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Commentary

A Nonhormonal Approach to Male Contraception?

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Since the recent overturn of Roe vs. Wade by the U.S. Supreme Court, attention has been brought to bear on the question of male contraception in the United States and other countries. While hormone-based approaches (those that inhibit the hypothalamic-hypophyseal-gonadal axis) are promising [1], side effects and the hesitancy of the pharmaceutical industry have hindered efforts in this direction [2]. But what about nonhormonal approaches to male contraception?

My initial research as a graduate student involved the effects of the glucose analog 5 Thio-D- glucose (5TG) on various tissues and organs in laboratory mice. 5TG is a synthetic analog of D-glucose where the ring oxygen is replaced by a sulphur atom. Administration of 5TG over a 3-week period resulted in no remarkable changes in any of the tissues examined, except the testes where spermatogenesis was inhibited [3]. Upon cessation of 5TG, sperm development and fertility resumed within 5 to 8 weeks. So, what is the reason for this effect by 5TG? It has been shown that 5TG inhibits cellular D-glucose uptake [4]. Other work has shown that spermatogenesis is sensitive to blood glucose levels [5]. Indeed, male diabetics have been found to have compromised fertility [6]. Mechanistically, this may provide a route to nonhormonal male contraception. A cautionary note should be added here, since follow-up studies with 5TG indicated that extended administration could result in irreversible sterility in addition to a diabetogenic effect [7]. However, there may be a positive side to this approach since the pharmacology of glucose uptake could make room for some creative drug discovery.

All tissues take up glucose through specific trans-membrane proteins known as glucose transporters (GLUTs). As of this writing, there are 14 specific GLUTs distributed among the various cells of the body [8]. For example, GLUT4 is the insulin-sensitive transporter found in muscle and adipose tissue. GLUT2 is expressed in β-pancreatic islet cells, the liver, and intestinal enterocytes [8]. The testis poses an additional challenge with the existence of the blood-testes-barrier (BTB), a complex of tight junctions between Sertoli cells (which aid in the development of maturing sperm cells) and the germ cells undergoing the process of spermatogenesis [9]. Sertoli cells express GLUTs 1, 3, and 8 with GLUT1 expression regulated by hormones during pubertal development [10]. Spermatogonia express GLUT3 and receive lactate from Sertoli cells through a specific uptake mechanism [10]. Each transporter exhibits unique kinetic properties that may serve specific needs of developing sperm cells. GLUT3 for instance, has the highest turnover number of the GLUT isoforms and a high affinity (low Km) for glucose [8]. Interestingly, it is not an insulin-dependent transporter (that role is owned by GLUT4). But GLUT3 and GLUT1 may be responsible for basal glucose transport throughout many tissues including testis and brain [8]. It has also been shown that unilateral cryptorchidism induced in rats is associated with a loss of GLUT3 degenerative changes in spermatogonia [11]. The bottom line is that a diverse pharmacology among specific GLUTs may allow for unique inhibitory drugs that only target spermatogenesis. Recent evidence for an allosteric site on GLUT1 in red blood cells [12] might provide even more selectivity for promising drugs. Of course dissecting the potential toxicity of glucose inhibitors from selective pharmacology will be a challenge, but the tools are available.

This approach to male contraception is but one path. Other nonhormonal options are also being pursued, including the retinoic acid receptor alpha where selective antagonists have been tested with positive results in murine models [13]. So, there are systems rich in complex pharmacology that may be promising. Clearly, the potential for male contraception exists in the technical arena. The real challenge is cultural. Are we ready to take the next step?

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