Rhinoviruses: The Quest for a Cure

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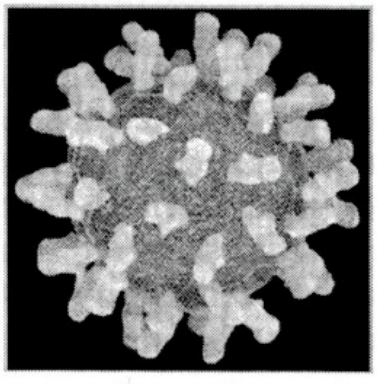
INTRODUCTION

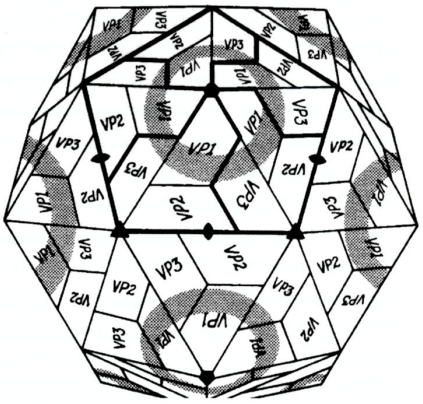
Rhinoviruses, also known as Human Rhinovirus, abbreviated HRV, are one of the many causes of the common cold. In fact, around 50 percent of all cold are caused by rhinoviruses, with the other major candidates being coronaviruses, influenza A or B virus, and minor causative agents like parainfluenza virus, respiratory syncytial virus, adenovirus, and enterovirus (Makela and Puhakka, 1997). However, due to the complex molecular structure of rhinoviruses, a cure for the common cold caused by HRV is still in the making. Several new treatments have been discovered, impacting the virus as different stages of its life, hopefully to prevent those colds that are cause by HRV. Most are still in the process of development, and some have adverse effects. Hopefully, in the near future, a cure will be developed, saving millions of people per year from that annual plague. (Greenberg, 2003).

INTRPDUCTION TO RHINOVIRUS

Rhinoviruses, or Human Rhinovirus are one of the most commonly studies viruses today. (Bella and Rossmann, 1999). The rhinovirus is a fairly small virus, only 30 nanometers, and it belongs to the Picornaviridae (pico means small, virdae, meaning virus) family of viruses. There are approximately 110-115 serotypes of rhinovirus, serotype being the testing of microorganisms for recognizable antigens on its surface.



HRV 16, computer simulated model developed by Purdue researchers
http://findit22.chipublib.org-Cold virus



Organization of the external viral proteins VP1, VP2, and VP3 in the icosahedral shell of HRV's and other picornaviruses. Each protein is repeated 60 times. The canyon is shown shaded. Taken directly from (Rossmann et al., 1999)

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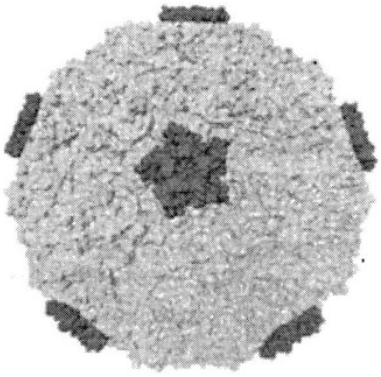
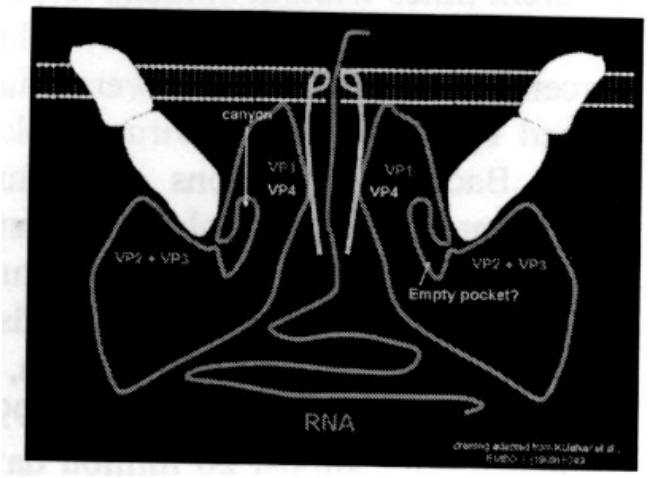
These numerous serotypes are what are responsible for the reinfection process, since different types could affect a person at different times without immune response. (Tolan, et al., 2007) according to a study done in 1997, when two hundred young adults were tested, 50 percent of the colds found were cause by rhinovirus, and the rest were caused by varying other viruses, like coronavirus, or influenza A and B virus. Bacterial infections that cause cold-like symptoms were rare, leaving proof that the cold is almost exclusively a viral disease. (Makela and Puhakka, 1997) According to studies, almost 30-50 percent of all adult colds, and 10-25 percent of colds in children are cause by rhinoviruses. (Bella and Rossmann, 1999) According to Stephen Greenberg, M.D., (2003), in 1996, the common cold was responsible for almost 20 million days of missed work, 22 million days of missed school, and 27 million physician visits in the U.S. In 1998, 76 million visits physicians were tracked up to the common cold, 50 percent of which is caused by HRV. In the United States each year, consumers seeking relief from cold symptoms spend $2 billiom-3 billion on over the counter products to prevent the common cold (Anzueto and Neiderman, 2003).

Rhinovirus is a non-enveloped virus that has only a single stranded, positive sense RNA molecule as its genome. (McCoy, 2004) The capsid is almost spherical, icosahedral in shape, and symmetrical. It is about 300 Angstroms in diameter, (about 30 nm) and is composed of around sixty copies of viral proteins. Theses viral proteins, specifically, VP1, VP2, VP3, and VP4, make up the surface of virus to create an exterior shell. VP4 specifically forms the interior or the capsid, which is in direct contact with the viral RNA (Bella and Rossmann, 1999). In fact, when the rhinovirus structure (specifically HRV 14) was mapped, all of the hypotheses about the structure were proven right (Rossmann, et al., 1985).



The 'starfish like' protuberance. Referenced from http://www.wikipedia.org



Rhinovirus complexing with the ICAM receptor allows entry into a host cell. http://pathmicro.med.sc.edu/virol/pol24.gif

VPI, VP2, and VP3 each take the shape of an eight-stranded molecule, each with a beta-pleated sheet structure, known as the beta-barrel, and the run anti-parallel to each other (Badger, et al., 1988). These fit together in a description like a 'jelly roll', and form the outer surface of the capsid. The capsid is around 5 nanometers thick. (Smyth and Martin, 2001) Unique to the

rhinovirus, at each five-fold vertex, the corners of the polygonal sphere, there is a 'star-fish like' protrusion or protuberance, made up of five copies of VPI, along with a 25 angstrom deep depression or canyon encircling it. This cavity is what makes the canyons. (Bella and Rossman, 1999)

VP4 is also shorter in the HRV, only around 70 residues, or portions of a larger molecule, added on, instead of around 240- 290 residues, like VP1-3, and it is lacking in any special structure. It is on the internal surface of the capsid, near the RNA, and has its N-terminus near the five-fold vertex, and the C-terminus near the three-fold axis of the capsid. VP4 is also covalently bonded to a myristic acid group, giving five symmetrically relates myristic acid groups near the five-fold vertex, and a channel running through the inner and outer surfaces of the capsid (Smyth and Martin, 2001). The protuberances are antigenically diverse among the different serotypes of the rhinovirus, making the canyons different as well (Talaro and Talaro, 2002). VP1-3 contain the antigenic sites that are important for the host immune response, so if they are diverse, that allows for reinfections (Greenberg, 2003).

