic process and the antiepileptogenic effects of early administration of brivaracetam (BRV), an FDA-approved ASM that targets the synaptic vesicle protein 2A (SV2A). Sprague Dawley rats were subjected to CCI and given a single i.p. injection of 21 mg/kg BRV immediately after injury, while the drug-control group received only the saline vehicle. Electrophysiological data of epileptiform bursts recorded from ex vivo neocortical slices within the first 4 weeks after injury were analyzed to assess changes in burst intensity with time after injury, as a metric of the progression of posttraumatic epileptogenesis. My analysis thus far indicates that the duration of epileptiform bursts increases progressively over the first weeks after injury, with evoked responses characterized by brief, interictal-like bursts during the early post-injury period (1 – 2 weeks) that progress to include prolonged, ictal-like bursts by 3 – 4 weeks after injury, reminiscent of a kindling-like phenomenon. Further analyses suggest that a single, post-injury dose of BRV may arrest this progression. Taken together, these analyses suggest that posttraumatic epileptogenesis may involve a progressive increase in cortical excitability with time after injury and that early administration of BRV after injury may interfere with this process.