FUNCTIONAL STATE OF THE HEPATOCYTE MONO-OXYGENASE SYSTEM IN RATS WITH DISTURBED HEPATIC INNERVATION

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Truncal and selective vagotomy, widely used in the treatment of peptic ulcers, are accompanied by morphological changes and functional disturbances of the liver cells [3-5]. It is important to study the functional state of the cytochrome P-450-dependent mono-oxygenase system of the liver, which plays a leading role in the metabolism of xenobiotics and endogenous compounds [1, 12], when the innervation of the liver is disturbed.

The aim of the present investigation was to study some parameters of the mono-oxygenase system of the liver at different times after bilateral subdiaphragmatic vagotomy.

EXPERIMENTAL METHOD

Noninbred male rats weighing 180-200 g at the time of the operation were used. Bilateral subdiaphragmatic vagotomy was performed as follows. The right and left branches of the vagus nerves were divided in the region of the lower part of the esophagus, below the diaphragm, and a segment of the nerve trunks 1.5-2 cm in length was removed. Animals undergoing a mock operation (laparotomy) served as the control. When 14 or 25 days had elapsed after the operation, after starvation for 18 h, the rats were decapitated in the morning and microsomes were isolated from the liver cells by differential centrifugation [7]. Each sample consisted of a pool of microsomes isolated from the liver of three rats. The protein concentration in the microsomes was determined by Lowry's method [10], the cytochrome P-450 concentration by the method in [13], the rate of demethylation of aminopyrine by the method in [9], in the modification [2], the rate of p-hydroxylation of aniline by the method in [11], and the rate of oxygen uptake in liver microsomes after the addition of 1 mM NADPH by a polarographic method [5] on the LP-7 polarograph (Czechoslovakia). The duration of hexobarbital sleep was estimated by the time the rats remained in the lateral position after intraperitoneal injection of hexobarbital in a dose of 100 mg/kg [8]. Student's t test was used for statistical analysis of the results. Differences were considered significant at the $p < 0.05$ level.

TABLE 1. Parameters of State of Hepatocyte Mono-Oxygenase System of Rats Depending on Time after Vagotomy (mean values and standard errors) (M ± m)

Experimental conditions	Cytochrome P-450 concentration, nmoles/mg microsomal protein	Rate of demethylation of aminopyrine	Rate of p-hydroxylation of aniline, nmoles/min/mg microsomal protein	Rate of O_2 uptake	Duration of hexobarbital sleep, min
Control	1.87±0.05 (n=5)	5.40±0.07 (n=6)	0.80±0.04 (n=6)	16.19±0.16 (n=6)	13.2±1.01 (n_1=6)
Vagotomy:					
14 days	0.90±0.07 (n=5)	2.10±0.07 (n=6)	0.58±0.03 (n=6)	10.0±0.42 (n=6)	32.5±1.15 (n_1=6)
25 days	1.23±0.04 (n=5)	3.90±0.08 (n=6)	0.70±0.05 (n=6)	11.98±0.18 (n=6)	24.5±0.62 (n_1=6)

Legend. n) Number of microsomal samples in group; n_1) number of animals in group.

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EXPERIMENTAL RESULTS

To investigate each parameter of function of the cytochrome P-450-dependent enzyme system five experiments were undertaken. Their results are given in Table 1.

Table 1 shows that virtually all the cytochrome P-450-dependent reactions investigated (except p-hydroxylation of aniline) are inhibited by vagotomy. The original parameters recovered to some degree 25 days after the operation (when differences from the "Vagotomy 14 days" group were highly significant), but their control levels were not restored (differences also highly significant). A rather different picture was observed with p-hydroxylation of aniline. Although the rate of hydroxylation of this substrate was significantly reduced ($p < 0.02$) 14 days after vagotomy, the value of this parameter was increased 25 days after the operation, when no significant differences could be observed compared with either the control or the other experimental groups.

The results suggest that vagotomy has an effect on the state of the cytochrome P-450-dependent mono-oxygenases that is to a certain extent specific: it mainly depresses the function of the enzymes responsible for metabolism of type I substrates (in this case aminopyrine and hexobarbital). Reduction of the activity of these enzymes after vagotomy explains the fall in the values of the cytochrome P-450 concentration, measured spectrophotometrically, and the rate of oxygen uptake, characterizing the process of electron transport in the NADPH-dependent mono-oxygenase system. The effect on activity of mono-oxygenases metabolizing type II substrates (aniline) is evidently weaker.

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