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Suggesting a new combination of antiviral agents: Targeting the Herpes Simplex Virus

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ABSTRACT

Herpes simplex is a viral disease caused by herpes simplex virus type 1 and type 2.Several broad spectrum drugs are available but most of the strains developed resistance against it. To overcome this problem, we are suggesting a new combination drug for the treatment of herpes simplex. The main aim of the hypothesis is to formulate a topical drug and an intravenously administered drug against herpes simplex virus. Chebulagic acid and Punicalagin inhibit HSV-1 entry at non-cytotoxic doses in A549 human lung cells. sodium is important to curb the proliferation and cell to cell spread of herpes simplex virus. TA205, an antitalin monoclonal antibody can be microinjected in human fibroblasts. It causes allosteric inhibition on integrin binding to the talin protein FERM domain. Sodium lauryl sulphate is a surfactant which enhances intra epidermal drug delivery without increasing transdermal delivery. Amphipathic DNA polymers work against HIV binding and entry. Candidate topical microbicides are efficient against viral entry and cell to cell spread by binding HSV glycoprotein B. Thus, a combination of the above mentioned drugs can be used to prevent HSV binding, cell to cell spread and infection.

INTRODUCTION

Herpes simplex is a viral disease caused by Herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) of herpes viridae family (Nahmias *et al*., 1971). All the members of herpes virus family cause latent infections and have linear, double-stranded DNA genome packed into an icosahedral capsid (Shukla *et al* 2001). The capsid is enclosed by a tegument which is a layer of proteins. A lipid bilayer membrane with embedded proteins and glycoproteins further cover the tegument. This genome is necessary for viral infectivity (Spear, 2004). To control herpes viruses, antiviral medications are used. These agents interfere with the replication of virus, slow down the replication rate of the virus effectively and provide a higher chance for the intervention of immune response. The enzyme thymidine kinase produced by the virus converts the drug from its prodrug form to monophosphate, diphosphate and triphosphate form (Miller *et al*., 1980).Sequentially hampered with viral DNA replication and interfered in its mechanism. Nowadays, several broad spectrum antiviral medicines are available.

These can be administered for controlling herpes outbreaks. Examples of these drugs are aciclovir (Zovirax), valaciclovir (Valtrex), famciclovir (Famvir), and penciclovir (Emmert, 2000). Some strains of the virus develop resistance to certain drugs that hamper their replication. Hence, to cure this disease, a drug with a suitable mechanism of action, had to be developed that would stop the virus from either entering or replicating within the host cell. This proves to be a difficult task as the drug would have to either bind to the virus to stop its fusion with the host or be a competitive ligand at the virus receptor in the host cell. Therefore, its chemical properties and physical conformation would have to be suitable for virus or ligand binding respectively. The process of hampering replication of virus genome in the host nucleus is also a major hurdle to cross to prepare a suitable drug.

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BACKGROUND STUDY

The number of individuals infected with sexually transmitted pathogens is increasing at an alarming rate worldwide. Herpes simplex virus type 1 (HSV-1) and HSV-2 are the most common causes of genital ulceration in developed countries. (Piret *et al*., 2002). It results in painful and recurrent lesions, systemic complications, and psychosocial unhealthy mental state. HSVs are transmitted by typically undesirable lesions and through viral shedding without obvious symptoms (Brugha *et al*., 1997). Five viral glycoprotein have important role in the viral entry process: gB, gC, gD, gH, and gL (Spear, 2004). gC is not necessary for entry. The initial interaction, i.e. binding to cells, is mediated by interactions of gC and/or gB with heparan sulphate proteoglycans (HSPGs). Filopodia, f-actin-rich membrane protrusions facilitate attachment by providing HSPGs-rich sites for this binding. gC is not necessary for viral entry; its absence causes a decrease in the overall binding of the virus to cell surfaces. (Shukla *et al*., 2001). After initial attachment, the penetration process begins. It depends on the cell type of host and the mode of entry. It may need a fusion of the virion envelope with the plasma membrane or with the membrane of an intracellular vesicle (Clement *et al*., 2006). Either ways, the membrane fusion needs essential participation of the viral glycoprotein gB, gD, gH and gL. While gD is not considered a fusion protein, other glycoprotein, specifically, gB and gH, demonstrate attributes of viral fusion proteins (Heldwein *et al*., 2006). Like the attachment process, membrane fusion also needs participation of the cellular receptors. Receptors for gD include herpes virus entry mediator (HVEM), 3-O sulphated heparan sulphate (3-O HS) and nectin-1 and -2 (Shukla *et al*., 1999).

