

Antiviral Therapy

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Diagnosis of Viral Infections

- **Clinical suspicion**
 - Is syndrome diagnostic of a specific entity?
 - Is viral disease in the differential diagnosis of a presenting syndrome?
- **Knowledge of appropriate specimen(s) to send**
 - Blood
 - Body fluids
 - Lesion scraping
 - Tissue
 - Proper transport is essential

Challenges to the Development of Effective Antiviral Agents

- Myriad number of agents
- Need knowledge of replication at molecular level to define targets
 - Viruses as intracellular parasites make targeting more difficult to avoid host toxicity
- Lack of culture systems for some agents hinders development
- High through-put screening plus 'rational' drug design are both labor intensive and expensive

Herpes Zoster



Challenges to the Development of Effective Antiviral Agents

- Pathogenesis of certain agents makes therapy a challenge even in the face of defined targets
- Clinical presentation of acute viral infections may be at peak of viral replication in vivo
 - May have a small window to intervene effectively
 - Need rapid diagnostic procedures

Progress in Antiviral Therapy

Herpesviruses (HSV, VZV, CMV)	Acyclovir, famciclovir, valacyclovir, ganciclovir, cidofovir, formivirsen, valganciclovir
HIV-1	25 approved agents
Influenza	Amantadine, rimantadine, zanamivir, oseltamivir
Resp. syncytial virus	Ribavirin
Hepatitis B	3TC, FTC, adefovir, tenofovir, entecavir, telbivudine
Hepatitis C	pegIFN-ribavirin
Papillomaviruses	IFN, ?Cidofovir
Poxviruses	?Cidofovir
JC virus	?Cidofovir

Non-HIV Antiviral Therapy: Targets

- Herpesviruses
- Respiratory viruses
- Hepatitis viruses
- Others

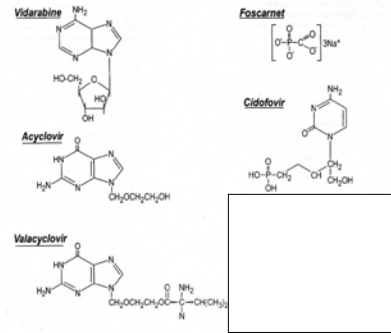
Anti-Herpesvirus Agents

Drug	Description	Active Moiety	Target Agents	Route of Admin	Toxicities
Foscarnet	Pyro-phosphate analog	Parent drug active	CMV, HSV	Intravenous	Renal, metabolic
Cidofovir	Nucleotide analog	Di-phosphate	CMV, HSV, HPV, pox	Intravenous	Renal, ocular
Formivirsen	Antisense oligo-NT: binds to CMV mRNA	Parent drug active	CMV	Intraocular	Ocular
Trifluridine	Nucleoside analog	Tri-phosphate	HSV keratitis	Topical	Ocular
Idoxuridine	Nucleoside analog	Tri-phosphate	HSV keratitis	Topical	Ocular

Anti-Herpesvirus Agents

- Acyclovir
- Valacyclovir
- Famciclovir
- Ganciclovir
- Valganciclovir
- Foscarnet
- Cidofovir
- Formivirsen
- Trifluridine
- Idoxuridine

Anti-Herpesvirus Agents



Anti-Herpesvirus Agents

Drug	Description	Active Moiety	Target Agents	Route of Admin	Toxicities
Acyclovir	Acyclic nucleoside	Tri-phosphate	HSV, VZV	Oral, intravenous, topical	Renal, Neuro
Val-ACV	Ester prodrug of acyclovir	Tri-phosphate	HSV, VZV	Oral	Renal, Neuro
Penciclovir	Acyclic nucleoside	Tri-phosphate	HSV	Topical	Local irritation
Famciclovir	Ester prodrug of penciclovir	Tri-phosphate	HSV, VZV	Oral	Headache, nausea
Ganciclovir	Acyclic nucleoside	Tri-phosphate	CMV, HSV, VZV	Intravenous, oral, intraocular	Hematologic
Val-GCV	Ester prodrug of ganciclovir	Tri-phosphate	CMV	Oral	Hematologic

Anti-Herpesvirus Agents

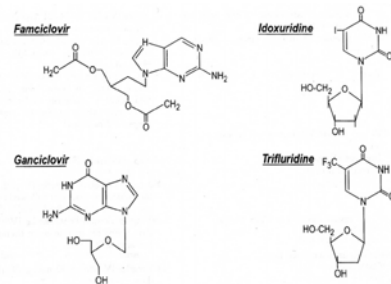


FIGURE 11-1. Chemical structures of antihherpesviral agents.

