

CELL DIVISION IN SOME MOUSE TISSUES AFTER ADMINISTRATION OF HYDROCORTISONE

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Hydrocortisone acetate was administered to mice for 6 days. The mitotic activity and duration of mitosis in the corneal epithelium during the morning and afternoon were unchanged. In the evening hydrocortisone accelerated mitotic cell division. There was no change in the number of cells beginning mitosis. Administration of hydrocortisone both accelerated mitosis and increased the number of cells starting to divide in the epithelium of the lower surface of the tongue. In the evening the stimulant effect of the hormone was much stronger than in the morning. The glucocorticoid hormone hydrocortisone can thus stimulate the entry of cells into mitosis and the process of mitosis itself; the intensity of the effect depends on the sensitivity of the tissue and on the time of day or night.

Adrenocortical hormones have a significant effect on the intensity of cell division in various tissues. It is generally accepted that glucocorticoids are inhibitors of cell division. However, tissues differ in their sensitivity to cortisone. Alov [1] found, in particular, that the mitotic index in the corneal epithelium decreases only after repeated injections of cortisone, whereas in the epithelium of the tongue the number of cell divisions is unchanged. Investigations by autoradiography have shown that changes in the mitotic cycle differ in severity in different tissues after administration of glucocorticoids [2, 3, 6, 7, 14]. These investigations showed that the main effect of glucocorticoids was to reduce the number of cells entering into the phase of DNA synthesis and to reduce the intensity of DNA synthesis. These results were obtained after administration of a single dose of hydrocortisone. There is no information in the literature on the effect of glucocorticoids on the parameters of the mitotic cycle, including the duration of mitosis, during their prolonged administration.

The object of this investigation was to study the effect of hydrocortisone on the duration of mitosis in the corneal and lingual epithelium of mice.

EXPERIMENTAL METHOD

Male mice weighing 25-30 g were used. Every morning for 6 days 38 mice received an intraperitoneal injection of hydrocortisone acetate in a dose of 15 mg/100 g body weight. The control group consisted of 30 mice. Control and experimental animals were sacrificed in groups of 3-4 at a time at 10 a.m., noon, and 2, 6, 8, and 10 p.m. In addition, some of the control and experimental animals were injected with colcemid in a dose of 5 mg/kg at 10 a.m. and 6 p.m. and sacrificed 4 h after the injection. Mitoses were counted in total preparations of the cornea and in histological sections through the tongue. About 40,000 cells in the cornea and 6000-8000 cells in the basal layer of the epithelium of the lower surface of the tongue were counted. The duration of mitosis was calculated by comparing the mean mitotic index (MI) and the index of metaphases blocked by colcemid (MI_{COI}) during the period of investigation, i.e., 4 h, using the equation

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TABLE 1. Effect of Hydrocortisone on Cell Division in Corneal Epithelium of Mice at Different Times of Day ($M \pm m$)

Time of day	Control			Experiment		
	MI (in %)	MI _{col} (in %)	t _m (in h)	MI (in %)	MI _{col} (in %)	t _m (in h)
10 a.m.- 2 p.m.	16,8±2,2 n=8	34,5±4,2 n=7	1,9	17,1±2,4 n=11	34,1±5,5 n=9	2,0
6-10 p.m.	9,5±1,9 n=9	12,6±3,1 n=7	3,0	3,0±0,6 n=9	8,8±1,8 n=9	1,4

TABLE 2. Effect of Hydrocortisone on Cell Division of Epithelium of Lower Surface of the Mouse Tongue at Different Times of Day ($M \pm m$)

Time of day	Control			Experiment		
	MI (in %)	MI _{col} (in %)	t _m (inh)	MI (in %)	MI _{col} (in %)	t _m (in h)
10 a.m.- 2 p.m.	13,6±2,2 n=8	50,9±8,6 n=5	1,0	10,1±0,7 n=10	79,1±8,0 n=9	0,5
6-10 p.m.	4,5±0,4 n=9	6,2±1,0 n=5	2,9	3,7±0,5 n=8	20,1±4,1 n=5	0,7

$$t_m = \frac{MI \cdot t}{MI_{col}}$$

where t_m is the duration of mitosis (in h) and t the duration of action of colcemid (4 h).

EXPERIMENTAL RESULTS

The experimental results are given in Tables 1 and 2.

The values of MI in the epithelium of the cornea and lower surface of the tongue were higher in the morning and afternoon than in the evening ($P = 0,24$ and $P = 0,001$, respectively). Duration of mitosis was shorter at times of high mitotic activity and increased in the evening, when the number of mitoses in the intact animals was small. These results agree with those obtained previously [8]. In the mice receiving hydrocortisone MI in the corneal epithelium did not differ from the control in the morning and afternoon. There was likewise no change in the value of MI_{col} or the duration of mitosis. In the evening, MI in the corneal epithelium of the experimental mice was one-third of its value in the control ($P = 0,006$). However, MI_{col} was virtually identical in the experimental and control groups (difference not statistically significant, $P = 0,158$). It is therefore reasonable to conclude that the duration of mitosis in the corneal epithelium is reduced by the action of hydrocortisone.

MI in the epithelium of the lower surface of the tongue in the experimental group did not differ significantly from the control in either the morning or the evening. However, MI_{col} in the experimental group was 1.5 times higher ($P = 0,019$) in the morning and 3.2 times higher ($P = 0,006$) in the evening than in the control group. The stimulation of entry of the cells into mitosis was thus much stronger in the evening than in morning.

These results show that hydrocortisone differs in its effect on cell division in different tissues. In the corneal epithelium the number of cells entering into mitosis per unit time was unchanged and only the process of cell division was accelerated in the evening. In the epithelium of the tongue hydrocortisone increased the number of dividing cells and shortened the duration of mitosis.

At the same time it must be noted that these two tissues were much more sensitive to hydrocortisone in the evening. Variation in sensitivity to different preparations in the course of the 24-h period has also been observed for other tissues [4, 5, 9-11]. Presumably glucocorticoids differ in their action on cells in different phases of the mitotic cycle. If hydrocortisone and cortisone depress DNA synthesis, as is clear from the literature, they cannot activate the preparation of the cell for division.

In the G₂-phase of the mitotic cycle the ribosomal and messenger RNAs necessary for entry of the cells into mitosis are synthesized [13, 15]. Cortisone and hydrocortisone induce the synthesis of RNA and of several enzymes [12]. The possibility cannot be ruled out that hydrocortisone stimulates preparation for mitosis and activates enzymes participating in mitotic cell division.

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