Inhibition of human large conductance calcium-activated potassium channels by a fungal toxin

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The aim of this research was to investigate possible receptor/ion channel sites of action of a fungal toxin (designated compound A) that produces ataxia, tremors, and hypersensitivity to external stimuli when injected into mice. Compound A is distinct among neurotoxins in that it has a long duration of action, producing tremors that can last for up to three days rather than only a few hours. It also inhibits electrically stimulated smooth muscle contraction, increases neurotransmitter release, and elevates blood pressure. These effects suggested the disruption of large conductance calcium-activated potassium (BK) channels, as they have important regulatory roles in smooth muscle contraction and in control of neurotransmitter release (Gribkoff *et al.*, 2001). We investigated this possibility using *hSlo* (α subunit) BK channels expressed in human embryonic kidney cells and patch-clamping. We discovered that compound A potently inhibits BK channel-activation at nanomolar concentrations in inside-out membrane patches. BK channel currents activated by depolarising voltage pulses in the presence of 10 μM free calcium were inhibited by compound A in a concentration-dependent manner. 100 nM compound A completely inhibited outward potassium currents in less than one minute. The concentration that produced half maximal inhibition was approximately 3 nM, indicating a high apparent affinity for BK channels. This is the first time a molecular site of action has been determined for a compound of this structural class and identifies a novel BK channel blocker.

Gribkoff V.K., Starrett J.E., Jr. & Dworetzky S.I. (2001) *Neuroscientist*, 7:166-77.