Medical Applications of Siderophores

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ABSTRACT
The literature survey presented in this review shows that the knowledge regarding the structure of various siderophores and the presence of microbial membrane receptors that operates in iron uptake from these iron-siderophore complexes have opened newer avenues for research. Siderophores and their substituted derivatives have a large number of applications in medical sciences. The most important application is selective drug delivery, a Trojan horse strategy, to defeat drug resistant bacteria. The Trojan horse strategy is most promising way to specifically attack multiple antibiotic resistant strains of bacteria associated with life threatening infections. Other major clinical applications include treatment of diseases like haemochromatosis, thalassemia, dialysis encephalopathy, removal of transuranic elements such as aluminium and vanadium and anti-malarial activity.

Key words: Siderophores, trojan horse strategy, medical applications

Siderophor’ların Tibbi Uygulamaları

ÖZET
Bu derlemede sunulan literatür taraması, çeşitli siderophores yapıları ve yeni araştırmalarla yol açan, demir siderofor komplekslerinden kaynaklanan demirin alınmasında faaliyet gösteren mikrobiyal membran reseptörlerinin varlığı ile ilgili bilgiler vermektedir. Siderophoresler ve onların türeverlerinin tip bilimlerinde çok sayıda uygulamaları vardır. En önemli uygulama, ilaca dirençli bakterileri yenmek için, Truva atı starejisi gibi selektif ilaç teslimidir. Truva atı stratejisi, hayatı tehdit eden enfeksiyonlar ile ilişkili bakterilerin, özellikle birden fazla antibiyotik dirençli susurlarına saldırmak için çok gececek vaat eden yoludur. Diğer önemli klinik uygulamaları, hemokromatoz, talasemi, diyaliz ensefalopatisi, alüminyum ve vanadıyum gibi uranyum ötesi elementleri kaldırılması ve sitma gibi hastalıkların tedavisini içerir.

Anahtar kelimeler: Siderophor, truva atı starejisi, tibbi uygulamalar

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INTRODUCTION

The concern over increasing antibiotic resistance in pathogenic bacteria, due to their capacity to adapt by natural selection, is wobbling the medical field all over the world. It has forced the pharmaceutical industries to search for newer effective antibiotics. To overcome the drug resistance problem, the sensible use of antibiotics available with us must be respected. One newer attitude that has been explored to resolve the problem is to smuggle the antibiotic molecule into the bacterial cell by binding it to a siderophore molecule (the Trojan Horse strategy).

Most organisms require iron as an essential element in a variety of metabolic and informational cellular pathways. More than 100 enzymes acting in primary and secondary metabolism possess iron containing cofactors (1). Although iron is abundantly present in the environment, ionic forms of iron are insoluble under physiological conditions and hence are difficult to assimilate for microorganisms (2). Three to four gram of iron is generally present in Human body, out of which haemoglobin and myoglobin acquire the major share of 70% (3). Mammalian iron-binding proteins, such as transferrin and lactoferrin, reduce the amount of iron available to the microbes. The iron acquiring skill of pathogens is essential for their ability to cause infection in animal hosts and to establish the host-parasite relationship (4 -7). Under such iron-depriving conditions, the aerobic and facultative anaerobic bacte- ria and other microorganisms frequently produce organic chelates that combine with inorganic iron and greatly enhance its solubility. These microorganisms also produce the unique outer membrane proteins (OMP’s) which serve to recognize process and transport the siderophore-iron complex (es) into cell. These chelates, which were designated earlier as siderochromes, sideramines, and sid- eromycins are now conveniently termed as Siderophores (meaning in Greek: sideros = iron and phores = bearer). Siderophores are technically defined as the ferric iron (meaning in Greek: sideros = iron and phores = bearer). Siderophores that contain nei-

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The obligate nutritional requirement for iron by multiple drug resistant pathogens can be exploited to control its infection. The three fundamental perceptions of iron dependant pathogen control include the Trojan horse concept to facilitate the cellular uptake of antibiotics, artificial iron starvation by using siderophores or antagonists that cannot be utilized as an iron source by the pathogen and inhibition of iron metabolism pathways (23). Siderophores and their substituted derivatives have a large number of applications in medical sciences: Siderophores have potential applications in the treatment of some human diseases and infections. These are as follows:

1. Selective Drug Delivery - Trojan horse strategy (Siderophore-antibiotic conjugates - Sideromycins)

Siderophores can be used for selective delivery of antibiotics in antibiotic resistant bacteria. It is a newer antimicrobial approach to defeat drug resistant bacteria. It is the potentially powerful application that uses the iron transport abilities of siderophores to carry drugs into cells by preparation of conjugates between siderophores and antimicrobial agents. It uses siderophores as mediators to facilitate the cellular uptake of antibiotics. This interaction of antibiotic with siderophores results in a formation of siderophore - antibiotic conjugates known as Sideromycins. These are the microbe selective compounds that put together two utilitarian molecules, a siderophore and an antibiotic, into one structural scaffold. The siderophore part of this conjugate is able to scavenge iron and is recognized by cellular Fe-Siderophore uptake systems, while the other part of conjugate bears an antibiotic activity that uses the siderophore as a Trojan horse and mediates iron transport mediated drug delivery.