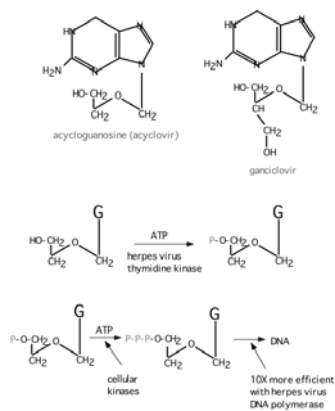
Acyclovir I

- Development represents a watershed in the field of antiviral chemotherapy
- Acyclic guanosine analog
- Active vs. HSV, VZV and modestly CMV
- Mechanism of action
 - Preferentially taken up by virally infected cells
 - Monophosphorylated by virally encoded thymidine kinases
 - Di- and triphosphorylation completed by cellular kinases
 - ACV-TP is the active moiety
 - Competitive inhibitor of viral DNA polymerase
 - Cellular DNA polymerases much less susceptible to inhibition
 - Leads to viral DNA chain termination

Anti-Respiratory Virus Agents

- Amantadine
- Rimantadine
- Zanamivir
- Oseltamivir
- Ribavirin

Acyclovir: Mechanism of Action



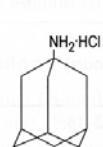
Amantadine and Rimantadine

- Tricyclic amines
- Active vs. influenza A only at clinically achievable concentrations
- Mechanism of action
 - Interference with function of viral M2 protein
 - M2 protein acts as an ion channel facilitating the hydrogen ion mediated dissociation of the matrix protein from the nucleocapsid
- Pharmacology:
 - Orally bioavailable
 - Amantadine: renal excretion
 - Rimantadine: hepatic metabolism and renal excretion
- Major toxicity
 - Neurotoxicity: amantadine > rimantadine
- Useful for treatment and prophylaxis of influenza A infections
 - Should not be used when amantadine resistant strains are in circulation
- Resistance mediated by mutations in M2 coding region

Acyclovir II

- Pharmacology
 - Administered by oral, intravenous and topical routes
 - Oral bioavailability 15-30%
 - $T_{1/2}$ 3 hrs
 - Primarily renally excreted
- Toxicities
 - Headache, nausea
 - Renal
 - Neurologic
- Resistance
 - Mediated by mutations in viral thymidine kinase and/or viral DNA polymerase genes
 - TK-deficient and TK altered virus can be produced
 - Clinically significant infections can be caused by drug resistant HSV and VZV

Amantadine



Rimantadine

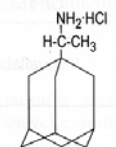


FIGURE 11-7. Chemical structures of amantadine and rimantadine.

Influenza Virus Replication Cycle

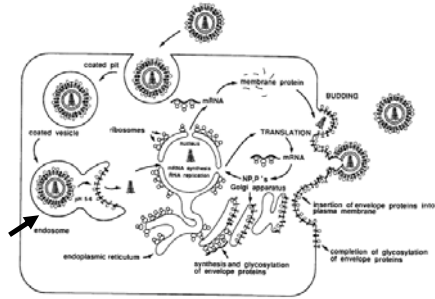
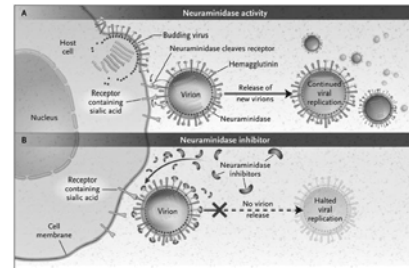


FIG. 13. Schematic diagram of the life cycle of influenza virus. See text for details of the model.

