

Utility of infertile male models for contraception and conservation

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Abstract

Epididymal defects in infertile domestic species and transgenic mice demonstrate the role of the epididymis in influencing sperm function. Spermatozoa from these males cannot negotiate the female tract as they fail to regulate their volume. The latter is necessary to counter the osmotic stresses encountered in the female tract. Reduced epididymal provision of osmolytes or their premature loss is discussed as probable causes of failed volume regulation. Measuring cell volume regulation for diagnosis of male infertility and blocking it as a means to male contraception are briefly considered.

Unchecked human population growth is destroying habitats supporting vulnerable and endangered species. Genome resource banks have been established to preserve spermatozoa of genetically valuable individuals. As cryopreservation stresses spermatozoa osmotically, this process could jeopardise volume regulation with consequences for fertility. Knowledge of sperm volume regulation and the uptake of organic solutes may permit improvement in sperm storage and prevent osmolyte-related cryodamage.

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1. Introduction

Evidence for the involvement of the epididymis in infertility of some domestic species has been known for about 40 years (see Cooper, 1992) and more recently several transgenic mice have displayed a similar infertility phenotype (see Cooper et al., 2004; Andersen et al., 2003). The cause of infertility appears to be dysfunction of the volume regulatory ability of spermatozoa that swell and have difficulty negotiating selective obstacles within the female tract (Yeung et al., 2000). The concept of sperm volume regulation is discussed here in relation to utilising this phenomenon for diagnosing infertility, developing contraceptives and improving sperm preservation.

2. Infertility and sperm volume regulation

2.1. Post-testicular infertility in stud males

One of the earliest reports of non-testicular infertility in bulls was an individual of the Jersey breed named “Dag”, which gave its name to the defect (Blom, 1966). Ejaculated spermatozoa from this male were sharply angulated at the midpiece/principal

piece junction, at the site of the distal cytoplasmic droplet. Ultra-micrographs revealed several axonemal profiles observed within one plasma membrane indicating that the sperm tail was coiled through more than 180°. Such coiled or rolled ejaculated spermatozoa have been confirmed in infertile Swedish Red, White Jersey and Hereford bulls (Swanson and Boyd, 1962; Cupps and Briggs, 1965; Gustafsson, 1965, 1966; Koefoed-Johnsen and Pederson, 1971; Bech and Koefoed-Johnsen, 1973; Gustafsson et al., 1972, 1974; Wenkoff, 1978; Kojima, 1978) and infertile Swedish Landrace, Welsh, Hampshire, Yorkshire and mongrel boars (Einarsson and Gustafsson, 1973; Kojima, 1978; Hirao and Kubota, 1980; Holt, 1982; Kunavongkrit et al., 1988), mongrel dogs (Kawakami et al., 1988) and stallions (Hellander et al., 1991).

The cause of the abnormality was sought by increasing the ejaculation frequency, in order to empty distal caudal sperm reserves, and this was effective in many males in reducing the percentage of coiled spermatozoa to 10–20% from 60–80% (Swanson and Boyd, 1962; Hopwood et al., 1963; Gustafsson et al., 1972, 1974). The observations imply that spermatozoa from the proximal cauda, moving into the distal cauda after its depletion by multiple ejaculation, were less affected than those initially in the distal cauda. This suggested that the problem was caused by the time spermatozoa spent in the distal cauda epididymidis. For other males, however, the percentage of coiled spermatozoa only decreased to 50% (Gustafsson, 1965), sug-

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gesting that even more proximally-derived spermatozoa were affected by this condition.

More information on the local origin of the defect was obtained from spermatozoa recovered and fixed from several epididymal regions of Dag defect bulls (Koefoed-Johnsen and Pederson, 1971; Wenkoff, 1978) and boars (Einarsson and Gustafsson, 1973; Holt, 1982). From these, many different epididymal profiles of coiled spermatozoa were observed. In some males, sperm flagella were largely straight until they entered the distal cauda, as suspected from the multiple ejaculation studies, whereas in others the increase in coiled spermatozoa occurred in the proximal cauda, distal, middle or proximal corpus or even in the distal caput. That the angulation was occurring within the epididymal canal implicates the epididymis and rules out the composition of seminal plasma being a determinant of the abnormal morphology.

Whilst being a rather good indication that epididymal dysfunction was the cause of infertility in these males, which were otherwise healthy and reproductively active, interest in the topic waned until a similar phenomenon was found in certain transgenic mice.

