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RATIONAL DESIGN OF ANTIVIRAL AGENTS

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HISTORICAL PERSPECTIVE

The search for novel chemotherapeutic agents for the treatment of viral infections has resulted in the discovery and development of a number of breakthrough drugs, such as acyclovir for the treatment of herpes simplex virus infections (1) and azidothymidine for the treatment of AIDS (2) within the past decade. These discoveries have served to quiet the skeptics who had previously maintained that viral replication is inseparably linked to cellular metabolism, and therefore, antiviral agents are inherently toxic. As our understanding of the replication strategies employed by the various virus families has evolved, new molecular targets for chemotherapeutic intervention have been identified, and novel classes of synthetic antiviral agents have been discovered. Nowhere has the rate of progress in this area been as noticeable as in the case of human immunodeficiency virus (HIV), the etiologic in AIDS. Since the first reports of the isolation and identification of this new virus in 1983 (3, 4), an effective antiviral agent (azidothymidine) has been discovered, developed, and marketed, and a number of viral-specific targets have been identified (5).

Beginning with the discovery in 1950 of methisazone, a compound effective in inhibiting pox virus replication (6), serendipity has played a major role in the identification of new classes of antiviral agents. Since inhibition of

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virus-induced cytopathic effect was the endpoint used in most of the earlier screening procedures, the mechanism of action was rarely determined until many years after the initial discovery. In the case of methisazone, it was not until 23 years after the initial discovery that the compound was shown to inhibit processing of structural proteins produced late in infection (7).

Over the nearly four decades following the discovery of methisazone, a number of new classes of synthetic antiviral agents have been discovered that inhibit a range of steps in the replication cycle of a number of different virus families. The antiviral drugs that are currently commercially available are found in Table 1. In addition to these agents is a group of compounds too numerous to list here that have either failed to clear the safety and efficacy hurdles required for regulatory approval, or are currently in development. As with methisazone nearly 40 years ago, serendipity has been responsible for the identification all of the synthetic small molecular antivirals discovered to date.

ANTIVIRAL DRUG DESIGN

Rational drug design, defined as the directed synthesis of new compounds based on an understanding of a prototype drug/viral structural or functional protein interaction at the atomic level, is only now becoming a viable alternative to empirical screening.

Table 1 Commercially available antiviral drugs

Virus family	Antiviral agents	Mechanism of action
Herpesvirus	idoxuridine (8)	altered transcription following incorporation into viral DNA (9)
	vidarabine (10)	inhibition of viral DNA polymerase (11)
	trifluridine (12)	DNA fragmentation following incorporation (9)
	acyclovir (13)	DNA chain termination following incorporation and inhibition of viral DNA polymerase
Human Immunodeficiency Virus	azidothymidine (2)	inhibition of reverse transcriptase (15)
Ortho- and Paramyxoviruses	amantadine (16)	uncoating inhibition (17)
	rimantadine* (18)	uncoating inhibition (17)
	ribavirin (19)	depletion of intracellular guanine pools, inhibition of viral RNA polymerase, alterations of 5' capping of mRNA (20)

*-not available in the U.S.

The most significant technical advance that is beginning to make rational antiviral drug design a reality has been in the area of x-ray crystallography of macromolecules, ranging in size up to spherical viruses with a diameter of 300Å. Following years of computational and technical development, the structure of the first spherical plant virus, tomato bushy stunt virus, was solved at 2.9Å resolution in 1978 (21). It was not until 1985 that the structure of the first animal virus, human rhinovirus-14, was solved (22). This significant advance was followed soon thereafter with the structural determination of human poliovirus (23), and mengovirus (24). It is likely that the structure of canine parvovirus (25) will be solved in the near future.

While the science of macromolecular crystallography was evolving, a number of pharmaceutical research laboratories were discovering compounds effective in inhibiting the replication of the picornaviruses (26), a major cause of viral-associated morbidity in humans. The picornavirus family consists of two major groups of viruses associated with human disease: the rhinoviruses and enteroviruses. The approximately 100 serotypes of rhinoviruses are the etiologic agent in the majority of the mild upper respiratory illnesses known as the common cold (27). The 68 serotypes of enteroviruses, consisting of the polio-, coxsackie-, and echoviruses, cause a spectrum of clinical syndromes ranging in severity from mild upper respiratory disease with or without myalgia and fever to myocarditis, aseptic meningitis, and neonatal sepsis.

