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ERECTILE DYSFUNCTION

Too much ROCK — erection block

A new study shows that mRNA expression of Rho kinase 2 (*ROCK2*), but not *ROCK1*, is upregulated in corpus cavernosum tissue (CCT) of men with erectile dysfunction (ED) who are refractory to phosphodiesterase type 5 (PDE5) inhibitor treatment. Combined ROCK and PDE5 inhibition resulted in enhanced relaxation of precontracted ED CCT.

Men with diabetes or nerve injury after radical prostatectomy and ED often do not respond to PDE5 inhibitor treatment, possibly owing to a decreased supply of NO from cavernous nerves. "Increasing evidence in animal models that mimic these clinical situations shows an upregulation of ROCK, which makes smooth muscle cells hypercontractile and less prone to relax during sexual arousal," explains Maarten Albersen, corresponding author of the new study. "However, whether these findings apply to human tissue has not previously been studied."

The team collected CCT from 21 men who were refractory to PDE5 inhibitors and opted to receive an inflatable penile prosthesis, and from 5 men without ED using needle biopsy. Owing to the small size of the control samples, comparative *ROCK1* and *ROCK2* expression levels were measured by qPCR only. Analysis showed no difference in *ROCK1* levels between ED CCT and controls, but relative expression of *ROCK2* was significantly upregulated in tissue from men with ED ($P < 0.05$). In ED CCT, the researchers confirmed protein expression of ROCK1 and ROCK2 in cavernous smooth muscle cells via immunofluorescence.

> expression of *ROCK2* was significantly upregulated in tissue from men with ED

Previous studies in animals showed that ROCK inhibition supports erectile activity and has additive effects to PDE5 inhibition. Hence, the team used organ bath experiments to test possible effects in human ED CCT. Tissue strips were precontracted with phenylephrine. Addition of the ROCK inhibitor Y-27632, which inhibits both ROCK1 and ROCK2, resulted in significant tissue relaxation compared with vehicle (~86%; $P = 0.0016$). When CCT was preincubated with the PDE5 inhibitor vardenafil (resulting in ~24% relaxation) subsequent addition of Y-27632 caused an additional relaxation of ~74% compared with vehicle.

"In this study, we combine results on ROCK expression with functional data in the human setting for the first time, confirming that ROCK might be an interesting target for ED treatment," Albersen told *Nature Reviews Urology*. "Several ROCK inhibitors are being developed for indications such as hypertension. A ROCK2-selective inhibitor might be more effective in ED and have fewer off-target effects, and combination of PDE5 and ROCK inhibition might enable reduced doses and enhanced effects in the penis."

Clemens Thoma

ORIGINAL ARTICLE Uvin, P. *et al.* Additive effects of the Rho Kinase Inhibitor Y-27632 and vardenafil on relaxation of corpus cavernosum tissue of patients with erectile dysfunction and clinical phosphodiesterase type 5 inhibitor failure. *BJU Int.* http://dx.doi.org/10.1111/bju.13691 (2016)
FURTHER READING Sopko, N. A. *et al.* Understanding and targeting the Rho kinase pathway in erectile dysfunction. *Nat. Rev. Urol.* **11**, 622–628 (2014)