Antiviral Agents

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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

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

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

Herpes Zoster

Progress in Antiviral Therapy

Herpesviruses (HSV, VZV, CMV)	Acyclovir, famciclovir, valacyclovir, ganciclovir, cidofovir, formivirsen, valganciclovir
HIV-1	22 approved agents
Influenza	Amantadine, rimantadine, zanamivir, oseltamivir
Resp. syncytial virus	Ribavirin
Hepatitis B	3TC, FTC, adefovir, tenofovir, entecavir
Hepatitis C	pegIFN-ribavirin
Papillomaviruses	IFN, ?cidofovir
JC virus	?Cidofovir
Picornaviruses	?Pleconaril
Rhinoviruses	Tremacamra (rsICAM-1)

Non-HIV Antiviral Therapy: Targets

- Herpesviruses
- Respiratory viruses
- Hepatitis viruses
- Others

Anti-Herpesvirus Agents

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

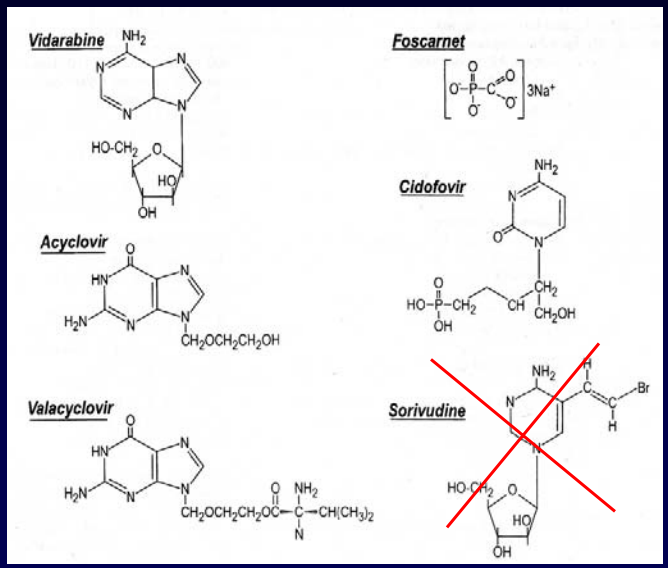
Anti-Herpesvirus Agents

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

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



Anti-Herpesvirus Agents

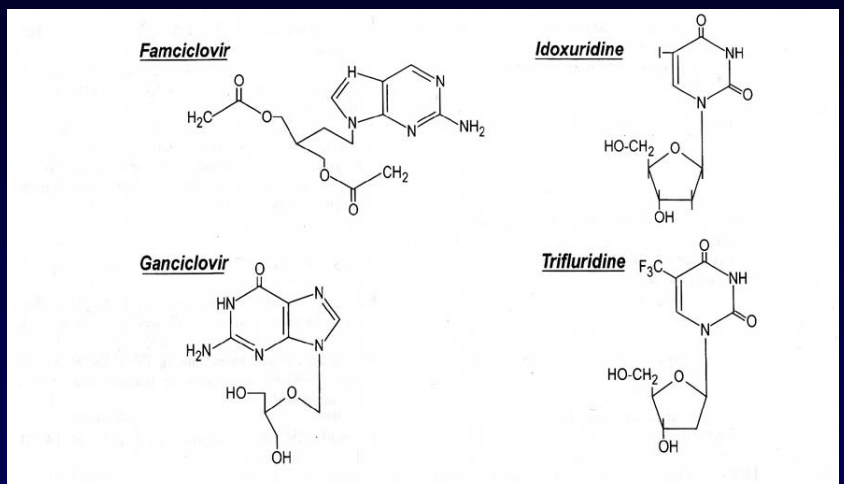
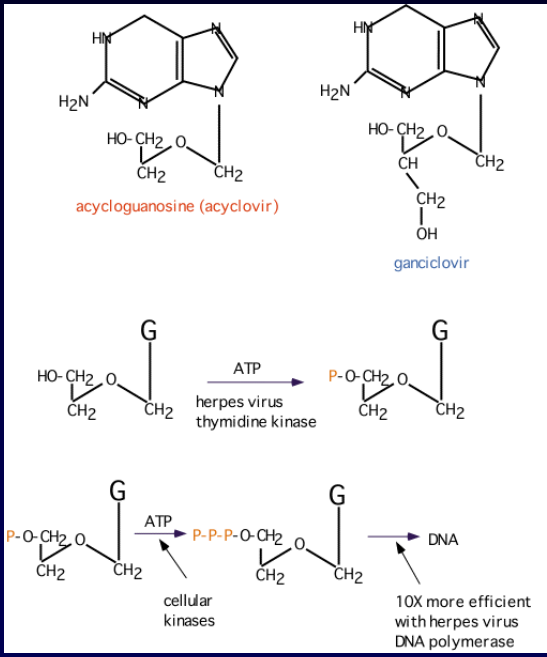


FIGURE 11-1. Chemical structures of antiherpesviral agents.

