http://dx.doi.org/10.7124/bc.000ABB

Protonated nucleotides as a promising class of APIs

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Background/Aim. Medicines based on nucleic acid derivatives, primarily nucleotides (N), are effective, non-toxic and widely used in medical practice. However, the currently known drugs based on N are used only in indeprotonated (D) forms. We studied the mechanism of action, antiviral, antitumor and cardioprotective properties of protonated (P)N, which still remain outside the attention of researchers. **Methods.** We used spectrometry methods, such as circular dichroism and reflectance anisotropy, determination of antiviral and antitumor activity in tissue culture, and cardioprotective action in rats. **Results.** It was shown that both forms of N interact with proteins in the medium affinity zone of $10^{-5} – 10^{-8}$ M. This interaction is based on proton-ion exchange, which significantly changes the conformation of proteins. However, the action of PN and DN on proteins is multidirectional in nature. PNs reduce protein stiffness, changing its conformation, thus increasing its surface area. DNs, on the contrary, make the protein molecule more rigid, reducing its surface area. The specified properties of PNs and DNs are often accompanied by opposite biological properties. PNs are especially valuable in the creation of active pharmaceutical ingredients (APIs) with increased efficiency and therapeutic effect, increased biological activity, and prevention of an unwanted immune response. Such APIs allow to reduce and optimize the treatment time, as well as reduce the total cost of treatment. A positive result is provided by the use of purine and pyrimidine PNs to boost the interaction between the protein-ligand and the protein-receptor, with an optimal ratio between PN and target proteins of 0.1 μM/10 mM. The recombinant proteins of cytokine and hormonal nature are used to create PN compositions. PNs themselves exhibit properties of antiviral APIs. In the cell culture of DNA-containing herpes virus, PNs have an efficiency index (IS) equal to 1082. When using PN in experiments with RNA-containing influenza virus, the IS is equal to 400. It is believed that antiviral APIs with IS=15 are already promising for further research. PNs demonstrate antitumor activity in tumor cell cultures in concentration from 1 μM to 10 mM with no toxic effects. At the same time, in concentrations from 1 μM to 1 mM, PNs stimulate the division of normal cells. The studies on rats revealed cardioprotective effect of purine PNs in concentrations from 1 to 10 mg/kg of animal weight, reducing the accumulation of uric acid by 10 times, which is characteristic of the known medicinal preparation based on inosine. **Conclusions.** The ability of protonated forms of nucleotides to bind to proteins has been established, changing their conformation in the direction of reducing their rigidity, which ultimately provide the antiviral, antitumor, and cardioprotective effects.

K e y w o r d s: Protonated nucleotides, circular dichroism, reflectance anisotropy, antiviral, antitumor, cardioprotective properties.