

New Progress in Pharmacochemistry of Anti Enterovirus 71

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Keywords: Enterovirus 71, Capsid protein inhibitor, Anti virus, Therapeutic drugs

Abstract: Although great progress has been made in the research and development of new drugs against enterovirus 71, the prevention and treatment of enterovirus 71 still relies on vaccines in most cases. Therefore, it is an urgent task to speed up the research and development of anti enterovirus 71 drugs. With the development and integration of multiple disciplines, the research and development directions of anti enterovirus 71 drugs are more diverse. At present, there are further research results on the crystal structure of capsid protein and some key proteases in clinical research. In the future development of anti enterovirus drugs, we can continue to design reasonably on this basis. In this paper, through consulting the relevant literature in recent years, the chemical research of anti enterovirus 71 was summarized and analyzed, in order to provide reference for related people.

1. Introduction

Enterovirus is the general term of a class of viruses, including poliovirus, Coxsackie virus, icov and new enterovirus type 68-71. Enterovirus 71 (EV71) is the main pathogen of hand foot mouth disease in China. Enterovirus 71 infection can cause encephalitis, meningitis, stomatitis, pharyngitis and other diseases. In serious cases, death may occur. At present, there is no specific drug for the treatment of enterovirus 71 infection. This paper reviews the progress of antiviral drugs from the perspective of pharmacochemistry.

2. Structural life cycle mechanism and clinical manifestations of enterovirus 71

2.1. Structure of enterovirus 71

Enterovirus 71 has no envelope and protuberance, and its diameter is about 25 nm. VP1, VP2 and VP3 of viral capsid protein are located on the surface of capsid, while VP4 is located in the inner of capsid, which connects with the core of enterovirus.

2.2. Life cycle and invasion mechanism of enterovirus 71

At present, there is no clear view on the mechanism of the life cycle of enterovirus 71. Because the life cycle of enterovirus 71 is mostly similar, we can choose the replication mode to speculate the life cycle of enterovirus 71. All enterovirus life cycle starts from the binding of one or more host

cell surface receptors with the virus. Under the host's endocytosis, the virus can reach the cell smoothly. The change of pH in the cell or the binding with the internal body receptor will cause the aggregation of virus capsid protein^[1-2]. In this way, viral RNA can be released through the pores on the surface of the capsid, and the release pathways of different enterovirus RNA will be different.

When the released viral RNA reaches the cytoplasm, a single polyprotein will be synthesized, and then hydrolases 2A ~ 3C and 3D will be added, and the polyproteins will be hydrolyzed into 10 different proteins. Enterovirus genome replication occurs on the membrane structure induced by the virus, also known as the replication organelle. At this time, the replication template of enterovirus is (+) RNA. Under the interaction of RNA polymerase, it copies (-) RNA, and then repeats this action repeatedly. The newly cloned RNA is then used as a template for further replication, or packaged into new virus particles for efflux. The packaging of virus particles is composed of VP0, VP1 and VP3 proteins, which can be packaged into protoplasts and pentagons, and then assembled on the newly replicated RNA to realize the replication and binding process of new virus particles and viral RNA^[3-4]. The newly synthesized RNA can process VP1 into VP2 and VP4 through induction, which can generate mature virus particles.

Viral proteases 2a and 3C can not only effectively hydrolyze viral polyproteins, but also hydrolyze some proteins in host cells, which can effectively optimize their own transcriptional replication and diffusion. Through this role, the host's resistance to virus can be greatly reduced.

3. New development of anti enterovirus 71 drugs

The physiological cycle of virus can be roughly divided into invasion, RNA replication, protein synthesis and virus release. Usually, the physiological cycle of each virus can be used as the basis when designing the target of anti enterovirus drugs. However, most of the clinical studies in this area are focused on virus invasion inhibitors, virus replication inhibitors and so on.