As for the receptors on the VP molecules, the rhinovirus can be grouped into two-three different types based upon receptors. The first major group, compromising around 91 serotypes have a cell surface glycoprotein known as intracellular-adhesion molecule-1, known as ICAM-1. The minor group, around 10 serotypes, binds to molecules of LDLR, low density lipoprotein receptors. The last group has a receptor that is yet to be discovered (Bella and Rossman, 1999). The LDL receptor that HRV serotype 2 bound to is also known as alpha-2-macroglobulin receptor, or a low density lipoprotein receptor related protein (Hofer, et al., 1993) Dr. Michael Rossmann, with Roland Ruecker at the University of Purdue in 1985 actually discovered the 3-D structure of the rhinovirus, and came up with the canyon hypothesis (Radetsky, 1991).

MODE OF TRANSMISSION AMONG HUMANS

The rhinovirus usually attacks the upper repertory tract in humans. It can be transferred either through aerosol, which is the inhalation of small particles of virus, or through direct contact, by touching the nose with a contaminated hand. However, once it is inside the nose, it moves to the nasopharynx, lodging in the nasal mucosa epithelia cells. It binds to ICAM-1, or an LDL receptor, and infection begins among the host, or human cells (McCoy, 2004). The conjunctiva of the eye may be involved, but because HRV attaches to epithelial receptors, it is less so (Tolan, et al., 2007) Contagious behavior would be construed as nose blowing, sneezing, physically touching environmental surfaces or tissues with the nasal secretions. Within a household, 50 percent of the time infection spreads, but within a school, it ranges from 0 to 50 percent, leading scientists to believe that it requires long-term contact to take effect (Tolan, et al., 2007). The virus replicates in the ciliated cells in the nasal epithelium, although it has been found in research that the non-ciliated cells of the adenoid also may support HRV infection (Arruda, et al., 1991).

Viral shedding occurs in large amounts, specifically, as Robert Tolan, M.D. states, 'as many as 1 million infectious virions present per mL of nasal washings'. This shedding can occur before the host realized that he or she has a cold, and can last as long as 3-4 weeks after the HRV cold dissipates (Tolan, et al., 2007). According to studies, around 95 percent of people exposed to a

HRV strain that they have not previously encountered will develop an infection, and 75 percent of those who are infected display symptoms (McCoy, 2004).

SENSITIVITY

Uniquely among the common viruses, rhinovirus has a sensitivity to temperature. It can only thrive in a temperature between 33-35 degrees Celsius, unable to survive in a normal body temperature of 37 degrees Celsius. This also limits its choice of receptor binding, because it needs the receptors in the upper respiratory tract, and not in the lower respiratory tract, which has a higher temperature (Tolan, et al., 2007).

Rhinovirus also has a sensitivity to pH, because if the virus is swallowed, the decreased pH in the stomach will prevent infection. The rhinovirus capsid dissolves in low pH, which effectively destroys the virus (McCoy, 2004). It is stated that a pH of 3-5 renders that virus unstable (Fiala and Guze, 1970).

SYPMTOMS

Although rhinovirus infections affect people around the world at all seasons, it seems to be epidemic in fall and spring times, causing doctors to prescribe unnecessary antibiotics, which contribute to antibiotic resistance in bacteria that were present at the time (Rotbart and Hayden, 2000). Despite what a parent may tell a child, getting wet, chilled, or exposure to cold weather are not clinically proven to increase the likelihood of contracting HRV (Tolan, et al., 2007). However, according, to a study done in the fall months on 346 adults, 224 were diagnosed as having a cold due to HRV, showing that rhinovirus is the largest contributing virus causing colds during the fall months (Arruda and Pitkaranta, 1997).

Symptoms may begin within twelve hours after infection, and start with the release of cytokines to initiate an inflammatory response. This causes airway hyper-reactivity, and an influx of neutrophils in the nasal mucosa and secretions (Rotbart and Hayden, 2000).

The incubation period normally is 1-3 days, and the most common symptoms are rhinorrhea (runny nose), nasal stuffiness, and sneezing. Other symptoms could be a sore or scratchy throat, facial pressure, headache, cough, hoarseness, malaise, chills, or feverishness. Significant fever is uncommon in adults, but in infants and young children it is present more often (Rotbart, H., Hayden, F., 2000).

HRV can also cause upper and lower respiratory tract complications. Acute otitis media (AOM), could be caused by HRV induced infections, and most cases of acute sinusitis are thought to be a secondary bacterial infection from a primary case of HRV. In children with AOM, viruses have been detected in 11-41 percent of middle ear fluids, and rhinovirus constitutes 8 percent of that. In acute sinusitis, HRV has been detected in 40 percent of sinus brushings (Rotbart and Hayden, 2000). According to Robert Tolan, M.D., (2007) 24 percent of patients with AOM have rhinovirus in their nasopharyngeal secretions.

HRV can also exacerbate asthma in adults and children. In a two-year study done in adults with asthma from 19-46 years of age, colds were associated with 71 percent of exacerbations, and rhinoviruses are the most commonly identified pathogens, HRV also is associated with lower respiratory tract infections. Up to 40 percent of exacerbations in patients with chronic bronchitis are associated with HRV, and in infants younger than 12 months, HRV is

associated with lower respiratory tract illnesses that required hospitalization, including bronchiolitis, and bronchopulmonary dysplasia (Rotbart and Hayden, 2000). HRV may also cause laryngotracheobronchitis in infants, and in cystic fibrosis patients, rhinovirus is the culprit for 57 percent of respiratory exacerbations (Tolan, et al., 2007).

VIRUS ACTION AND INFECTION ATTACHMENT

The rhinovirus attacks a host using the established mechanisms of viral infection. Firstly, the viral capsid interacts with specific receptors on the cell membrane. The receptor binding sires on rhinoviruses are inside the canyon made by VP1-4, which surrounds each 'star-fish', five-fold axis (Smyth and Martin, 2002). When neutralizing antibodies were tested against rhinovirus' surfaces, it was discovered that the virus continued to evade antibody neutralization actions. The mutations in shape that caused this were located at four distinct antigenic surfaces, at the most exposed regions on the virus- on the rim of the canyon depressions. However, molecular residues at the bottom of the canyon are conserved, and immunologically secluded, and the canyon is too narrow to allow antibodies access to the receptor sites. This led to the discovery that the canyon is the receptor binding site, and that the rhinoviruses can hide their binding sites there, protecting them from antibody attack, while they created external residues to confuse the host's immune surface. This is known as the canyon hypotheses (Bella and Rossmann, 1999 and 2000). This protects the virus from any immune response that counteracts its cell receptor binding.