The antibiotic molecule recruits the siderophore as a "Trojan horse" vehicle, taking advantage of the Fe-siderophore uptake system, to enter the microbial cell. The drug conjugate usually also consists of a linker for attaching the drug to the siderophore. The linker allows controlled, chemical or enzymatic, release of drugs in the target bacterial cell. On reaching into the cell, the siderophore-drug conjugate kills the cell by releasing the drug or by acting as an intact antibacterial agent or by blocking further iron acquisition. The siderophore - antibiotic conjugates are of two types - natural and synthetic:

a. Natural Siderophore-antibiotic conjugates are:
   - Albomycins, ferrimycins, danomycins, salmycins (isolated from Streptomyces and Actinomycetes), microcins (isolated from enteric bacteria)
   - Albomycins-blocks protein synthesis by inhibiting t-RNA synthetase in E. coli

b. Synthetic Siderophore-antibiotic conjugates-These can be prepared – using antibiotics with improved cell permeability and reduced susceptibility to resistance mechanisms. Siderophores can be bound to potent antibiotics such as beta lactam (Carbacephalosporins), erythromycin, sulphonamides, spiramycin, vancomycin, naldixic acid, norfloxacin, etc. Antifungal agents - such as 5-flourouracil and neoeacins can also be conjugated and used against fungi. The results indicate that these conjugates give better results and this siderophores mediated drug delivery is remarkably effective. Microbes recognize the siderophore component as an iron delivery agent and assimilate the conjugate and commit suicide as the attached drug is lethal to them. The siderophore-antibiotic conjugates can also be used against pathoge
bacteria, which produce and use siderophores to acquire iron (24-29).

2. Use of Gallium as Trojan Horse to Iron Seeking Bacteria

It is well known fact that iron is critical for the growth of bacteria and for their ability to form biofilms in slime encased bacteria that cause many chronic infections. In a study carried out at university of Washington, gallium, a metal very similar to iron (looks like iron) was used instead of iron. Because of structural similarity to iron, gallium is also chelated like iron by siderophores and siderophores are recognized by the cellular receptors on bacterial cells that allows the molecule (Siderophore-gallium complex) to enter inside the bacterial cells. Gallium was found to act as Trojan horse to iron seeking bacteria and killed them and inhibited biofilm formation. Gallium was also found effective against multiple antibiotic resistant strains of Pseudomonas aeruginosa. In mice, gallium treatment blocked both chronic and acute infections caused by Pseudomonas aeruginosa. This approach is under trial and results are promising (30).

3. Treatment of Iron Overload Diseases

Some siderophores are used in the treatment of acute iron intoxication and chronic iron overload diseases associated with excessive blood transfusions. In acute iron intoxication and chronic iron overload diseases, siderophores can be used as chelating agents, which are able to bind with iron to produce complexes that lead to formation of ferrioxamine. The ferrioxamine is soluble in water and readily excreted through the kidneys. It binds with iron in the blood and enhances its elimination via urine and faeces. Hence, it is of value in the treatment of acute iron intoxication and chronic iron overload diseases. Thus, it can be used to decrease the iron overload in the body.

These acute iron intoxication and chronic iron overload diseases include:

a. Haemochromatosis

Haemochromatosis is a disorder in which there is a prog ressive increase in the iron content of the body causing deposition of iron in the liver, heart or pancreas. It is the most common form of iron overload disease that occurs as a primary haemochromatosis (hereditary due to genetic abnormalities) or as a metabolic disorder. It causes body to absorb and store too much of iron from gastrointestinal tract. Haemosiderosis is a secondary haemochromatosis caused by excessive blood transfusions. Secondary haemochromatosis occurs as a result of severe chronic haemolysis, multiple frequent transfusions, excessive parental iron supplements and excess dietary iron intake. Clinically, haemochromatosis is manifested as joint pain - most common (Arthritis), fatigue, lack of energy, abdominal pain, loss of sex drive, heart problems, liver disease, such as cirrhosis, damage to pancreas, abnormal pigmentation of skin and damage to adrenal glands.

