Erectile dysfunction

Promising advances in gene therapy for ED, but only in rodents: Rats!

Mike Cummings, Consultant Physician and Honorary Reader, Queen Alexandra Hospital, Portsmouth

There has been much excitement in the last decade or so about the feasibility of using the technique of gene therapy for the treatment of chronic disorders, such as cystic fibrosis and diabetes. On first glance, the prospect of incorporating gene therapy into the advancement of the management of erectile dysfunction (ED) may seem 'excessive'. However, further reflection raises some intriguing possibilities. In this issue, we report on two studies that introduced genetic material into the corpora cavernosa of rats with diabetes with the subsequent expression of proteins that enhance erectile performance. The results of the first study indicate an increase in the production of vasoactive intestinal polypeptide, which is involved in penile smooth muscle relaxation (Shen et al, 2005; see below); the second study realises an increase in levels of neurotrophin-3 that may protect nerves from damage (see right).

These studies show that by using gene therapy to modify the availability of certain endogenous proteins, it is possible to uniquely study the mechanisms underlying diabetic ED in vivo. These findings may then underpin any pharmacological advances in the treatment of ED resulting from diabetes.

Also raised is the possibility that the technique of gene therapy per se may be used to treat the condition. Given the psychosocial misery associated with ED, this may appear an attractive prospect for some. However, scientifically this is a very long way off. At present the science is limited to rats, and other disease models in rodents have had their problems. For instance, hypoglycaemia resulting from uncontrolled insulin secretion in rats with diabetes receiving gene therapy aimed at enhancing beta cell function may draw a similar parallel in gene therapy for ED – with the prospect of unwanted priapism. Moreover there are many difficult ethical dilemmas to overcome. Nevertheless, gene therapy offers much potential.

Bennett NE, Kim JH, Wolfe DP, Sasaki K, Yoshimura N, Goins WF et al (2005) Improvement in erectile dysfunction after neurotrophic factor gene therapy in diabetic rats. *The Journal of Urology* **173**(5): 1820–4

Shen Z-J, Wang H, Lu Y-L, Zhou X-L, Chen S-W, Chen Z-D (2005) Gene transfer of vasoactive intestinal polypeptide into the penis improves erectile response in the diabetic rat. *British Journal of Urology International* **95**(6): 890–4

BRITISH JOURNAL OF UROLOGY INTERNATIONAL

ED in rats improved by gene transfer

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 The transfection of the corpus cavernosum in rats, with streptozotocin-induced diabetes, with vasoactive intestinal polypeptide (VIP) cDNA in order to observe any changes to erectile function was the main aim of this study.

2 The rats were injected with saline solution, saline solution with the naked DNA vector, or saline solution containing the VIP pcDNA expression vector. Following injection the intracavernosal pressure (ICP) was measured at four timepoints: at time of injection; 3 days post-injection; 7 days post-injection; and 14 days post-injection.

3 The ICP results for each injection group across all timepoints were not significantly different within the groups. The VIP pcDNA injection group had significantly higher ICP results than the other two groups.

4 The main conclusion the authors draw from their work is that the pcDNA vector is easily incorporated by corpus cavernous tissue and its expression of VIP is sustained for greater than 14 days; they also conclude that ICP with greater VIP expression is significantly higher.

Shen Z-J, Wang H, Lu Y-L, Zhou X-L, Chen S-W, Chen Z-D (2005) Gene transfer of vasoactive intestinal polypeptide into the penis improves erectile response in the diabetic rat. *British Journal of Urology International* **95**(6): 890–4

THE JOURNAL OF UROLOGY

Gene transfer technology useful for ED in rats

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 This group has previously reported the use of gene transfer technology for pyridoxine treatment. In this study they created non-replicating herpes simplex virus (HSV) vectors expressing either LacZ (control) or neurotrophin-3 (NT3; a neurotrophic factor).

2 Rats with induced diabetes (using streptozotocin) had either the LacZ or NT3 HSV vectors introduced directly into their cavernous nerve sheath. Four weeks later the rats underwent analysis for intracavernous pressure and histological analysis for LacZ or neuronal nitric oxide synthase in the major pelvic ganglia (MPG).

3 β-galactosidase staining for LacZ revealed positive neurons in the MPG, indicating successful uptake and expression of the HSV vectors.

4 Maximal intracavernous pressure (induced by electrical stimulation) was significantly higher in the NT3 rats than the LacZ rats (43.8 cmH_2O vs 15.1 cmH_2O, respectively; P=0.03), indicating a relief from erectile dysfunction (ED) symptoms. There were significantly more neurons positive for neuronal nitric oxide synthase in the NT3 group than in the LacZ group in the MPG.

5 The authors make clear in their discussion that this article does not offer direct hope for ED relief for humans just yet, but as the technique seems to work in rodent models, it can be developed for future use.

Bennett NE, Kim JH, Wolfe DP, Sasaki K, Yoshimura N, Goins WF et al (2005) Improvement in erectile dysfunction after neurotrophic factor gene therapy in diabetic rats. *The Journal of Urology* **173**(5): 1820–4

'The slow release of bFGF in the corpus cavernosum region can aid in sustaining erectile function by preserving smooth muscle integrity.'

