SEARCH OF NEW DRUGS ACTIVE AGAINST EPSTEIN-BARR VIRUS

Zabolotny Institute of Microbiology and Virology of the NAS of Ukraine, Kyiv

Epstein-Barr virus (EBV) is the representative of the family of Herpesviridae. Infectious mononucleosis is considered clinical form of primary human EBV infection after that the virus is retained in human organism during all life with the subsequent reactigation under influencing of different factors, both internal condition of an organism, and environment that results in clinical presentations of a miscellaneous degree of complication. EBV can be the agent to cause miscellaneous lymphomas such as nasopharyngeal carcinoma, carcinoma of parotid glands, stomach adenocarcinoma and other diseases. As well as other herpesviruses EBV affects central and peripheral nervous systems.

Summarize above it is possible to conclude that a modern arsenal of antitherpetic substances is rather miscellaneous. However, despite of it herpes as ARVI remains difficult controlled infection. It is caused as genotypical features of pathogen so and long-lived persistence of virus in organism and formation of resistant strains to antiviral drugs. Therefore search for new antitherpetics is still important.

In the laboratory of viruses reproduction IMV of NASU drug screening of the miscellaneous nature with the purpose of detection of new substances with the expressed activity against EBV is carried out permanently. Among developments of the Ukrainian scientists and pharmacists it is possible to mark out numbers of substances of miscellaneous nature, which have shown rather high anti-EBV activity and low cytotoxicity, that was revealed in our investigations. There are substances of nucleoside nature, such as 6-Azacitidin and its derivative, threecyclic nucleosides, iodine-contained drugs, such as Amizon and its derivative; drugs based on the plant extractions Proteflasid and Altabor. Antiviral activity of these investigated preparations and their new properties such as apoptosismodulatory were studied. That is the relevant feature outgoing from many-sided nature of EBV developments in clinical practice in particular its transforming capacity.

Thus, the obtained data will allow creating new antiviral drugs based on such substances for control of human diseases caused by EBV.

Questions regarding chemotherapy of virus infections are central to a number of problems of infectious pathology. Obligatory intracellular parasitism of viruses substantially defines the importance of creating antiviral preparations, which would selectively inhibit virus specific processes that proceed in a cell. It is known that many inhibitors of virus-specific processes, which are known to influence the metabolism of a cell, cause a toxic action. It essentially explains the existence of only a limited set of the antiviral preparations applied in clinical practice. For the last 30 years, some tens of antiviral preparations that pertain to various groups of substances have been introduced. Interest in search of active preparations on model herpes viruses increases. Human herpes viruses are found worldwide and they are among the most frequent causes of viral infections in immunocompetent as well as in immunocompromised patients.

Viruses affect the infected cells in different ways. Along with the deep alternations of the metabolic processes and their re-direction on the synthesis of the virion components, infection may lead to the changes of the functional state and regulatory processes in the cell. Molecular processes connected with an expression of early genes often are targets for antitherpetic preparations used in medical practice. Therefore, it is important to study the influence of nucleoside preparations on virus specific enzymes of nuclear synthesis. This provides a necessary basis for the elaboration of the principles of the correction of infectious, immunosuppressive and carcinogenic impact of viruses and development of efficient eithiotropic therapy means.

The Epstein-Barr virus (EBV) belongs to the family of Herpesviridae, whose characteristic feature is their ability to establish a life-long persistent infection in human organism with further reactivation, e.g. after the change of immune status of the patient under pressure of various ecological factors or stress. EBV causes infectious mononucleosis and it is associated with several human neoplasms – Burkitt’s lymphoma, Hodgkin’s disease, AIDS-associated B-lymphoma, primary CNS non-Hodgkin’s lymphoma, stomachic adenocarcinoma, X-linked lymphoproliferative syndrome, nasopharyngel cancer and posttransplantation lymphoproliferative syndrome. Some representatives of Herpesviridae family, primarily EBV, herpes simplex virus, cytomegalovirus and human herpes virus type 8 pertain to AIDS-associated viruses; they take part in pathogenesis of this symptomocomplex [2-8]. The search for the novel antiviral substances active against Epstein-Barr virus (EBV) is a topical problem, EBV like other herpesviruses affects central and peripheral nervous system being involved in the pathogenesis of meningoencephalitis, arachnoencephalitis and menigitis. There are no effective drugs for treatment of different clinical forms of EBV-infection up to date. Ganciclovir, vidarabine, foscarnet, cydofovir have some anti-EBV activities. That’s why the development of a new EBV inhibitor remains to be the actual problem of virology and medicine in total.

