The Discovery and Characterization of Steroidal Blockers of CatSper

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The cation channel of sperm (CatSper) is the principal entry point for calcium in mature spermatozoa. CatSper knockout mice are completely infertile with no other observable phenotypes, and genomics studies in men have shown its requirement in humans. CatSper is activated by the steroid progesterone and prostaglandin E₁ (PGE₁). Once bound, these compounds elicit a large calcium influx into the flagellum of the sperm, which propagates towards the head and induces hyperactivated motility (HAM) in sperm. HAM is required to penetrate the viscous fluid of the upper reproductive tract and the zona pellucida surrounding the egg. By systematically modifying the steroid backbone of progesterone we have discovered three steroidal compounds that block the progesterone-induced calcium influx observed in a fluorescence-based assay. The details of the discovery and characterization of these blockers, as well as differences to t-type calcium channel blockers will be discussed.