PHARMACEUTICAL SCIENCES

SOME EXAMPLES OF THE USE OF INTERDISCIPLINARY CONNECTIONS IN TEACHING BIOORGANIC CHEMISTRY TO FUTURE DOCTORS

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Modern biology, chemistry, medicine and pharmacy know compounds containing S-S and Fe-S bonds. The biological role of these compounds is significant and cannot be overestimated. When studying "Bioorganic Chemistry", we draw the attention of students of the specialties "Medicine", "Pediatrics", "Dentistry" to the mechanism of disulfide bond formation when considering the topics "Alcohols and thioalcohols", "Proteinogenic amino acids, peptides, proteins", "Heterocyclic

compounds". We consider it expedient to use the interdisciplinary connections of bioorganic chemistry with medical and biological chemistry, pharmacology, endocrinology and other disciplines, which we have decided to cite on specific examples. So, when considering the topic "Alcohols", we focus on thioalcohols and their features. Thiols (thioalcohols) are oxidized to dialkyl disulfides under mild conditions:

$$2C_2H_5 – SH \rightarrow H_5C_2 – S – S – C_2H_5.$$

This reaction is reversible - under the action of reducing agents, the disulfide turns into two thiol molecules:

$$R – S – S – R + 2\,[H] \rightarrow R – SH + HS – R.$$

When considering the topic devoted to proteinogenic amino acids and proteins, we pay attention to the structure of cysteine. Cysteine (containing a thiol group) upon oxidation forms cystine (the structural fragment is a disulfide bridge that forms the tertiary structure of the protein). When studying this topic, we focus the attention of students on the peculiarities of the formation of disulfide bonds. Disulfide bridges are formed during the oxidation of the protein molecule of amino acid cysteine residues, giving the polypeptide chain a coiled shape. Disulfide bonds are important in the formation of the tertiary structure of proteins. The destruction of these bonds leads to the destabilization of this level of structure and the protein's loss of its biological activity.

Among the functional groups of protein molecules are sulfur-containing groups (sulfhydryl (thiol –SH) group of cysteine, disulfide group of cystine, and thioester group of methionine), which are characterized by high reactivity and a variety of chemical reactions. Compounds with such groups are reactive, namely, they can undergo a wide range of chemical reactions, including alkylation, acylation, oxidation, thiol disulfide exchange, formation of semimercaptals, mercaptides, mercaptols, and charge transfer complexes. The reactivity of the SH group in native proteins varies widely. On this basis, three types of thiol groups are distinguished: 1) easily accessible, 2) less accessible and 3) "masked". SH-groups of the first type easily react with sodium nitroprusside and mild oxidizing agents (ferricyanide,

iodobenzoate). Thiol groups of the second type do not give a nitroprusside reaction and interact with rather strong oxidizing agents (iodine) and mercaptoforming agents. The "masked" include thiol groups, which can be detected only after protein denaturation.

It is known that there are two general types of disulfide bonds: structural and functional. As was traditionally believed until recently, only structural disulfide bonds belong to proteins secreted into the bloodstream. Intramolecular disulfide “links” additionally stabilize the native conformation of secretory proteins in the extracellular environment. It is believed that structural S-S bonds formed during thiol-disulfide transitions during renaturation or post-translational processes contribute to the correct folding of the protein, reducing the entropy of its unfolded form. Some disulfide bonds in the structure of secretory proteins play a functional role: there are two types of functional disulfides: catalytic and allosteric. The catalytic bond has been well studied so far. It is typical of the active sites of enzymes that provide thiol-disulfide metabolism in other proteins. These enzymes belong to the class of oxidoreductases. Allosteric bonds have been discovered only recently.

They have been found to control protein function through their key role in shaping the active/inactive conformation of a protein, providing a change in structure by reduction or oxidation.

Disulfide bonds play an important role in ensuring the folding and functioning of secretory proteins.

These bonds are critical in stabilizing the final protein structure, as cysteine mispairing can prevent proteins from reaching their native conformation or even misfold the polypeptide chain. It is traditionally believed that reversibly denatured proteins restore their original conformation when transferred to a suitable environment. However, the denaturation process not only contributes to the undesired convergence of individual reactive groups, the exposure of previously hidden amino acid residues, but also causes the formation of new covalent bonds.