Such approaches to treatment of virus infections are known at present:

• effective antiviral chemicals include: nucleoside analogs; viral DNA polymerase and thymidine kinase are targets for them. Miscellaneous natural substances are investigated; their mechanism of action is still insufficiently studied;

• immunomodulator drugs are active preparations with immunostimulating properties in relation to cell and humoral immunities.

Summarize above it is possible to conclude that a modern arsenal of antitherpetic substances is rather miscellaneous. However, despite of it herpes as ARVI remains difficult controlled infection. It is caused as genotypical features of pathogen so and long-lived persistence of virus in organism and formation of resistant strains to antiviral drugs. Therefore search for new antitherpetics is still important.

The role of interferon in treatment of diseases caused Epstein-Barr virus among doctors remains ambiguous as there are no works precisely proving his efficiency. Though the role of preparations of interferon in correction of immune system of the person is unconditional, at the given diseases as one of properties EBV is negative influence on system of the immune answer of an organism. Most the positive effect is observed at application of interferon of type an alpha [11].

Edward Gershburg and Joseph S. Pagano [10] in 2005 have presented the review of chemical preparations that are active against EBV. All modern spectrum of preparations existing in the world which are perspective in relation to Epstein-Barr virus is analysed in given paper.

to their approach all preparations can be related conditionally to following groups.

The first group includes noncyclic analogues of nucleosides (Aciclovir, Ganciclovir, Penciclovir, Valaciclovir, Malgnan-clovir, Famciclovir); noncyclic analogues nucleotides (Cidofovir, Adenos; Foscarnet and other substances). A target of all above-mentioned substances is viral DNA-polymerase and thymidine-kinase.

Natural substances the mechanism of action of which is insufficiently investigated belong to the second group.

All above represented preparations are strong inhibitor of virus reproduction, but not all of them are perspective for clinical applications as strongly differ by toxicity, this aspect is very actual, especially concerning children and youth. All these components have a number of lacks (toxicity, insufficient bioavailability and risk of occurrence new resistant strains). So in case of heavy defeats of nervous system caused EBV, prolonged intravenous introduction ganciclovir is necessary that increases undesirable toxic action by various bodies and systems of a macroorganism [1].

It is caused by genotypic features of the activator, duration of virus persistence in an organism, and formation of strains resistant to anti-virus preparations. Therefore, search new antiterphetic preparations remains actual.

Materials and methods. Cell and virus. The line of lymphoblastoid B-cell Raji infected by EBV was used as a model of EBV-infection in vitro. Cultural medium of B95-8 cells producing the EBV was used as a virus-containing material after a differential centrifugation. The nutritional media for Raji cells consists of medium 1640 with supplement of 10% embryonic serum, 2 mM glutamine and antibiotics. The Raji cells were infected during 60 minutes at the temperature 37° C. Upon the exposure, cells were washed and medium without serum was added.

PCR. An inhibition of reproduction of EBV in cell culture by drugs was determined by reduction of genome equivalents of EBV DNA on a cell in treated versus untreated cells. To determine it, a quantitative PCR was applied using primers and reagents of "AMPLY-SCence-Biotech" (Russia) and programme "Biotest A".

MTT method. The CD_{50} were also determined by colorimetric method using the dye MTT (Sigma Chemical, St. Louis, Mo.). 25 μl of RPMI 1640, containing 5 mg of MTT/ml, added in each well of the microtitration plate. Incubation continued for 3 h at 37° C. The contents of each well removed (after centrifugation under 1000g during 10 min) and 200 μl of 96% ethanol added to extract the dye. After 10 min of gentle agitation at 37° C the optical density (OD) at 540 nm was measured using microwell plate reader (Dynatech, Sweden). The percentage of MTT conversion in its formazan derivative for each well was calculated comparing the OD at 540 nm (OD_{540}). The line of Raji cells infected by EBV used as a model of EBV-infection in vitro. An inhibition of reproduction of EBV in cell culture by drugs was determined by reduction of a number of genome-equivalents of EBV DNA on a cell.