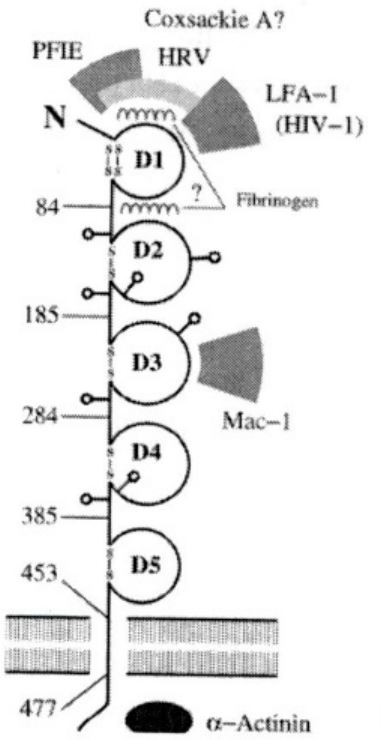
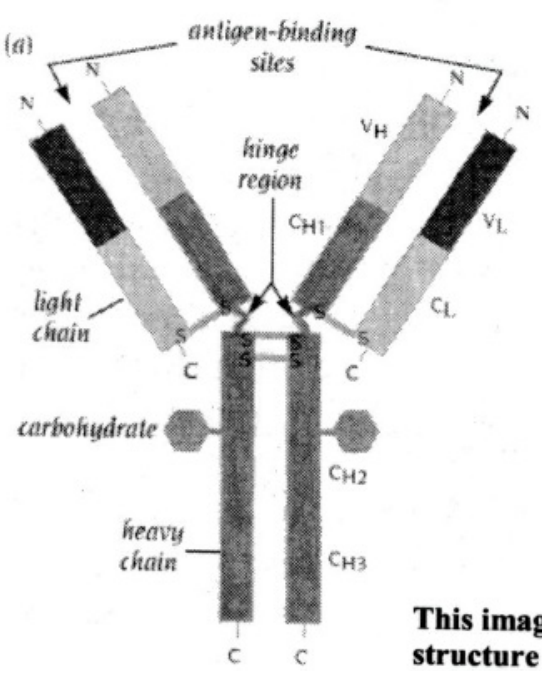


Fig 1. Domain structure if ICAM-1. Each Ig domain is represented schematically by a circle closed by one or two disulfide bonds. Amino acid numbers indicate the beginning and end of each domain. Approximate locations of relevant binding sites are shown. Lollipop-shaped structures indicate N-linked glycosylation sites. (Bella and Rossmann, 2000)



This image from Branden & Tooze shows the structure of an IgG immunoglobulin molecule.
http://images.google.imgres?imgurl=http://pps00.cryst.bbk.ac.uk/course/section11/IgG.gif&imgrefurl=http://pps00.cryst.bbk.ac.uk/course/section11/immunog.html&h=349&w=285&sz=19&hl=en&start=3&tbnid=SsURfzzb9uyQjM:&tbnh=120&tbnw=98&prev=images%3Fq%3Dimmunoglobulin%2B%26gbv%3D2%26vnum%3D10%26h1%3Den

The ICAM-1 receptor is a glycoprotein cell adhesion molecule (hence, CAM), that has an extracellular component made up of immunoglobulin chains. Immunoglobulin (Ig) chains are the building blocks of antibodies, molecularly described as two sets of beta-pleated sheets running antiparallel to each other and linked by disulfide bonds. ICAM-1 has five Ig chains, also known as domains, along with a transmembrane region into the cell, and a short cytoplasmic domain inside the host cell. It has been described as a lollipop structure, due to the several domains connected (Bella and Rossmann, 1999). The ICAM molecule has five immunoglobulin like domains, known as D1-D5 respectively. D2-D4 are glycosylated, and D1 is the primary binding site for rhinoviruses, and for the ligand that ICAM-1 binds naturally, known as lymphocyte function-associated antigen 1 (Olsen, et al., 1993). Some rhinoviruses have been known to stimulate the ICAM-1 expression on host cells to increase the chance of infection (Tolan, et al., 2007).

UNCOATING

When HRV attaches to the ICAM-1 receptor, this initiates entry into the host cell. During the un-coating stage of viral infection, the RNA across the host cell membrane into the cell, but the actual mechanism is still not known for HRV (Bella and Rossman, 2000). ICAM-1 is a transmembrane protein, and its two terminal ends show an Ig like-fold, solidifying the structure hypothesis. On the tip of domain D1, there are three loops important for HRV binding, known as DE, BC, and FG. HRV is usually specific by species, and does not recognize ICAM-1 in any other species other than human, and also ignores similar CAM receptors, like ICAM-2 or ICAM-3 (Bella and Rossmann, 1999).

Richard Colonno, a scientist from Merck Laboratories, actually was the first one to discover the I-CAM receptor, along with the receptor antibody to prevent HRV from bonding to the host cell. In a method known as “Colonno’s brute force method”, he performed 8,000 different tests, and discovered that the I-CAM antibody prevented mice nasal cells from becoming infected (Radetsky, 1991). Colonno discovered, using receptor antibody that he developed, that HRV used the canyon to bind to its ICAM receptor, and discovered the location of the plaques and residues inside the canyon (Colonno, et al., 1985). 20 out of 24 HRV serotypes tested proved positive for the ICAM receptor, and the I-CAM antibody that Colonno developed seemed to prevent receptor binding for 78 out of 88 serotypes tested (Colonno, et al., 1985).

Uncoating is the second step on rhinovirus infection of a host cell. The HRV must have a stable enough capsid to be able to transport itself to the host cell and bind with a cell receptor, but it also must be able to disassociate when needed to allow the RNA genome to enter the host cell. However, research has shown that the crucial step for rhinoviruses is the loss of the VP4 protein. It seems that the myristic acid that is covalently bonded to the VP4 terminal end can interact with the host cell membrane, causing the release of VP4, and the genome, allowing the RNA to enter the cell. The acid lies near the inner edge of the five-fold channel, allowing the genome to leave the capsid through the channel. However, the capsid must disassemble enough to allow this to happen. Uncoating mechanisms have been tested and observed with HRV14, in

which acid conditions were introduced, or as with HRV16, a preparation of its receptor was exposed to it, initiating uncoating (Smyth and Martin, 2002).

In addition, there is a canyon contained within VP1, known as a pocket, which is hydrophobic. Structural analysis has shown that there is a fatty acid in the pocket, known as a pocket factor. This pocket factor has an 'inhibitory but reversible' effect on uncoating. This allows the pocket to stabilize the capsid until it is time for it to disassemble when faced with a host cell. Residues inside the pocket become more stable, along with the N-terminal end of VP3, which allows the protein to stabilize (Smyth and Martin, 2002). This pocket factor fatty acid also protects the virus in between its cell to cell transit, between neighboring cells (Xing, et al., 2003). So, when the rhinovirus binds to the cellular receptor, it causes the virion particle to disintegrate, and the RNA genome is released directly into the host cell (Sompayrac, 2002).

