Hepatitis C virus (HCV) entry is a multiple-step process involving a number of host factors and hence represents a promising target for new antiviral drug development. In search of novel inhibitors of HCV infection, we found that a human apolipoprotein E (apoE) peptide, hEP, containing both a receptor binding fragment and a lipid binding fragment of apoE, specifically blocked the entry of cell culture grown HCV (HCVcc) at sub-micromolar concentrations. hEP caused little cytotoxicity in vitro and remained active even if left 24 hours in cell culture. Interestingly, hEP inhibited neither HIV-HCV pseudotypes (HCVpp) nor HIV and Dengue virus (DENV) infection. Further characterization mapped the anti-HCV activity to a 32-residue region that harbors the receptor binding domain of apoE, but this fragment must contain a cysteine residue at the N-terminus to mediate dimer formation. The anti-HCV activity of the peptide appears to be dependent on both its length and sequence and correlates with its ability to bind lipids. Finally, we demonstrated that the apoE-derived peptides directly blocked the binding of both HCVcc and patient serum-derived virus to hepatoma cells as well as primary human hepatocytes.

CONCLUSION: apoE peptides potently inhibit HCV infection and suggest a direct role of apoE in mediating HCV entry. Our findings also highlight the potential of developing apoE mimetic peptides as novel HCV entry inhibitors by targeting HCV-host interactions.