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

Acyclovir: Mechanism of Action



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

Anti-Respiratory Virus Agents

- Amantadine
- Rimantadine
- Zanamivir
- Oseltamivir
- Ribavirin

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 in 2006-07 season due to circulation of amantadine resistant strains
- Resistance mediated by mutations in M2 coding region

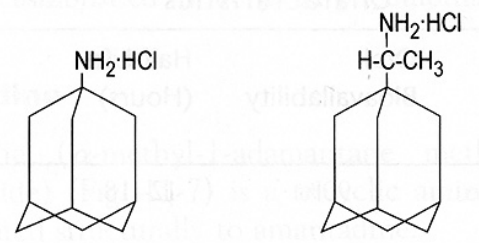


FIGURE 11-7. Chemical structures of amantadine and rimantadine.

Influenza Virus Replication Cycle

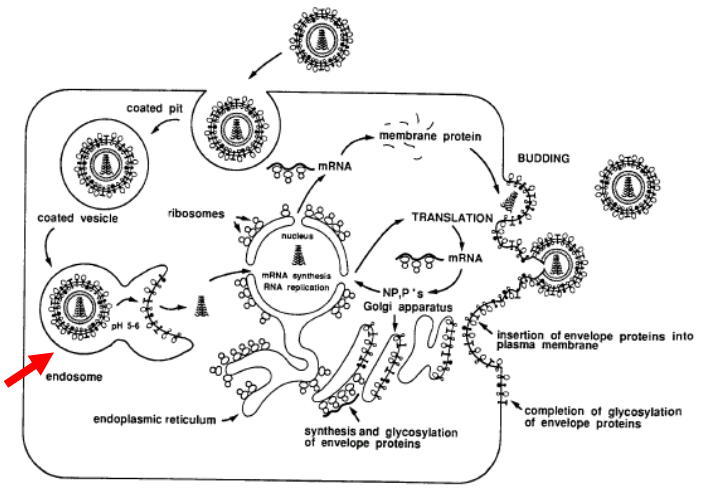


FIG. 13. Schematic diagram of the life cycle of influenza virus. See text for details of the model.

From Fields *Virology*

Uncoating of Influenza Virus

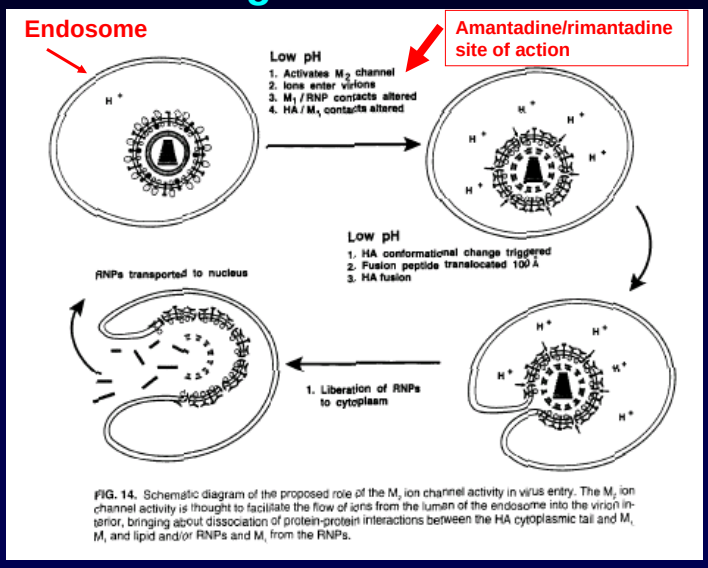


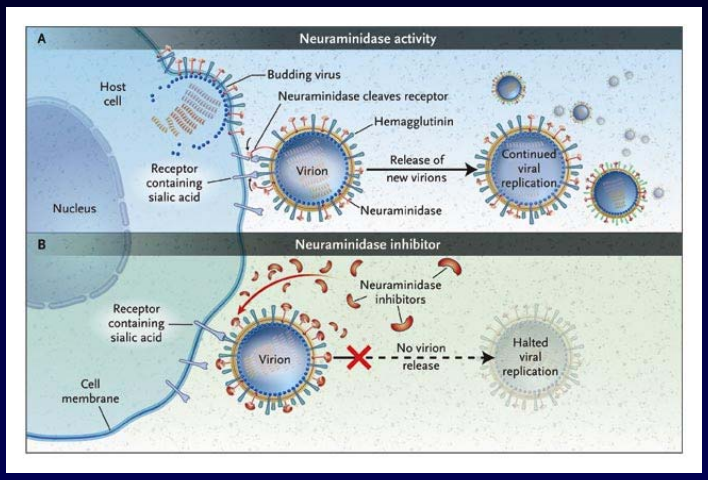
FIG. 14. Schematic diagram of the proposed role of the M_2 ion channel activity in virus entry. The M_2 ion channel activity is thought to facilitate the flow of ions from the lumen of the endosome into the virion interior, bringing about dissociation of protein-protein interactions between the HA cytoplasmic tail and M_1, M_1 and lipid and/or RNPs and M_1 from the RNPs.

