microscopy as an adjunct to conventional toxicology and pathology.

With the sequencing of the human genome and the explosive growth in the use of mouse models – it is estimated that in 2001, >6 million transgenic and knockout mice were bred for research purposes [1] – it became obvious that the Duke team had something that would be of value not only to pathologists but also to scientists working with genetically altered animals. John C. Waterton, who is Associate Director in Enabling Science and Technology at AstraZeneca (Macclesfield, UK) and looks after the company's global imaging capabilities, believes that MR microscopy will be of great use for the field of drug discovery. 'I think it is particularly valuable to understand the phenotype of knockouts and other transgenics in order to support target validation. I can think of many examples where our view on the validity of a target has been changed by the phenotype of a knockout.'

Limitations and solutions

However, Waterton stresses that it is important to realize that the approach described by the Duke group has been optimized for post-mortem specimens and that its exquisite resolution is not readily applicable to *in vivo* experiments.

He is also concerned that interpretation of the data is still time-consuming because of unsolved informatics problems. 'There is a risk that in taking that approach, you might do very elegant experiments that deliver too late, the company has already made the decision to proceed or not to proceed with a drug discovery project aimed at a given target.' Johnson agrees that this is an issue but says, 'There are many bioinformatics solutions coming from out of the clinical arena and we are adapting those.'

These problems can hopefully be solved over time. Meanwhile, Johnson has founded a company, MRPath (Durham, NC, USA), to offer MR microscopy scanning services and viewing software to the wider research community. The price for a whole-mouse study is currently not set but they expect to push the price down to less than US$200 per animal in the next year. Johnson says, 'Our vision is, you send us the animals, we fixperfuse and scan them immediately and within 24 hours you find your MR microscopy data on your desktop.'

References

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CNS-targeted sexual dysfunction drug for men and women

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A novel drug has been developed for the treatment of erectile and sexual dysfunction that works through the CNS and could potentially avoid the side effects associated with the traditional phosphodiesterase (PDE) inhibitors. Moreover, because of its different mode-of-action, this drug could have potential for the treatment of female sexual dysfunction (FSD).

Most erectile dysfunction (ED) drugs work through the vascular system but PT141, from Palatin Technologies (Princeton, NJ, USA; http://www.palatin.com), targets receptors in the CNS and could offer therapy for those previously unresponsive to conventional vascular treatments.

The occurrence of sexual dysfunction is widespread: one-third of men aged 40–70 years reported some form of ED [1] and researchers believe that ~40% of women also suffer from a sexual problem at some point in their lives [2].

Current treatments

The market was, until recently, dominated by sildenafil citrate (Viagra™; Pfizer, Sandwich, UK) [3]. Recently, drugs such as vardenafil (Bayer, Leverkusen, Germany) [4] and Cialis™ (Lilly, Indianapolis, IN, USA) [5], were thought to be more potent and produce fewer side effects than sildenafil. However, these drugs are PDE inhibitors, which target the vascular system and stop the breakdown of cGMP, produced by nitric oxide (NO), which is released upon sexual stimulation, thus resulting in an erection. Alternative treatments include Y27632 (Welfide Corporation, Osaka, Japan) [6], which blocks Rho-kinase activity, inducing erections in a NO-independent manner, and Uprima® (TAP Pharmaceuticals, Lake Forest, IN, USA)

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[7], or apomorphine hydrochloride, which activates dopamine D1 and D2 receptors at sites in the brain and spinal cord.

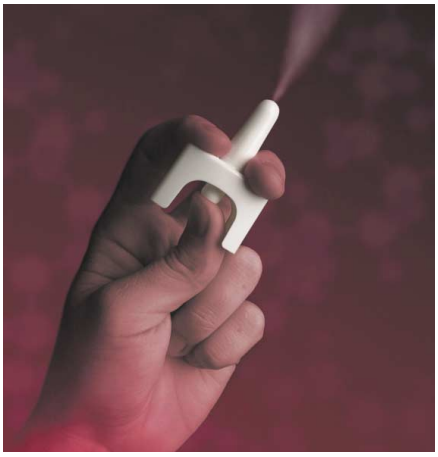
There are, however, problems with current treatments. Sildenafil is ineffective in 30–40% of patients; those with nerve damage in the penis following prostatectomy or as a result of diabetes. It also has side effects including headaches, nasal congestion and dyspepsia. Moreover, drugs that work as PDE inhibitors can interact with drugs for cardiac treatment, especially nitrate drugs.

