The role of BK channels in ataxia and tremor produced by fungal toxins

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Paxilline and lolitrem B are neurotoxic indole diterpenes that produce tremor and loss of coordination in animals. Both compounds inhibit large conductance calcium-activated potassium (BK) channels. Until now, it has not been known whether these effects on motor function are due to BK channel inhibition. Using BK channel knockout mice (BK -/-) and their wild-type littermates as controls, we investigated whether BK channels are involved in the tremor and ataxia induced by these compounds. Mice were administered with 4 mg/kg lolitrem B or 8 mg/kg paxilline in 9:1 DMSO-water by intraperitoneal injection. Tremor was assessed using a standard mouse bioassay and graded on scale from 1 to 5. A tremor score of 1 is mild tremor induced by activity and 5 is a severe spontaneous tremor. Ataxia was measured using an accelerating mouse rotarod to monitor changes in sensorimotor coordination and balance. All animal procedures were approved by the AgResearch Animal Ethics Committee (AE Application 10419). When dosed with either lolitrem B or paxilline, wild type mice became ataxic and measured around 3 on the tremor scale – continuous low intensity tremors with spontaneous severe tremor when handled. No ataxia or tremor effects were seen in control mice injected with DMSO-water. The symptoms seen in wild type mice dosed with toxin were absent in BK -/- mice. The phenotype of BK -/- mice includes mild ataxia and low baseline tremor, but even with high doses of toxin, there was no change in tremor or ataxia. This demonstrates that the tremorgenic and ataxic effects of these toxins are mediated through BK channels. We also found that the ataxic effect of paxilline required the BK channel β4 subunit, and is therefore centrally-mediated.