It is estimated that, on average, preschool children experience six to ten colds per year and adults have two or five colds per year (28). From the limited epidemiologic data available, there are five to fifteen million enteroviral infections occurring each year in the United States (29). These data provided the incentive for pharmaceutical firms to pursue antiviral drugs effective in inhibiting picornavirus replication. The majority of the synthetic agents coming out of broad based screens have been found to possess a common mechanism of action; inhibition of the virion uncoating process (Figure 1). Uncoating is the step following adsorption to and penetration of the cell membrane, which involves release of the viral nucleic acid from the viral protein shell (capsid) into the cytoplasm. Representatives of the structurally diverse class of uncoating inhibitors studied most extensively to date include dichloroflavan (30–32) Ro 09-0410 (33, 34), RMI 15,731 (35) R61-837 (36) and disoxaril (37–40) (Figure 2)

All of the picornavirus uncoating inhibitors are extremely hydrophobic in nature, such that in the cases of dichloroflavan and Ro 09-0410 they can only be dissociated from the virion by nonpolar solvents such as chloroform (31, 34). The nature and specificity of the presumed hydrophobic binding of these compounds to the virion, and an understanding of how the compound/virion interaction results in uncoating inhibition were unknown until the structure of an inhibitor bound to human rhinovirus-14 was solved to atomic resolution using x-ray crystallography (41). This pivotal study pinpointed the binding

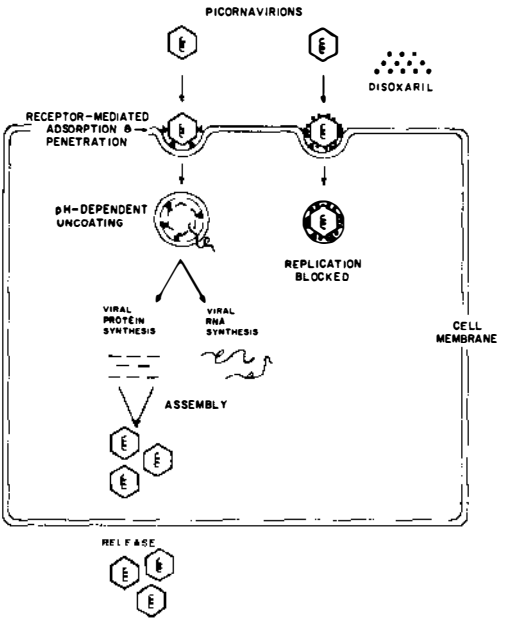

Figure 1 Schematic representation of the picornavirus replication cycle, noting the uncoating step blocked by disoxaril and other agents (Figure 2). Reproduced with permission from *J. Med. Chem.*

site of a disoxaril homologue (addition of a methyl group on the oxazoline ring) within a hydrophobic pocket inside VP_1, one of the four viral capsid proteins (Figure 3). The availability of this pocket suggests that it plays a functional role, such as providing the necessary flexibility in the capsid to allow disassembly or uncoating to occur. The binding of a hydrophobic molecule in the pocket may serve to make the capsid structure more rigid and resistant to uncoating forces. Alternatively, the compounds may act to hold the capsid together via the strength of the hydrophobic interactions.

An examination of the hydrophobic binding site revealed two features important for drug design. First, the compounds appear to form only one weakly directional hydrogen bond between Asn^{219} and a hetero nitrogen of the compound, with the remainder of the binding energy apparently contributed through hydrophobic interactions. The design of agents to increase binding affinity presents a novel set of problems in that no other reported drug/"receptor" interactions are so highly dependent on hydrophobic binding. The initial attempts at drug design have, therefore, focused on ways to more completely fill the binding pocket. In this regard, enantiomeric effects of substituents on the oxazoline ring of a disoxaril homologue (Figure 3) that

