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Baclofen suppresses epileptiform activity by disrupting spiking rhythmicity

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Epileptic seizures are triggered in the brain by widespread epileptiform field potentials, as a result of uncontrolled, synchronous multi-spiking in neurons. It is hypothesized that highly rhythmic spiking in epileptiform potentials will resonate between neuronal populations and facilitate propagation in the brain. Pharmacological agents that reduce rhythmicity of epileptiform activity may therefore have antiepileptic potentials. We hypothesize that $GABA_B$ receptor activation may reduce firing rhythmicity of epileptiform activity via inhibition of membrane excitability.

We employed the non-linear Lempel-Ziv (LZ) complexity analysis (Lempel and Ziv, 1976) to quantify firing rhythmicity in epileptiform potentials, hypothesizing that higher rhythmicity of spiking will yield a lower LZ complexity value. Control and epileptiform population spikes (PSs) were elicited in granule cells of the dentate gyrus in mouse (male Balb/c mice 1-3 month-old) hippocampal slices in the absence and presence of the $GABA_A$ receptors using the antagonist, bicuculline (10 μM), respectively (Foster et al., 2013). Due to reduced synaptic inhibition, the epileptiform PSs displayed 2-3 additional spikes and significantly increased PS area-under-the-curve (Foster et al., 2013). However, the LZ complexity was significantly reduced from 0.184±0.065 for control PS to 0.077±0.056 for epileptiform PS ($n = 6$, $P < 0.01$, One-way ANOVA followed by Tukey's multiple comparisons), demonstrating that the epileptiform PSs display a high firing rhythmicity. Applying the $GABA_B$ receptor agonist baclofen (10 μM) in the presence of bicuculline significantly increased LZ complexity to 0.159±0.070 ($P < 0.05$, $n = 6$), a value similar to that of the control PS, although the additional epileptiform spikes were not abolished. Furthermore, the baclofen-induced effects were inhibited by the selective $GABA_B$ receptors antagonist CGP55845 (1 μM) ($P < 0.01$).

$GABA_B$ receptor activation therefore suppressed bicuculline-induced epileptiform activity in the dentate gyrus by decreasing firing rhythmicity, revealing a novel antiepileptic action for $GABA_B$ receptor agonists. Furthermore, this novel approach of using LZ complexity analysis may be further explored to discover new antiepileptic targets.

Lempel A and Ziv J IEEE Trans Inform Theory 22:75–81, 1976

Foster JD et al. Br J Pharmacol 168:1808–1819, 2013