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Nitric Oxide: A Double Edged Weapon for Sperm Functions

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Oxidative Stress (OS) status has emerged as a promising field in the reproductive physiology. OS can be defined as the imbalance between pro-oxidative and anti-oxidative molecules in a biological system, which arises as a consequence of excessive production of free radicals and impaired antioxidant defense mechanism. Those free radicals derived from oxygen are called reactive oxygen species (ROS). ROS include superoxide (O_2^-), hydrogen peroxide (H_2O_2), peroxyl (ROO^-) and hydroxyl (OH) radicals. Those derived from nitrogen are called reactive nitrogen species (RNS). RNS include nitric oxide (NO^-), nitrogen dioxide (NO_2) and peroxynitrite anion ($ONOO^-$). RNS are often considered to be a subclass of ROS.

Recent information on the NO has proved its importance as an intercellular and intracellular messenger controlling many physiological processes. It is also a mediator of cytokines and growth factors in various cell types. NO is synthesized form L-arginine by the action of nitric oxide synthase (NOS), an enzyme existing in three isoforms. Two of them, endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS), collectively called as constitutive nitric oxide synthase (cNOS), are responsible for continuous basal release of NO and both, require calcium/calmodulin for activation. The other one is called as inducible nitric oxide synthase (iNOS), is responsible for prolonged release of NO and does not require calcium/calmodulin for activation. It is expressed in response to inflammatory cytokines and lipopolysaccharides.

Low concentration of NO increased the motility and viability of spermatozoa. However, high concentration of NO decreased the sperm motility and viability. The bimodal motility response to various concentrations of NO releasing compounds could be due to dual nature of NO, as both a transduction molecule at low concentration and a cytotoxic effector at high concentrations in systems.

NO inhibits cellular respiration by nitrosylation of heme in mitochondrial enzymes, aconitase and glyceraldehyde-3-phosphate dehydrogenase, leading to a depletion of ATP and consequent loss of motility in the spermatozoa. The primary mechanism of NO induced sperm damage is likely to be the inhibition of mitochondrial respiration and DNA synthesis. NO induced toxicity is also mediated indirectly through its interaction with superoxide anions and formation of peroxynitrite anion, which when protonated, decomposes to form hydroxyl and nitrogen dioxide radicals, both of which are cytotoxic agents.

NO can act as a free radical scavenger and inactivate superoxide, thereby preventing cell toxicity at low concentration. Peroxynitrite decomposes to form the reactive hydroxyl radical. Moreover, peroxynitrite and its metabolite are capable of inducing cytotoxicity by inducing LPO, nitrosation of several tyrosine molecules that regulate enzyme function, signal transduction and sodium channel inactivation.

Excessive NO contributes to the formation of peroxynitrite, a highly toxic anion of lipid peroxidation (LPO) of sperm membrane. Peroxynitrite is not a free radical because the unpaired electrons of NO and superoxide combine to form a new nitrogen-oxygen bond in peroxynitrite, but it is a strong one or two-electron oxidant and nitrating agent. The sperm plasma membrane is largely composed of PUFAs which are susceptible to oxidative damage due to the existence of double bond. The sperm membrane contains almost 50 per cent decosahexaenoic acid, which contains six unsaturated double bonds in every molecule. As the LPO cascade proceeds in sperm, almost 60% of the fatty acid is lost from the membrane. LPO affects membrane structure and functions such as fluidity, ion gradients, receptor transduction, transport processes and membrane enzymes. Peroxides, products of LPO constitute a potential hazard to the structural and functional integrity of spermatozoa.

Spermatozoa mitochondrial membrane potential (MMP) loss is preceded by permeability transition pore (PTP). The PTP is a multi-component protein that regulates oxidative phosphorylation, aggregates in mitochondrial membranes and induces cell death, when it turns into a non-specific channel. Another mechanism associated with MMP loss is the coordination between numerous B-cell lymphoma (BCl-2) proteins to induce mitochondrial outer membrane permeabilization, and this mechanism is strictly associated with caspase activation. NO induces a dramatic increase in percentage of spermatozoa with caspase activity. NO stimulates proteins of the BCl-2 family, followed by releasing of mitochondrial cytochrome C and concomitant activation of caspase 9 and 3, which results in disruption of MMP.

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