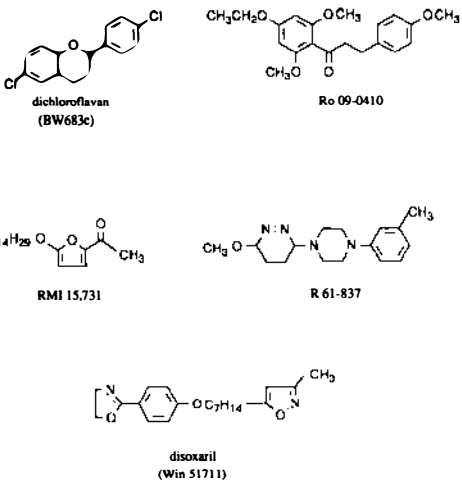

Figure 2 Inhibitors of picornavirus uncoating.

alter the binding affinity to the virion and the in vitro antiviral potency have been described, and explained on the basis of improvements in the hydrophobic interactions of alkyl substituents and Leu^{106} and Ser^{107} of VP_1 (42).

The second feature of importance in drug binding is the large conformational changes that occur in VP_1 following drug binding. The amino acid side chains in the center of the pocket, such as Met^{221}, are displaced by up to 5.5Å when the uncoating inhibitors are bound (Figure 4). The relevance of these conformational changes to uncoating inhibition is unknown, although it is speculated that the altered conformation may be more stable and resistant to forces involved in the pH-mediated uncoating process than is the native conformation. It is interesting that compounds with antiviral potencies that vary over a 120-fold range all induce the same conformational changes in the virion (43).

In an effort to develop a greater understanding of the nature of the drug/virus interactions, viruses resistant to the WIN compounds have been isolated and characterized (43). The majority of the high resistance mutants have been mapped to two sites, Val^{188} and Cys^{199}, within the drug binding pocket. In all cases, the substitutions found in the highly drug resistant mutants have been to amino acids with larger side chains. In the case of the $Val^{188} \rightarrow$ Leu mutation, drug binding is significantly reduced consistent with the decrease in antiviral potency. These results are consistent with the hypothesis that resistance to high concentrations of drug is a result of steric hindrance to drug binding.

Mutants with resistance to low concentrations of compound have been isolated and sequenced, and have been found to map to numerous sites more

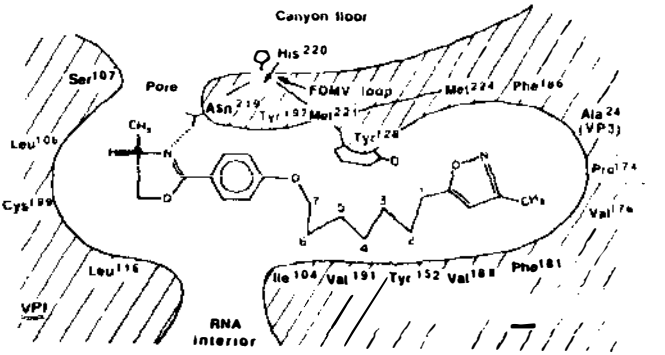

Figure 3 Diagrammatic view of the binding site of WIN 52084 within VP_1 of human rhinovirus-14. Reproduced with permission from *Science*.

than 3Å from the drug binding pocket (Beverly Heinz, personal communication). How these amino acid substitutions alter drug sensitivity is the subject of current studies. It is possible that these mutations affect the conformational shifts required for the compounds to enter the pocket, and thereby decrease binding affinity. Alternatively, the mutations may affect interactions by reducing the inherent stability of the virion, such that the antiviral agents are unable to bind within the capsid on stabilize the virion sufficiently to prevent uncoating. Whatever the results show, these mutants will be extremely informative in understanding the picornavirus uncoating process and how these agents work to prevent it.

Only the WIN compounds have been studied extensively to date using x-ray crystallography. Presumably all of the other picornavirus uncoating inhibitors, however, bind to this same site. This is suggested by their size and physical properties. Recent preliminary studies have shown that mutants resistant to dichloroflavan are cross-resistant to R61-837 (D. Tyrrell, personal communication). If confirmed, these results would provide strong evidence for a shared binding site.