REPLICATION

Replication is the next step in the viral infection process. The RNA moves through a membrane pore that is generated by the N-terminals of VP1 and VP4, during the uncoating process. It has been suspected, but never proven, that the RNA leaves through one of the 12 vertexes at the starfish shaped protuberances. It has been theorized that the virion undergoes conformational changes after the RNA leaves, which leads to capsid disassembly, but it has never been shown. ICAM-1 also locks the virus in an 'open state' so that the RNA can be released without the virion folding in on itself. When the virus expands, by locking the ICAM receptor in place, which allows for movement of the RNA out of the virion. Once the RNA exits, this leads causes rearrangements in the virion cell, namely that the VPI molecule twists, allowing for a larger molecule that eventually disintegrates (Xin, et al., 2003). The RNA genome is then injected into the cell from the acidic endosomes that internalize the virus, like the myristic acid groups of the VP4 (Smyth and Martin, 2002).

Rhinoviruses trigger a chemokine and cytokine response once they have entered and started infecting the cell. This response exacerbates the symptoms of the common cold, and some asthma patients, due to the inflammation that results (Virus Weekly, 2007). The cytokines, specifically are interferon-gamma and interleurkin-6 and interleurkin-8, along with interleukin-1 alpha. (Anzueto and Niederman, 2003). This leads to nasal discharge, nasal congestions, sneezing, and throat irritation (Tolan, et al., 2007). The immune response attracts immune cells, and sends chemical messages to neighboring blood vessels, causing leaking of capillaries, glandular secretion, and causes stimulation of nerve fibers. This causes the sneezing and coughing reflexes, in addition to a pain sense (McCoy, 2004).

The RNA rhinoviruses is a positive sense RNA, meaning that it serves as the viral mRNA, and can be immediately translated by the host cell without involving DNA. The RNA contains between 7500 to 8300 nucleotides, and encodes a single large polyprotein (Belsham and Sonenberg, 1996). The complete HRV genome has been mapped for rhinovirus-14, which has 634 non-coding nucleotides, 6537 coding nucleotides, and again a 47 nucleotide region of non-coding nucleotides. The molecular structure of HRV is most closely associated with enteroviruses, another of the family picornavirdae (Stanway, et al., 1984). It is translated one time by the ribosomes of the host cell, and then the polyprotein created divides itself up into several viral proteins. One viral protein created is the viral RNA polymerase, which then makes complementary copies of the original viral RNA, which are negative strands, in the sense that

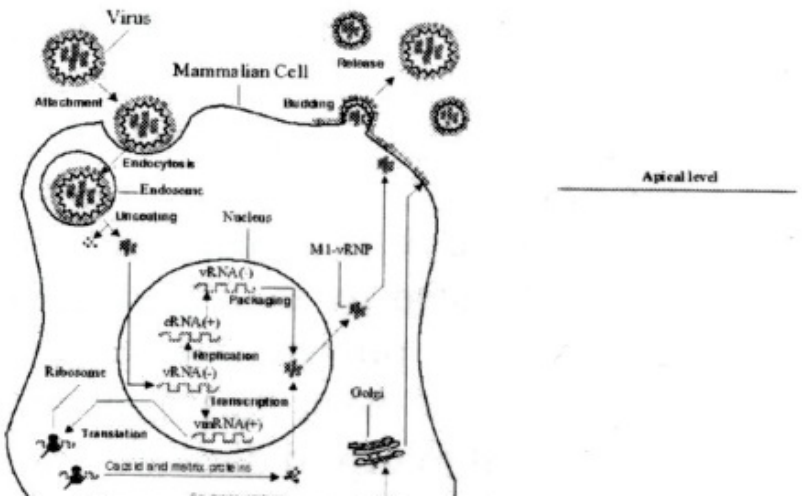
they are the exact opposite of the original strand. These copies of the viral RNA are then copied again, so complementary, positive sense strands are then created, and translated to make new viral proteins (Sompayrac, 2002).

These new viral proteins then undergo processing by virus-encoded proteases, and finally produce the mature virus proteins. This mature viral protein contains about 11 different polypeptides plus some partially processed products. Four of these proteins, with around 60 copies of each one, make up the virus capsid, and other proteins are involved in replication (Belsham and Sonenberg, 1996). The virion capsid protects the many copies of the virion, until the rhinovirus leaves the cell (Sompayrac, 2002). The virus inhibits the host cell's own transcription and translation, modifies or destroys the intracellular membranes of the cell (e.g., the organelles), destroys the cell itself through lysis, and finally releases the mature viruses, ready to infect the next cell (Belsham and Sonenberg, 1996).

The RNA genome is replicated though a RDRP, a RNA-dependent RNA polymerase which is a double stranded RNA intermediate to help the replication process. The host cell ribosomes are taken over, and initiated by an IRES, an internal ribosome entry site (Belsham and Sonenberg, 1996). The IRES allows the ribosomes to begin translating the original RNA genome without the "cap" structure normally present in a genome (Sopayrac, 2002).

The 5' terminal end, or UTR, untranslated coding region, of the RNA is uncapped, which is unusual. The rhinovirus 5' UTR is able to direct protein synthesis without mRNA, and is now referred to as an IRES, or a ribosome landing pad. The IRES is located about 150 bases from the initiation codon on the 3' UTR, but the distance can be greatly modified with little or no effect on rhinoviruses. Rhinoviruses do translate poorly, due to the fact that they, unlike DNA, do not have a checking factor built in to check the nucleotides before translation (Belsham and Sonenberg, 1996). The process by which the cell recognizes the IRES sequence is not known, but many initiation factors as well as other specific cellular proteins help. Three factors have been identified so far, polypyrimidien tract binding protein, La auto antigen, and PCBP (poly(rc) binding protein). The binding of PCBP to the 'clover lead' RNA at the 5' end enhances viral translation (Gamarnik and Adino, 1998).

To prevent interference from the host cell, the HRV encodes a protein that disrupts the normal cap-dependent initiation of the host cell. This shuts down all protein synthesis from capped, cellular mRNAs, except from its own uncapped RNA genome. It only takes about eight hours for a rhinovirus to reproduce, and to make thousands of new viruses (Sompayrac, 2002).



IMMUNE RESPONSE

The body's natural immune response does try to prevent the inhalation of these virions. HRV enters into the lowest part of the nasal cavity, and starts its replication there, without moving deeply into the lower respiratory and digestive systems to be destroyed by the acidic contents of the stomach. This internal defense prevents rhinoviruses from causing intestinal or gut infections. However, there is another defensive immune response. When cells are under attack by a virion, they produce 'warning-proteins' known as Interferon-alpha and interferon-beta. Interferon binds to receptors on uninfected cells, alerting those cells to virion invasion. These cells then spontaneously destroy themselves, to limit the spread of the virus. It is the presence of a large quantity of double stranded RNA in the cell that causes it to produce interferon (Sompayrac, 2002).

HRV however, has a way to deal with the interferon signaling problem. It interferes with the production of interferon by shutting down the host cell's system for transporting interferon out of the cells. So, HRV infected cells produce very little interferon. This also means that HRV has not built up any resistance to interferon as an anti-viral mechanism. HRV is mainly destroyed in the body by the innate immune system, by the phagocytes and NK cells, so that a rhinovirus infection is usually over in a few days. This causes a problem, because the infection is over so quickly that the adaptive immune system, like the B and T lymphocytes, are not activated, and neutralizing antibodies are not created for that infection. So, there is no way to prevent a second rhinovirus attack, even from the same strain of HRV, because there were no antibodies created from the first attack. And, HRV uses antigenic drift, so there are over one hundred different strains of HRV all around in the public. This is when mutations that are introduced during viral replication are used to produce different strains of the same virus. A person can continue being re-infected several times over a matter of weeks (Sompayrac, 2002).

