study of the effect of HBO on intact lung tissue [8]. The schedule and duration of HBO chosen evidently created conditions under the circumstances of the investigation which, on the one hand, maintained the necessary level of activation of metabolism in the lung tissue [3, 9] and, on the other hand, were insufficient to give rise to toxic lung damage by oxygen. The stimulus obtained as a result of this procedure evidently facilitates the formation of a stable defensive and adaptive response at different levels, including the whole organ (lung), even in the presence of severe diffuse involvement of this tissue. Our results, confirm the previous concept, according to which HBO has an adaptive effect also in acute respiratory failure due to the development of the so-called "wet lung."

LITERATURE CITED

1. A. B. Aksel'rod, in: A Manual of Hyperbaric Oxygenation [in Russian], ed. S. N. Efuni, Moscow (1985), pp. 197-201.
2. A. P. Zil'ber, Artificial Ventrilation of the Lungs in Acute Respiratory Failure [in Russian], Moscow (1978).
3. A. N. Leonov, Hyperbaric Medicine [in Russian], Vol. 2, Moscow (1983), pp. 7-9.
4. B. K. Namazbekov, "Hyperbaric oxygenation in the prevention and combined treatment of suppurative complications of operations on the lungs and pleura," Dissertation for the Degree of Candidate of Medical Sciences, Moscow (1986).
5. N. K. Permyakov, The Pathology of Resuscitation and Intensive Care [in Russian], Moscow (1985).
6. "Indications for and contraindications to hyperbaric oxygenation," in: A Manual of Hyperbaric Oxygenation [in Russian], ed. S. N. Efuni, Moscow (1985), pp. 390-393.
7. G. G. Rogatskii, Yu. V. Isakov, E. A. Pisarenko, and V. A. Strokov, Anest. Reanimatol., No. 3, 60 (1980).
8. G. G. Rogatskii, P. P. Golikov, M. A. Sapozhnikova, et al., Patol. Fiziol., No. 1, 56 (1987).
9. L. L. Shimkevich, Hyperbaric Medicine [in Russian], Vol. 2, Moscow (1983), pp. 45-47.
10. E. G. Damon and R. K. Jones, Physiologist, 14, No. 3, 127 (1971).
11. K. J. Dobuler, J. D. Catravas, and N. Gillis, Am. Rev. Resp. Dis., 126, No. 3, 534 (1982).

PHARMACOLOGIC ANALYSIS OF CHANGES IN MORPHOLOGY AND FUNCTION OF ADRENERGIC STRUCTURES OF THE PANCREAS IN LESIONS OF ITS ENDOCRINE AND EXOCRINE DIVISIONS

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The role of the sympathetic nervous system (SNS) in the regulation of the exocrine and endocrine functions of the pancreas is generally accepted. However, its role in the development of the various pathological processes and their pharmacologic correction by sympathicotropic agents have been studied very inadequately.

The aim of this investigation was to undertake a combined morphologic, biochemical, and pharmacologic investigation of the adrenergic components of the autonomic innervation of the pancreas in various types of experimental pathology of its exocrine and endocrine divisions.

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EXPERIMENTAL METHODS

Experiments were carried out on 250 noninbred male rats weighing 180-200 g and on 160 male Chinchilla rabbits weighing 2.8-3.2 kg, obtained from the Rappolovo Nursery, Academy of Medical Sciences of the USSR. Damage to the pancreas was produced in three ways: in series I acute pancreatitis was induced by cooling the pancreas with a jet of ethyl chloride [1], in series II the endocrine part of the gland was exposed to the action of alloxan (100 mg/kg, intravenously), and in series III Pean's forceps were applied to the reflexogenic pyloroduodenal region for 15-20 min [5]. The noradrenalin (NA) concentration in the pancreatic tissue was determined biochemically [4] and by the Falck–Hillarp histochemical method with glyoxylic acid. Blood catecholamines were measured by the method in [3]. The creatine phosphate (CP) concentration in the pancreatic tissue also was investigated [8]. Blood levels of sugar [9], ketone bodies [6], and insulin were determined by a radioisotope method using kits from CEA-Sorin (France).

