EFFECT OF TESTOSTERONE, ITS 5α-REDUCED METABOLITES, ESTRADIOL, AND PROGESTERONE ON EXPERIMENTAL DUODENAL ULCER FORMATION IN MALE RATS

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Testosterone (TS), the principal circulating androgen in mammals, realizes its effects in target organs mainly through metabolites formed in those organs in the course of its biotransformation [5, 13]. In some organs and tissues (the pituitary gland, hypothalamus, and skin) concrete physiological functions of various TS metabolites have been discovered [4, 6, 9]. However, this problem remains virtually unstudied as regards the intestine, in which a relatively high level of TS biotransformation has been found [3]. This fact is very important because, on the one hand, the intestine because of its large area can make an important contribution to the whole peripheral school of androgens and can directly influence their plasma concentrations, and on the other hand, we know that peptic ulcer affects predominantly men with a high circulating TS level.

The aim of this investigation was to study the role of TS metabolites formed in the intestine in the genesis of duodenal ulcer.

EXPERIMENTAL METHODS

Experiments were carried out on noninbred male rats (from the Central Laboratory Animals Nursery, Academy of Medical Sciences of the USSR), weighing 120-150 g. An experimental duodenal ulcer was induced by means of cysteamine, by the method in [10]. For 6 days the animals received various doses of TS, dihydrotestosterone (DHT), 17β-estradiol (17β-E_2), 5α-androstane-3β,17β-diol (3β-diol), and progesterone (PR), all from Koch–Light Laboratories, England, 5α-androstane-3α,17β-diol (3α-diol) (from Sigma, USA, and androst-4-ene-3,17-dione (A-dione), from Fluka (Switzerland), dissolved in 200 μl of a mixture of olive oil and ethanol (9:1 v/v), by a single intraperitoneal injection (0.01, 0.1, 1, 10, 100, 250, 1000, and 2500 μl/kg body weight). Control rats received the same volume of solvent. On the 6th day, besides an injection of steroids, the rats were given a subcutaneous injection of a solution of cysteamine hydrochloride (Fluka) in a dose of 350 mg/100 g. The animals were decapitated 24 h after injection of the cysteamine, and the stomach with the duodenum was removed. The state of the duodenal mucosa was assessed visually with the aid of a binocular microscope. Small erosions of the mucosa were classed as erosive duodenitis (1 point). If single ulcers were present the lesion was rated at 2 points, multiple ulcers at 3 points and penetrating or perforating ulcers at 4 points. Individual scores for each rat were added together and the total number of points divided by the number of animals in the group, thus giving an index of severity of the lesion (ISL), expressed as the average score. The frequency of the lesion (FL) also was calculated as the ratio of the number of animals with ulcers to the total number of rats in the group, surviving until the time of reading the results. For convenience in overall evaluation of the effect of various substances on ulcer formation, an ulcer index (UI) was calculated as the sum of the indices of severity of the lesion and twice its frequency (UI = ISL + 2FL). The significance of the difference between the groups of rats, in the case of ISL, was estimated by the Student's t test.

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TABLE 1. Changes in Severity of Lesion (M ± m) and Ulcer Index (UI) in Male Rats under the Influence of Different Doses of Sex Steroids

Dose, μg/kg	TS		DHT		3α-diol		3β-diol	
	M±m	UI	M±m	UI	M±m	UI	M±m	UI
1	1,71±0,54	3,42 (7)	1,00±0,25	2,00 (10)	1,93±0,50	3,86 (6)	2,15±0,39	4,30 (6)
10	0,64±0,31	1,28 (10)	1,33±0,23	2,66 (9)	0,51±0,48	1,02 (8)	1,28±0,48	2,56 (10)
100	1,78±0,6	3,57* (8)	1,60±0,45	3,20 (5)	1,27±0,04**	2,70 (10)	0,99±0,27*	1,98 (10)
250	0,79±0,27*	1,58 (9)	all rats were killed		1,19±0,39**	2,39 (9)	0,49±0,37*	0,98 (9)
1000	1,69±0,42	2,38 (8)	the same		0,53±0,38*	1,06 (8)	0,90±0,45	1,81 (9)
2500	1,77±0,54	3,55 (8)	» »		1,19±0,42**	2,39 (8)	1,74±0,31	2,58 (8)

TABLE 1 (continued)

Dose, μg/kg	A-dione		17β-E_2		PR	
	M±m	UI	M±m	UI	M±m	UI
1	0,44±0,31	0,88 (9)	0,28±0,31	0,56 (7)	1,41±0,38	2,83 (9)
10	1,00±0,28	2,00 (8)	0,89±0,27	1,78 (9)	1,99±0,60	3,99 (8)
100	0,60±0,32*	1,20 (10)	0,67±0,35*	1,34 (9)	2,10±0,53	4,19 (6)
250	0,20±0,21*	0,40 (9)	1,00±0,26*	2,00 (11)	1,41±0,4	2,83 (9)
1000	0*	0 (8)	0,50±0,35*	1,00 (8)	1,71±0,6	3,52 (9)
2500	0,22±0,24*	0,44 (9)	0,44±0,31*	0,88 (9)	1,71±0,52	3,52 (9)

Legend. Number of animals in group shown in parentheses. Control values were 1.71 ± 0.31 (10) and 3.42, respectively. *P < 0.001-0.02; **P < 0.25 compared with control.

