IRON UPTAKE AND INTRACELLULAR IRON DISTRIBUTION IN CULTURED RAT HEART CELLS: EFFECTS OF IRON CHELATORS.

B.R. Byers, C.V. Sciortino, P. Cox and P. Robinson

University of Mississippi Medical Center, Department of Microbiology, Jackson, MS 39216 USA.

ABSTRACT.

Primary cultures of beating rat heart muscle cells were shown to be a good model system for studies of iron uptake and intracellular iron metabolism. Iron uptake from several iron sources was rapid and ferritin was visualized (by electron microscopy) within 48-96 hours after addition of iron. Iron was distributed in various cellular fractions; an iron-containing cytosol component(s) (non-ferritin) that may represent a "pool" of iron was evident. The cultured rat myocytes were used to screen chelators that might become useful in therapy of human iron overload. One chelator, agrobaactin, was significantly more effective than the drug deferoxamine in reduction of iron uptake from transferrin-iron by the cells; however, enterobactin increased iron uptake from this source. Deferoxamine inhibited incorporation of iron into ferritin and increased the amount of iron in the non-ferritin cytosol fraction. Therefore, some of these chelators may be useful probes in studies of intracellular iron metabolism.

INTRODUCTION.

The essentiality of iron in most (if not all) biological systems is undisputed and the complex interactions of mammalian iron metabolism have been the subject of many studies. In humans iron absorption occurs mainly in the small intestine; mucosal cells pass the iron into circulation where the metal binds with the iron transport protein, transferrin. The transferrin-iron complex delivers iron to cells (probably through specific transferrin receptors on the surfaces of these cells),

Figure 1. Relationships in intracellular iron metabolism. Modified from Jacobs (3).

although other forms of iron also may be assimilated. There is no specific physiological mechanism for excretion of excess iron and iron overload caused by abnormally increased absorption or by parenteral intake can result in tissue damage and sometimes death. For example, persons with Cooley's anemia (homozygous \( \beta \)-thalassemia) require lifelong blood transfusions with the inevitable complication of iron toxicity that eventually is fatal, often from congestive heart failure. These aspects of mammalian iron metabolism are discussed fully in several excellent publications (e.g., 1,2,3).

Although the knowledge of movement of iron within the whole animal is extensive, less is known about the intracellular pathways of iron. Hypotheses explaining the intracellular flow of iron have been published (4,5,6). Iron is seen to enter the cells from transferrin-iron (or other iron-containing molecules) where the metal becomes associated with an unidentified molecule(s) to form a "pool" of available iron (Figure 1). Iron is delivered from the pool to iron-requiring cellular systems and to the storage depot, ferritin. Iron may be mobilized from ferritin for metabolic use. Overload of the pool may lead to toxic deposition of iron and consequent cell damage.

CELLULAR IRON METABOLISM: MODEL SYSTEMS.

As discussed by Bailey-Wood, et. al. (7), much of the knowledge of intracellular iron metabolism is derived from studies of erythrocytes (which are atypical in several ways) and there is need for model systems of single cell types for study of iron uptake and intracellular iron distribution. They selected Chang cells, a stable laboratory cell line that can be cultivated in suspension. In a series of studies with Chang cells (see reference 8 and publications cited therein) iron uptake and its distribution to various cell fractions (including ferritin) were described.