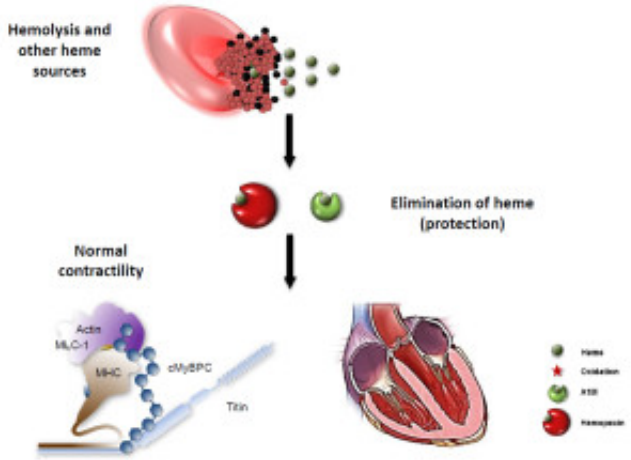
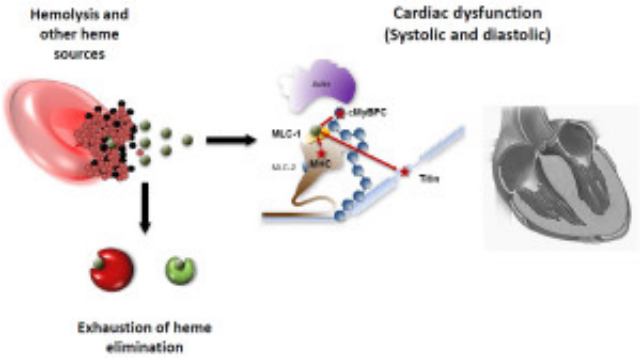
Heme: an old player with a novel mechanism in cardiac muscle contractility

Heme is a complex containing iron and protoporphyrin IX and it is commonly bound to proteins involved in oxygen transport, detoxification and energy production. However, this molecule has been known to have toxic effects in the heart. Therefore in the physiological environment this molecule has been under control by heme scavenger's proteins such as hemopexin and alpha 1 macroglobulin.



There are some diseases such as thalassemia and sickle cell disease in which the heme is found to be increased in the bloodstream and, as a consequence, in several tissues of the human body. In these diseases the patients present heart symptoms without a fully understanding of the mechanism of this condition. Furthermore, in 2013, researchers found increased levels of heme in hearts with heart failure diagnosis. All these conditions present heart problems in the first part of the bombing cycle called systole but specifically in the second part called diastole. The exact mechanism of this problem has not been elucidated completely. Heart failure is a condition that is present as the last stage of all cardiac diseases characterized by alteration in morphology and function of cardiac cells, and is considered as one of the most common cardiac diseases.

In our study, we measured the force generation of human cardiac cells in presence of calcium (active force generation) which represent the systolic phase and in absence of calcium (passive force generation) which represent the diastole. We found that heme exposure to the cardiac cells modified importantly the morphology and leads to the functional impairment of force generation. In this case heme altered both components of the force, decreased the active force generation and increase five folds the passive force generation.



These effects were avoided by exposure to heme scavenger's proteins, hemopexin and alpha 1 macroglobulin, which protect the cells for the toxic effects of heme. Another important finding was the direct binding of heme to a contractile protein (Myosin light chain 1). This binding allows heme to oxidize a specific aminoacid call cysteine, a common component of the contractile proteins. It is known that the oxidation of this aminoacid interferes with the normal function of the contractile proteins. We could identify the proteins involved in the first phase: myosin heavy chain, cardiac myosin binding protein c and titin for the second phase.

We would like to highlight the cardiotoxic effects of heme as the first molecule described that dramatically increases the passive force generation meaning an important increase in the stiffness of the heart. Taking together all these findings, heme effects fit with the definition of heart failure. Therefore heme may explain the mechanism of the dysfunction of the Talasemia, sickle cells disease and heart failure. On the other hand our findings suggest the potential to introduce novel therapeutic measures in order to modify the course of the chronic disease such as heart failure that leads to several impediments to continue everyday life tasks. In the future, this could lead to an improvement of the quality of life in these patients.

Publication

Heme-induced contractile dysfunction in Human cardiomyocytes caused by oxidant damage to thick filament proteins.
Alvarado G, Jeney V, Tóth A, Cs?sz É, Kalló G, Huynh AT, Hajnal C, Kalász J, Pásztor ET, Édes I, Gram M, Akerström B, Smith A, Eaton JW, Balla G, Papp Z, Balla J
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