'No significant differences were found between HbA_{1c} groups in those with diabetes for ≤5 years, but if duration of diabetes was >6 years, most men with HbA_{1c} ≥8.0 % suffered from severe ED.'

BRITISH JOURNAL OF UROLOGY INTERNATIONAL

HbA_{1c} level linked to ED severity

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

1 The objective of this study was to evaluate the association between the levels of glycosylated haemoglobin (HbA_{1c}) and the severity of erectile dysfunction (ED) in men with diabetes.

2 A total of 115 men were included in this study. All completed questions 1–5 and 15 of the International Index of Erectile Function (IIEF; the scoring of which allowed the severity of ED to be classified); all also had their fasting serum glucose and HbA_{1c} levels measured.

3 The men were divided into four groups according to their HbA_{1c} levels: <8.0 %; 8.0–9.4 %; 9.5–10.9 %; and ≥11 %. The severity of ED was correlated with HbA_{1c} levels and duration of diabetes (<5, 5–10 or >10 years).

4 Of all participants, 76 % were Caucasians, the rest being African-Americans. Eighteen per cent were smokers and 5.3 % heavy drinkers of alcohol.

5 Overall, ED was mild (as classified by the IIEF scores) in 31 % of the study population, moderate in 26 % and severe in 43 %. Significantly more men with low HbA_{1c} levels had mild than moderate ED. Among men with HbA_{1c} levels ≥8.0 %, significantly more had severe ED than moderate or mild. Statistical analysis showed that men with HbA_{1c} ≥11.0 % were even more likely to have severe ED. No significant differences were found between HbA_{1c} groups in those with diabetes for ≤5 years, but if duration of diabetes was >6 years, most men with HbA_{1c} ≥8.0 % suffered from severe ED.

6 In conclusion, this group has found a link between HbA_{1c} levels and severity of ED.

Rhoden EL, Ribiero EP, Riedner CE, Teloken C, Souto CA (2005) Glycosylated haemoglobin levels and the severity of erectile function in diabetic men. *British Journal of Urology International* **95**(4): 615–7

INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH

PDE5 inhibition improves ED in STZ-induced rats

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Phosphodiesterase-5 (PDE5) inhibition is already used as a treatment of erectile dysfunction (ED) in men with diabetes, although it has been shown to be more effective in men suffering from ED but with no diabetes.

2 This study investigated the effect of PDE5 inhibition on quantity of smooth muscle (SM) and endothelial cells in the vascular tissue of corpora cavernosa of rats with streptozotocin (STZ)-induced diabetes.

3 Further histological analyses were carried out for transforming growth factor-β1 (TGF-β1) expression in order to assess corpora cavernosa tissue for mitotic activity.

4 The STZ-induced rats had significantly lower SM and endothelial cell content as well as lower levels of TGF-β1 expression within the corpora cavernosa.

5 STZ-induced rats treated with DA-8159 (a PDE5 inhibitor) showed a clear increase in SM and endothelial cell content in the corpora cavernosa compared with untreated STZ-induced rats.

6 The authors conclude that their work suggests that treatment with DA-8159 can prevent the development of ED prior to the development of any related risk factors (such as long-term conditions like diabetes) and also provides evidence for its use in the treatment of ED in men with diabetes.

Ahn GJ, Sohn YS, Kang KK, Ahn BO, Kwon JW, Kang SK et al (2005) The effect of PDE5 inhibition on the erectile function in streptozotocin-induced diabetic rats. *International Journal of Impotence Research* **17**(2): 134–41

THE JOURNAL OF UROLOGY

bFGF sustains erectile function in rats with diabetes

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓✓

1 Some experimental success has been achieved in the past with inducing regeneration of corpora cavernosa tissue (particularly smooth muscle and endothelial cells) by introducing growth factors (such as vascular endothelial growth factor, insulin-like growth factor, and basic fibroblast growth factor [bFGF]) into the tissue. This approach is seen to have a better future than phosphodiesterase 5 (PDE5) inhibition for the treatment of erectile dysfunction (ED), as the efficacy of PDE5 is comparitively lower in animal models with diabetes than those without, due to damaged tissue.

2 The effect of injecting gelatin microspheres incorporating bFGF into the intracrural region of rats with streptozotocin-induced diabetes was investigated.

3 The use of microsphere technology allows the long-term sustained release of bFGF into the target tissue; this overcomes previous problems of short half-lives of growth factors.

4 This study does provide evidence for microsphere technology but states that it does not provide evidence for the restoration of severely damaged corpus cavernosum tissue.

5 The investigators conclude that the slow release of bFGF in the corpus cavernosum region can aid in sustaining erectile function by preserving smooth muscle integrity, suggesting that this technique could be used for the treatment of diabetes-induced ED.

Suetomi T, Hisasue S, Sato Y, Tabata Y, Akaza H, Tsukamoto T (2005) Effect of basic fibroblast growth factor incorporating gelatin microspheres on erectile function in the diabetic rat. *The Journal of Urology* **173**(4): 1423–8