tidylserine bonds in the MS itself, and also in the transport system at the level of components of CS, rather than slowing of the rate of GDH biosynthesis in MS. It is admitted that a central place in the mechanism chymotrypsin of labilization of these bonds is occupied by proteases (trypsin, chymotrypsin), the content of which in the pancreatic tissues and blood is substantially increased (three-fourfold). Additional indirect proof is given by the increase in the phosphatidylserine content (about twofold) in the pancreatic tissue.

Thus because of damage to membranes of the subcellular organelles of the pancreocytes in pancreatic necrosis, their function is disturbed and a phenomenon of "enzyme leakage" takes place [1], including leakage of GDH, into the cytosol, and subsequently into the blood stream and peritoneal cavity; this is an essential link in the chain of the pathobiochemical mechanism of damage and formation of acute pancreatitis.

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DETECTION OF SEQUENCES IN THE STRUCTURE OF INFLUENZA VIRUS PROTEINS SIMILAR TO VASOACTIVE INTESTINAL PEPTIDE

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In the course of their reproduction viruses utilize receptors of the host cell specific for certain neurotransmitters, including regulatory peptides. For instance, in order to infect B lymphocytes, Epstein–Barr virus utilizes the receptor [10], rubella virus uses the acetylcholine receptor [11], rheoviruses use the beta-adrenergic receptor [8], vaccinia virus the receptor of epidermal growth factor [9], and HIV virus uses the T4 receptor factor. These data indicate that viral proteins or their fragments can act successfully as agonists of many of the more important regulatory peptides.

This paper gives information on the discovery of amino acid sequences in the structure of influenza virus proteins similar to those of a regulatory peptide, namely vasoactive intestinal peptide (VIP). Comparison of these sequences is particularly interesting, first, because of the high concentration of receptors to this regulatory peptide in the upper respiratory tract, the lungs, and brain [14], i.e., of organs particularly intensively involved in influenzal infection, and second, because changes in the body observed following injection of VIP are similar to the pathological changes found in influenza.

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TABLE 1. Similar Amino Acid Sequences in Structure of VIP and in Structures of Proteins of Polymerases (PB1, PB2, PA), Hemagglutinin (HA1 and HA2), Neuraminidase (NA), Nucleoprotein (NP), Membrane (M1 and M2), and Nonstructural (NS1, NS2) Proteins of Influenza Virus

Parameter		VIP (1-28) 5 10 15 20 25 WSDAVFTCNYTRIRKQMAYKKYLNSILN	Degree of similarity (in SD units) and probability of incorrect conclusion on account of random similarity, per cent
PB1			
PB2			
PA			
HA1	(114—122)	DYEELREQL	4,99 SD 0,000025
	(128—131)	FERF	3,93 SD 0,003
	(128—131)	FERF	3,55 SD 0,01
	(175—180)	YPNLSK	4,12 SD 0,002
	(180—184)	KSYVN	4,01 SD 0,0025
	(210—215)	RKENAY	4,43 SD 0,0001
	(222—225)	NYNR	4,11 SD 0,001
	(236—252)	KVRGQAGRINYYWTLLR	3,65 SD 0,008
	(327—330)	TKLR	4,11 SD 0,0015
	(413—421)	EFDELEKRM	4,12 SD 0,0012
HA2	(463—470)	YEKVKSQL	4,5 SD 0,00008
	(500—505)	FYDYPK	3,67 SD 0,008
	(503—506)	YPKY	5,23 SD 0,00001
NA			
NP			
M1	(77—85)	RRFVQNALN	4,3 SD 0,0005
	(100—109)	YRKLKREIT	5,7 SD 0,000001
	(130—134)	LIYNR	3,8 SD 0,003
	(160—165)	RSHRQM	3,8 SD 0,003
	(229—233)	LKNDL	3,6 SD 0,009
M2	(36—40)	LHLIL	3,5 SD 0,007
	(48—53)	FKCIYR	5,6 SD 0,00001
NS1	(17—23)	HVRKQVA	4,34 SD 0,001
	(35—39)	RLRRD	4,79 SD 0,00008
	(62—70)	KQIVERILK	3,69 SD 0,004
	(124—139)	MDKNIILKANFSVIFD	3,62 SD 0,005
	(232—236)	RNKMA	3,5 SD 0,007

EXPERIMENTAL METHOD

Influenza virus A/USSR/77 (HlN1), whose primary protein structure has been decoded [1, 5], was used as the original material.

The search for identical sequences between VIP and influenza virus proteins was conducted by computer analysis. This kind of computerized search for similarity in two or more amino acid sequences is quickly becoming an important tool for research in molecular biology.

The computerized search for similarities in the primary structure of proteins is based on a "system of weights," characterizing the possibility of replacing one amino acid by another (including by itself), for similarity of fragments of sequences signifies that the amino acids of one fragment correspond to the amino acids of another fragment in the order of their sequence; the greater the total of the weights for replacement, the greater the similarity. It is interesting that a high weight of replacement signifies preservation of the replaced amino acid in one sense or other.

There are four basic approaches to construction of a matrix of weights: 1) a single matrix; 2) a matrix based on the genetic code; 3) a structural genetic matrix; and 4) a Dijkhoff matrix. This last matrix of weights, modified by Staden, enjoys the greatest popularity. We also shall use it in the present study.

