MECHANISM OF ACTION OF ANTIMICROBIAL PEPTIDES: DIFFERENT EFFECTS OF β-SHEET AND α-HELICAL PEPTIDES.

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We examined the effects of two β-sheet protegrins (PG-1 and IB-367) and two α-helical cathelicidin peptides (LL-37 and RL-37) on microbial membranes. When we performed permeability assays on membrane vesicles made of *E.coli* total lipid extract, PG-1 and IB-367 induced leakage of negatively and positively charged dye molecules. In contrast, LL-37 and RL-37 only induced the leakage of positively charged dye molecules. Both PG-1 and IB-367 caused rapid and extensive loss of K^+ from intact *E.coli*, and then caused them to swell. In contrast, LL-37 and RL-37 did neither. The mean diameters of liposomes prepared from *E.coli* lipids increased by 20-40% after exposure to IB-367 or PG-1. In contrast, exposure to LL-37 or RL-37 had no effect on vesicle size. We performed membrane permeability assays on *E.coli* ML-35p in the presence of polyethyleneglycols (PEGs) whose mean mass ranged from 60 to 1400 Da. The effects of the PEG-osmoprotectants indicated that the membrane pores formed by PG-1 and IB-367 were larger than those made by LL-37 or RL-37. Membrane conductance assays were done on planar lipid bilayers, and showed that LL-37 and RL-37 formed stable, well-defined channels, but PG-1 and IB-367 did not. Overall, these differences suggest that the β-sheet protegrins (PG-1/IB-367) and the primate α-helical cathelicidins (LL-37 and RL-37) act against bacterial membranes in very different ways to cause microbial damage.