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PASSAGE OF CHEMICALS INTO HUMAN AND ANIMAL SEMEN: MECHANISMS AND SIGNIFICANCE

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I. GENERAL CONSIDERATIONS ON THE SECRETORY MECHANISMS IN THE MALE REPRODUCTIVE TRACT

The male reproductive tract offers no barrier to many chemicals of exogenous origin. A number of such compounds cross into the fluids secreted by the testes and male accessory organs of reproduction, and ultimately pass into semen. This peculiar behavior of the male reproductive tract is largely inherent in the nature of the secretory mechanisms which operate in it. Furthermore, though the bulk of the material secreted by the epithelia which line the reproductive tract is composed of soluble substances, some of the secretory fluids also contain a variety of so-called débris or particulate matter in various shapes and sizes, sequestered from the secretory cells in the course of their activity.

A. Apocrine and Merocrine Secretory Processes

Two distinct mechanisms, namely an apocrine and a merocrine one, govern the secretory function of the male reproductive tract in mammals. The extent to which these two processes contribute quantitatively to the secretory activity in the male reproductive organs is still a matter of dispute but, in any case, it is subject to considerable interspecies variations as pointed out and extensively discussed in our monograph.[1] The apocrine mechanism is the one in which portions of the cytoplasm are discharged by the secretory cells together with the soluble secretory products. The merocrine mechanism on the other hand, is one in which the secretory cells remain intact in the course of their secretory activity. It is the apocrine mechanism which is responsible for the discharge of the seminal débris which, in most cases investigated, was found to consist of membrane fragments and portions of the apical cytoplasmic matrix. It is also the operation of the apocrine mechanism which probably provides at least partial explanation for the presence in the seminal plasma of so many enzymes, including those involved in glycolysis, which ordinarily one tends to associate with the intra- rather than extracellular milieu of the body. But there can be no doubt that the merocrine mechanism is also important for full secretory function of the epithelia which line the male reproductive tract as shown, for example, by the detailed study of the secretory mechanism operating in the ventral lobes of the rat prostate.[2]

of chemicals into semen is that the extent to which the apocrine and merocrine mechanisms operate in the male reproductive tract is different in the testis, epididymis, vas deferens, ampulla, seminal vesicle, bulbourethral (Cowper's) gland, urethral (Littré's) glands and other parts of the tract. In this respect, there is a particularly marked difference between the mechanism underlying the secretion of the clear, watery, and protein-poor fluid by the testis, an organ characterized by a dependence on the blood-testis barrier, and that operative in glands such as the prostate or the seminal vesicle, which are largely responsible for contributing particular matter or cellular detritus, usually referred to as the "debris", to ejaculated semen. From this it follows that in order to assess properly and to interpret correctly the results of analysis of a chemical in seminal plasma (the composite mixture of all the secretions which constitute the liquid portion of ejaculated semen), the question must be asked whether this particular chemical has found its way into the ejaculate via testicular plasma (the fluid portion of testicular semen), epididymal plasma (fluid portion of epididymal semen), vas deferens and ampullary secretions, or the secretory fluids contributed to the whole ejaculate by the seminal vesicles, prostate, Cowper's gland, and Littré's glands, respectively.

B. Exogenous and Endogenous Origin of Secreted Substances

Yet another question to be answered is whether a given substance detected in semen is of exogenous or endogenous origin. A typical example of exogenous substances is provided by foreign substances, drugs for example, which having been ingested or injected, then have passed (either in their original form or as metabolites) into the tissues and body fluids, including the male reproductive glands and their secretions. Endogenous substances are natural products of the body; that is, metabolites which having originated in the body itself, but outside the male reproductive tract, subsequently crossed into the secretory fluids of that tract.

