SILATRANES AS STIMULATORS OF GRANULATION TISSUE DEVELOPMENT

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According to several reports [1-8] some silatranes with the formula X— $\overbrace{Si(OCH_2CH_2)_3N}$, where X = C_2H_5O, $(CH_3)_2CHO$, $ClCH_2$, etc., are able to stimulate the reparative function of connective tissue. This is evidence that the further study of the organosilicon compounds as stimulators of repair processes is promising.

To examine the mechanism of this effect, the action of two silatranes and of their possible *in vivo* metabolites on biochemical parameters of connective tissue in a state of active proliferation was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 48 albino rats weighing about 180 g, divided into 8 groups (6 animals in each group). As experimental model, a circular skin defect with an implanted transparent plastic ring, preventing epithelization, was used [9].

Compounds chosen for testing, namely 1-(chloromethyl)silatrane (I) and 1-(ethoxy)silatrane (II), and also triethanolamine (III) and (chloromethyl) triethyoxysilane (IV), were applied daily to the surface of the defect in the form of a 0.5% or 5% liniment. On the 7th day, when the granulation tissue (GT) in the defect had attained maximal development, it was taken for biochemical analysis. A system of combined quantiative biochemical analysis, suggested for the study of different types of connective tissue [9], was used. The results were subjected to statistical analysis by the method in [10].

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TABLE 1. Changes in Biochemical Parameters of GT under the Influence of Liniment Base

Parameter studied		Control	Base lanolin + castor oil)
Weight of tissue, g		1,17±0,01	1,85±0,03
DNA	g/100g of dried defatted tissue	2,91±0,66	2,11±0,59
RNA		2,73±0,25	2,38±0,22
Hydroxyproline		2,04±0,04	2,49±0,40
Tyrosine		2,17±0,05	2,53±0,56
Arginine		3,64±0,35	3,52±0,47
Hexosamines		0,57±0,08	0,80±0,30
Hexuronic acids		0,64±0,07	0,44±0,14
Hexoses		2,13±0,17	3,31±0,43
Sialic acids		0,71±0,12	0,81±0,05

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TABLE 2. Changes in Biochemical Parameters of GT under the Influence of Silatrane Liniments

Parameter studied		Lanolin + castor oil	Liniment with I		Liniment with II	
			0,5 %	5 %	0,5 %	5 %
Weight of tissue, g		1,85±0,03	2,39±0,05	2,34±0,29	1,58±0,17	1,47±0,15
DNA	g/100g of dried defatted tissue	2,11±0,59	2,17±0,16	2,70±0,46	2,71±0,17	2,67±0,59
RNA		2,38±0,21	2,57±0,26	2,83±0,36	2,88±0,66	2,91±0,15
Hydroxyproline		2,49±0,40	4,34±0,54	3,73±0,26	4,00±0,27	3,46±0,28
Tyrosine		2,53±0,56	2,96±0,31	3,12±0,61	2,66±0,54	2,67±0,37
Arginine		3,52±0,47	3,45±0,57	4,31±0,73	3,39±0,34	3,33±0,90
Hexosamines		0,90±0,30	0,99±0,15	1,06±0,15	1,07±0,09	0,79±0,16
Hexuronic acids		0,44±0,14	0,55±0,05	0,77±0,12	0,79±0,11	0,61±0,12
Hexoses		3,31±0,43	2,77±0,23	4,73±0,80	2,60±0,33	3,68±0,64
Sialic acids		0,81±0,05	0,70±0,06	0,79±0,08	0,77±0,03	0,70±0,09

TABLE 3. Changes in Biochemical Parameters of GT under the Influence of Liniments Containing 0.5% of III and IV

Parameter studied		Lanolin + castor oil	III	IV
Weight of tissue, g		1,85±0,03	1,71±0,06	1,41±0,18
DNA	g/100g of dried defatted tissue	2,11±0,59	4,07±0,59	2,60±0,37
RNA		2,38±0,21	2,80±0,34	3,05±0,39
Hydroxyproline		2,49±0,20	3,15±0,23	3,80±0,29
Tyrosine		2,53±0,26	2,00±0,10	3,18±0,46
Arginine		3,53±0,37	4,08±0,24	3,77±0,59
Hexosamines		0,90±0,03	1,03±0,15	1,16±0,21
Hexuronic acids		0,44±0,04	0,58±0,14	0,74±0,14
Hexoses		3,31±0,43	2,43±0,51	2,62±0,62
Sialic acids		0,81±0,05	0,70±0,10	0,83±0,07

EXPERIMENTAL RESULTS

The liniment base used (a mixture of lanolin and caster oil in the ratio of 1:3) itself stimulates GT development. This stimulating action was manifested as a marked increase in the weight of GT, and also a change in some biochemical parameters (an increase in the content of hydroxyproline, hexosamines, and hexoses), but the inflammatory changes were intensified under these circumstances (concentration of sialic acids increased) and the level of glycosaminoglycans essential for optimal collagen fibrinogenesis (hexuronic acids) was reduced (Table 1).