From Fields Virology

Mechanism of Action of Neuraminidase Inhibitors



Moscona, A. N Engl J Med 2005;353:1363-1373



Uncoating of Influenza Virus

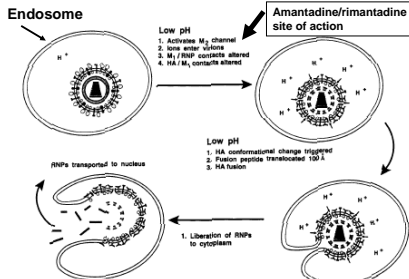


FIG. 14. Schematic diagram of the proposed role of the M₂ ion channel activity in virus entry. The M₂ ion channel activity is thought to facilitate the flow of protons from the lumen of the endosome into the virion, bringing about dissociation of protein-protein interactions between the HA cytoplasmic tail and M₂ and lipid and/or RNPs and M₂ from the RNPs.

From Fields Virology

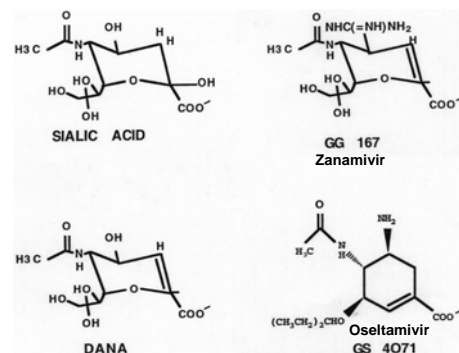
Zanamivir and Oseltamivir II

- **Pharmacology**
 - Zanamivir
 - Oral inhalation
 - Oseltamivir
 - Orally bioavailable
 - Converted from ester prodrug to active form
 - Renally excreted
- **Toxicities**
 - Exacerbation of reactive airway disease by zanamivir
 - Nausea and vomiting for oseltamivir

Zanamivir and Oseltamivir I

- **Active vs. influenza A and B**
- **Mechanism of action**
 - Viral neuraminidase catalyzes cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids, a process necessary for release of virus from host cell surfaces
 - Neuraminidase inhibitors thus prevent release of virions from infected cell

Zanamivir and Oseltamivir III



Zanamivir and Oseltamivir IV

- **Indications**
 - Treatment of influenza A and B within 24-48 hrs of symptom onset
 - Prophylaxis
 - N.B.: Neither drug interferes with antibody response to influenza vaccination
- **Resistance**
 - Incidence appears to be increasing
 - Ongoing surveillance necessary

Anti-Hepatitis B Virus Agents

- Interferon-alpha (pegylated)
- Lamivudine (3TC)
 - Nucleoside analog first developed for HIV
 - Lower dose used for HBV (100 mg/day)
- Emtricitabine (FTC)
 - Anti-HIV nucleoside analog with strong anti-HBV activity
- Adefovir dipivoxil
 - Nucleotide analog first developed for HIV but nephrotoxic at higher doses
 - Approved for HBV at lower dose (10 mg/day)
- Entecavir
 - Nucleoside analog with activity originally thought limited to HBV but recent reports indicate entecavir also has anti-HIV-1 activity and can induce resistance in HIV-1
 - Approved for use at dose of 0.5-1.0 mg/day
- Telbivudine
 - Nucleoside (thymidine) analog with activity vs. HBV but not HIV
 - Recently approved at a dose of 600 mg/day

Ribavirin I

- Synthetic nucleoside analog
- Active vs. broad range of RNA and DNA viruses
 - Flavi-, paramyxo-, bunya-, arena-, retro-, herpes-, adeno-, and poxviruses
- Mechanism of action complex
 - Triphosphorylated by host cell enzymes
 - For influenza
 - Ribavirin-TP interferes with capping and elongation of mRNA and may inhibit viral RNA polymerase
 - For other agents
 - Ribavirin-MP inhibits inosine-5'-monophosphate dehydrogenase depleting intracellular nucleotide pools, particularly GTP

Anti-Hepatitis C Virus Agents

- **Approved**
 - Interferon-alpha (pegylated)
 - Ribavirin
- **In development**
 - Protease inhibitors
 - Polymerase inhibitors

