Thesis Title Studies on the Ca^{2+}- ATPase of Thalassemic Red Blood Cell Membranes

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ABSTRACT

Thalassemia is a genetically inherited hemolytic disorder caused by imbalance synthesis of the globin chains. Accumulation of calcium ions has been reported in the thalassemic erythrocytes. Regulation of very low concentration of Ca^{2+} ions in normal human erythrocytes is accomplished by two mechanisms: slow inwards transport of the Ca^{2+} ions by selective permeability of the membrane and high efficiency protrusion of the Ca^{2+} ions by the membrane-bound Ca^{2+}-ATPase.

The abnormalities of the Ca^{2+} pump-ATPase have been elucidated by study of Arrhenius curve , response to calmodulin stimulation, Ca^{2+}-dependency, and the formation of phosphoenzyme intermediate. The Ca^{2+}-ATPase of erythrocytes from all types of thalassemias showed loss of calmodulin response, changes in the Arrhenius properties with the disappearance of the discontinuity at 32°C, a decrease in the value of activation energy at

temperture lower than 32°C, and an increase in the Ca^{2+}/calmodulin-independent ATPase activity. The Ca^{2+} pump-ATPase from all types of thalassemias showed loss in the ability to form phosphoenzyme intermediate. These observations suggest an uncoupling of the two activities, ATPase and Ca^{2+}-translocation, which locate on different active centers on the plasma membrane Ca^{2+} pump.

The cause of the damages to the thalassemic Ca^{2+}- ATPase was investigated by examining the oxidative effects of oxygen free-radicals. Normal erythrocytes were treated with various oxidants (phenazine methosulphate, phenylhydrazine, tert-butylhydroperoxide and xanthine oxidase) and the Arrhenius properties, calmodulin response, and Ca^{2+}-dependency were examined. The results showed that the changes in the properties of the enzyme from oxygen free-radical treated erythrocytes were very similar to those observed in thalassemic erythrocytes.

In addition, the effects of oxygen-free radicals to increase in Ca^{2+}-permeability have also been observed in experiments on human erythrocytes.

It was concluded in this study that an accumulation of Ca^{2+}ions in thalassemic erythrocytes could caused by both uncoupling of the Ca^{2+} pump and increase in Ca^{2+}-permeability. The effects could be the consequences of intracellular overproduction of oxygen free-radicals following precipitation of hemoglobin onto the erythrocyte plasma membrane.