DRUG DESIGN HURDLES

There are a number of lessons to be learned from the work with the picornavirus uncoating inhibitors that will be relevant to drug design of compounds that affect other steps in the replication cycle, once the target molecule's structure is determined. First, the structure generated by using x-ray crystallography is only a static representation of a macromolecule that obviously exists in nature as a dynamic entity. This fact is illustrated in the picornavi-

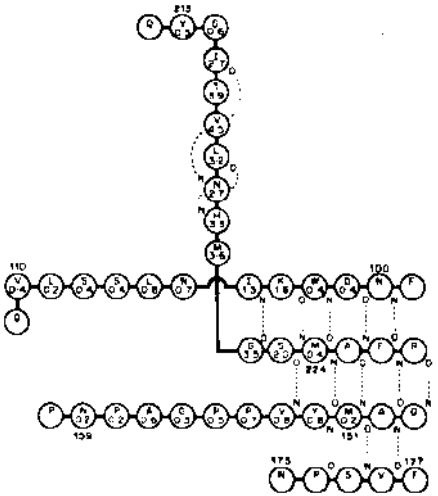

Figure 4 Hydrogen bonding diagram showing the Cα displacement in Å of the part of VP_1 affected by drug binding. The Cα displacement for Met^{221} is 3.6 Å, whereas the side chain movement is 5.5 Å. Reproduced with permission from *Proc. Natl. Acad. Sci.*

rus studies where examination of the native structure would not suggest that molecules such as disoxaril would bind, since Met^{221} of VP_1 blocks access to the pocket. To design an antiviral agent to block picornavirus uncoating simply by using the structure of the native virus would, therefore, have been virtually impossible. This result illustrates the need for the structure of the compound bound to the receptor, enzyme, or virus target of interest to be solved prior to initiating drug design.

A second observation from the picornavirus work relevant to any antiviral molecular target is the difficulty in relating the affinity of binding (Kd) to the target with the antiviral efficacy observed in vitro. With the picornavirus uncoating blockers, preliminary results suggest that the Kd for a number of radiolabeled compounds does not correlate perfectly with the in vitro minimal inhibitory concentration (MIC). This result is to be expected since factors such as penetration into the cell and metabolism of the compound by the host cells used in the 48–72 hr assay can affect MIC values. For this reason, the Kd values are of great importance in directing the design and synthesis of new compounds and must be considered as only one parameter in directing the synthesis of new molecules. Taken one step further, the obvious goal of any drug discovery program is to produce a bioavailable agent. Certainly Kd alone will rarely correlate with the in vivo efficacy of an agent. In the disoxaril series, where oral activity can be readily assessed in animal models of

human infection (44, 45), this problem is especially acute since the hydrophobic requirements for drug binding are at odds with the need for aqueous solubility in developing an oral dosage form.

There are two drug design problems particular to the picornavirus uncoating inhibitors. The first is the multitude of serotypes that must be inhibited by an agent before it is clinically useful. For all of the viruses whose RNA has been sequenced to date, amino acid substitution can be seen within the drug binding pocket despite the fact that this region is the most conserved part of the protein coat. The design of agents to maximize hydrophobic interactions within the binding pocket of one serotype could in fact reduce or eliminate activity against a serotype with a different complement of amino acids in the pocket. Structural data is necessary, therefore, on serotypes whose sensitivity to the class of compounds is most predictive of the sensitivity of the entire spectrum of serotypes. In this regard, rhinovirus type-14 (HRV-14) unfortunately appears to be a poor choice for use in drug design, since the structural modifications that improve activity against HRV-14 decrease activity against the majority of other rhinovirus serotypes.