3.1. Virus invasion inhibitors

(1) Capsid inhibitor

VP1 is a protein that can promote the effective binding of enterovirus to host cells. This protein has a hydrophobic cavity, which can bind to the receptor on the surface of host cell, so that the virus can enter the cell. If the compound is embedded into the hydrophobic pocket, the stability of VP1 protein can be greatly enhanced, thus effectively blocking the depolymerization of VP1 protein, preventing the virus from entering and avoiding shelling. In enterovirus 71, VP1 protein has a conserved hydrophobic pocket, which may be a potential drug binding target^[5-6]. In this regard, small molecule inhibitors can be designed to effectively prevent the conformational changes of hydrophobic pocket, so as to effectively inhibit the occurrence of virus shelling and avoid the release of virus gene in human body, so as to effectively treat enterovirus 71 and effectively control virus infection.

(2) Win series compounds

The early antiviral method is to use the capsid protein targeting virus, that is to use the capsid conjugate to occupy the hydrophobic pocket and replace the cystic factor to increase the stability of the particles, avoid binding with the receptor or release the genome.^[7-8] The clinical study of reversible capsid protein binding inhibitors is win series compounds. This discovery provides a very powerful direction for the research and development of targeted inhibitors. One of the most successful compounds was pleconaril, which showed no inhibitory effect on enterovirus 71 in human rhabdomyosarcoma cells. In 2002, it was reported in Taiwan that a virtual compound library was designed based on the framework of win series compounds. Among them, the minimum energy structure is very similar to VP1 pocket. On the basis of this virtual compound library, imidazolidone

derivatives have been found, which generally show good inhibitory effect on enterovirus 71.

According to related research reports, after the structural optimization of enterovirus 71 compounds with better activity, it was found that if carbonyl oxygen in imidazolidinone was replaced by sulfur atom, the activity of compounds would be greatly reduced. When the carbonyl group is replaced by the phenol group, the activity will also be significantly improved. [9-10] sults showed that among some cell compounds, the cells with high antiviral activity ranged from 3 to 5, among which 5 activity was the best. Some researchers have also optimized some of the structures and found that their activity has increased nearly 10 times.

(3) Enweximes

In the past few years, some researchers found compound 9 by screening bioactive compound library. This kind of substance showed good activity to PV and enterovirus 71 pseudovirus, and its activity was relatively improved in RD cell line.

3.2. Cell surface receptor inhibitors

[11-12]t, virus invasion and cell surface receptor binding is a very important link. In the process of virus invasion, human scavenger receptor has a direct promoting effect on enterovirus binding, which can make the virus reproduce under the condition of low sensitivity, and promote the pathological changes of cells (M27). For the mechanism of this phenomenon, clinical studies suggest that it may be related to the binding of scarb2 receptor on cell surface with the groove of viral VP1 capsid protein. This situation can greatly reduce the stability of virus particles, accelerate the depolymerization of virus capsid protein, thus greatly accelerating the invasion speed of virus. In addition, in recent years, relevant clinical studies have found that PSGL-1 is also a cell surface receptor when enterovirus invades leukocytes. However, in the presence of Rb2 receptors alone, the effect of Rb2 on enterovirus replication could not be enhanced by the presence of Rb2 receptors alone. Some progress has been made in the antiviral treatment of these cell surface receptors. For example, anti scarb2 antibody can inhibit the mild infection of enterovirus in a dose-dependent manner. Relevant studies have shown that sialidase can protect the susceptible intestinal cells from the influence of enterovirus 71 by clearing the sialic acid groups in plasma membrane proteins. At the same time, some studies have pointed out that in the environment of anti DC-SIGN antibody, the risk of enterovirus 71 infection in immature dendritic cells will be greatly reduced.

3.3. Viral RNA replication inhibitors

RNA replication is very conservative in all enterovirus replication, so blocking viral RNA replication is an effective way to block virus infection.

(1) Flavonoids

Related studies have shown that flavonoids can effectively inhibit virus replication in some traditional Chinese medicine ingredients. In the past, two flavonoid derivatives, compound 11 and compound 12, were found to be active against enterovirus 71 (EV71). In the related experiments, the toxicity of these two compounds to the cells was relatively low, but in the cell experiments against enterovirus 71 infection, it was found that the virulence of the infected virus also decreased with the increase of the dose of the two compounds [13]. These results indicate that these two compounds have certain inhibitory effect on enterovirus 71. In subsequent experiments, it was also found that the inhibitory effect of these two substances on the virus was due to its inhibitory effect on the replication of viral RNA without interfering with the internal activities of cells.

