ЛИТЕРАТУРА

1. Технический Регламент Таможенного Союза 007/2011. О безопасности продукции, предназначенной для детей и подростков: утв. Решением Комиссии Таможенного Союза от 23 сентября 2011 г. №797

2. Технический Регламент Таможенного Союза 008/2011. О безопасности игрушек: утв. Решением Комиссии Таможенного Союза от 23 сентября 2011 г. №798

3. Санитарные правила и нормы 2.4.7.14-34-2003. Игрушки и игры. Гигиенические требования безопасности. Методы контроля. Требования к производству и реализации: утв. Главным государственным санитарным врачом Республики Беларусь от 30 декабря 2003 г. № 213

МЕХАНИЗМЫ РАСПРЕДЕЛЕНИЯ ПОРФИРИНОВЫХ ФОТОСЕНСИБИЛИЗАТОРОВ В СЫВОРОТКЕ КРОВИ

PORPHYRIN PHOTOSENSITIZER DISTRIBUTION MECHANISMS IN BLOOD SERUM

И. В. Яковец[1,2,3*], И. В. Янковский[1], К. Н. Борисов[1], Т. Е. Зорина[1], Л. Н. Болотина[2,3], В. П. Зорин[1,4]

I. Yakavets[1,2,3*], I. Yankovsky[1], K. Borisov[1], T. Zorina[1], L. Bolotine[2,3], V. Zorin[1,4]

[1] Белорусский государственный университет, НИЛ биофизики и биотехнологии
г. Минск, Республика Беларусь
[2] Университет Лотарингии, CRAN, CNRS
г. Нанси, Франция
[3] Институт канцерологии Лотарингии
г. Вандовр-Нанси, Франция
[4] Белорусский государственный университет, МГЭИ им. А. Д. Сахарова БГУ
г. Минск, Республика Беларусь
yakavetsiv@bsu.by
[1] Belarusian State University, Biophysics and biotechnology laboratory, Minsk, Republic of Belarus
[2] CRAN, CNRS, Université de Lorraine, Nancy, France
[3] Institut de Cancérologie de Lorraine, Vandoeuvre-lès-Nancy, France
[4] Belarusian State University, ISEI BSU, Minsk, Republic of Belarus

Изучен новый метод флуоресцентного анализа процессов распределения неполярного порфиринового фотосенсибилизатора между основными белками сыворотки крови. Предложенный метод включает в себя использование циклических олигосахаридов (циклодекстринов) для предотвращения агрегации препарата и количественного определения основных характеристик его связывания с белками сыворотки крови на основании кривых конкурентного связывания.

In the present work, we have described new fluorescent technique to monitor the distribution processes of non-polar porphyrin photosensitizer between main blood serum proteins. The technique proposed includes the use of cyclic oligosaccharides (cyclodextrins) to prevent aggregation of the compound and to quantitatively estimate the main characteristics of porphyrin binding to the serum proteins.

Ключевые слова: порфирин, фотосенсибилизатор, сыворотка крови, процессы распределения.

Keywords: porphyrin, photosensitizer, blood serum, distribution processes.

It is well recognized that drug pharmacokinetics mainly defined by the interactions with plasma proteins after *i.v.* injection. The distribution between serum proteins governs drug transportation transport in the bloodstream and further permeation into the tissues. Thus, the evaluation of drug distribution mechanisms in blood serum proteins is very important to understand their pharmacokinetics features. In spite of the fact, there are a large number of physical-chemical methods for direct determination of the characteristics of affinity; most of them meet with difficulties, when dealing with non-polar compounds such as porphyrin photosensitizers. In the current work we have studied the distribution mechanisms of porphyrin photosensitizers in blood serum by means of fluorescent techniques.

Porphyrin derivatives, especially chlorins, are widely used in photodynamic diagnostic and therapy of oncological diseases [1]. Temoporfin (mTHPC), one of the most effective photosensitizer, in photodynamic therapy of solid tumors encounters several complications resulting from its insolubility in aqueous medium [2]. mTHPC molecules form aggregates in aqueous surroundings that complicates PS biodistribution in organism after injection in blood. The

aggregation leads also to the loss of mTHPC fluorescent ability and affects on their affinity to biological structures, such as plasma proteins and cell membranes. Therefore, mTHPC aggregation limits the range of methods to determine the quantitative characteristics of mTHPC distribution processes in blood serum.

