03.X-1

THE STRUCTURES OF ANTIVIRAL COMPOUNDS/RHINO VIRUS 14 COMPLEXES. By Thomas J. Smith[1], Marcia J. Kremer[1], Ming Luo[1], Gerrit Vriend[1], Edward Arnold[1], Greg Kamer[1], Michael G. Rossmann[1], Iwona Minor[1], James P. Griffith[1], Mark A. McKinlay[2], Guy D. Diana[2], and Michael J. Otto[2].
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The Sterling Research Institute has developed a family of compounds which inhibit the infectivity of several picornaviruses in both Hela cell cultures and some animal models. The basic structure of these compounds is an oxazoline ring attached to a phenoxy ring which is in turn connected to an isoxazole ring via an aliphatic chain. It is thought that these compounds inhibit infection by blocking the pH mediated uncoating of the capsid since they have been shown to stabilize the capsid against the effects of low pH and elevated temperatures.

The x-ray crystallographic structures of rhino 14 complexed with several of these compounds (WIN 52084, WIN 57007, WIN 51711, and WIN 52035) have been determined. WIN 57007, WIN 52084, and WIN 51711 have a seven carbon aliphatic chain with an ethyl, methyl, and hydrogen attached to C4 of the oxazoline ring respectively. WIN 52035 is similar to WIN 51711 except that the aliphatic chain is only five carbons long. These hydrophobic compounds bind to the interior of the β-barrel of viral protein 1 (VP1), causing large conformational changes in the region called the foot and mouth disease virus loop. The oxazoline end of the longer compounds (WIN 57007, WIN 51711, and WIN 52084) is positioned over the entrance to channels leading to the RNA core, and the phenoxy ring is stacked with tyrosine 197. With these longer compounds, there may be an important hydrogen bonding interaction between asparagine 219 and the oxazoline ring. In the cases of WIN 52084 and WIN 57007, the additions to the oxazoline ring point outwards through the pore to the outer surface of the capsid. The smaller WIN 52035 binds deep in the β-barrel rather than over the entrance to the internal channels, suggesting that the effecacy of the compounds is related to the presence of the ring structures in the β-barrel rather than blocking the entrance to the internal channels. Interestingly, while the conformational changes in the case of WIN 52035 are similar to the longer compounds, there are significant differences. From the position of all of these compounds in the aliphatic and aromatic environment of the β-barrel, it is clear why such hydrophobic compounds bind effectively.

These compounds probably block the uncoating process by stabilizing the VP1 β-barrel. It may be that the collapse of this β-barrel is an important step in the uncoating process.

03.X-2

THE STRUCTURE OF DNA AND HOW SMALL MOLECULES RECOGNIZE IT: OBSERVATIONS AT NEAR-ATOMIC RESOLUTION. Maxine J. McCall, Department of Inorganic Chemistry, University of Sydney, Sydney, N.S.W. 2006, Australia.

For a long time the structure of DNA was thought of as a monotonously repeating right-handed double-helix; in this view, any sequence-specific interactions with other molecules could only result from the recognition of DNA bases via hydrogen bonds to their exposed outer edges. During the past 10 years, high-resolution crystallographic analyses of DNA molecules, 6 to 12 base-pairs in length, have shown that these ideas are only partially correct. X-ray studies have shown that DNA can form a left-handed double-helix. They also have shown that there is a great deal of structural variation in the more commonly-occurring right-handed form and, further, that these variations are related to the sequence of nucleotides in the chain. The structures of just a few DNA-drug complexes have been solved, but these have already demonstrated that hydrogen-bonding to the base pairs is but one small facet of the molecular recognition of DNA. Other factors include the shape of the DNA surface presented to the drug, the deformability of the DNA structure near the binding-site, and even the ability to change from Watson-Crick to Hoogsteen base-pairs when the drug binds. Of course there are also many "invisible" kinds of electrostatic forces between drug and DNA which we can only guess at, and cannot yet calculate accurately.

Incidentally, it is well known that a variety of protein molecules (e.g. DNAaseI, transcription factor TFIIIA, and the histone octamer) recognize primarily the sequence-dependent aspects of DNA structure; and so there is no reason to think that small molecules will be any different.

The dependence on base sequence of the structure of DNA, both in its native form and in complexes with other molecules, will be reviewed. Particular emphasis will be placed on what we have learned from the crystallographic analyses, and how this relates to the intended design of molecules with specific biological properties. Given the many unexpected results already obtained in this field, the future looks bright for the continued employment of crystallographers.