Reproductive Biology and Endocrinology

BioMed Central

Review

Reactive oxygen species in spermatozoa: methods for monitoring and significance for the origins of genetic disease and infertility

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Published: 29 November 2005

Reproductive Biology and Endocrinology 2005, **3**:67 doi:10.1186/1477-7827-3-67

Received: 24 August 2005
Accepted: 29 November 2005

This article is available from: http://www.rbej.com/content/3/1/67

Abstract

Human spermatozoa generate low levels of reactive oxygen species in order to stimulate key events, such as tyrosine phosphorylation, associated with sperm capacitation. However, if the generation of these potentially pernicious oxygen metabolites becomes elevated for any reason, spermatozoa possess a limited capacity to protect themselves from oxidative stress. As a consequence, exposure of human spermatozoa to intrinsically- or extrinsically- generated reactive oxygen intermediates can result in a state of oxidative stress characterized by peroxidative damage to the sperm plasma membrane and DNA damage to the mitochondrial and nuclear genomes. Oxidative stress in the male germ line is associated with poor fertilization rates, impaired embryonic development, high levels of abortion and increased morbidity in the offspring, including childhood cancer. In this review, we consider the possible origins of oxidative damage to human spermatozoa and reflect on the important contribution such stress might make to the origins of genetic disease in our species.

1. Introduction – origins of genetic disease

The maintenance of genetic integrity in the male germ line has major repercussions for conception, the progress of pregnancy and, ultimately, the health and well-being of the progeny [1]. The human male contributes heavily to germ line mutations [2], and as such, is responsible for most of the dominant genetic diseases observed in our species. Indeed, in some cases, such as multiple endocrine neoplasia or achondroplasia (short-limbed dwarfism), the phenotype is invariably the result of mutations that can be traced back to the paternal germ line [2]. Epidemiological data also suggest that paternally derived genetic damage may contribute significantly to the aetiology of cancer in children and young adults [1,2].

These observations raise important questions about the aetiology of genetic damage in the male germ line and the causal links that exist between the induction of such damage and the inheritance of many childhood diseases. As early as 1912, Wilhelm Weinberg (cited in [2]) reported that children with dominant achondroplasia born to normal parents were among the last-born children in the family. Later work by Penrose [3] suggested that the effect observed by Weinberg was not actually correlated with birth order, nor surprisingly, maternal age. Rather, achondroplasia was a disease associated with paternal age. The implications of these findings were vast. Why is it that a much greater mutation rate apparently exists in the male germ line compared to the female? And why are several X-linked recessive and autosomal-dominant diseases correlated with paternal age?