A role for the Rho-kinase pathway in mediating smooth muscle tone of the porcine prostate and corpus cavernosum

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Background
Benign prostatic hyperplasia and erectile dysfunction are associated conditions, found commonly in ageing men. Current pharmacotherapies can be limited by sexual and non-sexual adverse effects, and around 40% of patients with erectile dysfunction do not respond to the main pharmacotherapy, phosphodiesterase-5 inhibitors, which are also contraindicated in patients with diabetes and cardiovascular disease. Since smooth muscle relaxation is a desired outcome of treatment for both conditions, the RhoA/Rho-kinase pathway has been under investigation to better understand the mechanisms involved in calcium sensitisation and smooth muscle tone, and to potentially establish this pathway as a novel target for treatment. The aim of this study was to investigate the role of the RhoA/Rho-kinase signalling pathway in mediating smooth muscle tone in porcine prostate and corpus cavernosum.

Methods
Strips of porcine prostate and corpus cavernosum were mounted in gassed Krebs-bicarbonate solution at 37°C and α1-adrenoceptor mediated contractile responses to phenylephrine were obtained in the absence and presence of the Rho-kinase inhibitors Y-27632, fasudil and GSK-269962.

Results
Phenylephrine evoked concentration-dependent contractile responses in porcine prostate and corpus cavernosum. In prostate, mean maximum contractions were inhibited in the presence of Y-27632 (10 μM) (67.9±7.8% inhibition, p<0.0001, n=8) and fasudil (30 μM) (49.6±8.5, p<0.001, n=9). Similarly, in corpus cavernosum maximum contractions to phenylephrine were inhibited by Y-27632 (68.2±6.1%, p<0.0001, n=9) and fasudil (52.7±5.2%, p<0.0001, n=9). The more potent Rho-kinase inhibitor GSK-269962 (100nM) also decreased maximum contractions to phenylephrine in prostate and cavernosum (by 22.8±11.2% (p=0.09) and 29.3±6.5% (p<0.001), n=8-9 respectively). Inhibition of contractions by GSK-269962 was significantly less than with Y-27632 and fasudil in both tissues (p<0.01).

Conclusion
The present study confirms that the RhoA/Rho-kinase signalling pathway plays a role in mediating smooth muscle tone in both porcine prostate and corpus cavernosum. The effects of the Rho-kinase inhibitors were similar in both tissues. The greater inhibitory effects observed with Y-27632 and fasudil versus GSK-269962 may be due to additional non-selective actions on other kinases involved in smooth muscle tone. Further elucidation of the precise role of the RhoA/Rho-kinase pathway may provide an alternative target for development of new treatments for erectile dysfunction and benign prostatic hyperplasia.