Macrophages do provide one helpful immune response to rhinoviruses, in that they produce interleukin-1, a cytokine that triggers a low fever. HRV can't tolerate higher temperatures, so it can help control the spread of the virus (Sompayrac, 2002). Interleukin-1 alpha, interleukin-6, and interleukin-8 have been found in nasal secretions, and are responsible for most of the symptoms (Anzueto and Niederman, 2003).

TREATMENT FOR HRV AND NEW DEVELOPMENTS

Because of the canyon hypothesis, along with the 'attack and surrender' mode of infection of the rhinovirus, a HRV vaccine is impossible, and even if it were possible, it would not be cost effective, due to the necessity of vaccination for over 100 different types of HRV, due to antigenic drift. However, anti-viral therapy has been developed for HRV.

The WIN-family of compounds are common anti-viral agents being tested as a defense against HRV. They bind to the pocket in VPI, which is hydrophobic, preventing the virus from binding to the host cell. Usually this pocket is filled with the 'pocket factor', a lipid compound, and when this pocket is filled with an anti-viral compound, it stretches the pocket, expanding the

beta-barrel, producing an open conformation, and preventing capsid uncoating (Hadfield, et al., 1999). There are currently nine WIN compounds being tested, yet only a few of them show efficacious results (Pevear, et al., 1989).

The WIN compounds generally contain three aromatic rings, known as A, B, and C. some rhinoviruses' pockets only interact with ring C, while others interact with A and B. Ring A is usually a methylisoxazole ring, ring B, a substituted phenoxy group, and ring C, a five-member heteroatom ring (Zhang, et al., 2004). Variations in the pocket if the rhinovirus, like a more hydrophobic 'toe end' of the pocket, and a more hydrophilic 'heel end', lead to the different bindings of the WIN compounds, and lead to different efficacies (Hadfield, et al., 1999).

WIN 54954

The WIN 54594 molecule is an oral anti-viral compound that is active against rhinoviruses and enteroviruses. It works by binding to the hydrophobic pocket inside the VP4 protein on the capsid surface, preventing the replication of the virus by interfering with the virus uncaoting process, and by changing the cell receptor site to not allow HRV to attach to the host cell. When WIN 54594 was tested in cell experiments, it inhibited 80 percent of the rhinovirus serotypes that were presented to it. As such, the developing scientists started to perform clinical trials on WIN 549594. However, when WIN 54594 was tested by volunteers in two different trials who were infected with HRV type 39 or type 23, it had minimal effect. The scientists that developed it feel that the reason was that the human nasal epithelial cells did not take up sufficient amounts of the drug to make a real difference in the sire of the viral infection. If the scientists refine the drug, it may have potent anti-viral effects (Turner, et al., 1992). It did reach phase II clinical trials, but due to the low efficacy in *vivo*, and some side effects, it was stopped (Hadfield, et al., 1999). The side effects included adverse effects of flushing and a rash (McKinlay, 2001).

WIN 52084

WIN 52084 is also another anti-viral molecule that attaches to the hydrophobic pocket in VPI on a rhinovirus capsid, preventing its attachment to the host cell, and limiting its uncoating mechanism. It also stabilizes the capsid, allowing it to be inactivated by temperature or acid related influences (Lewis, et al., 1998).

WIN 51711

WIN 51711 was a compound that bound to the viral capsid, specifically to the interior of VPU, preventing the virion from binding to the host cell receptor (Sperber and Hayden, 1988).

This WIN compound, known as disoxaril, had broad implications in inhibiting picornavirus activity, specifically HRV, and it interacts in a similar way to the other WIN compounds. However, when it entered phase I clinical trials, it failed toxicity tests, leading it to be stopped (Hadfield, et al., 1999).

PLECONARIL

According to the research in the United States, in 1994, there were 66 million cases of the common cold, caused by HRV. Pleconaril, a new oral drug developed, is a small molecule inhibition of rhinovirus that is developed for the entire picornavirus family (Pevear, et al., 1999). Pleconaril is {3- [3, 5 dimethyl-4-[(3-methyl-5-isoxazoly)-propyl]-phenyl]-

5(trifluoromethyl)-, 2, 4-oxadiazol}. It integrated into the pockets of the capsid at VP4, and inhibits the viral capsid uncoating. Pleconaril blocks the attachment to the host cell receptors, which in turn, inhibits viral replication. It was the first anti-picornavirus compound to be submitted to the FDA. In the clinical trials, it did reduce symptoms and duration of the colds, and with animals, it has penetrated the cells involved, and protected them. In phase II studies, it showed reduction of symptoms significantly, as compared with the placebo (Anzueto and Niederman, 2003). It is a WIN compound, WIN 63843, and is a third generation of the original two WIN compounds, WIN 51711 and WIN 54954, and is currently in phase III trials (Hadfield, Diana, and Rossmann, 1999). According to a 2004 report, it has been in the phase III trials, and is performing efficaciously (Zhang, et al., 2004).

Pleconaril has been tested on 1024 individuals who received it three times daily, and reduced the time to heal 3.5 days, instead of seven days. Individual symptoms also resolved themselves sooner in time to heal 3.5 days, instead of seven days. Individual symptoms also resolved themselves sooner in the pleconaril patients. The side effects seemed to be similar for both those on pleconaril and those with the placebo, and as such, it really has no adverse effects. It has a clinical (due to the reduction of symptoms) and antiviral effect (Rotbart and Hayden, 2000). However, because of safety concerns based upon potential drug-drug interactions, the FDA did not approve pleconaril, but new formulations are being considered (Greenberg, 2003).

INTRANASAL INTERFERON

Interferon molecules have antiviral, anti- proliferative, and immunological effects, mostly associated with the 'suicide' response of infected cells. Scientists have developed a synthetic copy, intranasal interferon-alpha2, (or intranasal interferon alfa-2 beta) which has activity against natural rhinovirus infections. However it has not been beneficial in treatment, due to the severe side effects of nasal irritation and bleeding (Anzueto and Niederman, 2003). In fact, after double-blind trials had been performed with interferon alfa-2 beta, there were no differences in the respiratory symptoms scores, and although there were less active viral particles in the nasal washings from those receiving interferon, there were instances of nasal bleeding, and was associated with toxicity to the volunteers (Hayden, et al., 1987). It still remains to be seen if other interferons or other methods can prevent these effects (Sperber and Hayden, 1988).

Interferon alpha administered intranasally through the major study worked very well in preventing HRV colds. Out of the 14 volunteers who received the placebo, 6 had definite rhinovirus infections, while 0 out of 10 with the interferon-alpha2 had been infected. During the third week of testing, interferon-dosed patients complained of nasal discomfort, nasal obstruction, and/or blood tinged mucus. The results tend to indicate the prevention of infection entirely, but due to the long term side effects, it cannot be prescribed long term. It has been administered through a spray and through drops, and has had a huge anti-viral effect. With regard to the drops, and a lower dosage of interferon, there was no intolerance, and it did prevent colds, but there were long term side effects. Possibly, for short term, this drug could be used (Farr, et al., 1984). However, due to the severe symptoms, it is not useful for treating the (generally mild) cold symptoms (Mossad, 1998).

