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Aprotinin, a protease inhibitor, as a drug against influenza

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Research efforts are focusing on development of new antiviral chemotherapeutic approaches that target either influenza virus replication itself or host factor(s) that are critical to influenza replication. Host mediated influenza hemagglutinin (HA) cleavage critical for activation of virus infectivity is such a chemotherapeutic target. Influenza pathogenesis develops through a “vicious cycle”: host proteases activate progeny virus which amplifies replication and stimulates protease activities in infected host. Aprotinin, a 58 amino acid polypeptide from bovine lung, is one of a family of the host-targeted antivirals that inhibits serine proteases involved in influenza virus activation. This drug was shown to suppress virus HA cleavage and multicycle reproduction of human and avian influenza viruses with a single arginine in the HA cleavage site. Site-directed structural modifications of aprotinin are possible to increase its intracellular targeting against cleavage of highly virulent H5 and H7 hemagglutinins possessing multi-arginine/lysine cleavage site. Additionally, serine protease inhibitors, including aprotinin, are known to target a number of host mediators of inflammation and down regulates their levels in virus-infected hosts. Aprotinin is a generic drug approved for intravenous use to treat pancreatitis and limit post-operative bleeding. As an antiinfluenzal compound, aprotinin can be delivered by two routes: (i) a middle-particle aerosol has been used for local respiratory application in mild-to-moderate influenza and (ii) an intravenous administration is proposed for severe influenza to provide both an antiviral effect and a decrease in systemic inflammation.