Results of work. The research work was given up to studying of antiviral action of nucleosides: 6-azacytidine, 2'-sec-o'-5-methyl-6-azacytidine, 2'-deoxy-23'-didehydro-6-azacytidine, 2'-deoxy-6-azacytidine to the reproduction of Epstein-Barr virus in Raji lymphoblastoid cells.

Cytotoxicity action of investigated preparations was characterized, and their doses that reduced the prolyphemative activity for 50% were determined. Minimal active concentrations, which inhibited of virus reproduction, were established. Determined selectivity index allow relating these substances to potential anti-EBV preparations. It was confirmed the worthiness of estimations of researches results for the obtained dates by the statistics methods. The obtained dates will be using for computing modeling of an interaction between structure and biological activity of substances, which will be using to prognosis of making a new high activity antiviruses medicinal preparations, 6-Azacytidine (2'-D-ribouranosyl-5-amin-1, 2,4-triazin-3(2H)-on; 6-AC) are an original structural cytidine analogue with the wide spectrum of biological activities (antiadenoviral, anti-HSV, anti-mycoplasmic, immuno-activating, antitumor) [9]. The objective of the present investigation was to study the activity of 6-AC against EBV, as well as its new analogues bearing. 6-Azacytidine, 6-AC acyclic derivative - 23'-sec-o'-5 methyl-6 Azacytidine (sec-o 6-AC), bi- and tricyclic nitrogen-containing structures (non nucleoside protease inhibitors) are widely used as potential antiviral agents. They are used against retroviruses and some herpesviruses. 23'-dideoxy-23'-didehydro-6-azacytidine (Ne1) and 2'-deoxy-6-azacytidine (Ne2) are original cytidine analogues. The concentrations of 6-AC and "sec-o"- 6-AC which inhibited the quantity of alive cells on 50% (CC_{50}) were equal to 96 and 200 μg/ml accordingly. The minimal inhibiting concentration (MIC) of 6-AC was equal to 0.5 μg/ml, because the amount of genome - equivalents of DNA EBV on a cell was reduced with 6.0 up to 3.1. Acyclovir has shown the considerably smaller activity against EBV; in concentration of 125-500 μg/ml it reduced the quantity of DNA EBV up to 6.5-4.8 genome-equivalents on a cell (7.12 without the inhibitor). The concentrations, which inhibited the quantity of alive cells on 50% (ID_{50}), were equal to substances Ne1 1 - 500 μg/ml and Ne2 - 250 μg/ml. The minimal inhibiting concentration (MIC) of Ne1 was equal to 4 μg/ml, because the amount of genome - equivalents of DNA EBV on a cell was reduced with 22.0 up to 10.4, MIC for Ne2 was equal to 16 μg/ml (the amount of genome - equivalents were reduced with 22 up to 7) (tab.1).

| Parameters cytotoxicity and anti-virus activity nucleosides (are synthesized in IMBG NASU) |
|---------------------------------|----------------|------------|-------------|-------------|-------------|
|                                | 6-azacytidine  | 23'-sec-o'-5-methyl-6-azacytidine | 23'-dideoxy-23'-didehydro-6-azacytidine | 2'-deoxy-6-azacytidine |
| CC_{50} 6-azacytidine           | 96 μg/ml       | 200 μg/ml  | 500 μg/ml   | 250 μg/ml   |
| EC_{50} 6-azacytidine           | 0,5 μg/ml      | 1 μg/ml    | 4 μg/ml     | 16 μg/ml    |
| IS      6-azacytidine           | 190            | 200        | 125         | 16          |

It was investigated the influence of 6-AC and acyclic derivative on CD95-mediated apoptosis in Raji cells infected by EBV as well as uninfected. It was shown that 6-AC in concentration 32 and 125 μg/ml strengthened the expression of CD 95-mediated apoptosis.

Hence, the index of selectivity (IS) was equal to 125 and 16 for 23'-dideoxy-23'-didehydro-6-azacytidine and 23'-dideoxy-6-azacytidine accordingly. It was investigated the influence of Ne1 and Ne2 on CD 95-mediated apoptosis in Raji cells infected by EBV.

