

Oral Session III

Mechanism of Action

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Mechanism of Action of Amantadine against the M2 Protein of Influenza A Viruses

A.J. Hay, R.J. Sugrue, S.A. Wharton and F. Ciampor*

Division of Virology, National Institute for Medical Research, Mill Hill, London, NW7 1AA; and

*Institute of Virology, Dubravska Cesta 9, 84246 Bratislava, Czechoslovakia.

Amantadine specifically inhibits the function of the M2 protein, a minor component of the virus envelope, which is involved in two stages of influenza A virus replication, in an aspect of virus uncoating distinct from membrane fusion *per se* and in preserving the structural integrity of the acid-sensitive haemagglutinin during its transport to the plasma membrane of infected cells. In the latter case, by causing a reduction in the pH of vesicles of the trans Golgi network, amantadine effects an M2-mediated conversion of HA to its low pH conformation and as a consequence blocks virus maturation. Evidence regarding the nature of this phenomenon together with the structural characteristics of the protein indicate that the M2 tetramer forms an ion channel, possibly involved directly in the transfer of H⁺. Its role in virus disassembly will be discussed. The location of amino acid changes which confer drug resistance within the transmembrane domain indicates that the antiviral action is analogous to the 'channel-blocking' anticholinergic activity of various adamantane derivatives.