SOLUBLE ICAM-1

Richard Colonno had discovered the difference in receptors among the different strains of HRV, determining what we know commonly now, that there are two major receptors, and most use ICAM-1. As many as 115 serotypes were discovered and out of the 24 tested, they all shared the same ICAM-1 receptor on the host cells (Abraham and Colonno, 1984). After Colonno used his "Brute Force Method' to discover an antibody, but as the synthetic antibody was not eventually cost effective, more scientists took on the race to find a different cure (Taubes, 1999).

Greve and McClelland discovered in 1989 the major HRV receptor on human nasal epithelial cells, known as the intercellular adhesion molecule-1, abbreviated ICAM-1. They discovered it by sending monoclonal antibodies to the host cells, and they recognized the ICAM-1 protein on the cell surface and bound to it (Greve, et al., 1989). They made the antibodies by injecting mouse cells with human HRV-infected cells, and so the mouse would then make antibodies for all the proteins on the host-cells surface. When they finally discovered that one of these monoclonal antibodies worked, it was against ICAM-1, already discovered as a cell receptor molecule by Springer, another scientist working at his own laboratory (Taubes, 1999).

Greves and McClelland, along with a different scientist, Hayden developed a synthetic of what is commonly known as soluble ICAM-1, or sICAM-1, a form of the receptor that was not bound to the cell wall but free to float in solution. This would act by competitive inhibition, attaching to the HRV before it would attach to the host cell's ICAM-1 (Taubes, 1999). Human cells naturally make a form of sICAM-1, but HRV acts on the cell to upregulate the membrane bound ICAM-1, and down regulates the sICAM-1 in the extracellular space, so that it can develop on the host cells and not be impeded by sICAM-1. So, a synthetic of sICAM-1, if developed into a usable drug, could have a large effect. sICAM-1 has been proven to have antiviral properties both *in vitro in* and *in vivo* (Whiteman, et al., 2002). The down regulation of ICAM is so strong that although the ICAM right after ICAM infection is upgraded to prevent the infection within the first 24 hours, it is almost immediately downgraded to the baseline level by day 9. The up regulation of ICAM is done in response to various stimuli, including ozone exposure, interleukin-5, TNF alpha (tumor necrosis factor-alpha), interleukin-1, and CD8 T lymphocytes (Winther, et al., 2002). Hayden performed four clinical trials on 196 student volunteers, with his version of soluble ICAM-1, known as Tremacamra. Virus shedding was detected from the experimentally induced HRV colds. Of the 177 subjects used to determine efficacy, 81 received Tremacamra, and 96 received placebo. There was a 45 percent drop in symptoms, a 23 percent drop in the clinical colds, and a 56 percent drop in mucus, and above all, even if the drug was administered after infection, it still reduced symptoms, and it has preventative measures (Turner, et al., 1999). A test in chimpanzees with rhinovirus-16 infection showed that the s-ICAM molecule was successful in preventing infection, through checking nasal washing and shedding (Huguenel, et al., 1997). Unfortunately, the development of Tremacamra has been halted. The reason given has been the only marginal clinical benefit observed in a highly controlled setting, with the drug being administered five to six times a day (McKinlay, 2001).

SOLUBLE LDL

Soluble forms of the LDL receptor have also been tested, but not extensively, due to the fact that only a few serotypes of HRV actually use the LDL receptor. It seems to inhibit infection by causing aggregation of the virus, unlike the sICAM molecule (Turner, 2000).

The LDL receptor was analyzed and then a synthetic was developed, containing the seven low density-lipid receptor ligand binding repeats that were found on original LDL in cells. The soluble LDL was tested against cells *in vitro* and found to bond to them, proving that the synthetic was identical to the biological LDL. When the group of HRV that uses an LDL receptor, HRV2, was tested against a synthetic soluble LDL receptor, it inhibited the HRV infection *in vitro*. The virion particles formed large aggregates, preventing binding to the LDL receptor in the host cell. In addition, some HRV particles were also prevented from binding to the host cell receptor due to competitive inhibition between the soluble LDL and the host cell LDL. More investigation is probably necessary on this compound (Marlovits, et al., 1998).

AG7088-RUPRINTRIVIR

AG7088 has been synthesized at Agouron Pharmaceuticals in San Diego, and is an antiviral compound, which inhibits the 3C protease in HRV. It was originally tested with cells in the laboratory, and delivered statistically significant results in inhibiting infection by HRV (Zalman, et al., 2000). And enzyme that is encoded by the virus, 3C protease, is the enzyme that cleaves the viral proteins from the polyprotein molecule created in the first step of translation. This allows the virus to replicate and assemble itself. So, some low-molecular weight drugs have been developed to inhibit the 3C protease and prevent HRV from translating. AG7088, one of these drugs, shows good in vitro activity against HRV, and is now being reformulated to maximize delivery to the nasal cavity (Anzueto and Niederman, 2003). In fact, when tested, AG7088 showed that it irreversibly inhibits the 3C protease, preventing translation (Binford, et al., 2004). It had been tested in 1999 on 868 subjects in a phase II study of naturally acquired picornavirus colds, and a trend was observed towards reduction of the total respiratory symptoms (McKinlay, 2001). Ag7088 was found to be active against 48 HRV numbered serotypes as well as 46 unnumbered types and 4 other picornaviruses (Binford, et al., 2004).

This AG7088, or known as Ruprintrivir, has reduced the number of cold victims in its study, from around 44 percent with HRV in the group to 70 percent on a placebo. It had no major side effects, just nasal irritation or blood-tinged mucus (Hayden, et al., 2003). Studies have shown that AG7088 did not prevent experimental rhinovirus infection, but it reduced illness severity. The side effects, nausea and taste disturbance, were mild (Greenberg, 2003). It was given as a nasal spray, and positively reduced the proportion of those subjects with a positive viral culture out of 202 subjects. The overall infection rate was reduced by 28 percent, but although it has antiviral effects, it didn't diminish the frequency of catching a cold (Hayden, et al., 2003). As such, AG7088 is being reformulated to maximize its effects, and to allow better delivery to the nasal cavity (Greenberg, 2003), with further phase II trials in play (McKinlay, 2001).

VIRAL CAPSID BINDING COMPOUNDS

There are many viral capsid binding compounds in existence, which have been used for picornavirus infections. These include amantadine, rimantadine, and zanamivir. However, with rhinoviruses, these drugs give no major clinical benefit. These drugs bind to the hydrophobic pockets in HRVs capsid, and then inhibit the uncoating of the virus and attachment via ICAM-1. In addition, the side effects of most of these drugs outweigh the slight benefits they give against HRV (Mossad, 1998). These compounds have been tried in influenza viruses, and had excellent

antiviral activity, but most have not demonstrated the same in human clinical trials of HRV. Many of these compounds have limitations in dosing, delivery, tolerance, bioavailability, solubility, and safety, and as such, only preclinical trials re performed with these agents (Anzueto and Niederman, 2003).