Treatment of haemochromatosis: Desferal is a chelating agent which binds with trivalent iron and form complexes that leads to formation of ferrioxamine. The complex ferrioxamine is soluble in water and readily excreted through the kidneys. It binds with iron in the blood and enhances its elimination via urine and faeces. Hence, it is of value in the treatment of haemochromatosis.

Doses and Administration: 6.0 gm in 24 hrs - not more than this is to be given intramuscularly or by slow subcutaneous injection or intravenous (IV) infusion. By intramuscularly or subcutaneous route it must be taken over 8-24 hrs due to its short duration of effect within body. Once its infusion stops, iron removal stops shortly thereafter, hence intermittent infusion has little effect on reducing iron overload. In chronic iron overload for infusion treatment the average daily dose of 1-4 gm (20-60 mg/Kg) depending up on iron overload is given by subcutaneous or intravenous route over a period of 12 hrs.

b. Sickle cell disease

It is a lifelong genetic disorder characterized by abnormal, rigid and sickle shaped red blood cells (RBCs) that needs repeated blood transfusions. Iron overload in these cases is likely to be detected after 20 transfusions. Iron overload can be detected by monitoring serum ferritin level but study of liver biopsy is more accurate test for the diagnosis. Desferal is the treatment for sickle cell disease.

c. Thalassemia major

It is a genetically transmitted haemoglobin abnormality that leads to anaemia. It needs multiple transfusions because of which iron overload is likely to occur after the first 10-20 transfusions (near the age of three years). Iron overload is monitored by serum ferritin level (serum ferritin level > 1000 microgram/L is an indicator) but this test is not reliable, hence for confirmation liver biopsy and MRI are used. Desferal is the drug used for the treatment of thalassemia major (31-35).

4. Siderophores in the Treatment of Malaria - Antimalarial Activity

Some siderophores have been found to be useful in the treatment of malaria caused by Plasmodium falciparum. Desferrioxamine B produced by Streptomyces pilosus (now produced by chemical synthesis also) is active against P. falciparum in vitro as well as in vivo. This agent enters the parasite and causes intracellular iron depletion. This agent conjugated with methylanthra nic acid shows 10- fold higher in vitro activity against P. falciparum, which could be increased further by using naldixidic acid as a conjugate against multidrug resistant P. falciparum. The mode of action of this conjugate is metal-catalyzed oxidative DNA damage (36-38).

5. Siderophores in the Removal of Transuranic Elements

The development of electricity generation by nuclear energy has led to increased human exposure to transuranic elements such as aluminium. Siderophores can be used to remove such elements from the body.

a. Removal of Aluminium

Aluminium overload occurs in dialysis encephalopathy (is a major complication of long - term dialysis, which is caused by the accumulation of aluminium in the brain) and dialysis patients with end stage renal failure (ESRF). In the treatment of chronic aluminium overload - Desferol can mobilize and chelate tissue bound aluminium forming an aluminiumoxamino complex, which are freely soluble in water and are readily excreted through the kidneys (urine) and may also be excreted in faeces. Desferol forms complex with aluminium ions, hence can be used in the treatment of aluminium overload. It is given as a single dose, slow intravenous infusion - 50 mg/kg (15 mg/kg/h). In children with ESRF - 15-20mg/kg is given. In chronic aluminium overload with ESRF -5.0 mg/kg IV infusion (15 mg/kg/h) once weekly for three months. Monitoring Criteria -Aluminium level is to be monitored properly. The aluminium level of 60 ng/ml and aluminium related bone diseases (diagnosed by bone biopsy) are the criteria for monitoring the same.

b. Removal of Vanadium

Desferal can also be used for removal of vanadium from the body. It has been found that in rats, desferal reduced the vanadium content in kidney by 20%, in lungs by 25% and in liver by 26%. It has been found that desferal increases the urinary and faecal excretion of vanadium. It is poorly absorbed through gastrointestinal tract (GIT). Inhalation causes adverse effects on the respiratory tract. Oral / inhalation exposures - affect blood parameters and create liver problems, neurological problems and problems in other organs. These effects have been studied in rats (39-42).

6. Other Uses of Siderophores

a. Deodorant - Siderophore from Klebsiella pneumoniae has been used in cosmetics as deodorant (43).

b. Cancer Therapy - Some siderophores, e.g. desraxoamine, O- trensox, desferriexochelins, desferrithiocin, tachypyrilide, have been found useful in cancer therapy (24).

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