Nature Reviews Urology | Published online 7 Feb 2017; doi:10.1038/nrurol.2017.21

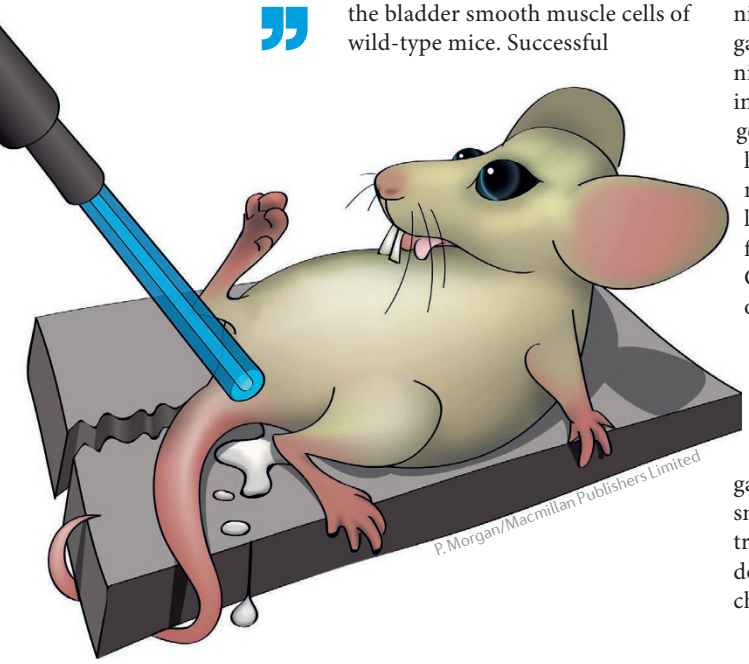
INCONTINENCE

Optogenetics enables control of micturition

> “…researchers have demonstrated the ability to control bladder function in mice…through light-sensitive ion channels…”

The urinary bladder is an electrically excitable organ that enables the storage and periodic elimination of urine. Until now, despite decades of research, the ability to control bladder function using an intermittently active intervention that targets only the bladder has largely eluded the research community. Now, however, researchers have demonstrated the ability to control bladder function in mice through transfection with light-sensitive ion channels, thus conferring the ability either to initiate or prevent micturition, in response to an external light source.

Researchers used adenoviral transfection vectors (as investigated in several clinical trials) injected into the detrusors of wild-type mice to selectively deliver channelrhodopsin (ChR2), a light-sensitive nonspecific cation channel, to the bladder smooth muscle cells of wild-type mice. Successful transfection was confirmed at 1 week after injection by the presence of the cotransfected enhanced yellow fluorescent protein.



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Researchers were then able to activate ChR2 in mice undergoing *in vivo* cystometry using transient blue-light illumination (473 nm, 63 mW for 1 s) at approximate 2-minute intervals, resulting in transient increases in intravesical pressure and voiding. These *in vivo* findings confirm the *in vitro* findings of blue-light evoked inward currents and membrane depolarization in isolated ChR2-transfected bladder smooth muscle cells, indicating that voiding is most likely the result of depolarization of smooth muscle cells *in vitro*. Further confirmation was provided by experiments using isolated *ex vivo* bladders exposed to the voltage-gated Na^+ channel antagonist tetrodotoxin or the voltage-gated Ca^{2+} channel antagonist nifedipine: tetrodotoxin, which inhibits neurogenic, but not myogenic contractions, did not affect light-evoked contractions, whereas nifedipine completely inhibited light-evoked contractions. These findings indicate that the effects ChR2 activation are not dependent on innervation of the bladder.

In addition to facilitating voiding, a similar approach was used to control prostaglandin E2 (PGE_2)-induced bladder overactivity. For these investigations, researchers used bladder smooth muscle cells isolated from transgenic mice expressing halorhodopsin (NpHR), a light-sensitive chloride channel. Experiments conducted in the presence of PGE_2, which is known to induce bladder overactivity *in vitro*, indicated that activation of NpHR using yellow light (598 nm) resulted in hyperpolarization of smooth muscle cells, and attenuation of PGE_2-induced overactivity in isolated bladder strips.

These findings reveal the intriguing possibility of using optogenetics to induce or prevent micturition. However, as outlined by the authors, several barriers to further testing and implementation of such approaches currently exist: transfection of human patients remains very much in its infancy as a technology and cannot be expected to confer robust expression of transfected proteins (although data from several clinical trials indicate short-term safety); furthermore, the size of the human bladder, relative to that of the mouse, means that a light-generating implant is likely to be required, with resultant challenges in maintaining battery life, possibly over a period of several decades.

Despite these challenges and the availability of a variety of nonsurgical (pelvic floor exercises, muscarinic receptor antagonists, β_3-receptor agonists) and surgical approaches (botulinum toxin injections and neuromodulation, among others) for patients with LUTS, this approach, unlike many others, directly targets the bladder and would most likely avoid many of the various adverse effects associated with other treatment modalities. In particular, the ability to achieve transient activation of detrusor smooth muscle might provide an alternative treatment for underactive bladder, for which few treatments are currently available.

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ORIGINAL ARTICLE Park, J. H. *et al.* Optogenetic modulation of urinary bladder contraction for lower urinary tract dysfunction. *Sci. Rep.* **7**, 40872; http://dx.doi.org/10.1038/srep40872 (2017)