A specific capsid-binding compound, BTA188, created in Australia, has been shown to inhibit antiviral activity. It had been tested, and inhibited 87 out of 100 specific serotypes of HRV, although it has yet to be tested on humans. BTA188 has been tested on dogs and rodents, with antiHRV activity, and a good uptake of the compound by the cells in question. This compound should undergo further testing and refining in the future (McKinlay, 2001).

ENVIROXIME

Enviroxime is an antiviral agent made from a benzimidazole derivative. It is believed that enviroxime works by inhibiting the viral RNA polymerase replication complex, (Sperber and Hayden, 1988) thus targeting viral replication inhibition of the virus. It inhibited the 3A coding region of the viral RNA, not letting it be translated, and effectively shutting down the process. However, its development has been halted, because it cannot be administered orally, and in clinical studies when it was administered nasally, it had limited antiviral activity. However, other similar compounds are under investigation (Anzueto and Niederman, 2003). Side effects were observed, like nausea and vomiting. There was limited antiviral activity in several trials. In a study with our sprays per day, there was no benefit shown, with no reduction in viral shedding or symptoms, and a study with six sprays per day showed the same results. It was also tested on naturally occurring HRV colds, with no specific advantages or antiviral effects.

However, although enviroxime had minimal antiviral effects, other similar compounds, like enviradene, are still under consideration, as are other methods of administering these compounds, like a topical delivery (Sperber and Hayden, 1988).

PIRODAVIR

Pirodavir, a substituted phenoxy-pyridanzinamine, is a compound that possesses anti-picornavirus activity (Tolan, et alk., 2007). Several pyridazinamines, like R61837, have already been tested to have clinical activity against many serotypes. It binds to the HRV capsid, and prevents capsid uncoating, cumulating in no infection. Four double-blind trials were performed on volunteer subjects experimentally induced with HRV colds, and pirodavir was administered intranasally. When sprays were given six times a day, colds developed in 100 percent of the placebo subjects, while only 58 percent of the pirodavir treated subjects became infected. Pirodavir also was associated with an unpleasant taste, but that was the only serious complaint. However, it would have to be administered with frequent nasal sprays daily during the duration of a cold (Hayden, et al., 1992).

However, clinical trials have not shown any decrease in rhinovirus viral shedding or symptoms, and as such, it has not been used for HRV (Tolan, et al., 2007). It was effective when given prophylactically, but had no effect on established infections (Turner, et al., 1999).

ZINC

There have been many studies done on the anti-viral effects of zinc on HRV. Some show that zinc beneficial, and some don't. Zinc's mode of anti-viral action is still subject to much discussion, although several theories include competitive inhibition, which prevents the HRV from binding to ICAM-1 blocking viral entry in to the cells, inhibiting viral capsid protein synthesis, stabilizing the membrane of the host cell, inhibiting prostaglandin metabolites, and increasing interferon production in the host cell (Mossad, 1998).

According to one study done on acute power upper respiratory infections, primarily caused by rhinoviruses, zinc gluconate lozenges were given to volunteers, and the duration of illness was not significantly reduced. The severity of the illness was reduced, but the adverse side effects, like nausea and altered taste, were reported by fifty percent of the volunteers. Therefore, according to that study, zinc lozenges were ineffective. The authors concluded that zinc had prevented rhinovirus replication by complexing with the capsid proteins, and preventing the proteases from binding to them (Smith, et al., 1989).

A study was performed by one group who found 40 percent reduction in symptoms, but they used unflavored zinc gluconate tablets and unflavored calcium tablets, leading to a difference in taste (Eby, et al., 1984). Another study performed also found significant reductions in symptoms by using zinc lozenges, but found no antiviral effects. This may have been due to the nasal washings used to dilute a sample for testing may have removed from the zinc, and the effect of zinc may have been only due to the actual presence of zinc in the sample at the time, instead of having an effect once it had just touched the viral sample, and didn't need to be actually present (Al Nakib, et al., 1987). It could be that the efficacy of the lozenge is related to the saliva concentration of zinc, and as such, the saliva can't impact the nasal mucosa, leaving most HRVs untouched, making all the lozenge studies invalid (Eby, 1988).

According to another study done by Gwaltney, Farr and colleagues, who tested zinc lozenges as well, zinc therapy did not reduce the viral symptoms, or alleviate the cold manifest symptoms. This study concluded that participants in other studies may have tasted the bad-tasting zinc lozenges and ascribed healing benefits towards them unduly, and as such, they developed a taste-matched placebo that also tasted bitter to prevent the volunteers from realizing which tablet was the active medication. They found that zinc truly had no noticeable effect (Farr, et al., 1987).

MAST CELL STABILIZERS

Mast cell stabilizers are those drugs like Nedocromil and sodium cromoglycate. They are administered intranasally or inhaled, and have reduced the severity of natural and experimental HRV colds. However, they prevent the chemokines and cytokines from being released, reducing symptoms, but they also do a small part in down regulating the ICAM-1 receptor, so the virus can't bond to the host cell. They have been shown to have no effect on viral shedding or viral response to the infection, so although they have some anti-viral effects, it is minimal (Mossad, 1998).

AQUEOUS IODINE

There have been many studies and arguments, some of which that are still going on regarding the method of transmission of HRV. In the University of Virginia, Jack Gwaltney wanted to prove that HRV colds spread through direct contact, like touch. He, and a colleague,

Owen Hendley, developed an iodine solution that killed the virus through hand contact. However, the solution smelled bad, and turned skin brown, but those who used the solution had 40 percent fewer colds. Elliot Dick of the University of Wisconsin, developed what was known as virucidal facial tissues, known as Dr. Dick's Killer Kleenexes, D2K2 for short. In a test, 60 percent of those who used cloth handkerchiefs developed a cold. Elliot Dick also tested for the mode of transmission. He discovered that HRV developed through aerosol contact, not through touch, through an experiment with human volunteers. The D2K2 tissues were marketed under 'Avert', from the Kleenex Company, but didn't sell so well. In addition, Gwaltney, the chief proponent of the touch transmission hypothesis found that they only worked 10 percent of the time in his study (Radetsky, 1991).

ACID SOAKED TISSUES

Jack Gwaltney, along with his colleagues, developed the virucidal nasal tissues. These were nasal tissues, like Kleenex, that had been impregnated with malic and critic acids, along with sodium lauryl sulphate. The idea was to reduce the pH in the nasal cavity, causing spontaneous capsid disassembly to prevent HRV infection. Working against a placebo of saccharin acid, they caused a 14 percent drop in cold infection rate. So, when used, these virucidal tissues may have a small effect, but not a major one (Farr, et al., 1988).

Gwaltney continued to submit his theory developed in 1978 that HRV was transmitted by hand to hand contact. Although iodine is probably the most effective in preventing the spread by touch, it comes with side effects listed earlier…Under Patent 6034133, Jack Gwaltney, Owen Hendley, and Deborah Thacker registered their idea for a virucidal hand lotion, which contained the same ethyl alcohol, citric acid, and malic acid of the tissues, and was not dangerous to the skin. According to a study done against iodine, this lotion was just as effective at halting the spread of the virus, due to lowering the pH to around 3 (Hendley, et al.-Patent, 2000).

