Hemozoin Formation is a Key Mechanism to Allow Oogenesis and Vectorial Capacity in a Triatomine Insect

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Introduction: Hematophagous organisms release large amounts of heme during blood digestion. Free heme is pro-oxidant and cause membrane destabilization but several organisms detoxify heme through its crystallization into hemozoin (Hz). Hz formation is inhibited by quinoline drugs and their potent antimalarial effects are thought to be a consequence of redox imbalance promoted by uncrystallized heme. However, there is no direct evidence to support this proposal.

Objective: Determine biochemical, cellular and physiological consequences of inhibition of Hz formation by quinidine in *R. prolixus*, a vector of Chagas' disease

Material and Methods: Heme, Hz, hemoglobin urate and lipid peroxides were determined by colorimetric assays. Biliverdin levels in the heart were determined by HPLC. Reactive species in posterior midgut were assessed by dihydroethidium fluorescence. Posterior midguts were observed by transmission electron microscopy. Parasites viability was measured by cell counting.

Results and Discussion: Quinidine severely affected midgut Hz formation. In posterior midgut, reactive species levels were significantly increased and ultrastructural analyses revealed reduced densities of mitochondria and presence of numerous structures similar to autophagosomes. Nevertheless, expression of some autophagy related genes does not increase. We observed increased hemeand lipid peroxidation levels, parallel to reduced urate content in the hemolymph. Protein levels of RHBP in hemolymph were increased by quinidine. Despite there is no increase of a heme oxygenase product (biliverdin) in the heart, free heme levels were increased on this tissue. Besides that, Hz formation impairment leads to a decrease of egg laying which is reversed by the administration of an antioxidant (urate) in the diet. Additionally, *Trypanosoma cruzi* infection of insects was reduced by quinoline treatment. **Conclusions**: Impairment of heme crystallization in an insect model promotes redox imbalance with systemic cellular and physiological consequences. Furthermore, inhibition of Hz formation by quinidine could be used to control vectorial transmission of Chagas' disease.

Keywords: heme, hemozoin, *Rhodnius prolixus*