The current model for membrane fusion suggests that the binding of gD to one of its cognate receptors induces conformational changes in gD that mobilizes a fusion active multi-glycoprotein complex involving gB, gD, gH and gL (Atanasiu *et al*., 2007). The release of the viral nucleocapsid and tegument proteins into the host cytoplasm occurs after the fusion of viral envelope with a cell membrane which causes content mixing. Thereafter, HSV nucleocapsids dissociate with tegument proteins and bind a microtubule (MT)-dependent, minus end- directed motor, dynein (Sodeik *et al*., 1997). Although most of the tegument proteins are necessary for activation and modulation of viral gene expression and shut-off of host protein synthesis, some may also participate in dynein-propelled transport of the nucleocapsids along MT toward the nuclear membrane for uncoating and the release of viral DNA into the nucleus. Transcription, replication of viral DNA along with the assembly of progeny capsids takes place within the host nucleus (Akhtar and Shukla, 2009).For the primary episode of genital herpes; it's a common practice to prescribe an antiviral medicine. If an antiviral medicine is administered within five days of the symptoms onset, sores and blisters are usually much lesser. First episode of genital herpes is when the patient has no pre-existing antibodies against HSV-1 or -2 and is usually severe and prolonged, lasting up to 21 days (Cusini *et al*., 2001). The gels that are available in the market, example Tromantadine, prevent the entry and spread of the virus. This is done by making changes in the surface composition of epithelial cells of the skin. They suppress the release of genetic material by the virus (Rosenthal *et al*., 1982.) Another example is of Zilactin, a topical pain killer barrier treatment. This forms a protective shield at the site of application of the gel to prevent a sore from getting bigger by an increase in size and to decrease the viral spreading that happens in the healing process.Novartis produces a drug called Lipactin which is available over-the-counter. It is a local application gel which has been clinically proven to decrease symptoms and to heal a Herpes simplex infection episode. Originally, aciclovir was the prescribed drug and a typical constituent of this class of drugs. It is now readily available in nonspecific brands of drugs at a much reduced price. Valaciclovir and famciclovir—prodrugs of aciclovir and penciclovir, respectively have better bioavailability than acyclovir (Tyring *et al*., 1998) when administered orally and have greater solubility in water.

OUR HYPOTHESIS

The main aim of the hypothesis is to formulate a topical application drug and an intravenously administered drug against Herpes simplex virus causing herpes infection in humans.

Constituents

Integrins

These are dimeric receptors that have a αandβ subunit .These are adhesion receptors that mediate signalling in cells. Talin is a cytoskeletal protein that has a globular head and a flexible rod domain. It is an important constituent of adhesion and joining of integrins with actin filaments. Talins interact with integrins and activate them, thereby increasing their ligand binding affinity (Wegener *et al*., 2006).

When talin head fragments are overexpressed experimentally into Chinese hamster ovary (CHO) cells expressing integrin $\alpha_{IIb}\beta_3$ leads to activation of receptors. Conversely, talin knockdown by transfection of small interfering RNAs into cells inhibits cellular activation of β_1 and β_3 integrins.

Talin binding to the integrin β tail activates integrins, and disruption of the integrin-talin interaction prevents integrin activation .To hamper the binding, adhesion of the virus to the host cell wall and to inhibit stress fibre formation, a monoclonal antibody TA205 can be used that causes allosteric inhibition on integrin binding to the talin protein FERM domain (Xing *et al*., 2006).TA205, an anti-talin monoclonal antibody, is microinjected into human fibroblasts (in vivo studies). The integrin$\alpha_{IIb}\beta_3$ binding to the talin head domain is inhibited due to the conformational changes of talin FERM domain due to biding of TA205.Experiments proved that TA20 inhibited the binding of αβ sub units of integrin to both full –length talin (by 50%) and the talin head fragment (complete inhibition). (Baodong *et al*., 2005)Another way of inhibiting the binding of talin to integrins is by using phosphatidylinositol phosphate kinase type Iγ-90