EXPERIMENTAL RESULTS

The histochemical investigations showed that the pancreas is rich in adrenergic fibers, which are located mainly in the walls of blood vessels, where they gave intense fluroescence in the control animals. In acute pancreatitis severe dystrophic changes were observed in the stroma and the exocrine part of the pancreas, although damage to the endocrine part was slight. There was a significant decrease in the number of fluorescent fibers per unit area, and the intensity of their fluorescence in all parts of the gland was reduced by half, and some of them became bead-shaped.

In the group of animals exposed to cold twice a day for 2 days and subsequently treated with benzohexonium, the intensity of fluorescence was significantly higher and was close to that observed in the control animals. Thus the use of the ganglion blocker prevented exhaustion of the mediator in adrenergic nerve structures developing during excessively strong stimulation of the pancreas.

In the case of damage to the endocrine part of the pancreas by alloxan, on the 30th day after its injection, when the animals had signs of diabetes, besides hyperglycemia and hyperketonemia, their immunoreactive insulin (IRI) level also was observed to be lowered and the blood catecholamine concentrations were raised, mainly on account of adrenalin. It can be tentatively suggested that the predominant increase in the adrenalin concentration was due to activation of its synthesis in the adrenals, for adrenalin gives rise to a stronger mobilizing effect than noradrenalin [7]. Single injections of the α-adrenoblocker dihydroergotoxin (0.066 mg/kg) or the β-adrenoblocker propranolol (3 mg/kg) into the animals did not cause any change in the blood IRI level. Meanwhile, in the control rabbits, α-adrenoreceptor blockade caused a fall, whereas β-adrenoreceptor blockade caused a rise of the IRI level in response to injection of adrenalin in a dose of 5 mg/kg. Desensitization of the adrenoreceptors of the islet cells to adrenalin during diabetes is evidently due to disturbance of carbohydrate and lipid metabolism, for we know that adrenoreceptors are related in their chemical structure glycoproteins that are incorporated into the cell membrane [7].

The histochemical study of the adrenergic structures of the pancreas showed that the intensity of fluorescence of the adrenergic plexus of the vessels in animals with alloxan diabetes was much weaker than in the control, and the number of varicose expansions was significantly reduced. The results are evidence that selective damage to the endocrine part of the pancreas gives rise to secondary morphological and functional changes in adrenergic nerve structures of the pancreas, which may play an essential role in the pathogenesis of disturbances of the functions of the gland as a whole.

Cathecholamine deprivation of the adrenergic structures of the pancreas also developed in another experimental model of pancreatic damage obtained by excessively strong stimulation of the reflexogenic zone of the duodenum, which is intimately connected by innervation and function with the pancreas. Biochemical tests showed that the NA level in pancreatic tissue 3 h after stimulation was only 4%, rising to 36% of the control value after 48 h. Administration of the NA precursor L-dopa, formation of which is the limiting stage of catecholamine biosynthesis [2], before stimulation prevented the fall of the NA concentration in the gland, whereas injection fo L-dopa for 2 days after the operation restored the NA concentration to the control level (Table 1). The positive effect of L-dopa indicates that the fall of the concentration of NA is the results of its inadequate resynthesis, compared with its excessive utilization. The protective action of L-dopa also was manifested in rela-

Table 1. Effect of Neurotropic Drugs on NA and CP Concentrations in Pancreatic Tissue of Animals Subjected to Stimualtion of the Pyloroduodenal Region

Substance tested, nmoles/g	Group of animals	Drug and time of injection	Control	Stimula-tion	Stimula-tion + drug	Drug alone
NA	Rats	Dopa (10 mg/kg) before stimulation	5,35±0,23	0,24±0,16*	5,10±0,10	4,60±0,30
		Dopa (10 mg/kg) for 2 days after stimulation	4,45±0,11	1,65±0,15*	4,38±0,15	4,73±0,14
CP	Rabbits	Dopa (10 mg/kg) before stimulation	0,36±0,02	0,05±0,02*	0,032±0,004	0,30±0,04
		Dopa (10 mg/kg) for 2 days after stimulation	0,22±0,02	0,10±0,02*	0,24±0,02	0,26±0,02
		Benzohexonium (10 + 5 mg/kg) before stimulation	0,25±0,05	0,03±0,01*	0,29±0,02	0,11±0,03*
		Atropine (1 mg/kg) before stimulation	0,49±0,03	0,09±0,02*	0,25±0,02	0,26±0,04*
		Phenoxybenzamine (15 mg/kg) before stimulation	0,29±0,03	0,04±0,02*	0,93±0,14*	0,15±0,04*
		Propranolol (10 mg/kg) before stimulation	0,40±0,01	0,05±0,02*	0,39±0,02	0,15±0,03*

