Proposal for the action mechanism for angiotensin II and derivatives on Plasmodium sporozoite membrane

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Introduction: Malaria is an infectious disease responsible for approximately one million deaths annually. Peptides such as angiotensin II and its analogs are known to have antimalarial effects against *Plasmodium*. However, their mechanism of action is still not fully understood at the molecular level. **Objective:** In the work reported here, we investigated this issue by comparing the antimalarial activity of angiotensin II with that of its enantiomer, its isomer with reversed sequence and its lactam bridged analogs, the so-called VC5 peptides. **Methodology:** Peptides were synthesized manually and tested against *Plasmodium* sporozoites. Results were obtained by fluorescence microscopy of stained sporozoites nuclei, conformational analysis were performed by Circular Dichroism in four different solvents. **Results:** Data from fluorescence microscopy indicated that the antiplasmodial activities of both *ent*-AII and *ent*-VC5 were as high as those of the related peptides AII and VC5, respectively. In contrast, *retro*-AII had no significant effect against *Plasmodium gallinaceum.* Conformational analysis by circular dichroism suggested that AII and its active analogs usually adopted a β-turn conformation in different solutions. In the presence of membrane-mimetic micelles, AII had also a β-turn conformation, while *retro*-AII was random. Molecular dynamics simulations demonstrated that the AII chains were slightly more bent than *retro*-AII at the surface of a model membrane. At the hydrophobic membrane interior, however, the *retro*-AII chain was severely coiled and rigid. AII was much more flexible and able to experience both straight and coiled conformations. **Conclusion:** We took it as an indication of the stronger ability of AII to interact with membrane headgroups and promote pore formation.

Keywords: Malaria, Peptides, Angiotensin II, Molecular Dynamics, Mechanism

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