From Fields *Virology*

Zanamivir and Oseltamivir I

- Active vs. influenza A and B
- Mechanism of action
  - Neuraminidase inhibitors
    - 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
  - Oseltamivir is an ester prodrug of GS4071, oseltamivir carboxylate
    - Transition state analog of sialic acid
      - Binds to viral neuraminidase

Mechanism of Action of Neuraminidase Inhibitors



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

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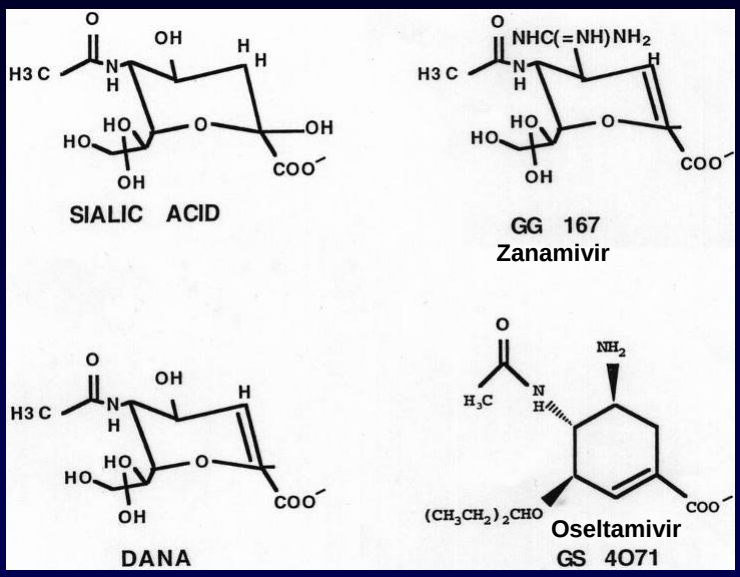
Zanamivir and Oseltamivir II

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

Zanamavir and Oseltamivir III



Zanamivir and Oseltamivir IV

- Indications
  - Treament 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
  - Reports appearing
  - Incidence may be increasing

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

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)

Anti-Hepatitis Agents

- Hepatitis B
  - Interferon-alpha (pegylated)
  - Lamivudine
    - Nucleoside analog first developed for HIV
    - Lower dose used for HBV (100 mg/day)
  - 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 limited to hepatitis B
    - Most recently approved anti-HBV agent at dose of 0.5-1.0 mg/day
- Hepatitis C
  - Interferon-alpha (pegylated)
  - Ribavirin

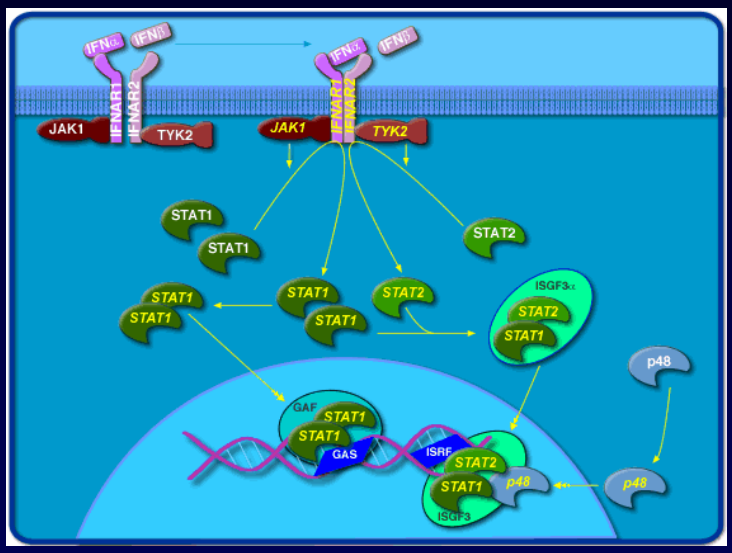
Interferons I

- 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

Interferon Mechanism



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

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

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)

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