EFFECT OF NITROFURAN PREPARATIONS ON SPERMATOGENESIS

I. F. Yunda and Yu. I. Kushniruk

UDC 612.616.2.014.46:[615.221.547.722.5

The effect of nitrofurantoin and furagin on spermatogenesis was studied in experiments on male albino rats. The preparations studied were found to have a specific gonadotoxic action. The processes mainly affected were spermiogenesis and the late stages of the cycle of the spermatogenic epithelium. These disturbances were accompanied by a decrease in the nucleic acid content in the cells, especially in the series of spermatocytes and spermatids. There was a parallel decrease in the concentration of spermatozoa and in the duration of their motility. Recovery from these disturbances took place only after a complete period of spermatogenesis although the number of tubules with desquamated spermatogenic epithelium continued to be increased.

Besides the main causes of disturbances of the reproductive function in the male, considerable importance is attached at the present time to the harmful effect of chemicals and drugs on spermatogenesis [4, 5, 10, 13]. In this respect special attention has been paid to 5-nitrofuran derivatives, the harmful effect of which on spermatogenesis has been known for a long time [14]. However, the mechanism, character, and persistence of the cell damage produced by these preparations have not yet been finally settled [3, 7, 13], so that it is impossible to estimate the degree of their harmfulness to testicular function.

The effect of nitrofurantoin (furadonin) and furagin on the spermatogenic function of the testis was accordingly studied in experiments to determine the character and persistence of the cell damage and also the RNA and DNA content in the cells of the spermatogenic epithelium.

EXPERIMENTAL METHOD

Experiments were carried out on 90 sexually mature male albino rats to which a suspension of the compounds for study was administered daily by gastric tube in therapeutic and toxic doses for 1 month. Control animals received drinking water in the same way. At the end of the experiment the animals were decapitated and the testes and their appendages removed. To verify the recovery of testicular function some rats were sacrificed 18 and 48 days later (the duration of spermiogenesis and spermatogenesis). The index of spermatogenesis [9], the mean number of spermatogonia per tubule (in 20 tubules), and the number of tubules with desquamated spermatogenic epithelium and with the 12th stage of meiosis (the metaphase of the second maturation division) was counted. To evaluate spermiogenesis the number of tubules containing spermatozoa in the various stages of development was counted. These last three indices were expressed as percentages of 100 tubules examined. Spermatozoa were studied in a suspension obtained from the tail of the epididymis [1]. DNA was detected by Feulgen's reaction and RNA by Brachet's method. Altogether 100 cells of each cell generation were studied entirely in tubules in stage VIII of the cycle of the spermatogenic epithelium.

EXPERIMENTAL RESULTS

The experiments showed that the nitrofurans, unlike antibiotics damaging the spermatogonia [6], had a harmful effect on the late stages of spermatogenesis. The processes of spermiogenesis were most

Clinic for Sexual Disorders, Kiev Scientific-Research Institute of Urology. (Presented by Academician of the Academy of Medical Sciences of the USSR, A. I. Cherkes.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 77, No. 5, pp. 68-70, May, 1974. Original article submitted June 20, 1973.

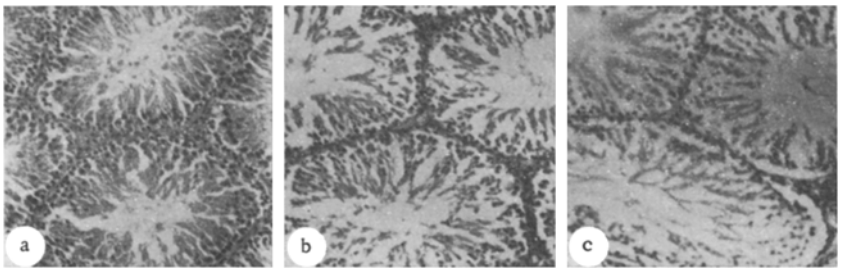

Fig. 1. Morphological changes in the spermatogenic epithelium under the influence of nitrofurans: a) testis of control rat; b) arrest of spermatogenesis in a rat receiving therapeutic doses of nitrofurantoin; c) the same in a rat receiving toxic doses of furagin. Hematoxylin-eosin, 220×.

severely affected, as shown by a reduction in the number of tubules containing spermatozoa. For instance, in animals receiving therapeutic doses of nitrofurantoin the number of these tubules fell to 43.5% below the control ($P > 0.01$), whereas in rats receiving toxic doses it fell by 50.3% ($P < 0.01$). Almost the same decrease in this index was observed in animals receiving therapeutic and toxic doses of furagin (by 42.95%, $P > 0.01$, and 55.2%, $P < 0.01$, respectively). The late stages of the cycle of the spermatogenic epithelium also were severely damaged, for in most of the seminiferous tubules spermatogenesis was arrested at the primary spermatocyte stage (Fig. 1).