(PIPKIγ-90)1 which binds talin and competes for talin binding to integrin β tails. It's over expression can stop integrin activation. (Bate *et al*., 2003)

Chebulagic acid (CHLA) and punicalagin (PUG)

These are hydrolysable tannins that are isolated from the dried fruits of *Terminalia chebula* Retz. (*Combretaceae*). These inhibit HSV-1 entry at noncytotoxic doses in A549 human lung cells (Lin *et al*., 2011).Experiments showed that both tannins act against HSV-1 viral particles to inactivate, prevent binding, penetration and cell-to-cell spread(Buzzini *et al*., 2008). It also suppressed secondary infections. Prior treatment of host cell with tannins could not protect the host against HSV-1. Tannins, being natural compounds, were able to block polykaryocyte formation which is mediated by expression of recombinant viral glycoproteins that take part in attachment and membrane fusion. Thus, their inhibitory activities targeted HSV-1 glycoproteins (Serrano *et al*., 2009). It was shown that CHLA and PUG blocked interactions between cell surface glycosaminoglycans and HSV-1 glycoprotein, leading to difficulty in the binding of virus to the host cell. The antiviral activity from the two tannins depends on heparin sulphate availability in cells. It was greatly reduced in mutant cell lines unable to produce heparan sulphate and chondroitin sulphate. This could be avoided by reconstitution of heparan sulphate biosynthesis in cells. It is thus, acceptable that the hydrolysable tannins CHLA and PUG may be useful as competitors for glycosaminoglycans in the regulation of HSV-1 infections and it may decrease the risk for development of viral drug resistance during therapy with nucleoside analogues (Lin *et al*., 2011).

Sodium lauryl sulphate (SLS)

SLS is an anionic surfactant .It increases the fluidity of epidermal lipids and hence enhances penetration into the skin (Froebe *et al*., 1990). Under the site of application, SLS diffuses in several directions due to an increase in fluidity of the lipids. It also follows the radial path of diffusion (Patil *et al*., 1995.). SLS could thus increase intra epidermal drug delivery without increasing transdermal delivery (Piret *et al*., 2000). Furthermore, SLS is a potent inhibitor of the infectivity of various HSV strains at quite low concentrations and under very mild conditions. Taken together, these properties suggest that SLS could be a potential candidate for use in combination with antiviral agents in topical formulations. Sodium lauryl sulfate (SLS) incorporated in topical gel formulations of foscarnet,the conjugate base of the chemical compound with the formula $HO_2CPO_3H_2$, has been tested in mice against herpes simplex virus type 1 (HSV-1) cutaneous infection. The gel formulation containing 3% foscarnet, after a single application, when given 24 h post infection showed a slight effect on the development of herpetic skin lesions (Pechère *et al*., 1998). On the other hand, when 5% SLS is added to this gel formulation it greatly reduced the mean lesion score. The foscarnet gel formulation containing SLS has an improved efficiency due to an increased penetration of the antiviral agent into the epidermis. *In vitro*, SLS decreased the infectivity of herpes viruses for Vero cells (Feizi *et al*., 2013) it is a concentration dependent reaction. SLS also inhibited the damage caused to cells due toHSV-1 strain F. Combinations of foscarnet and SLS resulted in sub synergistic to sub antagonistic effects, depending on the concentration used. Foscarnet has a detrimental effect on human fibroblast cells as it decreases its viability, in a dose dependent manner, in phosphate-buffered saline. (Willers *et al*., 1999) This toxic effect was reduced tremendously when foscarnet was incorporated into the polymer matrix. The presence of SLS in the gel formulations could not alter the viabilities of these cells. The use of gel formulations containing foscarnet and SLS could represent an attractive approach to the treatment of herpetic mucocutaneous lesions, especially those caused by acyclovir-resistant strains. (Piret *et al*., 2000).Also SLS is non toxic to skin, because it is used in toothpastes and shampoo.