The second problem affecting drug design in the picornavirus area is the hydrophobic nature of the binding. An illustration of the difficulties in trying to design a "piece of grease" to fit into a "greasy pocket" is the flip-flop in orientation seen when the alkyl chain length of the compounds was reduced from seven methylene units to five (Figure 5). In this case, the surprising 180° change in orientation still results in the same conformational change in VP_1, and the conservation of a probable hydrogen bond between with the nitrogen

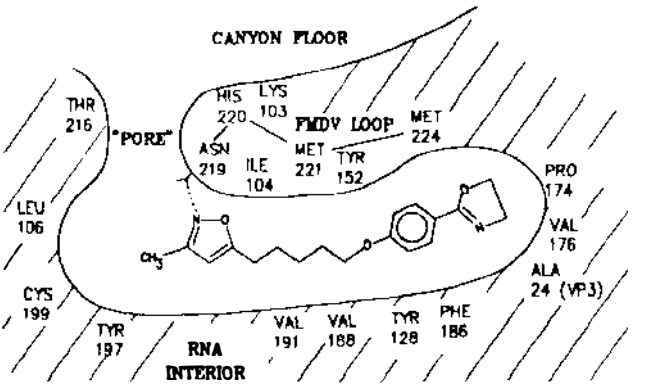

Figure 5 Diagramatic reprcsentation of a compound possessing on 5 methylene unit alkyl bridge (as opposed to 7 in Figure 2) bound to rhinovirus-14. Note that the hydrogen bond is conserved despite its shift in orientation. Reproduced with permission from *Proc. Natl. Acad. Sci.*

on the isoxazole ring. In the absence of strong hydrogen bonds to anchor the compounds to the pocket, the orientation of any designed compound will have to be examined crystallographically.

FUTURE PROSPECTS FOR ANTIVIRAL DRUG DESIGN

Our understanding of the molecular biology and biochemistry of viral infection has increased greatly in recent years. With the urgent need to discover agents effective in inhibiting replication of HIV, researchers have rapidly applied the emerging technologies, such as crystallography, to their drug discovery programs.

In the case of HIV, numerous enzyme, regulatory factors, and receptor targets have been identified and molecularly based screens have been established. Many of these proteins have been expressed, purified, and in some cases crystalized. It is reasonable to expect that inhibitors of the key steps in the virus replication cycle will be discovered within the next five years. It is also likely that the structure of these essential viral proteins with inhibitor bound to them will be solved at atomic resolution. Once these hurdles are surmounted, true drug design can begin.

One possible target for HIV chemotherapy is inhibition of uncoating. Based on the probable homology of HIV core protein structure and the conservation of folding motif in capsid proteins of RNA viruses, it is possible that a hydrophobic binding site, similar to that found in picornaviruses, will be found in HIV (46).

The most important ingredient in a drug design program is the obvious need to predict the activity of a molecule before the effort is invested to synthesize it. While a certain amount of success can be had by viewing a ligand/protein structure on a graphics terminal, the multiplicity of possible conformations the ligand and protein can assume make it exceedingly difficult to make accurate predictions with any regularity. Recent developments in the use of thermodynamic calculations and molecular dynamics simulations permit consideration of previously impossible computational problems through the use of supercomputers and new computational approaches.

The thermodynamic-cyclic perturbation approach to thermodynamic calculations is likely to be increasingly used in the future. (47). Since the free energy change of binding of a drug to a protein or virus would be exceedingly difficult, if not impossible, to calculate, this method enables one to calculate the relative free energy change for the binding of two different compounds. These calculations will enable the researcher to predict whether a compound proposed for synthesis is likely to possess a greater binding affinity to the target.

The second promising application of computational chemistry to drug

design is molecular dynamics simulation (48). The object of this exercise is to simulate the dynamics of the drug/protein interactions based on the dynamical trajectories of each atom. This type of analysis can help identify areas of the drug where considerable movement is occurring when bound to the target, suggesting that the conformation of the drug may need to be constrained to maximize activity. This analysis may also suggest ways in which the drug is exerting its effect on the protein. In the case of the picornavirus work, these studies may help explain how drug binding induces such large conformational changes in the virus capsid, and why disassembly process is inhibited.

SUMMARY

Examining the change in the state of the art of antiviral drug discovery, from the discovery nearly 40 years ago of a smallpox drug (methisazone) of unknown mechanism of action to the analysis of an antiviral agent bound to a virus at atomic resolution, gives the reader an appreciation for the magnitude of the advances in the science of antiviral chemotherapy. The clinical success of amantadine, acyclovir, and azidothymidine have proved that antiviral chemotherapy is a reality. The next step will be to apply the new tools of x-ray crystallography and computational chemistry to the antiviral challenges that lie before us.

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