International Journal of Impotence Research (2005) 17, 546
 0955-9930/05 $30.00
www.nature.com/ijir

Perspectives
PDE5 inhibition and fibrosis

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Editor's Note: Can PDE5 inhibitors inhibit fibrosis? Is this a direct effect of PDE5 inhibitors on the fibrotic cascade? If this hypothesis is found true, then an entire new algorithm for treatment of ED and other diseases may be realized. Three recent manuscripts this year discuss this question. Dr Jackie Corbin, a renowned PDE5 expert, offers a perspective in light of its potential clinical relevance.

International Journal of Impotence Research (2005) **17,** 546. doi:10.1038/sj.ijir.3901362

Three recent reports (Valente EG, Vernet D, Ferrini MG, Qian A, Rajfer J, Gonzalez-Cadavid NF. L-arginine and phosphodiesterase (PDE) inhibitors counteract fibrosis in the Peyronie's fibrotic plaque and related fibroblast cultures. *Nitric Oxide* 2003 Dec; 9(4): 229–244; Ahn GJ, Sohn YS, Kang KK, Ahn BO, Kwon JW, Kang SK, Lee BC, Hwang WS. The effect of PDE5 inhibition on the erectile function in streptozotocin-induced diabetic rats. *Int J Impot Res* 2005 Mar–Apr; 17(2): 134–141; and Kang KK, Ahn GJ, Sohn YS, Ahn BO, Kim WB. DA-8159, a new PDE5 inhibitor, attenuates the development of compensatory right ventricular hypertrophy in a rat model of pulmonary hypertension. *J Int Med Res* 2003 Nov–Dec; 31(6): 517–528) suggest beneficial effects of chronic elevation in tissue cGMP levels for treating diseases associated with fibrotic lesions such as Peyronie's disease, diabetes, and right ventricular hypertrophy. Doses of sildenafil that were nearly equivalent to those given to men with erectile dysfunction were antifibrotic in rat penile tunica albuginea after several weeks of treatment. In addition, this treatment increased cavernosal endothelial and smooth muscle cells and decreased TGFβ1 expression. The latter protein is believed to inhibit smooth muscle growth. In fibroblast cultures, similar antifibrotic-like effects were observed with sildenafil, L-arginine, or 8-Br-cGMP treatment, and it was presumed that each acted by causing elevation in cGMP levels or by mimicking cGMP. Elevation in cAMP by pentoxifylline was also effective. It is not surprising that cGMP and cAMP elevation caused a similar effect since these two cyclic nucleotides are known to produce the same effects in many, although not all, signaling pathways in which they participate. A new PDE5 inhibitor, DA-8159 from the Dong-A Pharmaceutical Company, was also antifibrotic for penile corpus cavernosum when administered to streptozotocin diabetic rats or for right ventricular myocardium when administered to rats made pulmonary hypertensive by monocrotaline treatment. Again, the results imply that chronic elevation in tissue cGMP levels in the affected tissues could be beneficial in preventing or reducing fibrosis in some human tissues. The mechanisms for the apparent cyclic nucleotide effects are uncertain, but the modifications in each study suggest that long-term cyclic nucleotide elevation in these tissues modifies either gene expression or protein synthesis/degradation to produce the effects. Perhaps vasodilation caused by cGMP elevation improves corporal oxygenation, which prevents tissue deterioration. The results so far are very encouraging, although the apparent alteration in cellular protein profiles that takes place could potentially cause some undesirable effects in addition to the beneficial effects observed.

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Received 16 May 2005; accepted 2 June 2005