Legend.. Sample for determination of NA contained pancreatic tissue from 4-6 animals. *$p \leq 0.05$.

tion to the tissue energy resources. The concentration of the high-energy compound CP in the pancreatic tissue 3 h after stimulation was 14% of the control level, but preliminary injection of L-dopa prevented its fall. Meanwhile, L-dopa was effective also when used after stimulation, i.e., when the imbalance of the tissue energy resources had already developed. Whereas the CP concentration in the pancreatic tissue of the animals 2 days after the operation was 45% of the control level,in animals receiving L-dopa after the operation, the CP concentration was identical with normal values (Table 1). There is reason to suppose that the beneficial action of L-dopa on the energy supply of the tissue is effected mainly through normalization of the NA level in the pancreatic tissue.

Other evidence of the important role of SNS in the development of pancreatic lesions induced by stimulation of the duodenal reflexogenic zone is given by the results of experiments involving the use of drugs preventing neurotransmission in the autonomic ganglia and synapses of effector organs. Preliminary injection of the ganglion blocker benzohexonium prevented the fall of the CP concentration induced by trauma to the pyloroduodenal region. The peripheral muscarinic chloinolytic atropine protected the pancreas insufficiently effectively against the development of a deficiency of energy resources in its tissue. Meanwhile the use of drugs preventing the conduction of sympathetic impulses showed that they have a distinct protective action. The α-adrenoblocker phenoxybenzamine and the β-adrenoblocker propranolol were shown to prevent exhaustion of CP in pancreatic tissue due to excessively strong stimulation (Table 1). To summarize the results of the experiments with peripheral neuroblockers it can be concluded that the last stage in the transmission of efferent impulses causing a disturbance of energy metabolism in the pancreas after stimulation of the pyloroduodenal region is composed mainly of sympathetic nerves. Participation of adrenergic mediation in the development of pancreatic lesions in response to excessively strong stimulation also was confirmed by experiments with NA. Intraperitoneal injection of large doses of this mediator (2.5 mg/kg) caused a sharp fall of the pancreatic tissue CP level by 83%, i.e,. the same as was observed during stimulation of the reflexogenic zone of the duodenum.

These results showed that some pathological processes in the pancreas, associated with damage to its endocrine and exocrine parts, are characterized by considerable morphological and functional changes in sympathicoadrenal structures. This suggests that the SNS plays an essential role in the etiology and pathogenesis of many pancreatic diseases, and that, consequently, their treatment and prevention by sympathicotropic drugs is a promising new development.

LITERATURE CITED

1. A. S. Kanayan, N. K. Permyakov, G. P. Titova, and K. P. Arabadzhyan, Arkh. Patol., 46, No. 4, 64 (1984).
2. M. Tulczinski (ed.), Laboratory Methods of Clincial Investigation [in Russian], Warsaw (1965), pp. 326-327.
3. S. Z. Langer, Neutrotransmitter Systems [Russian translation], Moscow (1982), pp. 38-59.
4. A. F. Maslova, Biokhimiya, 24, No. 2, 181 (1959).
5. É. Sh. Matlina and T. B. Rakhmanova, Methods of Investigation of Some Systems of Humoral Regulation [in Russian], Moscow (1967), pp. 136-141.
6. T. N. Nikova and N. N. Kuznetsova, Problems in Gastroenterology [in Russian], Erevan (1985), pp. 72-77.
7. P. Felig, Endrocrinology and Metabolism, McGraw Hill, New York (1981).
8. A. Ennor and H. Rosenberg, Biochem. J., 51, 606 (1952).
9. J. H. Roe, J. Biol. Chem., 212, 335 (1955).