



The application of gene therapy to the treatment of erectile dysfunction

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During the past two decades the application of the results of basic medical research to the clinical environment has resulted in vast improvements in the understanding, diagnosis and treatment of erectile dysfunction. Intracavernous injection therapy, vacuum devices, surgical implantation of prosthetic devices, intraurethral suppositories, and most recently, oral medications provide urologists with a therapeutic arsenal sufficient to correct even the more severe forms of organic impotence. In short, erectile potency can be effectively restored in every man who possesses the requisite desire and motivation. However, despite their documented efficacy, all available treatment options have significant side effects. Therefore, there is still much room for improvement, and this is where the application of the techniques of molecular biology to the study of erectile physiology/dysfunction will open up exciting new opportunities for the treatment of erectile dysfunction.

In particular, the recent commercialization and popularization of molecular biological techniques, such as Northern, Western and Southern blots, and the polymerase chain reaction, has allowed for the identification, isolation, sequencing, synthesis, cloning and foreign expression of numerous genes and gene products. Moreover, the more widespread application of these techniques has allowed investigators to more precisely evaluate the contribution of individual genes to cellular responses. The incredible fidelity of replication and relative ease of incorporation of the genetic material in diverse cell types *in vitro* has made gene therapy an attractive therapeutic option in many areas of clinical medicine. Gene therapy has traditionally been utilized to correct diseases/disorders that have an underlying genetic component, that is, the introduction of foreign genetic information into human cells usually either restores/supplements defective functions, or conversely, functionally antagonizes the effects of expression of a mutant

genetic function. In this regard, it should be emphasized that the absence of compelling evidence either for, or against, a genetic basis for, or a genetic predisposition to, erectile failure does not obviate the potential utility of gene therapy for the treatment of erectile dysfunction.

In fact, as erectile dysfunction is most frequently the result of an altered balance between contraction and relaxation of corporal smooth muscle cells, any genetic therapy that restores this delicate balance might well be expected to restore potency. In this regard, we have previously shown that potassium (K) channels are a convergence point for mediating the effects of a diverse array of physiologically relevant substances on corporal smooth muscle tone. Thus, K channels are thought to participate in the modulation of both contraction and relaxation responses in corporal smooth muscle. As such, K channels represent a logical first target for exploring the effects of altered gene expression on erectile physiology, by virtue of their ability to alter the response of corporal smooth muscle cells.

Therefore, as a first step toward demonstrating the possible utility of genetic therapy to the treatment of human erectile dysfunction, we chose to examine the effects of a single intracavernous injection of naked cDNA encoding one particular subtype of K channel, the human smooth muscle maxi-K channel, *hSlo*. The effects of over-expression of this K channel on erectile physiology were examined in a rat model *in vivo* using the nerve-stimulated intracavernous pressure response as an objective index of altered corporal physiology. Our exciting preliminary results indicated that in all cases, the injection of *hSlo* cDNA resulted in a dramatically greater intracavernous pressure response in the injected animals, than that observed in age-matched control animals that received injection of vehicle only (Christ *et al. Int J Impot Res* 1996; **8**: 103; Christ *et al. J Urol* 1997; **157**: 414). Moreover, these effects were apparent for a minimum of 1–3 months post-injection. Presumably, the efficacy of gene therapy is related to the improved hyperpolarizing ability of the corporal smooth muscle cells that have incorporated and expressed the foreign human K channel

gene. The improved hyperpolarizing ability would result from the reciprocal inhibition of transmembrane flux through L-type voltage-dependent calcium channels, thus, ultimately resulting in diminished intracellular calcium concentrations, and thus, enhanced smooth muscle relaxation. Clearly, the precise cellular distribution and longevity of the *hSlo* cDNA has not yet been verified. However, extrapolating these results to the clinic, if equally successful, a patient could receive 3–4 injections/year, rather than 3–4 injections/week, and maintain his erectile potency in the absence of the necessity for any other form of treatment. This would represent a clear advance over all other forms of therapy currently available. In light of the fact that the human genome project is expected to provide another 70 000–100 000 genes that will be candidates for gene transfer, the future of the genetic therapy of human erectile dysfunction seems bright indeed.

The penis is an organ particularly suited for the use of gene therapy as a means of altering a disease process. Of predominant importance is that the penis is an external organ that is easily accessible for the insertion of the gene product. Because of its position on the body a tourniquet can be placed at the base of the penis limiting the egress of the gene product into the general circulation until it is taken up by the target cells. In addition, the blood flow within the penis at rest is very low at about 5 ml/min further enhancing the uptake of the gene product

into its intended target. The target, vascular smooth muscle cells have a low turnover rate. Therefore, the effects of a newly introduced gene may last for weeks to months.

The type of gene to be introduced into the cells can be tailored to have one of several effects. They can express products that are lacking because of a missing or defective gene, they can express products that protect the cell from cytotoxic agents or in turn express products that make it more vulnerable to such agents. Another possibility is to express additional products in order to produce supra physiological responses in otherwise normal cells.

The method of introduction of the gene product into the cells can be done in several ways. The manufactured (recombinant) is added to another vector so that it can cross the cell membrane and enter the cytoplasm of the target cells. The vectors used to date include plasmids i.e., naked DNA, liposomes, adenoviruses and retroviruses. The viruses are the most efficient vectors but they have drawback of producing an immune response with repeated use or even injuring the target cells. Liposomes and plasmids are less efficient vectors but do not cause immune responses in the host. The presence of gap junctions, which allow the penis to function as a syncytial network, compensate for inefficient introduction of recombinant genes into the cells. Thus, even a small percentage of cells with the new gene product may be sufficient to allow the supra physiological response to be effective.