Can spermatozoa be targets for drugs? If so, what are the consequences of such drug exposures? Is there a need for pre-conception counselling for men?

Drugs that affect sperm structure or function, male-mediated developmental toxicity, prevention, tests to detect damage to spermatozoa

B.F. Hales and B. Robaire

There are more than 100,000 chemicals in our environment. Men are exposed to chemicals in air, water, and food, in daily life, in occupational settings, and as drugs. Some of these chemicals do target spermatozoa (Chapter 28). Chemicals may have adverse effects on male germ cell numbers, decreasing production by blocking mitosis and/or meiosis, or increasing cell death by inducing apoptosis, an active process by which cells commit suicide. Alternatively, chemicals may affect germ cell quality, without an accompanying effect on sperm counts. Finally, chemicals may disturb the male germ cell genome, by mutating the DNA sequence itself, or alter the epigenome (Chapter 9), by affecting modifications to the DNA bases or to the proteins that make up male germ cell chromatin.

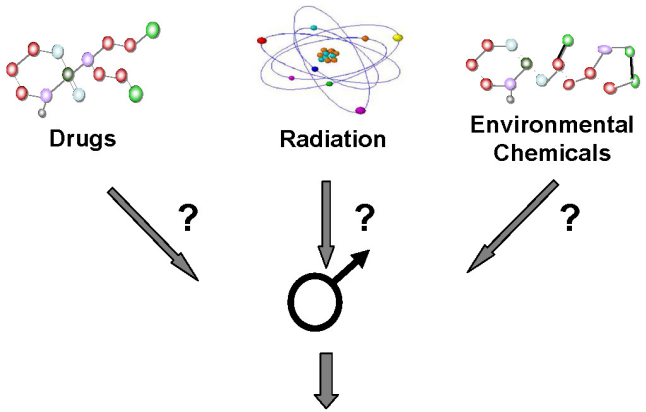

FIG. 1. Environmental factors and xenobiotics can affect male germ cells with consequences for future generations.

Male germ cells are engineered to fertilize an oocyte and to provide a paternal genome to the conceptus; chemicals that target male germ cells may decrease their fertilizing ability or induce post-fertilization adverse effects on progeny outcome. The success of in vitro fertilization techniques is a direct measure of fertilizing ability. In vitro fertilization technology is well established in humans and certain animal models, such as mice, but less successful in other common lab species, such as rats. An in vitro fertilization assay with rat zona-free oocytes revealed that sperm fertilizing potential was reduced by treatment of rats with toxicants, such as m-dinitrobenzene and ethylene glycol monomethyl ether, that did not affect sperm motility. Although there are very few human studies, in IVF-treated women there was no increased risk of spontaneous abortion attributable to paternal exposure to welding or pesticides. When other parameters that do not distinguish between an effect on fertilizing ability and early pregnancy loss, such as cycle-specific fertility rates, time to pregnancy, cumulative percent pregnant, and fecundability are assessed, effects have been reported after paternal exposures to common environmental toxicants, such as lead.

Adverse progeny outcomes might include early or late pregnancy loss, preterm delivery or delivery of a small-for-gestational age infant, malformations, behavioral abnormalities, or even childhood cancer. There is convincing evidence from animal studies that paternal exposures to specific environmental or therapeutic agents do result in a higher incidence of adverse progeny outcomes. A wide range of environmental chemicals (e.g., lead, dibromochloropropane, phthalates) and drugs (e.g., the anticancer alkylating agent, cyclophosphamide) produce abnormal progeny outcomes after paternal exposure. From the timing between toxicant exposure and the effect on offspring, one can deduce the stage specificity of the susceptibility of germ cells during spermatogenesis to damage.

A number of epidemiology studies show that certain paternal occupations, e.g. as a welder, painter, auto mechanic, greenhouse worker or fireman, involving exposure to metals, combustion products, solvents, or pesticides, are associated with altered sperm quality, and an increase in time to pregnancy, spontaneous abortions, birth defects, or childhood cancer. Life style exposures, such as paternal smoking, have been linked to an increased incidence of childhood lymphomas. Therapeutic drug exposures may also be of concern with respect to progeny outcome. After men are treated with anticancer drugs, there is a high incidence of transient or permanent infertility. The extent to which the sperm produced during recovery from chemotherapy are “normal” deserves further investigation. However, when these men have fathered children, the proportion of malformed children has not been higher than in control groups.

It is very difficult to associate a paternal exposure with a specific birth defect or childhood cancer since the numbers in the studies are normally low, exposure assessment methods are frequently imprecise, and the outcomes are rare; thus, the lower limits of the confidence intervals surrounding the risk estimates are often less than half a unit away from the null value. One should not automatically dismiss cause-and-effect relationships only on the grounds that they are small.

It is of concern that the germ cell line of progeny may be affected, thus increasing the risk for subsequent generations. Generally, the basic premise has been that the chemicals that are capable of affecting subsequent generations do so by inducing mutations in the germ cell genome. Studies with human populations and mice have provided evidence that paternal irradiation exposures result in elevated mutation rates in progeny. However, in recent years it has become evident that the male germ cell transmits more than its genome, as specified by DNA sequences, to the conceptus. In animal studies, there is a large gap between the generally low rate of genetic "damage" induced by many chemicals after the exposure of male germ cells and the associated adverse progeny outcomes. This gap has led to the hypothesis that a key mechanism by which chemical perturbation of sperm may lead to heritable alterations in progeny is epigenetic, i.e. the alteration of DNA function without affecting DNA sequence, regulated by modifications to histones (Chapter 9). Deregulation of the programming of the paternal genome may be responsible for altered expression of genes and impaired post-implantation development.

Future research is needed to elucidate the implications to public health of the finding in animal experiments that chemical exposures may have transgenerational effects. Nevertheless, there is already suggestive evidence from human studies indicating that this is possible. There are reports of altered sex ratios in children born after exposures to chemicals such as dioxins; one explanation for these observations could be an effect on the survival of Y bearing sperm. Defects in DNA methylation of paternally imprinted genes may contribute to imprinting errors and disease in children conceived with assisted reproductive techniques (ART), perhaps due to the in vitro culture conditions.

It is apparent from both animal and epidemiological studies that there are paternal exposures to chemicals that result in abnormal progeny outcome. Men exposed to certain chemicals because of their occupation should be made aware that there is concern with respect to an increased risk of adverse progeny outcome. Paternal counseling, after a chemical exposure or treatment with drugs that are known to be toxic to male germ cells, would be greatly facilitated by the development of a battery of new tests to detect the effects of exposure on sperm chromatin and function.

Handbook of Andrology – Can spermatozoa be targets for drugs?

Suggested reading

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