

Targeting ryanodine receptors for relief from increased myogenic tone following subarachnoid hemorrhage

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ABSTRACT

Vasospasm following subarachnoid hemorrhage (SAH) is a major contributor to poor outcome following cerebral aneurysm rupture. Research has suggested that a contributing factor to vasospasm following SAH is a decrease in calcium spark frequency due to increased inhibition of ryanodine receptors (RyRs) by FKBP 12.6 binding protein (FKBP 12.6). Calcium spark stimulation of large-conductance calcium activated potassium (BK) channels represents a prominent vasodilation pathway. The objective of this study was to investigate the proposed involvement of FKBP 12.6 in vasospasm by examining whether pharmacological agents that prevent interactions between FKBP 12.6 and RyRs cause significant dilation in arteries from SAH model animals. Isolated superior cerebellar arteries from control and SAH model rats were mounted on a pressure myography chamber and diameter changes were analyzed using edge detection software. Assessment of myogenic tone at 60 mmHg showed that SAH arteries experienced significantly more tone than control arteries. Paxilline was shown to cause significant constriction in control arteries but elicited little response in SAH arteries, suggesting decreased BK channel activity. Rapamycin and FK-506, two chemicals that form complexes with FKBP 12.6, were applied in order to increase the activity of RyRs and alleviate the increase in myogenic tone. At various concentrations, neither rapamycin nor FK-506 was able to produce a significant change in arterial diameter. In summary, this study was able to show physiological differences between SAH and control arteries related to myogenic tone and BK channel activity. However, the vasoconstriction of arteries following SAH could not be alleviated with rapamycin.