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**MAIN FACTORS AFFECTING SPERM MOTILITT**

Sperm motility is highly dependent on several metabolic pathways and regulatory mechanisms. Besides the involvement of specific gene defects, any abnormalities of these factors could be responsible for cases of poor sperm motility and consequently infertility.

**Pathways and regulatory mechanisms involved in sperm motility**

The calcium (Ca2+) pathway and the cyclic adenosine monophosphate (cAMP)-dependent protein kinase or protein kinase A (PKA) pathway are two important metabolic pathways involved in the regulation of sperm motility.[1](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref1),[2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref2) These pathways involve calcium ions, adenylyl cyclases, bicarbonate ions, different membrane channels, and phosphorylation events. All are responsible for the acquisition of competences that will enable sperm to fertilize the oocyte, namely capacitation, hyperactivity, and acrosome reaction.Cellular levels of cAMP are controlled by adenylyl cyclases (ACs) that catalyze an intramolecular cyclization of ATP to cAMP under release of pyrophosphate.[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref3) The mammalian ACs can be separated into two distinct types, transmembrane AC enzymes (tmACs) and soluble AC (sAC, also known as AC10). Soluble AC is directly activated by bicarbonate and Ca2+ and acts as a sensor for ATP, Ca2+, and bicarbonate/CO2 /pH at various intracellular locations. Soluble ACs are the only signaling proteins known to be directly regulated by bicarbonate. Mammalian tmACs, in contrast, are not responsive to bicarbonate. Instead, they are mainly regulated by heterotrimeric G-proteins, as part of the G-protein coupled receptor pathways.[3](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref3),[4](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref4) Both ACs are known to play an important role in male fertility. Transmembrane AC is involved in the basic mechanism for motility activation through cAMP-dependent protein phosphorylation and in progressive motility.[5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref5),[6](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref6) Soluble AC is the predominant adenylyl cyclase responsible for the generation of most cAMP in spermatozoa and plays a critical role in cAMP signaling and is involved in the increase in beat frequency in spermatozoa.[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref7),[8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref8) Inactivation of sAC gene leads to male sterility given the lack of forward motility.[9](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref9) Cyclic AMP is thus essential for sperm motility regulation and fertility with reduction of cAMP levels associated with reduced sperm motility.

Calcium is a fundamental regulatory factor for sperm capacitation, hyperactivation, and acrosome reaction. At low intracellular Ca2+ concentrations, flagella beat symmetrically but when Ca2+levels rise in activated sperm (Ca2+ of 10–40 nM), the waveform becomes more asymmetric, and sperm becomes hyperactivated (Ca2+ of 100–300 nM).[12](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref12),[13](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref13)However, high levels of Ca2+ (about 9 μM) suppress motility. This inhibition seems to be due to a decrease of protein phosphorylation (caused by substrate depletion or to conformational changes) induced by Ca2+, which prevents substrate-kinase interactions.[14](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref14),[15](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref15)Calcium is also involved in the regulation of dynein-driven microtubule sliding.[16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref16)Calmodulin is a key axonemal Ca2+ sensor, and the calmodulin-dependent kinase may mediate this Ca2+ signal. These complexes, localized at the sperm axoneme, are regulated by the central pair complex and radial spokes. Calmodulin regulates motility through direct interaction with protein kinases,[17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref17) phosphatases,[18](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref18) and sAC).[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref7),[8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref8)

Bicarbonate (HCO3−) ions also play a critical role in the regulation of sperm function (ion of the female reproductive tract transported into sperm during capacitation. An increase in Ca2+ stimulates sAC; it converts ATP to cAMP and increases cAMP levels.[19](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref19),[20](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref20) As HCO3− is required for Ca2+ uptake, it causes the same effects. The treatment in vitro with HCO3− evokes Ca2+ entry, which rapidly increases flagellar beat frequency but decreases flagellar beat asymmetry.[21](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref21)As a result, serine/threonine PKA is activated, which then phosphorylates serine and threonine residues on neighboring proteins to trigger a cascade of protein phosphorylation events.[22](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref22) The presence of proteins in the fibrous sheath (FS) with PKA anchoring sites strongly suggests that one of the major roles of this structure is to anchor PKA in the principal piece of the flagellum. Cyclic AMP promotes both capacitation and the acrosome reaction and activates PKA).[22](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref22),[23](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref23),[24](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref24) PKA subunits are expressed differentially. The regulatory subunit RIα is expressed throughout male germ cell development, RIIα only appears at the late stages in spermatogenesis, and the catalytic subunit Cα2 is only expressed in sperm. It is believed that the activation of PKA increases flagellar beat frequency and tyrosine phosphorylation to prepare the capacitated sperm for fertilization.[22](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref22)PKA localizes at the principal piece of the flagellum, and Cα2 null males are completely infertile.[25](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref25),[26](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref26)

Several Ca2+-permeable-specific channels have been found in sperm based on immunostaining or on the presence of transcripts in spermatogenic cells, such as high voltage-gated Ca2+ channels, cyclic nucleotide-gated channels, cation channels of sperm (CatSper), and transient receptor potential channels). These are a family of alkalinization-activated cation channels (CATSPER-1-4) that are highly conserved in humans. They are the principal Ca2+ channels activated by progesterone in human sperm.[27](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5227674/#ref27) Mutations in these channels were associated with human infertility and also suggested as a target for development of a male contraception. Thus, it is likely that Ca2+ plays different roles in distinct stages of the sperm journey.