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Mode of Action of SP-303 against Respiratory Syncytial Virus (RSV)

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A natural product polyphenolic polymer of molecular weight 2100, designated as SP-303, has been found in previous studies to have antiviral activity against certain orthomyxo and paramyxoviruses, including RSV (P.R. Wyde, et al. 1991 Antiviral Res. Suppl. I :67, #45). In that study RSV was inhibited by 50% at a concentration of 5 ± 1.6 μM (11 ± 3 μg/ml), and the 50% cytotoxic dose in HEp-2 cells was 121 ± 41 μM (254 ± 86 μg/ml). For this study experiments were done to determine the mode(s) of inhibition of RSV by this compound, including virucidal and interferon induction tests. The 99% virucidal concentration was 69 μM (144 μg/ml). SP-303 did not induce interferon. To answer the question whether SP-303 inhibition of RSV infection might occur inside or outside of the cell, assays were done to determine if radiolabeled SP-303 penetrated cells. After a 2 h exposure to the compound, less than 1% of [^{3}H] SP-303 penetrated HEp-2 cells, implying that the compound did not inhibit virus replication by penetrating cells. This suggested that the attachment, fusion or penetration stages of the infectious cycle of the virus might be inhibited by SP-303. The compound did not inhibit RSV-induced cell to cell fusion. SP-303 did inhibit attachment of infectious virus in a syncytia-forming assay. In a radiolabeled virus particle attachment assay, the ED_{50} for inhibition of attachment was 29 ± 2.6 μM (60 ± 5.42 μg/ml). SP-303 also inhibited virus penetration as detected by plaque assay. The ED_{50} for inhibition of penetration was 769 nM (1.67 μg/ml). Additional experiments were performed to show that SP-303 did bind specifically to purified virus (K_d = 23 ± 10 nM, β_{max} = 9.6 ± 3 pmoles). These results suggest that the interaction of SP-303 with RSV causes an inhibition of penetration of RSV into cells, and that this inhibition is an important mode of inhibition of RSV infection.

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LY217896: Studies on the Mechanism of Antiviral Activity. J. M. Colacino*, G. M. Birch, and J. C. Tang. Lilly Research Laboratories, Indianapolis, Indiana 46285, USA.

LY217896 (LY; 1,3,4-thiadiazol-2-ylcyanamide) is a 2-substituted thiadiazole that is an effective inhibitor of influenza A and B viruses *in vitro* and in the mouse infection model. Recent experiments have helped to explain partially the underlying mechanism of antiviral activity. Similar to that of ribavirin or 2-aminothiadiazole (ATD), the *in vitro* anti-influenza activity of LY is reversed by an equimolar or 10-fold excess amount of guanine or guanosine. Like ribavirin, LY (1 or 10 μg/ml) effected a selective decrease in the levels of intracellular pools of GTP in MDCK cells. The extent of antiviral activity or cytotoxicity of LY is positively correlated with the amount of LY metabolite formed intracellularly as detected in perchloric acid soluble cell extracts. A cell line resistant to 50 μg/ml LY (LY^r) was derived from parental MDCK cells. LY^r cells were able to undergo log phase replication in LY (1 μg/ml) and were unable to metabolize the compound. Furthermore, LY had no antiviral activity against influenza A/Ann Arbor or vaccinia virus (VV) in LY^r cells (IC_{50} >100 μg/ml). In contrast, LY inhibited influenza A/Ann Arbor (IC_{50} = 0.7 μg/ml) or VV (IC_{50} = 0.07 μg/ml) in the parental MDCK cells. Similarly, ribavirin was much less active against VV in LY^r cells (IC_{50} = 5 μg/ml) than in parental, susceptible cells (IC_{50} = 0.3 μg/ml). Taken together, these data indicate that the mechanism of antiviral activity of LY may be similar, in some respects, to that of ribavirin.