ANTIBIOTICS

According to studies, although antibiotics are commonly prescribed for HRV, there is no clinical benefit or antiviral activity. A study of 1,500 children found that antibiotics did not affect the HRV caused colds. Some cold sufferers, around 20 percent, according to a Swiss study, have pathogenic respirator bacteria, like *streptococcus pneumonia*, *Haemophilus influenzae* and *Moraxella catarrhalis*, for which the antibiotics may be helpful, especially if treated with amoxicillin clavulanate. However, for those patients without bacteria, the antibiotics do not help, and in fact, cause five times more gastrointestinal intolerance and reactions. So, antibiotics should not be prescribed for HRV (Rotbart and Hayden, 2000). However, doctors continue to prescribe unnecessary antibiotics, leading to $37.5 million in 1994 spent for HRV related prescription of antibiotics, contributing to drug-resistant bacteria (Mossad, 1998).

Several studies continue to have been performed, using demethylchlortetracycline, amoxicillin and cotrimoxazole, and cephalexin. The effects for all these studies were mostly gastrointestinal, but most had positive effects. According to a review of all the studies, it states that antibiotics are probably beneficial for acute purulent rhinitis, but they support the 'no

antibiotics' as the first line of defense due to the unclear studies and the side effects (Arroll and Kenealy, 2006).

A study was done on 109 patients with COPD (chronic obstructive pulmonary disease), and were observed for twelve months while receiving erythromycin therapy. The results showed that 76 percent of those who did not receive the therapy caught a cold while 13 percent who received the erythromycin therapy caught a cold and since HRV is the major cause of the common cold, antibiotics may be beneficial (Suzuki, et al., 2001).

In a recent study, the antibiotic erythromycin did inhibit HRV infection in tracheal epithelial cells. It reduced the susceptibility of reinfection, the nuclear factor-kB activation, the number of acidic endosomes, and the cytokine production. The study suggested that erythromycin reduces the ICAM-1 receptor and blocks the rhinovirus' entry into the cell by way of the endosomes. This is the first time that macrolide antibiotics have actually helped in an experimental way. However, when clinical trials were performed, the macrolide antibiotic did no better than a regular antibiotic, trimethoprim-sulfamethoxazole (Suziki, et al., 2002).

Corticosteroids have been shown to inhibit the rhinovirus action through inhibiting interleukin activity, specifically NF-kappa B activity, but these steroids actually increase virus replication, having no anti-viral activity as was once thought (Turner, 2000).

NF-Kappa B is a substance used to indicate to cells to produce tumor necrosis factor-alpha. This factor, TNF-alpha, is used to exacerbate virus infections by starting the body's immune responses. When HRV infects the cells, stimulating macrophages, these factors are released, leading to the inflammatory responses (Laza-Stanca, et al., 2006).

NITRIC OXIDE

When HRV attacks a human system, it caused interleukin production, specifically IL-8 and IL-6, causing inflammatory measure. However, when a nitric oxide donor, specifically 3-(2-hydroxy-2-nitroso-1-proplyhydrazino)-1 propanamine, also known as NONOate, was applied, it inhibited the rhinovirus replication and the cytokine production from the body by releasing nitric oxide. This nitric-oxide releasing effect may have both an anti-inflammatory and an antiviral effect (Sanders, et al., 1997). It seems likely that the release of NO may inhibit early events in the viral infection process. NO has been tested in other picornaviruses, and had an effect against the replication of these viruses, and as such, further testing will be done to see it is has the same effect on HRV (Sanders and Proud-patent, 1998).

R61837

R61837 is another compound that inhibits the replication of rhinoviruses. When tested in vitro, it inhibited 74 percent of the HRV serotypes. When administered intranasally in frequent dosages, starting 1 hour before an HRV cold infected a subject and continuing for six days afterwards, it reduced the symptoms and mucus production, along with inhibiting the replication process. Further studies on this compound need to be done (Sperber and Hayden, 1988).

PDTC

PDTC, or pyrrolidine dithiocarbamate, is another antiviral compound, which works against all tested HRV serotypes yet. However, the studies are not conclusive as to how exactly it prevents HRV infection. The studies suspect that metal irons are involved in some way, since

adding metal ions to PDTC blocks its antiviral effects. PDTC actually inhibits NF-kappa, which had been adding metal ions to PDTC actually inhibits NF-kappa B, which had been mentioned earlier, and PDTC inhibits the polyprotein processing of HRV. However, how it accomplishes this is still not understood. More research on this antiviral drug is needed to come to more conclusive results (Krenn, et al., 2005).

NATURAL REMEDIES

There have been some natural anti-viral remedies as well for rhinovirus. A Chinese herb Agastache folium, had been used for the common cold, and a company named Roche extracted a chemical from the herb that stopped HRV from multiplying within cells. It binds to the capsid surface of rhinoviruses to prevent them from infecting a host cell by binding to the host cell receptor. However, its effect and anti-viral activity is not well known yet, and the chemical, Ro-09-0415 is undergoing testing (Scott, 1987).

Ro-09-0415 is actually a phosphorylated ester attached to the original antiviral flavone from the Chinese herb. It seemed to absorb well, but ineffective eventually, in large dosages, like 1200 mg attached to cells (Sperber and Hayden, 1988).

A different capsid binding agent, Ro-09-0410, was developed, also from the same compound. It also seemed to have adequate levels in blood, but the drug was undetectable in nasal washings, and seemed to have no anti-viral effect, and actually increased mucous production, which didn't alleviate symptoms (Sperber and Hayden, 1988).

DICHLOROFLAVAN

Dichlorofalvan is another capsid-binding agent, preventing viral uncoating and attachment to the host cell receptor. It inhibited viral activity best when it was added together with the virus, but it did show antiviral activity even when it was added replication of a single cycle of HRV (Tisdale and Selway, 1983). When it was administered orally three times daily, it was ineffective in inhibiting HRV infection. When tested in nasal washings, it was not detected, despite adequate levels of the drug administered. When it was administered intranasally, a high level of the drug was detected, proving that intranasally was the correct application. However, when the nasal drops were administered five times daily, they failed to reduce HRV infections, showing that adequate levels of the drug were not taken up by nasal cells (Sperber and Hayden, 1988).

CONCLUSION AND SUMMARY

Rhinoviruses are one of the most common and well known pathogens to date. They were the first virus crystal structure mapped, and the quest for the cure for the common cold is well known and documented, including its mode of attack, and how it affects a host cell. There are even many old proverbs regarding rhinoviruses that have sprung up since ancient times. From England, "stuff a cold starve a fever", from Germany, "sauerkraut is good", and from India, "one cold in the head is as bad as ten diseases'. Many doctors go by the proverb, "untreated colds last a week; medical attention can end them after seven days" (Biddle, 2002). William Osler, a John Hopkins doctor, stated "there is just one way to treat the common cold-with contempt". For colds are the cause of more sickness in the world than all other disease combined. (Radetsky, 1991).

Unfortunately, the cure for this pathogen has eluded scientists for decades. New treatment have sprung up, like soluble ICAM-1 or pleconaril, and natural antiviral compounds like zinc or dichloroflavan. Each has a different antiviral effect, from inhibiting the replication of the virus to preventing binding to the host cell receptor. Hopefully, the scientists and 'cold-warriors' battling this insignificant virus will eventually find a cure for the common cold, caused by the most perfect pathogen, human rhinovirus.

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