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Cell functions impaired by frataxin deficiency are restored by drug-mediated iron relocation

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Abstract

Various human disorders are associated with misdistribution of iron within or across cells. Friedreich ataxia (FRDA), a deficiency in the mitochondrial iron-chaperone frataxin, results in defective use of iron and its misdistribution between mitochondria and cytosol. We assessed the possibility of functionally correcting the cellular properties affected by frataxin deficiency with a siderophore capable of relocating iron and facilitating its metabolic use. Adding the chelator deferiprone at clinical concentrations to inducibly frataxin-deficient HEK-293 cells resulted in chelation of mitochondrial labile iron involved in oxidative stress and in reactivation of iron-depleted aconitase. These led to (1) restoration of impaired mitochondrial membrane and redox potentials, (2) increased adenosine triphosphate production and oxygen consumption, and (3) attenuation of mitochondrial DNA damage and reversal of hypersensitivity to staurosporine-induced apoptosis. Permeant chelators of higher affinity than deferiprone were not as efficient in restoring affected functions. Thus, although iron chelation might protect cells from iron toxicity, rendering the chelated iron bioavailable might underlie the capacity of deferiprone to restore cell functions affected by frataxin deficiency, as also observed in FRDA patients. The siderophore-like properties of deferiprone provide a rational basis for treating diseases of iron misdistribution, such as FRDA, anemia of chronic disease, and X-linked sideroblastic anemia with ataxia.

Topics: aconitate hydratase, iron, mitochondria, deferiprone, chelating agents, cytosol, iron chelating agents, dna, mitochondrial, oxidation-reduction, adenosine triphosphate

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Drugs Used to Treat Iron Deficiency Anemia. The following list of medications are in some way related to, or used in the treatment of this condition. Select drug class. All drug classes - iron products (51) - vitamin and mineral combinations (7) - phosphate binders (2). Rx. OTC. Brand names: Feosol Original, Slow Fe, FeroSul, Fer-In-Sol, Slow Release Iron, Ferrousal, Fer-Iron, Fe Caps, Fer-Gen-Sol, Feratab, Ferra T.D. Caps, Ferro-Bob ...show all. Drug class: iron products. For consumers: dosage, interactions, For professionals: A-Z Drug Facts, Prescribing Information. The function of frataxin is not clear but it is involved in assembly of iron-sulfur clusters. It has been proposed to act as either an iron chaperone or an iron storage protein. Reduced expression of frataxin is the cause of Friedreich's ataxia. Contents. Frataxin mRNA is predominantly expressed in tissues with a high metabolic rate (including liver, kidney, brown fat and heart). Mouse and yeast frataxin homologues contain a potential N-terminal mitochondrial targeting sequence, and human frataxin has been observed to co-localise with a mitochondrial protein. Furthermore, disruption of the yeast gene has been shown to result in mitochondrial dysfunction.