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Medical applications of algae, cyanobacteria and their toxins

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Gambierol and analogs reverse paralysis caused by d-tubocurarine and botulinum type-A neurotoxin at vertebrate neuromuscular junctions

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Abstract: Gambierol is a marine polycyclic ether toxin, first isolated with ciguatoxins by Satake, Murata, and Yasumoto (1993) from cultured *Gambierdiscus toxicus* dinoflagellates, collected in French Polynesia. The chemical synthesis of gambierol and truncated analogues has been achieved successfully allowing detailed analyses of their mode of action. Interestingly, gambierol and analogs inhibit voltage-gated K⁺ (Kv) channels. It is well known that Kv channels play important roles in modulating acetylcholine (ACh) release from motor nerve terminals of vertebrate neuromuscular junctions. Therefore, the aim of our study was to investigate the action of synthetic gambierol and analogues on K⁺ currents in nerve cells and nerve terminals, using electrophysiological techniques. In addition, gambierol was studied on neuromuscular junctions in which muscle nicotinic ACh receptors have been blocked with d-tubocurarine (postsynaptic block), or in junctions in which quantal ACh release has been greatly reduced (presynaptic block) by botulinum neurotoxin type-A (BoNT/A). This neurotoxin induces a selective proteolytic cleavage of SNAP-25 an important nerve terminal protein for the neurotransmitter release process. Our results showed that gambierol and analogues inhibited Kv channels in neuronal cells in a concentration-dependent manner. Also, nanomolar concentrations of gambierol prolonged the duration of the presynaptic action potential in motor nerve terminals, as revealed by focal current recording. This indicates that Kv channels in nerve terminals were also blocked by the polyether. The loading of the calcium-sensitive dye Fluo-3/AM to frog motor nerve terminals and the use of spectrometric imaging techniques showed that gambierol increased the transient calcium fluorescence signals in response to 1-10 Hz nerve-stimulation, indicating that blockade of Kv channels enhanced calcium entry into nerve terminals. At the neuromuscular junction, such actions of gambierol are essential for increasing nerve-evoked quantal ACh release and can explain the observed reversal of the neuromuscular block produced by d-tubocurarine, a competitive inhibitor of the muscle nicotinic ACh receptor. Interestingly, gambierol also increased the quantal content of endplate potentials in BoNT/A-intoxicated mouse neuromuscular junctions. These results indicate that blockade of Kv channels and enhanced calcium entry into terminals by gambierol increased the probability of quantal ACh release, supporting the view that SNAP-25 cleaved by BoNT/A can enter into the protein-complex required for calcium-dependent neurotransmitter release. In conclusion, our results suggest that gambierol and analogues can have potential medical application in neuromuscular pathologies in which it is necessary to antagonize pre- or post-synaptic neuromuscular blockade, or both.

Disclosure of Interest: None Declared