The search for local similarities between influenza virus proteins and a number of neuropeptides is based on an idea put forward initially in [7]. During successive advance of a neuropeptide along a protein, we can distinguish regions for which there is minimal probability of obtaining similarity corresponding to these regions (the sum of the weights for replacement) accidentally. Thus any widening or narrowing of the corresponding regions will lead to an increase in probability that similarity was obtained due to random causes. This algorithm having been realized, we can precisely indicate the boundaries of the regions of similarity and the probability of obtaining such similarity through random causes (the probability is indicated in units of standard deviation of the standard normal distribution). The exact indication of the boundaries of the regions of greatest similarity is the

main advantage of this algorithm compared with traditional algorithms for searching for local similarities by the examination of fixed-length windows.

In the present study we used a program of rapid search of maximally nonrandom regions of similarity of two sequences, written in "SI" language for a computer of the class whose algorithm was presented at the Third All-Union Working Conference on Computerized Methods and on a Databank for Molecular Biology [2]. To construct a complete map of local similarity of two proteins, each with 200 amino acids, for this program requires 50 min of computer time, with a frequency such as 4 (vgHz). The program picks out all similar fragments of the two sequences whose probability of random similarity is below the level assigned by the user.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that no amino acid sequences similar to VIP were found in the protein structure of the polymerases (PB1, PB2, PA), in neuraminidase (NA), or nucleoprotein (NP). Several regions of amino acid sequences similar to VIP (with different degrees of similarity, expressed by the value of SD) were found in the structure of hemagglutinin (HA1 and HA2) and of membrane (M1 and M2) and nonstructural (NS1) proteins. For instance, about 13 regions with an amino acid sequence similar to that of VIP were found in the hemagglutinin molecule: nine regions in the structure of HA1, located mainly in its receptor part (from 115 to 230 aa); four regions in the structure of HA2. It is interesting to note that most of the above-mentioned regions in the structure of HA1 and HA2 have similarity with the C-part of the VIP molecule (from 10 to 28 aa) and that only one region in the structure of NA2 (from 500 to 505 aa) has similarity with the N-terminal part of the VIP molecule.

Regions with similarity to VIP also were found in the structure of influenza virus membrane proteins M1 and M2. In most cases these regions also were similar to the C-terminal part of the VIP molecule, with the exception of one region in the structure of protein M2 (from 48 through 53 aa), which had a similar fragment in the N-terminal part of the VIP molecule.

For nonstructural influenza virus proteins NS1 and NS2 a region similar to the C-terminal part of VIP was found only in the structure of NS1.

Thus sequences common with the VIP molecule were found in the structure of three of the eight influenza virus A/USSR/77 proteins studied (HA, M, and NS). What can be the functional significance of these groups of amino acid residues common with VIP in the structure of influenza virus proteins? We know that VIP causes relaxation of smooth muscles of blood vessels and the respiratory passages. A similar picture is observed in the host in the case of influenzal infection. Hence it can be postulated that the similarity between the manifestations of the action of VIP and of influenza virus on the body is due to the presence of common amino acid sequences in the structure of influenza virus proteins and the VIP molecule, although this hypothesis requires experimental confirmation. Besides the properties of VIP listed above, in recent years information has been obtained to show that VIP is connected with the immune system. It has been shown, for instance, that the C-part of the VIP molecule (from 14 to 28 aa) depresses activity of natural killer cells, and that a pentapeptide TCNYT, with the property of agonist for the T4-receptor, is located in the N-terminal part of the molecule [13, 14]. It has also been found that VIP has an immunodepressive action similar to the action of HIV (human immunodeficiency virus), and a similar pentapeptide TCNYT has also been found in the structure of the membrane protein of HIV (gp120) [13]. It was shown above that a similar fragment is found also in the structure of influenza virus proteins and, in particular, in the molecule of the HA2-conservative part of hemagglutinin (from 500 through 505 aa), and in membrane protein M2 (from 48 through 53 aa). Of course there are as yet no grounds for asserting that because the influenza virus has in its protein structure a fragment similar to pentapeptide TCNYT from the amino acid sequence of VIP, it possesses similar immunodepressive properties, although the fact that immunodepression exists in association with influenzal infection is beyond dispute [6, 12].

The discovery of sequences similar to interleukin-2 in the N-region of the hemagglutinin of several different strains of influenza virus is further proof of the functional role of these domains in the realization of the mechanisms of immunodepression during influenzal infection [3].

It is also important to note that the immunodepressive action of influenza virus, by analogy with data obtained for HIV [10], may be not only the result of viral infection, but also the result of accumulation of degradation products of viral proteins in the host's blood. This concept deserves particular attention in connection with the use of killed influenza vaccines in practice.

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FUNCTIONAL CHARACTERISTICS OF CHEMICALLY MODIFIED HEMOGLOBIN DURING CIRCULATION IN THE BLOOD STREAM

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Research into the production of an artificial oxygen carrier (AOC) based on chemically modified hemoglobin (Hb) has led to the obtaining of several compounds possessing oxygen-transport characteristics close to the properties of normal human blood, and capable of remaining for a long time in the blood stream [1, 6, 8]. The most widely used of these Hb derivatives is polyhemoglobin (PHb), which contains in its composition a covalently bound regulator of reversible oxygenation, namely pyridoxal-5-phosphate (PP) [5, 7], and which several workers regard as a potential AOC [4, 8]. One of the principal conditions for its suitability as an artificial substitute for erythrocytes, besides its long life in the blood stream, is the fact that its initially high functional activity remains unchanged during circulation, and it is this feature which determines its ability to maintain pO_2

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