Effects of lolitrems isolated from endophyte on human BK channels

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Lolitrems are a family of structurally related indole diterpenoid compounds produced by endophyte–grass symbioses[1]. Lolitrems have been isolated from ryegrass seed infected with *Neotyphodium lolii.* Lolitrem B, the major toxin responsible for ryegrass staggers syndrome in grazing animals, produces tremors when injected into mice[2]. Recently we discovered that lolitrem B potently inhibits *hSlo* large conductance calcium-activated potassium (BK) channel currents at nanomolar concentrations[3]. BK channels are expressed in most tissues, except for the heart, and regulate important physiological processes . They have a role in the regulation of blood pressure and are implicated in hypertension. In the brain they modulate action potential waveform, repetitive firing, and neurotransmitter release. BK channels are activated in response to depolarizing voltages and to increased intracellular calcium.

31-*epi*lolitrem B is an isomer of lolitrem B but unlike lolitrem B it does not produce tremors in mice[4]. We investigated whether 31-*epi*lolitrem B inhibits BK channel function or not. Human BK channel alpha subunits (*hSlo*) were expressed in human embryonic kidney cells and macroscopic currents recorded from inside-out membrane patches. We found that 100 nM 31-*epi*lolitrem B decreased *hSlo* potassium currents by 94%. The concentration-dependence of inhibition by 31-*epi*lolitrem B will be determined and compared with that for lolitrem B. This research identifies the lolitrem structural class of indole diterpenes as a family of novel BK channel blockers. The discovery that a non-tremorgenic lolitrem inhibits BK channel function is particularly significant as it may have potential as a pharmaceutical.

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