2.2. Post-testicular infertility in transgenic mice

At least four transgenic mouse models display a similar sperm phenotype to the Dag defect males: angulated spermatozoa associated with male infertility. They are the *c-ros* knockout mouse (Sonnenberg-Riethmacher et al., 1996; Yeung et al., 1998), the SHP1 phosphatase mutant (Keilhack et al., 2001), the GPX5-Tag2 transgenic mouse (Sipilä et al., 2002) and the ApoER2 knockout mouse (Andersen et al., 2003). Ros-1 is an oncogene associated with epithelial-mesenchyme relationships during organ development; in the mouse, it is down-regulated post-natally in every organ that expresses it, except the proximal caput epididymidis where it is up-regulated around puberty. In *c-ros* knockout mice, the adult organ lacks the initial segment of the epididymis (Sonnenberg-Riethmacher et al., 1996) although the rest of the caput differentiates normally (Avram and Cooper, 2004). A natural mutant of the SHP-1 phosphatase gene causes sterility in mice and specifically results in hyperphosphorylation of *c-ros* protein. Both SHP1 and *c-ros* are co-expressed in the initial segment that is lacking from the mutant. In GPX5-Tag2 transgenic males, the epididymis-specific GPX5 promoter was used to target the simian large and small T antigens to the epididymis. These males have an initial segment that may even be hypertrophied. The apolipoprotein E receptor 2 binds the low-density lipoprotein and is associated with neuronal development. It is expressed in the initial segment of wild-type males but knockout males lack this epithelial region.

In all these models an epididymal defect in the caput is associated with male infertility and an identical sperm phenotype as the Dag defect males, suggesting that an epididymal dysfunction is associated with a sperm malfunction. Most is known about the *c-ros* knockout males, which can be used interchangeably with vasectomised males for stimulating pseudopregnancy. In these mice, spermatozoa fail to reach the oviduct despite normal numbers in the uterus (Yeung et al., 2000). It is now known that the

Table 1

Osmolality of fluids (mmol/kg) from male and female mice and men^a

Species (strain)	Fluid	Genotype	Mean $\pm$ S.E.M. (range)	Ref.
Mouse				
(FLBV)	Cauda epididymidis	WT	396 $\pm$ 8	1
		TG	358 $\pm$ 10	1
(129Bl6)	Cauda epididymidis	HET	480 $\pm$ 19	2
		KO	484 $\pm$ 24	2
(C57Bl6/Ola29)	Cauda epididymidis	WT	415 $\pm$ 12	3
		KO	427 $\pm$ 27	3
(C57Bl6/Ola29)	Seminal vesicle	HET	305 $\pm$ 7	4
		KO	298 $\pm$ 9	4
(B6D2F1)	Seminal vesicle	WT	298 $\pm$ 7	4
(C57Bl6)	PC uterine contents	WT	327 $\pm$ 8	5
Human				
	Testicular (spermatocele) fluid		280 $\pm$ 4	4
	Vas deferens fluid		342 $\pm$ 5	6
	Unliquefied ejaculate after 5 min		294 $\pm$ 4	7
	First portion of split ejaculate after 5 min		304 (281–308)	8
	Cervical mucus		287 $\pm$ 31	9
	Uterine fluid		284 (276–298)	10
	Hydrosalpinx (tubal) fluid		271	11
			268–280	12
	Follicular fluid		300–305	13
			280 $\pm$ 9	14

1, Sipilä et al. (2002); 2, Andersen et al. (2003); 3, Yeung et al. (1999); 4, Barfield and Cooper, unpublished observations; 5, Yeung et al. (2000); 6, Hinton et al. (1981); 7, Cooper et al. (2005); 8, Björndahl and Kvist (2003); 9, Rossato et al. (1996); 10, Casslén and Nilsson (1984); 11, Ng et al. (2000); 12, Granot et al. (1998); 13, Menezo et al. (1982); 14, Edwards (1974).

^a PC, post-coital; TG, transgenic; WT, wild-type; HET, heterozygous; KO, knockout.

spermatozoa are mainly straight within the epididymis (about 20% are angulated in the cauda: Yeung et al., 1999) but undergo flagellar angulation upon entry into the uterus (Yeung et al., 2000) or in routine incubation media (Yeung et al., 1998, 1999). The significance of these observations is that flagellar angulation is now known to indicate a swollen spermatozoon (Yeung et al., 2002) so that angulation implies that the spermatozoa are unable to regulate their volume. Regulation of volume is necessary because murine spermatozoa suffer a hypotonic insult upon ejaculation into the female tract (Table 1). Thus, spermatozoa should experience swelling as water enters the cell, and they presumably regulate their volume in order to remain straight and to negotiate the uterotubal junction in this species. The fact that demembration with detergents straightens the flagella confirms that the spermatozoa are held in the angulated position as a result of membrane tension.

Unlike the *c-ros* knockout males where flagellar angulation occurs after release from the epididymis, in the GPX5-Tag2 and ApoER2 knockout males, the percentage of coiled spermatozoa within the epididymis reached 80% in the proximal and distal cauda. Some spermatozoa from the ApoER2 knockout mice and none from the GPX5-Tag2 males straighten out upon demembration, suggesting that the normal process of flagellar disulphide oxidation upon maturation within the epididymis restrains the flagellum in the swollen conformation. Despite the morphological defect in transgenic *c-ros* knockout mice, they swim with

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