EXPERIMENTAL RESULTS

All the steroids except PR were able to prevent ulcer formation, as was shown by a decrease in the values of ISL and UI compared with the control, but the effect depended on the nature of the steroid and the dose given. In a dose of 1 μg/kg the greatest decrease in ISL and UI was given by 17β-E_2 and A-dione (ISL was 0.28 ± 0.31 and 0.44 ± 0.31, UI 0.56 and 0.88, respectively). DHT was sufficiently effective (ISL was 1.0 ± 0.25, UI was 2), but 3α-diol and 3β-diol did not inhibit ulcer formation in this dose. With an increase in the dose up to 10 μg/kg the steroids could be arranged in the following order of ability to inhibit ulcer formation: 3α-diol > TS > 17β-E_2 > A-dione > 3β-diol > DHT > PR (Table 1).

In a dose of 100 mg/kg A-dione and 17β-E_2 prevented ulcer formation more effectively than the other steroids (ISL was 0.6 ± 0.32 and 0.67 ± 0.35, UI was 1.2 and 1.34). In a dose of 1000 μg/kg A-dione completely prevented ulcer formation (ISL was 0, UI was 0), whereas 17β-E_2 and the diols were very effective in this respect (ISL was 0.50 ± 0.35, 0.53 ± 0.38, and 0.90 ± 0.45; UI was 1.0, 1.06, and 1.81 respectively for 17β-E_2, 3α-diol, and 3β-diol).

If the dose effect of each steroid (except DHT) are examined, the same general rule can be observed: the dose–effect curves are wave-like in character and have two minima in each dose range. We observed dose–effect curves of the same character for the action of TS and its 5α-reduced derivatives on the secretion of luteinizing hormone by the pituitary and the concentration of LHRH in the hypothalamus [2].

The report that TS stimulates proliferation in the rat intestine [12] suggests that the formation of TS derivatives, which is observed in the intestine [3], may be aimed, among other things, at intensifying this effect. According to our own data, A-dione (the principal metabolite of TS) causes the strongest antiulcerative effect, whereas 17β-E_2, which can be formed from A-dione or TS, reduces ILS and UI more strongly than the other steroids and in a smaller dose. This is in good agreement with the concept that the effects of androgens are realized through estrogens formed in the target organ by aromatization [7].

Estrogen therapy of duodenal ulcer was suggested more than 30 years ago, but it has not achieved widespread recognition because of the undesirable effects of feminization in men [11]. These results not only confirm the role of sex steroids (including 17β-E_2) in the pathogenesis of duodenal ulcer, but they also directly indicate that their metabolites are involved in this process. A further study of A-dione and the diols from this standpoint may be useful. A-Dione is almost as effective as 17β-E_2 in preventing the development of duodenal ulcer, but in this case it may not have such a powerful feminizing action. Androgens,

diols by nature, are known to have a mitogenic effect in other organs [8]. These compounds exhibit their antiulcer effect in very small doses, and as was shown previously, their metabolic products are excreted quite rapidly by the organs [1]. The study of metabolism of sex steroids in biopsy material from patients with duodenal ulcer would be of considerable interest in this connection.

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PREVENTION OF WOUND SUPPURATION

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Known methods of wound disinfection, including external aplication of antiseptic solutions, are only relatively effective. It will be evident that after abundant irrigation with antiseptic soltuions microorganisms will nevertheless remain in the tissues and will induce suppurative inflammation of the wound [1-6, 8].

The reason for intensive irrigation was that the agents of suppurative processes find in a wound favorable conditions for growth and multiplication, for necrotic tissues and blood clots are present there. Conditionally pathogenic bacteria, in dead tissues, are not exposed to the lethal action of factors of the cellular and humoral defense of the organism.

We have accordingly studied the action of 0.3% NaCl solution on the length of stay of conditionally pathogenic microorganisms in a wound. The safety and harmlessness of injection of 0.3% NaCl solution is not an antiseptic. The mechanism of the prophylactic action of the hypotonic solution is evidently associated with the effect of a combination of physical factors on cells of conditionally pathogenic microorganisms. The detailed investigation of the mechanism of its action is therefore indicated through the joint efforts of clinicians, microbiologists, and physicists.

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