Today drug-resistant strains of virus diseases have been documented in every country as well as multidrug-resistant strains. Thus the development of new drugs is one of the essential problems for modern chemotherapy in combating such infections. New series of Triazine Bearing Tricyclic Bases and their N-Glycoside Derivatives were synthesized as potential antiviral agents. These bases present the biosources of isosalloxasine chromophore of natural flavin mononucleotides.N-Glycoside Derivatives were stereo-specifically prepared by glycosylation of corresponding bases with tetraacetyl ribose precursor, followed appropriated chemical modifications. Search of new effective preparations capable to inhibit herpesviruses reproduction is stipulated by their certain resistance to different groups of chemical preparations. New Triazine Bearing Tricyclic
Bases and their N-Glycosidic Derivatives structures are widely used as potential antiviral agents.

The first stage of investigation of substances was the analysis of their cytotoxicity for cell line Raji. We have studied in concentrations of 1000 to 0.1 µg/ml. The concentrations, which inhibited the quantity of alive cells on 50% (IC50) were equal to substances Triazine Bearing Tricyclic Bases - 750 µg/ml, N-Glycoside Derivatives N1 - 625 µg/ml and N-Glycoside Derivatives N2 - 125. The minimal inhibiting concentration (MIC) of N1 and N2 was equal to 1 µg/ml, because the amount of genome - equivalents of DNA EBV on a cell were reduced by 28, 0 up to 14. Hence, the index of selectivity (IS) was equal to 750 and 625 for Triazine Bearing Tricyclic Bases N1 and N2 (tab.2).

| Table 2. Parameters cytotoxicity and anti-virus activity Triazine Bearing Tricyclic (are synthesized in IMBG NASU) |
|-----------------|-----------------|-----------------|
| Triazine Bearing Tricyclic Bases N1 | Triazine Bearing Tricyclic Bases N2 | N-Glycoside Derivatives |
| CC 50 | 1780 mM | 2170 mM | 590 mM |
| EC 50 | 2.7 mM | 2.86 mM | 4.7 mM |
| IS | 625 | 750 | 125 |

During last decades more and more attention is given to creation of preparations for pathogenetic therapy with the polynuclear pharmacological action, which is capable essential to influence on immunity, to adjust the basic exchange processes, and also to have anti-inflammatory effect. One of successful elaborations of the Ukrainian pharmacologists is the new non-narcotic analgesic Amizon with expressed antiphlogistic, antipyretic, interferon gene and immunomodulatory properties. Amizon – the derivative of isonicotinic acid (N-metyl-4-benzyl urea-pyridinit iodidum).

The objective of the present investigation was to study the activity Amizon, as well as derivative, in which structure there is no iodine, against Epstein-Barr virus. To study the cytotoxicity of investigated drugs they were entered into the culture of the replication of the virus on 50 %, that was shown by reductions of 0.1, 0.5, 1, 5, 10 µg/ml. The analysis of obtained data allowed to determine concentrations, which oppressed the replication of the virus on 50 %, that was shown by reduction of the number of genomic equivalents of EBV DNA on a cell testified. ED50 for Amizon has compounded 0.1 µg/ml, for it derivative - 5 µg/ml (tab.3).

| Table 3. Parameters cytotoxicity and anti-virus activity of Amizon and his Derivative (are synthesized in IFT AMNU) |
|-----------------|-----------------|-----------------|
| Amizon | Derivative N1 | Derivative N2 |
| CC 50 | 840 µg/ml | 2100 µg/ml | 2200 µg/ml |
| EC 50 | 0.1 µg/ml | 5 µg/ml | 5 µg/ml |
| IS | 8400 | 400 | 440 |

Thus, the low toxicity of investigated drugs was shown and their effective doses were determined. Proceeding from the index of selectivity that is 8400 for Amizon, 400 for the its derivative, it is possible to make a conclusion about their availability for the further researches as of drugs that are active against an Epstein-Barr virus. Furthermore obtained data testify to importance of presence of iodine in structure of drug, as, apparently from the received data, the activity of derivative, not containing iodine, is below more than in 20 times.

