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DIVISION OF STELLATE RETICULOCYTES IN THE RAT LIVER AFTER VAGOTOMY

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Diurnal fluctuations in mitoses in stellate reticuloendotheliocytes of the intralobular capillaries of the rat liver under normal conditions and after bilateral subdiaphragmatic vagotomy were investigated. The largest number of mitoses was found in all the animals during the morning, between 3 and 7 a.m. The number of mitoses in the vagotomized and laparotomized animals fell gradually until 10 p.m. After vagotomy the number of mitoses in the stellate reticuloendotheliocytes, just as in the hepatocytes also, was more than twice as high as in the control; the character of the curve reflecting the diurnal rhythm of mitosis in the denervated liver was the same as in the control.

KEY WORDS: reticuloendotheliocyte; mitotic index; hepatocyte.

Many surgeons who use the operation of selective subdiaphragmatic vagotomy for the surgical treatment of severe forms of peptic ulcer have recently become interested in the consequences of this operation and, in particular, its effect on the morphological and physiological state of the abdominal organs. Considering the practical importance of this problem, Eletskii and his colleagues [7-9] have studied the character of the morphological and physiological changes in the digestive glands of the subdiaphragmatic region after bilateral subdiaphragmatic vagotomy and, in particular, processes of compensation and proliferation arising in the denervated organs under these conditions. It has been shown, for instance [12], that vagotomy in rats does not lead to increased mitotic activity in the acinar cells of the exocrine portion of the pancreas. However, the worker concerned did not study the diurnal rhythm of mitosis in the denervated pancreas. The present writers showed previously that bilateral subdiaphragmatic vagotomy in rats leads to increased mitotic activity in the hepatocytes (low mitotic activity) and enterocytes (high mitotic activity) by roughly two to three times the control value. The character of the curve reflecting mitotic activity in the course of the 24-h period in these organs was unchanged after vagotomy (Fig. 1). A similar pattern of change in mitotic activity also was found later in the glandular cells of the exocrine portion of the pancreas [7].

Analysis of data in the literature and our own observations shows that the dynamics of diurnal rhythms of mitosis in the various organs and tissues has not only its similarities, but also considerable differences [1-3, 6]. According to certain observations [11], rhythms of mitosis in different tissues of the thyroid gland (the stroma and glandular cells) of adult rats, and also in the hepatocytes and Kupffer cells, exhibit tissue-specific features and differ from one another.

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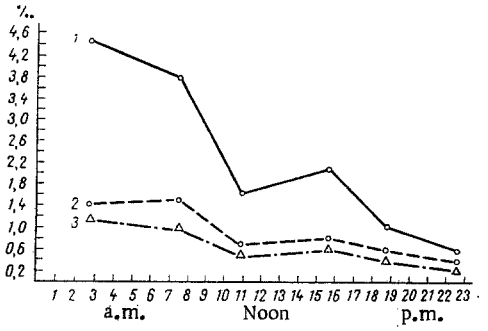

Fig. 1. Changes in number of mitoses in hepatocytes of normal and denervated rat liver: 1) vagotomy; 2) laparotomy; 3) control. Abscissa, time of day; ordinate, number of mitoses (in ‰).

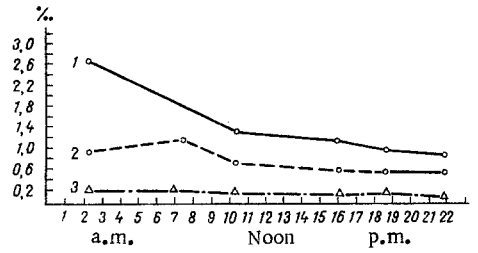

Fig. 2. Changes in number of mitoses in stellate reticuloendotheliocytes of normal and denervated rat liver. Legend as in Fig. 1.

TABLE 1. Number of Mitoses in Stellate Reticuloendotheliocytes of Normal and Denervated Rat Liver

Time of sacrifice of animals	Control		Laparotomy		Vagotomy	
	count 1	count 2	count 1	count 2	count 1	count 2
2:15-2:50 a.m.	0,21	0,2	1,15	1,07	2,73	2,6
7:15-7:45 a.m.	0,21	0,2	1,24	1,18	1,89	1,82
10-10:40 a.m.	0,17	0,15	0,76	0,7	1,49	1,30
3-3:40 p.m.	0,17	0,16	0,65	0,53	1,29	1,18
6:15-6:50 p.m.	0,16	0,16	0,51	0,5	0,80	0,79
10-10:35 p.m.	0,13	0,12	0,45	0,42	0,62	0,6

The object of this investigation was to study diurnal fluctuations in mitosis in the stellate reticuloendotheliocytes of the intralobular capillaries of the rat liver.

EXPERIMENTAL METHOD

Just as in the previous investigation [4] noninbred albino rats weighing 150-180 g were used. All the animals (135) were divided into three groups: the control group of rats (no operation), rats undergoing laparotomy, and rats subjected to bilateral subdiaphragmatic vagotomy. The animals of all three groups were kept under ordinary animal house conditions with natural lighting and free access to natural food and water. The rats were killed 1 week after the operation. Material for investigation was taken every 4 h during the 24-h

period: at 3, 7, and 11 a.m. and 3, 6, and 10 p.m. At each of these times seven or eight rats from each group were used. Mitoses in the stellate reticuloendotheliocytes were counted in 3000 cells in each animal. To determine the precise number of mitoses the colcemid method was used, for colcemid is known to block mitosis in metaphase. Colcemid was injected into all rats 4 h before sacrifice, in a dose of 3 μg/100 g body weight. The number of mitoses was counted under the immersion objective (objective 90, ocular 10). The numerical results were subjected to statistical analysis by the Fisher–Student method.