Aciclovir

The sugar ring in aciclovir is replaced by an open-chain structure. Viral thymidine kinase was 3000 times more effective in phosphorylation than cellular thymidine kinase. It converts aciclovir into acyclo-guanosine monophosphate (acyclo-GMP) (Trousdale *et al*., 1980.) Then acyclo-guanosine triphosphate (acyclo-GTP) is formed by the action of cellular kinases which has more than 100 times greater affinity for viral than cellular polymerases. Acyclo-GTP gets incorporated into viral DNA which results in premature chain termination. Aciclovir does not have a 3' end even though it resembles a nucleotide. Therefore, after its insertion into a replicating DNA strand, no further nucleotides can be added. Also, viral enzymes cannot remove acyclo-GTP from the replicating chain. Thus, there is inhibition in further activity of DNA polymerase.

Amphipathic DNA polymers

Amphipathic DNA polymers have potent activity against HIV binding and entry (Cardnin *et al*.2009) .This class of compounds disturbs the binding of the virus to heparin sulphate and hence prevents infection (Guzman *et al*.2008). The antiviral activity does not depend on the sequence of the particular polymer. It depends on the size of the polymer. The most potent activity was found for analogues of 40 nucleotides in length. REP 9 and REP 9C block HSV-2 binding and entry. These drugs are active even after the entry of the virus. They inhibit viral gene expression and block HSV induced apoptosis. For the study of the mechanism of these drugs, REP 9 and REP 9C were fluorescently tagged and then inserted into human epithelial cells. The delivery of these drugs was abundant in the infected cells as compared to the non-infected cells. This class of drugs exhibit no cytotoxicity. They retained cytotoxic activity in the cervicovaginal secretions when virus is introduced in the seminal plasma. When REP 9C (which lacks CpG motifs) was compared to REP 9, it exhibited comparable antiviral activity as REP 9 but it was not associated with splenomegaly. This suggests that the direct antiviral activity of APs is the predominant therapeutic mechanism *in vivo*.

Moreover, REP 9C, which is acid stable, was effective when administered orally in combination with known permeation enhancers. (Guzman *et al*., 2008)

Topical Microbicides

Candidate topical microbicides bind herpes simplex virus glycoprotein B and prevent viral entry and cell-to-cell spread (Chenshenko *et al*., 2004). Topical microbicides are designed to prevent acquisition of sexually transmitted infections. Nonoxynol-9, the only commercially available spermicide, damages epithelium and may enhance human immunodeficiency virus transmission. Herpes simplex virus (HSV) and human immunodeficiency virus bind heparan sulphate provided the rationale for the development of sulphated or sulfonated polymers as topical agents. Although several of the polymers have advanced to clinical trials, the spectrum and mechanism of anti-HSV activity and the effects on soluble mediators of inflammation have not been evaluated. The present studies address these gaps. The results indicate that PRO 2000, polystyrene sulfonate, cellulose sulphate, and polymethylenehydroquinone sulfonate inhibit HSV infection 10,000-fold and are active against clinical isolates, including an acyclovir-resistant variant**.** (Anderson *et al*., 2004) The compounds formed stable complexes with glycoprotein B and inhibit viral binding, entry, and cell-to-cell spread. The effects may be long lasting due to the high affinity and stability of the sulfated compound-virus complex, as evidenced by surface plasmonresonance studies (Keller *et al*., 2004). The candidate microbicides retain their antiviral activities in the presence of cervical secretions and over a broad pH range. There was a little reduction in cell viability following repeated exposure of human endocervical cells to these compounds, although a reduction in secretory leukocyte protease inhibitor level was observed (Newcomb *et al*., 2005).

MECHANISM

Intravenous administration

The drug is designed to stop viral entry and replication. Monoclonal antibody can only be administered orally and acts as a first line of defence against viral penetration. Thus, it prevents the entry of the virus by blocking the integrin receptor. There is another way in which the drug can enter i.e. through the glycoproteins that is stopped by the amphipathic DNA molecule. Even after being stopped at these stages the virus enters, there is aciclovir to stop its replication. Thus, the newly designed drug hinders viral entry as well as growth. Thus, it will be more effective than the already existing drugs. The brief description of mechanism of the above three ways of prevention of viral existence is given below:

A monoclonal antibody TA205 can be used which cause allosteric inhibition on integrin binding to the talin protein FERM domain to hamper the binding. TA205 is an anti-talin monoclonal antibody which is microinjected into human fibroblasts. The integrin αIIbβ3 binding to the talin head domain is inhibited due to the conformational changes of talin FERM domain due to binding of TA205. Experiments proved that TA20 inhibited the binding of αβ subunits of integrin to both full –length talin (by 50%) and the talin head fragment (complete inhibition) (Baodong *et al.*, 2005).