(2) Isoflavones.

Isoflavones widely exist in edible plants in nature. This kind of material has very significant application effect in anti influenza, anti-virus and so on. At present, a large number of studies have

confirmed that isoflavones have a significant inhibitory effect on viral RNA replication.

(3) Pyrazolopyrides

2C protein plays a very important role in the whole life cycle of virus, which is equivalent to the role of RNA helicase and molecular chaperone. This situation is indispensable in the replication cycle of many enteroviruses. Moreover, the small RNA virus has obvious conservative characteristics in 2C protein^[14]. Therefore, the broad-spectrum antiviral drugs targeting 2C protein have a very good development prospect. At present, many studies have indicated that pyrazolopyridyl derivatives play an important role in antiviral activity, and their target is protease 2C.

(4) Natural product osw-1

The natural product osw-1 has great potential in the research and development of enterovirus drugs. Some researchers have used enterovirus 71 and other enteroviruses to test the activity of this substance. The results show that osw-1 has a good inhibitory effect on enterovirus.

(5) Fluoxetine

Many researchers have found a series of 2C protease inhibitors by high-throughput screening, among which fluoxetine has a good inhibitory effect on virus activity. After further comparative study, only fluoxetine can bind to RC protein cavity and inhibit the protein active products.

3.4. Inhibitors of viral protein synthesis

Protease 2a and 3C play an important role in enterovirus protein synthesis. 2A protein series is highly conserved. 3C protease activity is similar to serine protease in structure. In practical use, as long as one of 2A or 3C proteases is inhibited, good antiviral effect can be achieved. However, due to the poor pharmacokinetic parameters, it is difficult to widely use peptide covalent inhibitors. The derivatives of phenylthioketones introduce phenylpropenyl to the dominant skeleton atoms, thus greatly enhancing the inhibitory effect of the compounds on 3C protease.

It has been found that some peptide compounds can inhibit virus replication by binding with 2A protease active center. Lu Ping Qu Wei is also a successful polypeptide 3C protease inhibitor, but this kind of substance has no obvious remission effect on patients with natural infection of HRV. Therefore, the current clinical for its research to stop processing. At present, the most effective 3C protease inhibitor found in clinic is peptide like food with natural substrate. This substance covalently combines with cysteine in protease active center, which has very significant antiviral effect and can block the replication of virus genome^[15].

3.5. Vaccines

In addition to anti enterovirus memory drugs, vaccines are also very important in the prevention and treatment of this disease. At present, it is aimed at enterovirus epidemic. The vaccines mainly include pre inactivated virus vaccine, live virus detection vaccine and so on. Compared with other types of vaccines, pre inactivated virus vaccine has stronger immunogenicity, and a new generation of inactivated whole virus vaccine of enterovirus 71 can be developed more quickly based on the existing inactivated polio vaccine technology. In the practical clinical application, enterovirus 71 vaccine strain has good immunogenicity, and its clinical application response is becoming more and more extensive.

4. Conclusion

It is very important to study and understand the life cycle model of enterovirus 71 (EV71) for the development of anti enterovirus 71 drugs. In the design of drugs, it is necessary to pay attention to

the toxic effects on cells after drug Miss target. From the current development situation, enterovirus 71 skeleton inhibitor is the main direction of future research and development. With the development of the drug resistance of the virus strain, it will increase. In traditional enterovirus prevention and treatment drugs, the activity of compounds is usually reduced to enhance their antiviral activity. In the future, we can turn our attention to multi-target and multi-point synergistic inhibitors, and find new targets from the level of proteomics, so as to screen out suitable new compounds and effectively improve the activity of compounds against virus mutants. In general, on the basis of the existing pharmacological strategies and methods, we need to further explore new strategies, new methods and new targets, so as to effectively promote the development of anti enterovirus 71 drugs.

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