



Iron gies in systemic metal overload, neurodegeneration and cancer.chelating strate.

Autorzy

Elżbieta Gumienna-Kontecka

Monika Pyrkosz-Bulska

Agnieszka Szebesczyk

Małgorzata Ostrowska

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Streszczenie

Iron is a trace element required for normal performance of cellular processes. Because both the deficiency and excess of this metal are dangerous, its absorption, distribution and accumulation must be tightly regulated. Disturbances of iron homeostasis and an increase in its level may lead to overload and neurodegenerative diseases. Phlebotomy was for a long time the only way of removing excess iron. But since there are many possible disadvantages of this method, chelation therapy seems to be a logical approach to remove toxic levels of iron. In clinical use, there are three drugs: desferrioxamine, deferiprone and deferasirox. FBS0701, a novel oral iron chelator, is under clinical trials with very promising results. Developing novel iron-binding chelators is an urgent matter, not only for systemic iron overload, but also for neurodegenerative disorders, such as Parkinson's disease. Deferiprone is also used in clinical trials in Parkinson's disease. In neurodegenerative disorders the main goal is not only to remove iron from brain tissues, but also its redistribution in system. Few chelators are tested for their potential use in neurodegeneration, such as nonhalogenated derivatives of clioquinol. Such compounds gave promising results in animal models of neurodegenerative diseases. Drugs of possible use in neurodegeneration must meet certain criteria. Their development includes the improvement in blood brain barrier permeability, low toxicity and the ability to prevent lipid peroxidation. One of the compounds satisfying these requirements is VK28. In rat models it was able to protect neurons in very low doses without significantly changing the iron level in liver or serum. Also iron chelators able to regulate activity of monoamine oxidase were tested. Polyphenols and flavonoids are able to prevent lipid peroxidation and demonstrate neuroprotective activity. While cancer does not involve true iron overload, neoplastic cells have a higher iron requirement and are especially prone to its depletion. It was shown, that desferrioxamine and deferasirox

are antiproliferative agents active in several types of cancer. Very potent compounds with possible use as anticancer drugs are thiosemicarbazones. They are able to inhibit ribonucleotide reductase, an enzyme involved in DNA synthesis. Because the relationship between the development of overload / neurodegenerative disorders, or cancer, and iron are very complex, comprehension of the mechanisms involved in the regulation of iron homeostasis is a crucial factor in the development of new pharmacological strategies based on iron chelation. In view of various factors closely involved in pathogenesis of such diseases, designing multifunctional metal-chelators seems to be the most promising approach, but it requires a lot of effort. In this perspective, the review summarizes systemic iron homeostasis, and in brain and cancer cells, iron dysregulation in neurodegenerative disease and possible chelation strategies in the treatment of metal systemic overload, neurodegeneration and cancer.

Słowa kluczowe

cancer, chelating agents, Iron, iron overload, neurodegeneratives diseases

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