

“Taste” takes Control of “Testes”: A New Trick for an Old Gene Family

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The TAS1R taste receptors, best known as sugar and amino acid sensing in taste cells and in the gastrointestinal tract, are required for proper sperm formation, according to a very new study in mice. These extraoral “taste” molecules seem to directly participate in the sperm development and maturation, a process that normally occurs at the late stage of spermatogenesis.

Mice and humans each have three types of TAS1R receptors: TAS1R2+TAS1R3 form a sweet receptor, and TAS1R1+TAS1R3 form an umami receptor. TAS1R3 is the common subunit and may also serve as a low-affinity sweet receptor alone. The TAS1R receptors have also been implicated in male reproduction. In mice, for instance, T1R2 is expressed in the primary spermatocyte or spermatogonial cells, as revealed by a T1R2-LacZ knock-in mouse model. TAS1R1 is also found to be expressed in mouse spermatozoa and has been implicated in regulating basal Ca²⁺ and cAMP concentrations in spermatozoa.

To examine the function of TAS1R receptors more closely, Mosinger et al. first examined the expression pattern of *Tas1r3* gene and its associated heterotrimeric G protein gustducin α -subunit *Gnat3* gene in the male reproductive system using *in situ* hybridization [1]. They found that *Gnat3* and *Tas1r3* were both expressed in testis, with strong positive signals being detectable in the elongating and elongated spermatids. Of note, expression of these two genes appears to be specific to testes because they were not found in epithelial cells in epididymis, or

in ovaries, although TAS1R1 expression in ovaries has been reported.

Further evidence for a direct role of TAS1R3 and GNAT3 in the modulation of sperm formation is provided by using a mouse model that expressed a humanized form of TAS1R3 susceptible to inhibition by the antilipid medication clofibrate. Sperm formation in animals without functional TAS1R3 and GNAT3 is significantly impaired, with malformed and immotile sperm. In addition, clofibrate inhibition of humanized TAS1R3 in the genetic background of *TAS1R3*^{-/-}, *GNAT3*^{-/-} doubly null mice led to inducible male sterility. Closer analysis revealed that TAS1R3 and GNAT3 may affect cAMP levels and Ca²⁺ signaling in spermatids, thus resulting in disruption of several critical pathways required for normal sperm development.

A number of natural and synthetic anti-sweet or sweet-modifying substances/ antagonists exist. The long-term biological effects of these compounds in humans are not well known, although some reports point to male infertility. To this end, this study suggests that inhibitors of human TAS1R3 together with nonspecific G protein inhibitors, or mutations in these genes, could result in infertility or sterility, which should shed light on some forms of idiopathic male infertility.

Reference

1. Mosinger B, Redding KM, Parker MR, Yevshayeva V, Yee KK, et al. (2013) Genetic loss or pharmacological blockade of testes-expressed taste genes causes male sterility. *Proc Natl Acad Sci U S A* 110: 12319-12324.

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