does not increase during the period of the rhythm but, on the contrary, it has a tendency to fall.

Injection of thyroxine caused no significant change in the mean 24-hourly number of DNA-synthesizing cells compared with the control (469 ‰ on the 5th day and 454 ‰ on the 6th day). The 24-hourly pools of DNA-synthesizing cells differed only a little from each other (530 and 517 ‰) and from the control. During the 2nd day of the experiment some fluctuations were observed in the value of RI, but they were not significant. At all points of the investigation RI did not differ significantly from the control. Thus during administration of thyroxine also, changes in MI and RI with time were not synchronized.

The results of this investigation indicate that similar chronobiological principles govern the response of dividing tumor cells to the action of thyroxine as in the case of cells of normal tissues, and are expressed as rhythms of sensitivity of the tissues to this hormone. Meanwhile thyroxine has no appreciable effect on the number of DNA-synthesizing tumor cells, changes in which did not have the character of a circadian rhythm in either the control or the experimental animals. Cells characterized by rhythmic entry into mitosis cells entering the S period from the G_1 phase did so nonrhythmically and they had no such rhythm of sensitivity to thyroid hormone. Injection of thyroxine into animals likewise is not accompanied by an increase in the pool of dividing cells in EAT, whereas such an increase does occur in normal tissue [3].

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EFFECT OF *SCHIZANDRA CHINENSIS* LIGNANS ON CELL DIVISION IN THE CORNEAL EPITHELIUM AND TONGUE OF ALBINO RATS EXPOSED TO CHRONIC COLD STRESS

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KEY WORDS: stress; pathological mitoses; DNA synthesis; *Schizandra chinensis* lignans; adaptation.

In previous investigations the writers showed that chronic exposure to cold stress causes activation of DNA synthesis in the corneal and lingual epithelium of albino rats [6]. This phenomenon was interpreted as a structural trace of adaptation [5], aimed at restoring tissue homeostasis, when disturbed as a result of the damaging effect of stress [1, 7]. The increase in frequency of pathological mitoses (PM) was characterized as a cellular manifestation of disadaptation [10]. Data in the literature indicate that preparation of *Schizandra chinensis* (Chinese magnolia vine) alleviate the course of the general adaptation syndrome (GAS) and possess adaptogenic properties [4].

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TABLE 1. Effect of *Schizandra chinensis* Lignans on Cell Division in Corneal and Lingual Epithelium of Albino Rats Exposed to Chronic Stress (M ± m)

Exptl. conditions	Cornea				Tongue		
	MI, ‰	PM, %	ILN, %	LI	MI, ‰	ILN, %	LI
Control	4,4±0,3	5,3±1,4	7,6±0,5	18,7±2,3	7,9±0,9	4,8±1,1	17,4±3,3
Cold	10,3±1,1*	10,4±1,2*	10,7±0,6*	28,1±2,9*	9,2±1,1	8,1±0,5*	27,8±1,7*
Cold+ Schizandra	9,7±1,1	6,2±1,1	7,9±0,8	17,8±2,7	7±0,5	6,4±0,6	25,7±1,7*
Schizandra	11,7±0,5	5,6±0,4	12,7±1,3*	21,8±2,8	5,4±0,6	6,8±0,4	27,7±2,7*

Legend. *) Differences significant compared with intact control.

The aim of this investigation was to study the possibility of correcting cellular manifestations of disadaptation following chronic exposure to cold stress by means of preparations of *Sch. chinensis*.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 180-200 g. Four groups of animals were used: 1) intact control, 2) animals exposed to stress for 28 days, 3) animals receiving the *Schizandra* preparation for 28 days, 4) rats receiving the *Schizandra* preparation and also exposed to chronic stress. The model of chronic stress was cooling the animals daily for 1.5 h to a temperature of 28-30°C for 28 days by the method described previously [6]. Preparations of lignans were obtained from the seeds by the method in [3] and given perorally in a dose of 1 mg/kg [4] by means of a metal tube daily for 18 days before the animals were cooled, in the form of a 0.02% solution in aqueous alcohol. There was two versions of the experiment: In the first the controls were intact animals, in the second rats receiving a 1.9% aqueous solution of ethanol in a dose of 5 ml/kg, which served as the solvent for the lignans, through the tube. Since differences between levels of proliferation in the intact animals and in the rats receiving 1.9% ethanol solution were absent, values obtained in the group of intact animals are given in Table 1 as the control. The animals underwent euthanasia at 4 p.m. (48 h after the final exposure to cold). The rats received an injection of [^{3}H]thymidine in a dose of 0.6 μ Ci/g (47 kCi/mmole) 1 h before sacrifice. The corneas were incubated at 37°C in medium 199 with [^{3}H]thymidine (2 μ Ci/ml) for 1 h. Histological preparations of the cornea and tongue and autoradiographs were obtained and the mitotic index (MI), PM level, index of labeled nuclei (ILN), and labeling index (LI) were determined by methods described previously [2, 8]. MI was expressed in promille, PM as a percentage of all mitoses, ILN as a percentage of the total number of cells in the stratum basale, and LI as the mean number of tracks above a labeled nucleus. Altogether 56 animals were used in the experiments. The results were subjected to statistical analysis by Student's test.

