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Studies on the antiviral activity of lactoferrin and ribavirin upon hantavirus

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Bovine lactoferrin (LF) and ribavirin (Rbv) were tested as antiviral agents against Seoul type hantavirus (SR-11 strain) *in vitro*. Hantaviral foci number in Vero E 6 cells infected with SR-11 were reduced with LF treatment by 5 days post infection. When LF was added at the time of infection, the 50% effective dose (ED₅₀) was 2,500 µg/ml, while pre-treatment with LF was highly efficacious having an ED₅₀ of 39 µg/ml. Conversely, 1 hr pre-treatment with Rbv revealed no inhibition of viral focus formation but significantly reduced the number of viral foci (ED₅₀ : 10 · µg/ml) when used from the time of viral infection. One hour pre-treatment of the cell monolayer with LF and subsequent addition of Rbv revealed a synergistic anti-hantaviral effect against SR-11, < 20 focus forming units (FFU) / ml as compared to 105 FFU / ml in the control. One hour treatment of SR-11 with LF prior to virus inoculation gave an ED₅₀ of 312.5 µg/ml. Whereas, washing the LF-pretreated cell monolayer with phosphate buffered saline (PBS) demonstrated minimal focus reduction, suggesting that LF lightly adheres to cells. These results indicate that LF has anti-hantaviral activity *in vitro* and inhibition of virus adsorption to cells which play an important role in revealing the anti-hantaviral activity of LF.

Mechanisms of anti-hantaviral activity of bovine lactoferrin (LF) or ribavirin (Rbv)

were investigated. Hantavirus focus formation at 48 h was 15% of the control in cells treated with 400 µg/ml LF for 1 hr at 37 C prior to viral infection. Post infection treatment of 100 µg/ml Rbv also inhibited the focus formation to 2.5% of the control. Combined LF pre- and Rbv post-infection treatment completely inhibited focus formation. Viral glycoprotein (G 2) and nucleocapsid protein (NP) syntheses were delayed in LF pre-treated cells up to 24 hours post infection (hpi) but became comparable to the control by 48 hpi. Further, LF inhibited viral yield at 24 hpi but could not inhibit viral yield after 48 hpi. However, Rbv was able to inhibit synthesis of viral proteins, (+) and (-) strand RNAs as well as inhibit viral yield after 24 hr. These results suggest that LF inhibits viral adsorption to cells while Rbv inhibits viral RNA synthesis. For *in vivo* trials of LF and Rbv, LF pre- and Rbv post-treatment were evaluated in suckling mice infected with hantavirus, which the survival rate was 7 %. LF concentrations of 40 and 160 mg/kg administered prior to viral challenge improved survival rates to 15% and 70%, respectively for single administration and 85% and 94%, respectively for double administration. Rbv concentrations of 25 and 50 mg/kg had survival rates of 68% and 81%, respectively. This suggests that both LF and Rbv are efficacious in hantavirus infection *in vivo*.