WORLD OF REPRODUCTIVE BIOLOGY

Progesterone and Endocannabinoid Interaction Alters Sperm Activation

A recent study in Science finds that α/β-hydrolase domain-containing protein 2 (ABHD2) is a novel nongenomic progesterone receptor that holds the CatSper cation channel open while progesterone elevates sperm cytoplasmic calcium ion (Ca2+) levels and triggers sperm hyperactive motility. ABHD2 functions as a lipid hydrolase, breaking down arachidonoylglycerols (2-AG/1-AG)—endocannabinoid components that inhibit CatSper channel functionality.

Miller et al. [1] identified this role of ABHD2 through a series of elimination-based experiments. After administering methyl arachidonoyl flourphosphanate (MAFP), a metabolic serine hydrolase inhibitor, they recorded an absence of progesterone-dependent CatSper activation. However, basal CatSper activity levels remained unchanged, suggesting the work of an indirect mechanism instead of a direct binding between progesterone and CatSper. Tests of lysophospholipids and endocannabinoids against CatSper channel activity unveiled 2-AG and 1-AG as the major inhibitors. Lipid analysis revealed arachidonoylglycerols primarily concentrated within the sperm plasma membrane; however, when the investigators treated membranes with progesterone, arachidonoylglycerol levels dropped severely.

This relationship between progesterone and selective endocannabinoids enabled the authors to focus their search for the nongenomic progesterone receptor. Earlier studies localized progesterone actions to the plasma membranes of cells, but the specific binding partner remained a mystery. Miller et al. designed a photoactivatable progestin analog (P4*) to open the CatSper channel and bind to neighboring molecules upon exposure to UV light. This approach uncovered ABHD2 as the progesterone-binding target that hydrolyzes AGs to increase CatSper activity.

Further, ABHD2 antibodies inhibited sperm activation when incubated with human spermatozoa. The authors tested ABHD2 effects on sperm arachidonoylglycerols; when they supplemented ABHD2 with progesterone, hydrolysis increased, marked by rising levels of glycerol and arachidonic acid (AA). These shifting levels created a feedback system to regulate the CatSper channel, progesterone, and endocannabinoids.

The authors speculate that the sperm plasma membrane continuously produces arachidonoylglycerols to keep the CatSper channel closed. Increases in progesterone interaction with ABHD2 correspond with arachidonoylglycerol decline, but this continues only as long as the nongenomic progesterone receptor remains stimulated. When progesterone signaling drops, AG levels restore in a time-dependent manner.

Miller et al. [1] demonstrate that progesterone-activated endocannabinoid depletion by ABHD2 is a general mechanism by which progesterone exerts its genome-independent action and primes sperm for fertilization. Modulation of ABHD2 function in males may be useful to improve fertility, identify the etiology of infertility, and develop novel contraceptive agents.

-- Katie Gerhardt

REFERENCES


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