EXPERIMENTAL RESULTS

The results (Table 1) confirm those of the writers' previous studies of stimulation of DNA synthesis and mitotic activity in the corneal and lingual epithelium of albino rats during chronic exposure to stress [6]. ILN in the corneal and lingual epithelium was increased by 1.4 and 1.7 times respectively. In both tissues LI, reflecting the rate of DNA synthesis, increased. Activation of DNA synthesis was accompanied by a corresponding increase in the value of MI in the cornea. The PM level, used as a test of cellular disadaptation, was increased in this case by 1.8 times. Administration of the *Schizandra* lignans into intact rats caused activation of DNA synthesis, manifested as an increase in ILN in the corneal epithelium by 1.7 times and LI in the tongue by 1.5 times.

Stimulation of cell division by lignans and chronic exposure to stress undoubtedly differ in nature. This is confirmed by stability of the PM level in the cornea of rats receiving *Schizandra* lignans. Stimulation of cell division by preparations of *Schizandra* is evidently based on the general acceleration of the cell cycle. Regarding the nature of activation of DNA synthesis during chronic stress, the writers have postulated its compensatory character [1, 7]. Stimulation of DNA synthesis under these conditions is aimed at normalizing tissue homeostasis when disturbed as a result of death of some of the cells during stress [1, 7]. Evidence in support of this view is given by elevation of the PM level. Administration of the adaptogenic preparation to rats exposed to chronic stress led to complete normalization of DNA synthesis in the corneal epithelium. The increase in MI in the cornea in this

version of the experiments was evidently due to changes in the circadian rhythm of mitosis [9] or other mechanisms [6]. It must be emphasized in particular that the PM level of stressed rats receiving *Schizandra* lignans was the same as in the intact control. In the lingual epithelium of the animals administration of the lignans led to normalization of the number of DNA-synthesizing nuclei, but LI remained increased.

Elevation of the PM level during exposure to stress exceeding the powers of adaptation of the animal, and also in the decompensated version of the GAS, was interpreted by the writers as a structural trace of disadaptation [10]. The ability of *Schizandra* lignans to prevent elevation of the PM level in stress is interpreted as a cellular manifestation of its adaptive properties. The absence of activation of DNA synthesis in the corneal epithelium, and also the weakening of this effect in the tongue can be explained as follows. By alleviating the course of the GAS during chronic exposure to cold, the *Schizandra* preparation weakened the harmful effect of stress, reduced cytolysis, and thereby abolished a powerful stimulus for cell proliferation. However, this hypothesis requires further experimental analysis.

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INDUCTION OF SENSITIVITY OF FIBROBLAST CULTURES TO PITUITARY GROWTH HORMONE BY A THERMOSTABLE SERUM FACTOR

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Many facts have now been published that have led to a critical attitude toward the generally held view that the mechanism of stimulation of growth processes by pituitary growth hormone (GH) is mediated by somatomedins. The direct effect of GH on growth of certain cells in culture [10] and also on growth of cartilage and bone tissue [11] has been described. Specific receptors for GH have been found in chondrocytes [9]. Acceptance of the direct growth-stimulating effect of GH on cells, it must be pointed out, does not exclude participation of somatomedins in the mechanism of its action, but through local (intracellular or intratissue) and not by distant mediators.

The possibility of stimulation of growth processes by GH in cell cultures provides the investigator with a convenient model with which to study the growth-stimulating activity of GH *in vitro*. To study the mitogenic activity of various growth factors cultures of fibroblasts are widely used [4, 8]. It has been shown that preparations of GH belonging to dif-

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