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BASIC RESEARCH

Mouse study shows spermatogenesis inhibitor is effective as a reversible male contraceptive

A novel small-molecule inhibitor of BRDT, a testis-specific member of the bromodomain and extraterminal (BET) subfamily of epigenetic reader proteins, has the potential to be used as a potent and reversible male contraceptive, according to a study recently published in *Cell*.

BRDT is expressed in pachytene and diplotene spermocytes and round spermatids, and is required for chromatin remodelling during spermatogenesis. BRDT polymorphisms have been shown to be associated with oligozoospermia and azoospermia, suggesting that it is a target for potential male contraceptives. Based on these data, a multinational team of researchers developed the small-molecule inhibitor JQ1, and investigated its effect on reproduction in male mice.

Juvenile and adult mice received daily intraperitoneal injections of 50 mg/kg JQ1 or vehicle for 3 or 6 weeks, after which testicular volume, semen parameters, and hormone levels were recorded. Testis volume was significantly reduced in all mice receiving JQ1 in a time-dependent manner. Furthermore, epididymal sperm number was reduced to 28% that of control-treated mice after only 3 weeks of treatment and 11% after 6 weeks, with an associated 4.5-fold reduction in sperm motility. Cross-sectional area of seminiferous tubules and number of tubules containing obvious and abundant round spermatids and spermatozoa were also decreased. Interestingly, serum luteinizing hormone, follicle-stimulating hormone and testosterone levels were not significantly different from control-treated

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mice, suggesting that the effects of JQ1 are specific to germ cells and do not affect the Leydig cells of the testis.

To elucidate the effects of JQ1 on fertility, mice received 50 mg/kg JQ1 or vehicle daily for 6 weeks ($n = 7$), after which they were mated with female mice whilst still receiving the treatments. After the first month of breeding, all control-treated mice had sired offspring, compared with only four of the JQ1-treated males. The three males that had not sired offspring demonstrated normal mating behaviour. A dose escalation study showed that total daily dose of 50–100 mg/kg was sufficient to produce a complete contraceptive effect in male mice. As reversibility is a key feature of any potential contraceptive, the team investigated the mating behaviours of mice after 1 month of recovery from JQ1 treatment. In the three mice most responsive to JQ1, induced infertility remained complete after 1 month. However, after only 1 further month, all three males sired litters containing a statistically similar number of pups to controls. 4 months after halting the regimen, testis volume, seminiferous tubule area, testis histology, sperm motility and sperm counts returned to control levels, consistent with a full recovery. No long-term effects of treatment were seen, and offspring of the JQ1-treated males exhibited normal mating behaviour and fertility, demonstrating that JQ1 did not confer any transgenerational effects on reproductive function.

The clinical potential of a selective and fully reversible male contraceptive in humans is huge and the team has already begun optimization of a BRDT-selective, drug-like molecule, with hopes to have human data available as soon as next year. Unlike some other proposed male contraceptives, JQ1 is nonhormonal, so testosterone levels and penis size would not be altered, and sexual function would not be affected.

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Original article Matzuk, M. M. *et al.* Small molecule inhibition of BRDT for male contraception. *Cell* **150**, 673–684 (2012)