Relatively little attention has been given so far to the ways in which chemicals can reach whole ejaculated seminal plasma, and the possibility of interactions between chemicals in the seminal plasma and the ejaculated spermatozoa. This, in spite of the existence of a large and fast growing literature on the subject of pharmacological effects exerted upon male reproductive function as a whole, by a variety of foreign chemicals, including substances as far apart as antispermatogenic (antifertility) agents, antiandrogens, narcotics, pesticides, all sorts of chemotherapeutic and industrial compounds, food additives, and many other substances; the literature on this subject has been extensively and repeatedly reviewed.[1,3-11]

II. ENTRY OF CHEMICALS INTO THE TESTIS AND TESTICULAR SEMEN

A. Role of Blood, Lymph, and Scrotal Skin

There are several ways in which foreign chemicals are able to penetrate into the testis. Blood and lymph (after absorption from the gastrointestinal tract) are the most obvious vehicle. An alternative route is occasionally provided by the skin (after local application), as shown by the behavior of 'Tris-BP' (tris[2,3-dibromopropyl]phosphate), a major flame-retardant chemical used at one time extensively for impregnating childrens' clothing. This mutagen and carcinogen has been known (since 1977) to produce testicular atrophy and sterility in rabbits after cutaneous application and, more recently, 2,3-dibromopropanol, a metabolite of Tris-BP and a mutagen itself, has been found in urine samples of children who had been wearing Tris-BP-treated sleepwear.[12] Potential adverse reproductive effects of Tris-BP and similar compounds are of special concern to instance, a group of compounds widely used in agriculture as powerful insecticides, easily penetrate the skin of cattle. When applied to the hairy parts of a bull's skin, they produce only a minor and transient decline in motility of ejaculated spermatozoa, but application to the scrotal skin lowers much more distinctly the quality of ejaculated bovine semen.[13]

B. Inhalation as Route of Entry

Inhalation of a toxic chemical constitutes yet another route along which that substance or its metabolites might enter the blood and ultimately reach the testis. Inhaled 1,2-dibromo-3-chloropropane, a soil fumigant against nematodes, possesses marked antispermatogenic properties. It causes severe degenerative changes in animal testes and atrophy of germinal epithelium in factory workers who had been chronically exposed to it.[14–15] Screening tests performed on 71 workers showed that in 15 of the men employed in the production of dibromochloropropane there was severe oligospermia in semen; patchy hyalinization, but with some production of spermatozoa continuing, was the main histological finding in their testes. However, when the examination of semen was repeated 18 to 20 months after the last contact with the nematocide, significant improvement in the sperm count was noted in ejaculates, thus indicating that recovery of spermatogenesis is possible following withdrawal of dibromochloropropane.[16]

C. Permeability of the Blood-Testis Barrier and Passage of Chemicals into Testicular Plasma

Notwithstanding the function of the blood-testis barrier, a variety of chemical substances, including some antifertility drugs, pass into the testicular plasma — that is the fluid composed of the secretions originating in the seminiferous tubules, tubuli recti, rete testis ("rete-testis fluid") and ductuli efferentes — which provides the suspending medium for the testicular spermatozoa (the latter still immotile and infertile) at the point of their entry into the caput epididymidis. The accessibility of testicular plasma to a selective range of compounds has been demonstrated amply thanks to the availability of microsurgical cannulation and catheterization techniques which permit the collection of substantial amounts of fluid from different regions of the exocrine system of the testis.

For example, to obtain testicular semen from the ductuli efferentes of a ram, one uses a special catheter, about 30 cm long and 0.5 mm wide, which can be directly inserted into this portion of the exocrine system, thus enabling one to collect 1 to 2 mℓ testicular semen per hour, without seriously disturbing the ram's feeding habits and other functions. Similar methods are available for various other animals such as the bull, rabbit, hamster, and rat. For the collection of fluid directly from the seminiferous tubules of a rat, a micropuncture technique is used resembling in principle the standard technique employed in the examination of kidney function. In addition to a method for collecting free-flowing fluid from a whole seminiferous tubule of the rat, one can use a microsurgical technique specially devised for obtaining fluid from different segments of a single tubule. Using methods of this kind it has been possible to demonstrate that such diverse substances as ethanol, glycerol, a variety of steroids (testosterone in particular), α-chlorohydrin, iodoantipyrine, methanesulphonate, dimethylnitrosamine, barbiturates, and sulphonamides, cross the blood-testis barrier and reach the testicular plasma.[17–23]

The permeability of the blood-testis barrier is, however, by no means the sole factor on which the composition of testicular plasma is normally dependent. The events leading to the passage of inositol into the testicular plasma may serve as an example. The ram rete-testis fluid normally contains inositol at a concentration level about 100 times higher than in blood plasma. Yet, upon i.v. infusion of radioactive inositol, little if any of the radioactivity can be demonstrated in the rete-testis fluid. However, upon administration

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