A Putative Role For TRPV4 Channels In The Hyperosmotic-Mediated Vasorelaxation Of Mouse Mesenteric Resistance Arteries

Hyperosmotic-mediated vasorelaxation (HOMV) has been reported in several vascular beds and TRPV4 channels have been implicated in both endothelium-mediated vasodilation (coupling to intermediate conductance Ca^{2+}-activated K^+ (IK_{Ca}) channels) (1) and responses to hyperosmolarity (2). The present study aimed to investigate if HOMV can be stimulated in small mesenteric arteries, and to establish the underlying mechanisms. Adult male C57B1/6J mouse mesenteric arteries were mounted in a wire myograph to measure isometric changes in vessel tension. In arteries pre-constricted with phenylephrine (1-5μM), HOMV was found to be endothelium-dependent so 100μM □-NAME and 5μM indomethacin were present throughout, meaning relaxation reflects only the opening of endothelial K_{Ca} channels. Acute application of 40mM hyperosmotic (HO) glucose or mannitol caused robust vasorelaxation (68.1% ± 6.33, n=6 and 65.8% ± 8.03, n=4 respectively, $P<0.05$). Inhibition of IK_{Ca} channels, but not K_{ATP} channels or small conductance Ca^{2+}-activated K^+ (SK_{Ca}) channels, with 1μM TRAM-34 significantly attenuated HOMV in response to HO glucose and mannitol (38.7% ± 6.60 and 21.4% ± 4.57 respectively, $P<0.05$, n=3) (**Figure 1**). Furthermore, inhibition of TRPV4 channels with 1μM GSK-2193874 was associated with a reduction in HOMV (27.1% ± 1.33 and 33.0% ± 1.96 for HO glucose and mannitol respectively, $P<0.05$, n=3) (**Figure 2**).

Figure 1

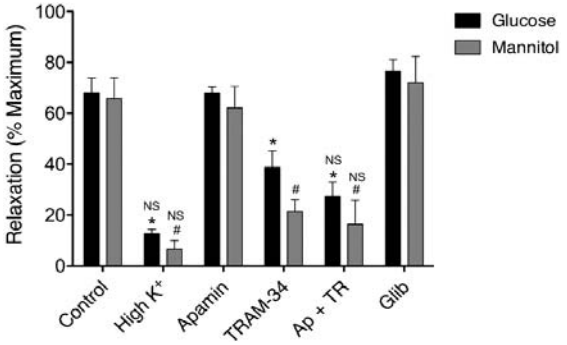
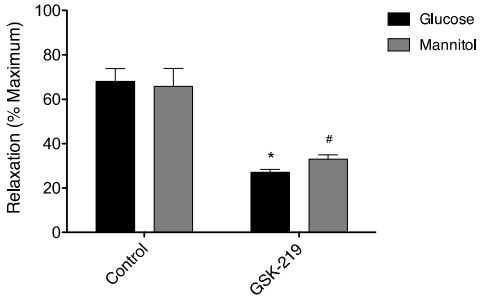


Figure 2



These results provide preliminary evidence for the recently characterised endothelial IK_{Ca}-TRPV4 functional module in mesenteric HOMV, as well as supporting a HO-responsiveness of TRPV4 channels. HOMV may contribute to various physiological and pathophysiological scenarios associated with the build-up of osmolites in or around resistance arteries (namely vascular changes in diabetes mellitus and functional hyperaemia); defining the underlying mechanisms will help us better understand its role in both health and disease.

(1) Zhang DX *et al.* (2009). *Hypertension* **53:** 532–8.
(2) Liedtke W and Friedman JM. (2003). *Proc. Natl. Acad. Sci. U.S.A.* **100:** 13698–703.