For women, most FSD disorders are caused by a combination of physiological factors (i.e. vascular, traumatic injury, neurological or hormonal factors) and psychological factors. Current treatments include oestrogen replacement therapy, sildenafil and apomorphine.

PT141

PT141 is a novel, nasally administered peptide for the treatment of sexual dysfunction. It is a synthetic modification of melatonin 2 (MTII), an analogue of the naturally occurring α-MSH (melanocyte-stimulating hormone peptide). Receptors for this class of molecules (melanocortin receptors) have a role in sexual behaviour [8,9]. PT141 binds to melatonin receptors in the hypothalamus, affecting an area of the brain involved in sexual arousal. It is believed that PT141 will work for most men, including those whose use of cardiac drugs precludes the use of PDE inhibitors. Moreover, PT141 can be administered ~30 min before intercourse, favouring this treatment over others, such as sildenafil, which takes >60 min to take effect.

Preclinical trials of PT141 showed an increase in the potency and safety profile of the drug by 200-fold, compared with MTII. Efficacy was evaluated by the ability of PT141 to cause penile erections in primates and rodent species [10]. Carl Spana, President and CEO of Palatin, said that, 'preclinical research with PT141



in several animal species suggested this drug is highly potent and has the potential to be free of the cardiac side effects found in many of today's treatments for ED.'

Meanwhile, because PT141 works by directly stimulating receptors in the CNS, the drug has potential for the treatment of FSD. Preclinical studies in female rodents showed enhanced sexual behaviour [11]: female rodents exhibited body movements to heighten sexual arousal in, and to actively solicit sexual contact from, male rodents (proceptive precopulatory behaviour). 'This study's results indicate that PT141 could have the potential to offer a unique treatment for women with desire disorders,' said Annette Shadiack, Director of Biological and Preclinical Research at Palatin.

Trial results to date

Phase I studies of a double-blind, placebo-controlled trial to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of single escalating doses of PT141, administered intranasally to healthy adult male subjects, showed positive results with participants tolerating treatment well at all dose levels. These trials showed a wide therapeutic window and good safety profile and suggest potential for best-in-class efficacy. Further studies measured the efficacy of the compound, using the RigiScan® Plus System (Timm Medical Technologies, Eden Prairie, MN, USA), which assesses the rigidity and tumescence of the penis. There were no significant changes in blood pressure, heart rate or respiration rate and no reports of side effects. By the intranasal route of administration, PT141 appears rapidly in the bloodstream (within 5 min) with maximum levels reached at ~30 min.

Perry B. Molinoff, Executive Vice-President of R&D, said, 'In our present studies, we demonstrated that PT141 could induce robust erections in a dose-dependent manner. The magnitude and consistency of the response make us optimistic that PT141 will be an effective treatment for patients suffering from ED.' Carl Spana added, 'We are excited about our ongoing Phase II efficacy trials in patients with ED, which we anticipate will conclude in the second quarter of 2002.' A Phase II study in women has recently been initiated.

Potential

Alan Gibson, Senior Lecturer in Pharmacology at the School of Biomedical Sciences (King's College London, UK) commented: 'Melanocortin receptor agonists represent an exciting new class of therapeutic agents for the treatment of ED, especially the psychogenic forms. Their novel mechanism-of-action should circumvent the problems associated with sildenafil, such as nitrate interactions, dyspepsia and visual disturbance. PT141 has major potential, having a convenient method of administration and rapid onset. The ability to increase desire should benefit women suffering from sexual arousal disorder. As always, however, there is a downside. The full side-effect profile is awaited and, unlike sildenafil, the melanocortin receptor agonists can directly induce erection in the absence of sexual stimulation, which raises some interesting ethical issues.'

References

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