The absence of the 4th layer (spermatozoa) and 3rd layer (spermatids) of the spermatogenic epithelium in some of the tubules led to a statistically significant decrease in the index of spermatogenesis, evidence of more severe disturbances in the testes [5, 6]. Despite the very small decrease in the number of spermatogonia in the experimental animals, the action of the nitrofurans on them must nevertheless be regarded as unfavorable. In turn, the damage to the spermatogonia and the spermatocytes developing from them led to the disappearance of these cells from the lumen of the seminiferous tubules, with the result that the number of tubules with desquamated epithelium was significantly increased. These changes corresponded to a marked decrease in the concentration of spermatozoa and a decrease in the period of their motility.

Histochemical investigations showed that the disturbances of spermatogenesis were accompanied by changes in the content and character of distribution of nuclear chromatin structures and of pyroninophilic granules in the cytoplasm, indicating a decrease in the RNA and DNA content of the cells. RNA was affected more severely, especially in the series of spermatocytes and spermatids. Since nucleic acids play an important role in the structure and function of the cell [2, 8, 12], the decrease in the nucleoprotein content observed in these circumstances was one of the important causes of the disturbance of spermatogenesis. The morphological and histochemical parameters studied returned to normal 48 days after the end of administration of the compounds, recovery taking place more slowly in the animals receiving the toxic doses. Even at the end of this period, however, the number of tubules with desquamated spermatogenic epithelium was still greater in the experimental animals by a statistically significant degree, which confirms the marked gonadotoxic action of the nitrofuran compounds studied.

LITERATURE CITED

1. G. M. Egorova, N. G. Ivanov, and I. V. Sanotskii, in: The Toxicology of New Industrial Chemicals [in Russian], No. 8, Moscow (1966), p. 33.
2. B. A. Ezdanyan, Morphological and Histochemical Changes in the Testis of the Albino Rat in Various States of the Organism and under Various Experimental Conditions, Author's Abstract of Candidate's Dissertation [in Russian], Moscow (1954).
3. V. M. Moshkova, General and Specific Action of 5-Nitrofurans, Author's Abstract of Candidate's Dissertation [in Russian], Moscow (1972).
4. I. V. Sanotskii, in: Pharmacology. Chemotherapeutic Substances. Toxicology, Problems in Pharmacology. Results of Science [in Russian], Moscow (1971), p. 107.
5. E. M. Chirkova, The Toxicological Characteristics of the Gonadotropic Action of Occupational Poisons (Some Immunocompounds, Organic Oxides and Peroxides, Halogenated Hydrocarbons, Benzene, Aminopyrimidine, Lead), Author's Abstract of Candidate's Dissertation [in Russian], Moscow (1970).
6. I. F. Yunda and Yu. I. Kushniruk, Antibiotiki, No. 1, 43 (1973).
7. L. Cieciura, Endokr. Pol., 13, 181 (1962).
8. R. Daoust and J. Clermont, Am. J. Anat., 96, 255 (1955).

9. L. C. Fogg and R. F. Cowing, Cancer Res., 11, 23 (1951).
10. B. W. Fox and M. Fox, Pharmacol. Rev., 19, 21 (1967).
11. C. P. Leblond and J. Clermont, Am. J. Anat., 90, 167(1952).
12. D. Mazia, Mitosis and the Physiology of Cell Division [Russian translation], Moscow (1963).
13. W. O. Nelson and D. Patanelli, in: Factors Acting on Fertility [Russian translation], Moscow (1970), p. 81.
14. J. T. Prior and J. H. Ferguson, Cancer (Philadelphia), 3, 1062 (1950).