Journal Homepage: -www.journalijar.com
INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)
Article DOI:10.21474/IJAR01/1874
DOI URL: http://dx.doi.org/10.21474/IJAR01/1874
ISSN NO. 2320-5407

RESEARCH ARTICLE

APPROACHES IN THE DEVELOPMENT OF VACCINES AGAINST HENDRA & NIPAH VIRUS A REVIEW.

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Manuscript Info

Manuscript History

Received: 12 August 2016
Final Accepted: 22 September 2016
Published: October 2016

Abstract

Hendra and Nipah viruses from genus Henipavirus are paramyxovirus that can cause diseases that passed between animals and humans. These viruses are responsible for causing diseases that occurs at irregular intervals at some places. Like other paramyxovirus, henipavirus also have the ability to escape the host immune response due to interferon protein; this is due to P gene. The P-gene is responsible for encoding four proteins – C, P, V, & W protein. Currently no vaccines or therapeutic remedies are available which can prevent henipavirus infection. Ribavirin which is used to treat various viral hemorrhagic fevers, in vitro studies of ribavirin against both hendra and nipah virus shows effective inhibition of hendra and nipah virus. The henipavirus have two envelope proteins F & G glycoproteins; the G glycoprotein is an attachment glycoprotein while F is the fusion glycoprotein. The recent tactic to prevent henipavirusinfection focused on direct medication by soluble forms of F & G viral glycoproteins to induce a protective immune response.

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Introduction:-

Hendra virus (HeV) and Nipah virus (NiV) from genus henipa virus are zoonotic paramyxovirus; they can cause disease which is passed between animals and humans (1). Hendra virus was first detected in humans in Australia in 1994 with horses as intermediate host. Fruit bats of Pteropous species of Australian flying fox show serological evidence of early exposure to Hendra virus (2).

Nipah virus was first detected in humans in Malaysia in 1998with Pigs as the intermediate host (3). The nipah virus was isolated from the cerebral fluid of an infected human (4) The name Nipah is come from the name of theriver in the village from which the first case had come (5). Different ELISA methods have been developed for the serological diagnosis of henipa virus infection (6).

There is no approved therapeutics modality againstHendra and Nipah virus and hence both are extremely pathogenic (7), this leads to the classification of Nipah and Hendra virus as biosafety level 4 pathogens (8). Recent investigations show that compounds which modulated ion flux particularly intracellular calcium ion flux induced a potent inhibition of henipa virus replication (9). Some of the compounds used as therapeutic drugs against henipavirus exert their effect via releasing intracellular calcium and thus it provides a novel antiviral mechanism (10).

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Currently there are no vaccines or therapeutic medicine specifically recorded to either prevent or treat patients infected withhenipaviruses (11), in a screening of over 8,000 low molecular compounds against live NipahVirus, three commercially available compounds are identified, providing a measure to immediately evaluate their mode of action (12). Brilliant Green (One of the identified compounds) was observed to induce a rapid and continuous rise in intracellular calcium concentration (9). further investigation reports compounds which inflect ion channel flux, mainly intracellular calcium flux, this results in a strong inhibition of henipavirus replication *in vitro*(9).*In vitro* studies of ribavirin shows effective inhibition of both Hendra and Nipah Virus (13), a recent *in vivo* study on a hamster model animals infected with Nipah virusreveals that the 5-ethyl analogue of ribavirin is capable to prevent mortality in five of six animals (14), it has been found by in vitro study on pseudo typed-VSV of HendraVirus, as *chloroquine*, is an efficient antiviral compound.But *in vivo* it does not shows any anti henipa virus effect (15), the major vaccination strategy to induce a protective immune response against henipa virus infection is thedirect immunization with soluble forms of F and/or G viral glycoprotein(16). In this form of vaccination several injections of recombinant proteins coupled to adjuvant are required to achieve a significant immune response (17). In few other vaccination strategies recombinant viral vectors are used to directly express the G and/or F glycoproteins of henipa virus in vivo (18).The hamsters and pigs can be protected against a challenge with wild-type Nipah virus by using recombinant vectors derived from vaccinia virus or canary poxviruses were shown to induce a humoral response against the Nipah virus G protein, (19).However, several other viral proteins are also encoded by these vectors, which may cause undesired immune response in humans (20). Immunization withadeno-associated virus (AAV) vaccines (expressing the Nipah virus G protein) in mice demonstrated that to induce a potent and long-lasting Antibody response a single intramuscular AAV injection was sufficient (21).

Structure of henipa virus:-

Henipaviruses are ***pleomorphic*** ranging in size from 40 to 600 nm in diameter. They have a lipid membrane above a shell of viral matrix protein, within the lipid membranespikes of F (Fusion) protein trimmers and G (Attachment) protein tetramers are Embedded (22). The G protein is responsible to attach the virus to the surface of a host cell via EPHB2 (Ephrin B2) (23). The viral membrane of henipavirus fuses the with the host cell membrane, via F protein releasing the virion contents into the cell (24). This results in the fusion of infected cells with the neighboring cells to form a syncytium (25). The Hendra virus and Nipah virus genomes are non-segmented, single-stranded anti-sense RNA (26). The genomes of both hendra and nipah virus are 18.2 kb in size and contain six genes relating to six structural proteins (27). With the help of RNA editingHenipaviruses can generate multiple proteins from a single gene (28), this results in insertion of extra guanosine residues into the P gene mRNA prior to translation (29). The synthesis of P, V or W proteins is decided by number of residues added (30). The functions of the V and W proteins are unknown however they might be included in disturbing host antiviral systems (31).

