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# Human neutrophil defensins inhibit infectivity of many influenza viral strains but increase infectivity of 2009 pandemic H1N1

**Tesfaldet Tecle[1], Mitchell R. White[1], Li Qi[2], Jeffrey Taubenberger[2] and Kevan L. Hartshorn[1]**

[1]Department of Medicine, Boston University School of Medicine
[2]Laboratory of Infectious Diseases, National Institutes of Allergy and Infectious Diseases, National Institutes of Health, USA

**Rationale**: Influenza A virus (IAV) remains a major cause of morbidity and mortality. Human neutrophil defensins (HNPs) are released in large quantities from neutrophil primary granules and have antiviral, antibacterial and immune modulatory effects that could be important during innate defense against IAV. The goals of this research were to determine the mechanisms of action of HNPs against seasonal IAV and compare these findings with its effects vs. the 2009 H1N1 pandemic IAV (pH1N1).

**Methods and Results:** HNPs had broad spectrum antiviral activity against various seasonal and laboratory strains of IAV as evidenced by decreased viral protein or RNA synthesis, or viral RNA release, from A549 cells. HNP did not reduce viral uptake by the cells but inhibited replication at an early phase of the viral life cycle. HNPs did not cause apparent degradation of viral membranes on electron microscopy but do cause viral aggregation and increase viral uptake by neutrophils or monocytes. These findings are being characterized further with confocal microscopy and other methods. The mechanism of viral neutralizing activity of HNPs differed from those of another human antimicrobial peptide produced by neutrophils, LL-37. Unexpectedly we found that HNPs increase infectivity of pH1N1 (in striking contrast to their inhibitory effects on seasonal H1N1 or H3N2 strains). We are investigating the mechanisms through which HNPs increase infectivity of pH1N1 and comparing the results with a large panel of synthetic defensins.

**Conclusions:** HNPs have mechanisms of antiviral and immune modulatory activity that are distinct from those of LL-37. Although HNPs have broad spectrum antiviral activity vs. seasonal and laboratory IAV strains they paradoxically increase infectivity of pH1N1. This could be a contributory factor to the increased severity of pH1N1 infection in some subjects.