Abstract

The aim of this bachelor thesis is to desbribe mechanisms of resistance to metronidazole in three anaerobic eukaryotic pathogens (*T. vaginalis*, *G. intestinalis*, *E. histolytica*). Diseases caused by these pathogens belong to the list of important but currently neglected diseases. Metronidazole acts only on microbes with an anaerobic metabolism. The drug enters the cell by passive diffusion and needs to be activated by reduction of the nitro group. Mechanisms of activation are different for every pathogen. Enzymes bound with energetic metabolism in hydrogenosomes, cytosolic thioredoxin reductase and nitroreductases play a major role in the activation. The drug damages cells in three ways – DNA damage, formation of covalent bonds with proteins, and covalent bonds with thiols. Pathogens have specific mechanisms to defend themselves against the drug. They can either down-regulate enzymes that activate metronidazole, reduce it to non-reactive aminoimidazole or they can increase the intracellular concentration of oxygen which leads to deactivation of the drug by futile cycling. These mechanisms are bound with physiological changes and subsequently with lowered viability of these pathogens. Furazolidone and benzimidazole derivatives are the best candidates to become an alternative to metronidazole for the treatment of trichomoniasis. Clinical trials are necessary for every probable alternative.