Cyclic cell-penetrating peptides as therapeutics for Neisseria gonorrhoeae infection

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Abstract Information

Background

Neisseria gonorrhoeae has quickly developed resistance to antibiotics and the rapid emergence of multidrug-resistant (MDR) strains could result in untreatable gonorrhea. We previously reported that a linear 12 amino acid cell-penetrating peptide (CPP) was bactericidal for MDR strains of N. gonorrhoeae. In the current study, we hypothesized that the potency of the CPP could be increased by cyclization to constrain secondary structure and increase stability.

Aim/Methods

We synthesized cyclic CPP using head-to-tail macrocyclization and performed bactericidal assays as a measure of potency. Survival of two MDR strains, F89 (WHO Y), H041 (WHO X), and one human challenge strain, FA1090 1-81-S2, was determined after treatment with increasing concentrations of the cyclic and linear CPP for 4 h. To assess anti-inflammatory activity, the expression of TNF-α by THP-1 monocytic cells infected with gonococci in the presence of increasing concentrations of CPP was quantified. To determine CPP activity in a more physiological environment, bactericidal assays were performed in the presence of THP-1 monocytic and ME-180 cervical cells in cell culture media containing 10% FBS for 4 h. Bactericidal activity of the CPP for three commensal strains, N. lactamica, N. flavescens, and N. subflava and for gram-positive Staphylococcus aureus was tested.

Results

The linear and cyclic CPP were bactericidal for all three gonococcal strains, however the strains were significantly more susceptible to cyclic CPP compared to linear CPP in the concentration range of 4-100 μM. Similarly, in the presence of THP-1 and ME-180 cells, the cyclic CPP was significantly more bactericidal than the linear CPP. The levels of TNF- secreted by THP-1 cells infected by gonococci were reduced to a greater degree by treatment with the cyclic CPP compared to the linear CPP. Commensal strains were more susceptible to the cyclic CPP, whereas S. aureus was resistant with an MIC of >100 μM.

Conclusions

The data supports our postulate that cyclization of CPP would increase potency for the bactericidal killing of gonococci. This increased potency is likely due to the more rigid conformation of the cyclic form, which could increase its penetration of bacteria or its affinity for DNA intracellularly.