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Poster presentation

Hyper-contractility and impaired cGMP signaling in the BK_{Ca} channel deletion model of erectile dysfunction

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Erectile dysfunction (ED) is frequently elicited by a multiplicity of pathogenic factors, predominantly by impaired formation of and responsiveness to nitric oxide (NO) and the downstream effectors soluble guanylate cyclase (sGC) and cGMP-dependent protein kinase I (PKGI). In smooth muscle, one important target of PKGI is the large conductance, calcium-sensitive potassium (BK_{Ca}) channel, which upon activation hyperpolarizes the smooth muscle cell membrane, causing relaxation. In our earlier report [1], we demonstrated that ablation of the gene, encoding for the pore-forming α subunit of the BK_{Ca} channel in mice (*Slo*$^{-/-}$) induced an increase of corpus cavernosum smooth muscle (CCSM) force oscillations, led to reduced nerve-evoked relaxations and ED. In our current work, we used this ED model to explore the role of the BK_{Ca} channel in the NO/cGMP pathway. Electrical field stimulation (EFS)-induced contractions of CCSM strips from *Slo*$^{-/-}$ mice demonstrated a 53% increase that could be reduced by sildenafil similar to levels observed in strips from wild-type (*Slo*$^{+/+}$) mice. In *Slo*$^{-/-}$ strips precontracted with phenylephrine (PE), SNP and sildenafil induced relaxations, which were diminished by 10% and 7% over *Slo*$^{+/+}$, respectively. Neither SNP nor sildenafil was able to reduce the enhanced force oscillations, which were induced by the loss of BK_{Ca} channel function. Yet, these oscillations could be completely eliminated by blocking L-type voltage-dependent calcium channels (VDCCs). The latter results indicate that loss of BK_{Ca} channel leads to ED and hyper-contractility likely due to instability of membrane potential which activates VDCCs. Moreover, since the relaxing effects of SNP and sildenafil were reduced in *Slo*$^{-/-}$, the ED phenotype in our BK_{Ca} channel deletion model could also be the consequence of an impaired NO/cGMP signaling pathway.

References

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