

The SOD1, SOD2 and GSTO2 are active and expressed in human sperm: their involvement in the physiopathology of varicocele-associated male infertility

Marta Santoreo¹, Vittoria Rago¹, Rocco Malivindi¹, Daniela De Rose¹, Rosario D'Agata², Giuseppina Peluso³, Giampiero Russo⁴, Francesca De Amicis¹, Saveria Aquila¹

¹ Department of Pharmacy and Sciences of Health and Nutrition, University of Calabria, Cosenza, Italia

² Department of Clinical and Experimental Medicine, University of Catania, Catania, Italia

³ Unit of Physiopathology of Reproduction, Annunziata Hospital, Cosenza, Italia

⁴ Family Counseling Center (ASP Cosenza), Health Center-University of Calabria, Cosenza, Italia

Testicular varicocele is strictly associated to male infertility. Nevertheless, the mechanism/s by which varicocele affects fertility remain undetermined. Recently, we showed that varicocele damages male gamete at molecular level, opening a new chapter in the already multifactorial physiopathology of varicocele.

Considerable evidence showed that the retinoic acid receptor α (RAR α) and its all-trans retinoic acid (ATRA) ligand, the active form of vitamin A, play key roles in sperm maturation. Previously, we showed in varicocele sperm a reduced RAR α expression and that ATRA influence sperm performance. To further define vitamin A significance in human sperm and in the varicocele physiopathology, we tested for the first time ATRA action on the antioxidant defense systems. Poor sperm quality compromises the fertilization process and one of the most important cause is the oxidative stress elicited by excessive ROS generation from sperm and/or by the disruption of the antioxidant defense systems in the male reproductive tract. Recently, many clinical trials have been performed to examine potential therapies for oxidant stress-induced infertility.

Herein, ATRA induced the superoxide dismutase and glutathione transferase activities, while it reduced the malondialdehyde and ROS production both in healthy and varicocele sperm. Interestingly, for the first time we showed that SOD1 and SOD2 have been localized in the acrosome and midpiece, GSTO2 in the acrosome, equatorial and subacrosomal regions. By Western Blotting analyses SOD1, SOD2 and GSTO2 expression were significantly lower in varicocele with respect to healthy sperm. Further, we showed that basal ROS production is elevated in varicocele with respect healthy sperm, and it decreased after ATRA treatment.

Sperm plasma membranes are particularly susceptible to oxidative stress owing to their high levels of polyunsaturated fatty acids that readily undergo lipid peroxidation, affecting the fluidity of the sperm plasma membrane and thus causing functional defects during capacitation, acrosome reaction and sperm-oocyte fusion.

In conclusion, our study describes a novel retinoids action as modulators of antioxidant defense systems in human sperm. Nonetheless, despite the open question of clinical efficacy for these anti-oxidant therapies, their low cost and toxicity, could offer a great advantage for both patients and clinicians, opening the possibility to consider this agent as potential therapeutic tool to ameliorate sperm performance also in pathological samples.

These novel findings further confirm the importance of vitamin A in male fertility and add new insights into the retinoids complex biological framework. Collectively, ATRA administration in procedures for artificial insemination or dietary vitamin A supplementation might represent a promising therapeutic approach for the management of male infertility.