Amphipathic DNA polymers have potent activity against HSV binding and entry. This class of compounds disturbs the binding of the virus to heparin sulphate and hence prevents infection. The antiviral activity is dependent on the sequence of the particular polymer and the size of the polymer.

Aciclovir

the sugar ring in a nucleotide is replaced by an open-chain structure which makes it 3000 times more effective for viral thymidine kinase in phosphorylation than the cellular thymidine kinase. Aciclovir is converted into acyclo-guanosine monophosphate (acyclo-GMP) which later forms acyclo-guanosine triphosphate (acyclo-GTP) by cellular kinases which has more than 100 times greater affinity for viral than cellular polymerases. Acyclo-GTP gets incorporated into viral DNA which results in premature chain termination. Aciclovir does not have a 3' end even though it resembles a nucleotide. Therefore, after its insertion into a replicating DNA strand, no further nucleotides can be added. Also, viral enzymes cannot remove acyclo-GTP from the replicating chain. Thus, there might be inhibition in further activity of DNA polymerase.

Local administration

Local application of the drug too includes prevention of entry of drug into the host cells through the glycoproteins by the presence of hydrolyzable tannins like Chebulagic acid (CHLA) and punicalagin (PUG). Sodium lauryl sulphate is added to help the entry of drug into the skin. DHPG is the substance that prevents replication after the virus may have skipped the first line of defence of drug and entered the cell. It will be more effective than aciclovir. As it is seen, the virus is free to enter through the integrin receptor. Thus the oral drug is more effective against the virus than the ointment. However, this problem is counteracted by using a better agent to stop replication than the one used in oral administration. But, it is strongly suggested that the oral drug is far more active against the virus. The following briefly puts across the functions of each of the components.

Chebulagic acid (CHLA) and punicalagin (PUG) are hydrolyzable tannins that are isolated from the dried fruits of Terminalia chebula Retz. (Combretaceae). These inhibit HSV-1 entry at noncytotoxic doses in A549 human lung cells. Tannins, being natural compounds, are able to block polykaryocyte formation which is mediated by expression of recombinant viral glycoproteins that take part in attachment and membrane fusion.

Sodium lauryl sulfate (SLS) is an anionic surfactant .It increases the fluidity of epidermal lipids and hence enhances penetration into the skin. Under the site of application, SLS diffuses in several directions due to an increase in fluidity of the lipids. It also follows the radial path of diffusion. SLS could thus increase intraepidermal drug delivery without increasing

transdermal delivery. Furthermore, SLS is a potent inhibitor of the infectivity of various HSV strains at quite low concentrations and under very mild conditions.

DHPG

dihydroxy propoxy methyl guanine is more effective than acyclovir in stopping replication of the virus in the host cell. The mechanism is similar to acyclovir: the presence of an open chain makes it more effective towards viral thymidine kinase. It is converted to acyclo-GMP followed by its conversion to acyclo-GTP. Due to the absence of the 3' end, nucleotides cannot be added. Thus viral replication will be hindered.

CONCLUSION

We have come up with two drugs one that would be administered intravenously andtopically to develop resistance against herpes simplex virus. The first drug will be taken intravenously as it contains a monoclonal antibody. The virus has two ways of entering into the cell: the glycoproteins and the integrin receptor.

The two components monoclonal antibody TA205 block integrin receptors and amphipathic DNA molecules block the glycoproteins. Even if the virus has entered the cell, aciclovir stops the replication of the virus inside the host cell. The topical application does not comprise of a component which blocks the integrin receptors. Certain strains of HSV have mutant genes in it developed resistance against aciclovir. However, the strains were still sensitive to the action of DHPG. The intravenously administered drug is better preferred over the local application as it counteracts all possible mechanisms of viral entry and replication. The reason for using aciclovir and not DHPG in the intravenously administered drug is that aciclovir has very little side-effects. Though its action is not as effective as DHPG, the combined action of the rest of the components of the drug balances this disadvantage.

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