In our study we used cyclic oligosaccharides (cyclodextrins) to prevent the photosensitizer aggregation and to calculate the binding constants of mTHPC to the main serum proteins. It is widely known that cyclodextrins readily form inclusion complexes with many drugs by incorporating a drug molecule or more commonly a lipophilic moiety of the molecule into the central cavity. It has been shown, that CDs efficiently form an inclusion complexes with mTHPC [3] and can be used in indirect techniques of binding constants determination.

To determine the mTHPC affinity to biological structures we have analysed the processes of mTHPC binding to methyl-β-cyclodextrin in the serum proteins solutions (human serum albumin, low and high density lipoproteins) and in the lipid vesicles suspensions. The obtained titration curves and previously determined binding constants values for the mTHPC association with methyl-β-cyclodextrin process were used to estimate relative mTHPC affinity to biological structures. The following values of the distribution coefficient were obtained: 2.6 $(mg/ml)^{-1}$ for human serum albumin, $4.8x10^2$ $(mg/ml)^{-1}$ for low density lipoproteins and $1.0x10^3$ $(mg/ml)^{-1}$ for high density lipoproteins. The ratios of mTHPC distribution coefficients in plasma com-pounds were in a good accordance to the data obtained by means of the gel-chromatography [4].

This study was supported by Belarusian Republican Foundation for Fundamental Research (grants Ф16МВ-006 and M16M-049), the Ministry of Education of the Republic of Belarus and French “Ligue National contre le Cancer”. We thank Biolitec Research GmbH (Jena, Germany) for providing us with mTHPC.

REFERENCES

1. *Bonett, R.* Hydroporphyrins of the meso-tetra(hydroxyphenyl)porphyrin series as tumour photosensitizers / R. Bonett [et al.] // Biochem. J. – 1989. – V. 261. – P. 277–280.

2. *Senge, M.* mTHPC – A drug on its way from second to third generation photosensitizer? / M. Senge // Photodiagnosis and Photodynamic Therapy. – 2012. – V. 9. – P. 170–179.

3. *Yakavets, I.* Soret band shape indicates mTHPC distribution between β-cyclodextrins and serum proteins / I. Yakavets, I. Yankovsky, L. Bezdetnaya, V. Zorin // Dyes and Pigments. – 2017. – V. 137. – P. 299–306.

4. *Reshetov, V.* Interaction of liposomal formulations of meta-tetra(hydroxyphenyl)chlorin (temoporfin) with serum proteins: protein binding and liposome destruc-tion / V. Reshetov [et al.] // Photochem. Photobiol. – 2012. – V. 88, № 5. – P. 1256–1264.

ВЛИЯНИЕ ПРОИЗВОДНЫХ В-ЦИКЛОДЕКСТРИНА НА БИОДОСТУПНОСТЬ И БИОРАСПРЕДЕЛЕНИЕ ТЕТРАПИРРОЛЬНЫХ СОЕДИНЕНИЙ

INFLUENCE OF B-CYCLODEXTRIN DERIVATIVES ON THE BIOAVAILABILITY AND BIODISTRIBUTION OF TETRAPYRROLE COMPOUNDS

И. В. Янковский[1*], И. В. Яковец[1,2,3], Л. Н. Болотина[2,3], В. П. Зорин[1,4]

I. Yankovsky[1*], I. Yakavets[1,2,3], L. Bolotine[2,3], V. Zorin[1,4]

[1] Белорусский государственный университет, НИЛ биофизики и биотехнологии, г. Минск, Республика Беларусь

[2] Университет Лотарингии, CRAN, CNRS, г. Нанси, Франция

[3] Институт канцерологии Лотарингии, г. Вандовр-Нанси, Франция

[4] Белорусский государственный университет, МГЭИ им. А. Д. Сахарова БГУ, г. Минск, Республика Беларусь

iv.yankovsky@gmail.com

[1] Belarusian State University, Biophysics and biotechnology laborator, Minsk, Republic of Belarus

[2] CRAN, CNRS, Université de Lorraine, Nancy, France

[3] Institut de Cancérologie de Lorraine, Vandoeuvre-lès-Nancy, France

[4] Belarusian State University, ISEI BSU, Minsk, Republic of Belarus

Цель данной работы – оценить влияние β-циклодексринов на биодоступность и биораспределение мТГФХ в различных биологических системах, включая процессы распределения в мышах-опухоленосителях.

The aim of this work was to evaluate the effect of β-cyclodextrins on mTHPC bioavailability and biodistribution in various biological systems including tumor-bearing mices.