EXPERIMENTAL RESULTS

The largest number of mitoses in the stellate reticuloendotheliocytes was found (as also for hepatocytes) in all the animals in the morning, between 3 and 7 a.m. (Figs. 1 and 2). The number of mitoses in the stellate reticuloendotheliocytes of the vagotomized and laparotomized animals fell gradually until 10 p.m. As Fig. 2 shows, after laparotomy the number of mitoses in the stellate reticuloendotheliocytes rose only a little and was highest in the morning. The largest number of mitoses in the stellate reticuloendotheliocytes was observed in the animals after vagotomy. It must be emphasized in this case that the character of the curve (monomodal) remained the same as in the control, intact rats.

There is evidence in the literature [11] that the mitotic index in the stellate reticuloendotheliocytes of the liver may correlate with the number of hepatocytes examined in the field of vision. To obtain more reliable results, the mitoses were first counted in the stellate cells relative to the mean number of hepatocytes (1000 hepatocytes) (Table 1, count 1), after which the mitotic index was counted (this is given in Table 1 in promille) per mean number of stellate reticuloendotheliocytes (3000 cells) (Table 1, count 2). After comparing the two methods of counting it was concluded that the relative data on the character of the diurnal rhythm of mitotic activity in the stellate reticuloendotheliocytes was the same in both cases. Such a comparison is useful, having regard to the difficulties which arise when counting reticuloendotheliocytes. The results thus show that curves reflecting diurnal fluctuations in the number of mitoses in the various tissues of the liver in rats differ somewhat both in amplitude and in character. After vagotomy the number of mitoses in the stellate reticuloendotheliocytes, just as in the hepatocytes, was more than doubled; the character of the curve reflecting the diurnal rhythm of mitosis in the denervated liver, moreover, was unchanged compared with the control.

When the results of these experiments are analyzed it must be remembered that in the course of development of denervation changes in the organs after bilateral subdiaphragmatic vagotomy two periods can be distinguished: the first, covering the first 4–5 days after the operation, in which stress is the predominant phenomenon, and the second, starting after 1 week, when processes induced by vagotomy itself, i.e., by denervation of the organ, begin to appear [9]. In this period the ultrametabolic shifts in the denervated liver exceed the normal limits and destructive processes begin to predominate. These observations show that at this period the parallel development of compensatory and proliferative processes also is observed in the denervated liver, and as was stated above, they are expressed as an increase in mitotic activity in the various tissues of the parenchyma of the organ. The diurnal rhythm of proliferation in the tissues of the denervated liver was, however, unchanged. Characteristically, 1 week after vagotomy, the ability of the liver [5] and pancreas [9] to respond to their specific food stimulus is unchanged, although the intensity of physiological processes in the denervated organ is sharply reduced, for many reasons (disturbance of the circulation within the organ, destructive processes, and so on). In other words, 1 week after vagotomy the denervated organ tries to compensate for the catastrophic denervation situation in which it finds itself, by manifesting its ability to function and to proliferate.

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EFFECT OF SIGETIN ON ANOVULATION IN RATS

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The effect of sigetin on anovulation was investigated in experiments on sexually mature female rats. Anovulation was induced experimentally by stress (keeping the rats under overcrowded conditions) and by unilateral ovariectomy (hemicastration). Treatment with sigetin in a dose of 10 mg/kg for 4-5 days restored normal ovulation. If large doses of sigetin (up to 30 mg/kg) were given for longer periods (2-3 weeks) no such effect was observed. The results of these experiments suggest that sigetin, in small doses, stimulates the secretion of luteinizing hormone.
KEY WORDS: hemicastration; stress; anovulation; sigetin.

Research is in progress in the Department of Pharmacology, Institute of Experimental Medicine, Academy of Medical Sciences of the USSR, to obtain therapeutic preparations with a selective type of action on the hypothalamo-hypophyseo-ovarian system. One such compound is sigetin, the dipotassium salt of disulfomeso-3, 4-diphenylhexane, which is similar to dihydrostilbestrol but differs from it in chemical structure by replacement of two hydroxyl radicals by potassium sulfonate radicals. As a result sigetin has lost some of its properties as an estrogen (the peripheral proliferative action on tissues and organs) but has retained its ability to give a central inhibitory action on gonadotropic function [3, 5] and also some of its pharmacological properties as an estrogen, as a result of which sigetin can be used with success in obstretrics to improve the uterine and placental circulation and for the relief of intrauterine fetal asphyxia [2].

Nowadays, following investigations by Hungarian research obstetricians and gynecologists [4] and also experimental studies in the present writer's department, further information has been obtained of the mechanism of action of sigetin. In particular, it has been shown that by binding with specific estrogen-sensitive receptors, sigetin can prevent the action of estrogens on them [1, 4]. This property enables sigetin to be used in clinical obstetrics for the treatment of anovulation and sterility in patients with hyperestrogenemia [1].

The object of the present investigation was to study the action of sigetin on ovulation in rats when delayed by hypoluteinemia and a deficiency of ovarian hormones in the blood.

EXPERIMENTAL METHOD

Sexually mature female rats with experimentally induced anovulation were used. Anovulation was induced by stress (by keeping the rats in overcrowded cages). Various types of experimental stress are known to be effective and to cause inhibition of secretion of gonadotropins, especially luteinizing hormones, and to block ovulation. This inhibition of gonadotropic function is explained by activation of secretion of ACTH.

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