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COMMENTARY

α_1-Adrenoceptors and ejaculatory function

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The abnormal ejaculation of semen is a typical but infrequent side effect of some α_1-adrenoceptor antagonists, particularly those with selectivity for α_{1A}-adrenoceptors such as silodosin or tamsulosin. Recent clinical studies suggest that this represents a relative anejaculation rather than a retrograde ejaculation. An elegant study in this issue of the journal using α_{1A} single and $\alpha_{1A/B/D}$ triple knock-out mice reports a similar phenomenon in rodents. Using a multi-disciplinary approach, the reduced ejaculation and related male infertility is shown to be caused by an impaired function of the vas deferens rather than by alterations in sperm formation, number or function. Similarities and differences between mouse and human data are discussed, particularly why a complete inhibition of all three α_1-adrenoceptor subtypes has the strongest effects in mice whereas apparently only α_{1A}-adrenoceptor-selective drugs impair ejaculatory function in humans.
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Abbreviations: KO, knockout; WT, wild-type

The abnormal ejaculation of semen is a typical but rather infrequent side effect of some α_1-adrenoceptor antagonists; its incidence appears to decline with age, and across age groups, it is not judged as particularly bothersome by most patients (van Dijk *et al*., 2006). While abnormal ejaculation has been reported most often with antagonists with selectivity for α_{1A}-adrenoceptors such as silodosin or tamsulosin, direct comparative studies with antagonists without subtype selectivity have not reported significant differences between drugs unless very large patient numbers were studied (van Dijk *et al*., 2006).

Originally, it had been assumed that such abnormal ejaculation is a consequence of smooth muscle relaxation in the prostate, urethra and bladder neck. Such relaxation implies a reduced resistance of the prostatic urethra and bladder neck for the ejaculate coming from the vas deferens. By analogy with the retrograde ejaculation often occurring after transurethral resection of the prostate, it had been assumed that abnormal ejaculation occurring during treatment with α_1-adrenoceptor antagonists also represents retrograde ejaculation. Accordingly, observed abnormal ejaculation had been coded as 'retrograde ejaculation' in several clinical studies, despite absence of positive proof that this actually had happened (van Dijk *et al*., 2006). However, more recent clinical studies have shown that abnormal ejaculation upon treatment with tamsulosin represents a relative anejaculation rather retrograde ejaculation (Hellstrom and Sikka, 2006; Hisasue *et al*., 2006). These clinical findings suggested a drug effect on semen formation and/or transport, rather than on urethral smooth muscle relaxation, as the cause of the abnormal ejaculation. Against this background, an article in the present issue of this journal provides a comprehensive analysis of the role of α_1-adrenoceptor subtypes in male sexual function based upon knockout (KO) mice (Sanbe *et al*., 2007).

A starting point of the mouse studies was the observation that α_{1A} KO mice had a somewhat, and $\alpha_{1A/B/D}$ triple KO mice a markedly, reduced fertility rate; experiments with different combinations of male and female wild-type (WT) and KO mice indicated that the impaired ability to induce pregnancy resulted from male infertility (Sanbe *et al*., 2007). Of note, impaired fertility had not been reported in men treated with any α_1-adrenoceptor antagonist (van Dijk *et al*., 2006), but this may partly relate to the fact that men treated with α_1-adrenoceptor antagonists for their voiding difficulties typically are in their mid-sixties, that is, in an age group where procreation becomes a relatively rare event. *In vitro* fertilization experiments with sperm from either α_{1A} KO or $\alpha_{1A/B/D}$ triple KO mice did not reveal any abnormality in sperm function; sperm number in testis, daily sperm production and sperm motility were similar to WT in either KO strain (Sanbe *et al*., 2007). Similarly, sexual behaviour was not altered in either α_{1A} KO or $\alpha_{1A/B/D}$ triple KO mice (Sanbe *et al*., 2007), which is in line with clinical findings detecting only very small, if any, adverse α_1-adrenoceptor antagonist effects on libido (van Dijk *et al*., 2006). Taken together these data

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demonstrate that reduced fertility and lowered sperm delivery to the uterus in α_1 KO mice did not result from reductions of sexual drive, sperm formation or sperm function, which left an impaired transport of sperm from the testes to the urethra as the primary candidate to explain the reduced fertility. The overall analogy with the clinical findings supports the idea that similar mechanisms may be involved in human abnormal ejaculation.

It has long been known that α_1-adrenoceptors play an important role in the control of vas deferens motility. Antagonist data in rats (Eltze *et al*., 2001) and humans (Noble *et al*., 1997) demonstrate that this motility enhancement is largely mediated by α_{1A}-adrenoceptors. Accordingly, α_{1A} KO mice exhibited markedly reduced contractile responses to noradrenaline or field stimulation *in vitro*, and in $\alpha_{1A/B/D}$ triple KO mice this response was abolished (Sanbe *et al*., 2007). Based upon these findings, it appears that functional α_1-adrenoceptors, particularly α_{1A}-adrenoceptors, are essential for the physiological contraction of the vas deferens and hence for sperm delivery from the testes to the urethra.

While these elegant studies clearly demonstrate a role for α_{1A}-adrenoceptors in vas deferens function and male fertility in mice and men, important questions remain to be answered. The most important one appears to be why α_{1A} KO causes some, and $\alpha_{1A/B/D}$ triple KO major, impairment of ejaculation in mice, whereas in humans α_{1A}-selective antagonists can cause abnormal ejaculation but antagonists without subtype selectivity fail to do so (van Dijk *et al*., 2006). Clearly, the antagonists without subtype selectivity are dosed clinically to reach at least similar occupation of α_{1A}-adrenoceptors as the subtype-selective ones (Taguchi *et al*., 1998). Several, as yet untested possible explanations come to mind: Firstly, it is possible that crosstalk occurs between the α_1-adrenoceptor subtypes, in which one can alter the function of others (Michel *et al*., 1994). Secondly, it is possible that the clinical differences between silodosin and tamsulosin as compared to other α_1-adrenoceptor antagonists do not, or at least not exclusively, relate to their subtype-selectivity. Additional properties of these drugs such as a proposed insurmountable antagonism in the vas deferens (Noble *et al*., 1997) or additional effects on other receptor systems, for example, dopamine and/or serotonin (Leonardi *et al*., 1997), should be considered. Finally, it has been proposed that abnormal ejaculation is not primarily regulated at the level of the vas deferens but rather at central nervous sites controlling its function (Giuliano *et al*., 2006).

In conclusion, the present study by Sanbe *et al*. (2007) demonstrates an important role of α_1-adrenoceptors, particularly α_{1A}-adrenoceptors, in vas deferens function, and inhibition of these effects can lead to male infertility. These findings may represent the mechanistic correlate of the clinically observed abnormal ejaculation with some α_1-adrenoceptor antagonists (van Dijk *et al*., 2006), but some inconsistencies between mouse and human data as well as alternative possibilities remain to be investigated.

Conflict of interest

In the field of α_1-adrenoceptor research, MCM has received research support, consultant and lecturer honoraria from Astellas, Boehringer Ingelheim and Schwarz Pharma.

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