The silatranes studied, especially I, had a positive action on the biochemical parameters of GT compared with the action of the liniment base (Table 2). Against the background of a reduction of the inflammatory phenomena, collagen and noncollagen proteins accumulated. In addition, the whole reparative process was intensified through the stimulation of cell proliferation, as shown by an increase in the DNA content in GT. Synthetic processes in GT cells also were intensified, as shown by an increase in the content of RNA and also by glycoproteins and glycosaminoglycans.

A similar but less marked effect was produced by compound IV, which can be regarded as a silicon-containing fragment of the I molecule. Under its influence the content of collagen, noncollagen proteins, hexosamines, hexuronic acids, RNA, and DNA increased (Table 3).

Triethanolamine (III), a hydrolysis product of silatranes, and which also is a fragment of their molecule although not containing silicon, had no such activity. It increased only the quantity of collagen in the tissue a little, but did not reduce the content of noncollagen proteins, not did it change the sialic acid level compared with the pure control. Although the DNA concentration achieved its highest value under the influence of III, the intensified cell proliferation in this case was not accompanied by the formation of corresponding quantities of intercellular biopolymers necessary for optimal intermolecular relations and, consequently, for the biomechanical properties of HT.

The results of the experiments with III suggest that the biological activity of silatranes relative to proliferating connective tissue is essentially determined by the presence of sili-

con in their molecule. However, the much stronger activity of I and III than of IV is evidence that the most important role in the effective manifestation of the function of silicon belongs to its introduction into the silatrane group $\overset{\downarrow}{Si}(OCH_2CH_2)_3\overset{\downarrow}{N}$. Organosilicon compounds with this structure are much more active than acyclic compounds.

The results confirm that an essential component in the mechanism of the stimulating action of silatranes on the course of repair processes and, in particular, on wound healing, is their effect on the proliferative-reparative function of connective tissue. According to the principal biochemical parameter of "maturity" of developing GT, namely the collagen content, the best effect was caused by liniments containing 0.5% of compounds I and II. This indicates that the local application of excessive doses of silatranes is contraindicated.

ROLE OF PHOTOPERIODICITY AND THE CIRCADIAN RHYTHM OF GLUCOCORTICOIDS IN SYNCHRONIZATION OF FREE-RADICAL OXIDATION FLUCTUATIONS IN RATS

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The antioxidative activity (AOA) and content of products of free-radical oxidation (FRO) of lipids significantly affect many parameters of cell metabolism: the permeability of cytoplasmic membranes [4], activity of enzymes bound with them [2], and so on. Circadian fluctuations in FRO of lipids and AOA have been described in man [6] and rats [1]. However, the role of various factors in the synchronization of these rhythms remains undecided.

There is information in the literature on the connection between rhythm of AOA and FRO of lipids with mitotic activity of cells [1] and the state of the multipurpose oxidase system of the endoplasmic reticulum of the liver [5]. Among other factors influencing these rhythms and possibly under their control are corticosteroids [7], the distinct circadian rhythm of which has been described many times [3].

The object of this investigation was to study artifical modification of the circadian rhythm of glucocorticoids and the light-darkness cycle on AOA and the content of products of FRO of lipids in the liver and erythrocytes of rats.

EXPERIMENTAL METHOD

The role of photoperiodicity in the synchronization of the above-mentioned rhythms was investigated in experiments with reversal of the light-darkness cycle. Adult male Wistar rats were used. The conditions of illumination were 12 h of light:12 h of darkness in one chamber and 12 h of darkness(12 h of light in the other, regulated automatically with simulation of dawn and dusk for 3 h. Transitions to total darkness and light occurred at 6 a.m. and 6 p.m. The experiments were carried out before and 14 days after reversal.

In another experiment noninbred female albino rats were given a single daily intramuscular injection of hydrocortisone acetate in a dose of 250 µg/100 g for 16 days in the morning or evening. The time of the injections was synchronized with the time of switching the light on (8 a.m.) and off (8 p.m.). Control animals were given an injection of physiological saline at these same times. In this particular experiment a sudden change of illumination was provided during the transition from darkness to light and vice versa. The experiments were carried out in June and July.

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