The presence of free thiols facilitates the course of thiol-disulfide exchange reactions with the formation of new intermolecular disulfide bonds, resulting in

protein aggregation. A mandatory additional condition for accelerating the formation of “correct” disulfide bridges is the optimization of the environment: the redox state of the buffer, temperature, disaggregant compounds and secondary structure stabilizers. It is known, for example, that human plasminogen easily forms aggregates in an acidic environment that are almost insoluble in neutral medium.

Disulfide bridges are present in the structure of the disulfide form of lipoic acid, a biologically active substance with vitamin activity, a coenzyme involved in redox processes and oxidative decarboxylation of oxoacids.

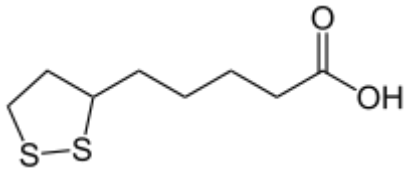

Fig. 1 Disulfide form of lipoic acid

Disulfide bridges are part of the pituitary hormones oxytocin and vasopressin.

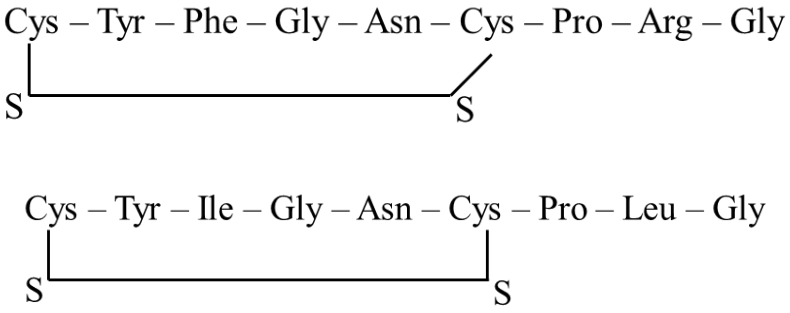

Fig. 2 The structure of vasopressin and oxytocin

The common structural element of these hormones is a peptide (containing nine amino acid residues with a disulfide bond between the fourth and ninth). These hormones differ only in two amino acid fragments: instead of leucine and isoleucine in oxytocin, vasopressin contains arginine and phenylalanine. It is the connection between structure and biological activity that we pay attention to when considering the topic “Proteinogenic Amino Acids. Peptides and proteins”. A slight difference in the structure of nonapeptides (differing by only two amino acids) determines the specific activity of each of these hormones.

Vasopressin (antidiuretic hormone) is a neurohypophyseal hormone synthesized in many mammals. Its main functions are water retention in the body and

narrowing of blood vessels. It plays a key role in homeostasis, regulating the level of water, glucose and salt in the blood. Vasopressin is an active stimulant of mental activity. It is produced in both female and male bodies. In contrast, oxytocin is produced only in the body of women. It is a hormone of the paraventricular nucleus of the hypothalamus that is transported to the neurohypophysis (posterior pituitary gland), where it accumulates and is released into the bloodstream. It has a stimulating effect on the smooth muscles of the uterine muscles.

A striking example of a biologically active compound containing several disulfide bonds is the pancreatic hormone insulin, which is constructed from two polypeptide chains: chain A (21 amino acids) and chain B (30 amino acids) - these chains are connected to each other by two disulfide bridges (due to thiol groups of cysteine); the third disulfide bridge is formed between two cysteine residues in chain A.

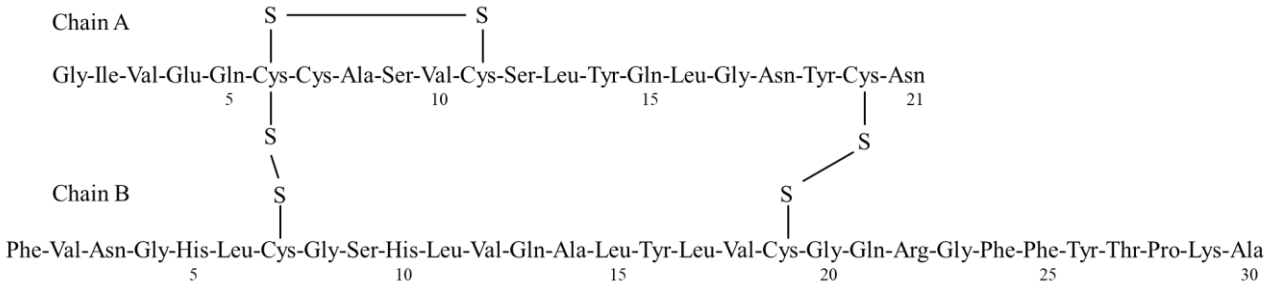

Fig. 3 The structure of insulin

Another interesting example of a biologically active compound with a disulfide group is a drug used to treat alcohol withdrawal syndrome - disulfiram (teturam, esperal, bis(diethylthiocarbamoyl) disulfide, 1,1',1",1'"-[disulfanedilbis (carbonotoylnitrilo)] tetraethane).