The aim of the study was to assay the anti-EBV activity of several substances prepared from the raw material of the plant origin, namely Proteflasid, Proteteflasid (Ecopharm Research and Production Company, Kyiv) represents the quercetin-containing herbal extract of wild grasses Deschampsia caespitosa L. and Calamagrostis epigeios L. The search of the novel antiviral substances active against Epstein-Barr virus (EBV) is a topical problem since the persistent EBV infection alters immune status promoting the development of adenocarcinomas and lymphoproliferative diseases. Moreover, EBV like other herpesviruses affects central and peripheral nervous system being involved in the pathogenesis of meningoencephalitis, arachnocephalitis and meningitis. The substances were assayed within broad concentration ranges. The maximally tolerable concentrations for the cell line being assayed amounted to 1000 µg/ml for Altabor and 150 µg/ml for Protetflasid. The inhibition of EBV reproduction was assessed by PCR technique estimating the number of EBV DNA genomic equivalents. Minimal effective concentrations amounted to 0.1 µg/ml for Protetflasid.

Altabor (Borschavovshvkyi Chemical and Pharmaceutical Plant, Kyiv) based on the polyphenols isolated from fructescences of the alder comprises monomers and oligomers of ellongotannins (no less than 60%), melanoid polymer (about 10%), and phenolic acids (ellagic, gallic, valonic acids as well as mono- and polysaccharides). The substances were assayed within broad concentration ranges. The maximally tolerable concentrations for the cell line being assayed amounted to 1000 µg/ml for Altabor and 150 µg/ml for Protetflasid. The inhibition of EBV reproduction was assessed by PCR technique estimating the number of EBV DNA genomic equivalents. Minimal effective concentrations amounted to 2 µg/ml for Altabor and 0.1 µg/ml for Protetflasid. Therefore, the chemotherapeutic indices for Altabor and Protetflasid were estimated as 500 and 1500, respectively (tab.4).

| Table 4. Parameters cytotoxicity and anti-virus activity of plant preparations |
|-----------------|-----------------|-----------------|
| Proteflasid | Altabor |
| CC 50 | 150 µg/ml | 500 µg/ml |
| EC 50 | 0.1 µg/ml | 0.1 µg/ml |
| IS | 1500 | 5000 |

Thus, the obtained data will allow creating new antiviral drugs for strive with human diseases caused by EBV based on such substances.

SEROLOGICAL DETECTION OF HIV-INFECTION AND ANTIGENIC MIMICRY

Lev Gromashevsky Institute of Epidemiology & Infectious Diseases, Academy of Medical Sciences of Ukraine, Kyiv, Ukraine

Carrying out HIV-infection diagnostics, a lot of factors should be taken into account. The authors discuss the role of different factors and pathogens in the development of false-positive answers, that is why a continuous perfection of diagnostic test-systems is necessary to avoid interference contribution to diagnostic faults.

Test-system specificity is a problem of the greatest importance in serological diagnostics. It is especially true for infections of enormous epidemiological and social impact including the HIV-infection.

HIV-like proteins and antibodies (Abs) against them are described in patients with numerous pathologies associated with autoimmune processes [17, 21-22, 28], some of them appearing to be free from autoimmune features [6, 9-10, 16]. False-positive answers (FPA) are often found in tumor-bearing patients with multiple myelomas, malignant lymph and blood conditions [23, 25], multiple warts causing antibody development against HIV core proteins [23].

According to generally known data, there is about 70 conditions or other factors whose presence is shown to be associated with FPA for sera being studied by different serological methods including also immunoenzyme analysis (IEA) which is thought to belong to the most sensitive and specific diagnostic approaches [28]. The FPA probability becomes higher proportionally to increase of foreign antigens and factors being in contact with patients investigated. Such cases may appear due to many situations accompanied by polyonal B-lymphocyte activation; independently on factor specificity having induced this process, a lot of Abs to different non-similar antigens raise usually and appear in blood sera [13].

Advances in molecular biology, especially the use of monoclonal antibodies (MAbs) in diagnostic field as well as study of amino acid and nucleotide sequences of enormous quantity of structures (for viruses, bacteria, and their hosts) led to publications proving immune relationship between structures of quite different origin, presence of similar or identical structures in evolutionary distant organisms including also different viruses [1, 2, 8, 14, 17-18, 20, 24, 26]. Now such phenomenon is known as molecular mimicry.

Anti-HIV antibodies cross-reacting with tissue structures may contribute to HIV-infection pathogenesis and numerous AIDS-accompanying autoimmune processes. HIV patients sera were found to contain antibodies to a lot of human cells (lymphocytes, platelets, neutrophils, erythrocytes) and their components (myelin, basic myelin protein, nucleus components, phospholipids, CD4, HLA etc [8, 18, 24, 26]. Now such phenomenon is known as molecular mimicry.

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