Ribavirin II

- **Pharmacology**
 - Aerosol and oral administration
 - Hepatically metabolized and renally excreted
- **Major toxicity**
 - Anemia
- **Indications**
 - Aerosol treatment of RSV in children
 - Effectiveness debated
 - Oral treatment of HCV (in combination with pegylated IFN-alpha)

Interferons I

- Part of cytokine repertoire
- Possess antiviral, immunomodulatory and antiproliferative effects
- **Types**
 - Alpha/Beta (leukocyte/fibroblast)
 - Coding genes located on chromosome 9
 - At least 24 subtypes of alpha, 1 of beta
 - Gamma
 - Coding gene located on chromosome 12
 - 1 subtype

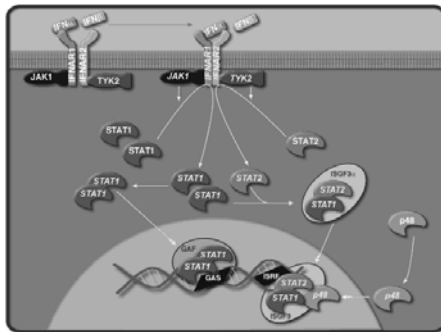
Interferons II: Mechanism of Action

- Act by inducing an antiviral state within cells
- Bind to specific receptors on cell surface
- Receptor associated tyrosine kinases activated
 - Tyk2 and JAK 1 for alpha and beta
 - JAK1 and JAK2 for gamma
- Cytoplasmic proteins [signal transducers and activators of transcription (STAT)] phosphorylated
 - Move to nucleus and bind to cis-acting elements in promoter regions of IFN inducible genes

Interferons IV

- Pharmacology
 - Injected IM or SC
 - Renal excretion and inactivation in body fluids/tissues
- Toxicities
 - Flu-like symptoms
 - Hematologic effects
 - Leukopenia and thrombocytopenia
 - Neuropsychiatric effects
- Antiviral indications
 - IFN-alpha (pegylated) SC for HCV (in combination with ribavirin)
 - Intralesional for condyloma acuminata
- Resistance can develop
 - Mutations in NS5A gene of HCV described

Interferon Mechanism



Passive Immunization for Viral Infections I

- Human immune globulin
 - Prevention of hepatitis A
 - Prophylaxis and treatment of enterovirus infections in neonates and in children with antibody deficiency
 - Treatment of B19 parvovirus infection in immunodeficient individuals
- CMV immune globulin
 - Prophylaxis of CMV in solid organ transplant recipients
 - Treatment of CMV pneumonia in combination with ganciclovir
- Hepatitis B immune globulin
 - Prophylaxis of hepatitis B infection
- Rabies immune globulin
 - Post-exposure prophylaxis for rabies (in combination with rabies vaccine)

Interferons III: Mechanisms of Action

- Synthesis of 2'-5' oligoadenylate synthetase
 - Activated by dsRNA
 - Convert ATP into a series of 2'-5' oligo(A)s
 - These activate RNAase L which cleaves single stranded mRNAs
- Synthesis of dsRNA-dependent protein kinase (PKR, eIF-2 kinase)
 - PKR activated by dsRNA and autophosphorylated
 - In turn, phosphorylates alpha subunit of eukaryotic initiation factor 2
 - Protein synthesis inhibited
- Induction of a phosphodiesterase with inhibition of peptide chain elongation
- Synthesis of MxA protein which can bind to cytoskeletal proteins and inhibit viral transcriptases
- Induction of nitric oxide by gamma IFN in macrophages

Passive Immunization for Viral Infections II

- Respiratory syncytial virus immune globulin
 - Prevention of complications of RSV infection in young children
- Palivizumab
 - Humanized RSV monoclonal antibody
 - Prevention of complications of RSV infection in young children
- Varicella-zoster immune globulin
 - Prevention of varicella infection in immunocompromised children and adults within 96 hours of exposure
- Vaccinia immune globulin
 - Available from CDC for complications of smallpox (vaccinia) vaccination

Conclusions

- **Field of antiviral therapy has matured dramatically in past 30+ years**
- **Greatest progress made for**
 - Herpesviruses
 - HIV
 - Respiratory viruses
 - Hepatitis viruses
- **Preventive vaccination remains the key to global control of viral infections**