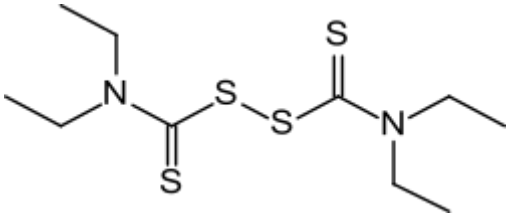

Fig. 4 The structure of disulfiram

Disulfiram causes impaired metabolism of ethanol in the liver, which is accompanied by accumulation of acetaldehyde (the drug blocks the breakdown of acetaldehyde, inhibits the synthesis of the enzyme acetaldehydrogenase) and leads to

headaches and discomfort when drinking alcohol.

Modern science knows iron-sulfur-containing proteins (n–Fe–S – proteins, where n is the number of iron atoms in the protein), which perform the function of transporting electrons in the processes of photosynthesis, synthesis of adenosine triphosphate, fixation of atmospheric nitrogen and carbon dioxide, and also take part in redox processes of various forms of life. In the active center, these proteins contain Fe (III) ions, which are covalently bound to −SH- groups of cysteine and inorganic sulfur. This topic is closely related to the topic "Chemical properties of bioelements" of the discipline "Medical Chemistry". We consider it appropriate to give students examples of such iron-sulfur-containing proteins: 2-Fe–S type (ferredoxin of chloroplasts, which is contained in plants and takes part in the processes of photosynthesis; adrenodoxin - takes part in the transfer of electrons during the hydroxylation of steroids); of the 8-Fe–S type (bacterial ferredoxin, which provides electron transfer, is a reducing agent in atmospheric nitrogen fixation processes; xanthine oxidase – an enzyme that participates in the oxidation reaction of purines; aldehyde oxidase – an enzyme that accelerates the oxidation reaction of aldehydes). When considering this topic, we draw the attention of students to the peculiarity of the structure of Fe–S proteins, which is connected with the unique structure of iron and sulfur atoms in the form of a cubic lattice ("cage"). It is connected to four cysteine residues of the polypeptide chain.

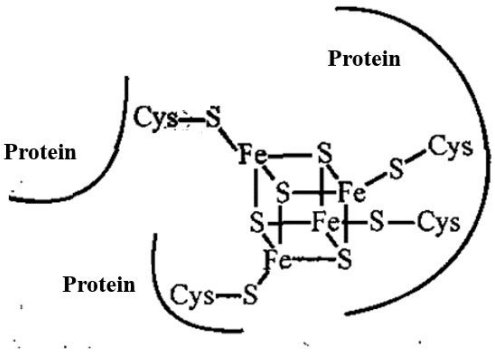

Fig. 5 Special structure of Fe-S proteins

Thus, we have reviewed the mechanism of formation of disulfide bonds, formation of dialkyl disulfides; the role of disulfide bridges in maintaining the structure and functions of secretory proteins; the structure and biological role of

pituitary hormones (oxytocin and vasopressin, which are nonapeptides, contain one disulfide bond each and differ by only two amino acids, but such a small difference in structure determines the specific action of each of them); the structure of the pancreatic hormone insulin, which contains 51 amino acid residues and three disulfide bonds; the structure and biological activity of the drug for the treatment of alcohol withdrawal syndrome - disulfiram; the structure of iron-sulfur-containing proteins (ferredoxin of chloroplasts and bacteria, xanthine oxidase, aldehyde oxidase) and their biological role.

We emphasize attention the positive result of using the examples given in the article when teaching the discipline “Bioorganic Chemistry” to future doctors; we consider it expedient to use interdisciplinary connections of bioorganic chemistry with medical and biological chemistry, pharmacology, endocrinology and other disciplines; this approach to teaching promotes the interest of students in the future profession.

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