Epidemiology:-

The basis for the epidemiology of Hendra and Nipah virus throughout the vary of their prevalence is determined by the sources that maintain them and the by the mode of transmission of viruses to the human population (32). Pteropid fruit bats family *Pteropodidae*, have been distinguished as the common reservoir hosts of henipaviruses (33). Both Nipah and Hendra virus are endemic, highly pathogenic and capable of infecting most of the mammalian species in nature and under experimental conditions (34). Field studies in Malaysia shows that there are various factors that could have led to the transmission of the virus from the reservoir bat species to commercial pig farms. (35). The common practice of large scale farming, without the application of sufficient biosecurity practices certainly promote the transmission of the virus once it was imported into the national swine herd (36). The passage of transmission in crowded populations is well identified as a primary aspect in aiding the genesis of the Malaysian outbreak in the swine population (37). The incubation time ranged from few days but in most of the cases between 1 to 3 weeks (38). Prior signs and symptoms are often nonspecific: headache, dizziness, fever, myalgia, (39). Neurological symptoms are the prevalent features within a week, despite of 14–29% also exhibit respiratory involvement (40). Symptoms of Hendra virus infection of humans may be respiratory, along with hemorrhage and edema of the lungs, or encephalitic, resulting in meningitis (41). In horses, infection mostlyresults inpulmonary edema, congestion and or neurological signs (42).

Henipa virus outbreaks in india& Bangladesh:-

DATE	LOCATION	DETAILS
January 31–23 February 2001	Siliguri, India	66 cases 74% mortality rate. 75% of are hospital employees. (43)
April – May 2001	Meherpur, Bangladesh	13 cases,9 fatalities (44)
January 2003	Naogaon District, Bangladesh	12 cases,8 fatalities. (44)
January– February 2004	Manikganj and Rajbari districts, Bangladesh	42 cases ,14 fatalities. (44)
19 February – 16 April 2004	Faridpur District, Bangladesh	36 cases , 27 fatalities 92% of cases are in close contact with at least one other nipah virus infected person. (45)
February – May 2007	Nadia District, India	50 suspected cases, 3–5 fatalities. (46)
February – March 2008	Manikganj and Rajbari districts, Bangladesh	Nine cases , 8 fatalities. (46)
February 2011	Hatibandha, Lalmonirhat, Bangladesh	21 schoolchildren are due to Nipah virus infection. IEDCRhas confirmed the infection is due to this virus. (47)

Henipa virus outbreaks in Australia:-

DATE	LOCATION	DETAILS
August 1994	Mackay, Queensland	Two horses one human die. (48)
September 1994	Hendra, Queensland	20 horses died. Two humans infected, and one die (48)
October 2004	Gordonville, Cairns, Queensland	One horsedies. (48)
July 2008	Redlands, Brisbane, Queensland	Four horses died due to Henda virus. Two veterinary workers infected. A nurse involved in caring for the infected horses was also hospitalized. The Biosecurity Queensland website shows that 8 horses died during this incident. (48)
20June 2011 – 31July 2011	Mt Alford, (near Boonah) Queensland	Three horses die due to hendra virus. And dogs which are in contact with infected horses are also affected (48)
19 July 2012	Rockhampton, Queensland	One horse died.
4 July 2013	Macksville, New South Wales	Six year old castrated male horse died. (49)
9 July 2013	kempsey, New South Wales	Thirteen year old unvaccinated quarter horse died. (49)
1 June 2014	Beenleigh, Queensland	Horse euthanized. (49)
June – july2015	Murwillumbah Kairi	1 horse dies. (49)

Mechanism of transmission of henipa virus:-

Like other paramyxoviruses, henipavirus infection of the host cell is mediated by two membrane anchored surface glycoprotein's- an attachment (G) and fusion (F) glycoprotein (50). The G glycoprotein is present as tetramer anchored in the lipid membrane of the virus which appears to be associated with the trimeric F glycoprotein prior to receptor binding (51).Following binding of G to its ephrin receptors, conformational changes are expect to occur within the G glycoprotein oligomer (52).The receptor assurance of the G glycoprotein in turn elicit a conformational change in the F glycoprotein, leading to the stripping of the fusion peptide (53)which forms a physical link between the viral and cellular membranes. At the end of the fusion process nucleo capsid enters into the cytoplasm of the cell and results in onset of viral replication (54). The utilization of ephrin-B2 and ephrin-B3 as the receptor on the host

cell leads to basic similarities in the disease processes caused by Hendra and Nipah virus regardless of the species infected (55). Isolation of virus from the nasopharyngeal secretions of Nipah virus infected patients and from the dissection of organs of a fatally infected Nipah virus patient, suggested that the primary site of virus replication could be the lymphoid and the respiratory tissues (56).

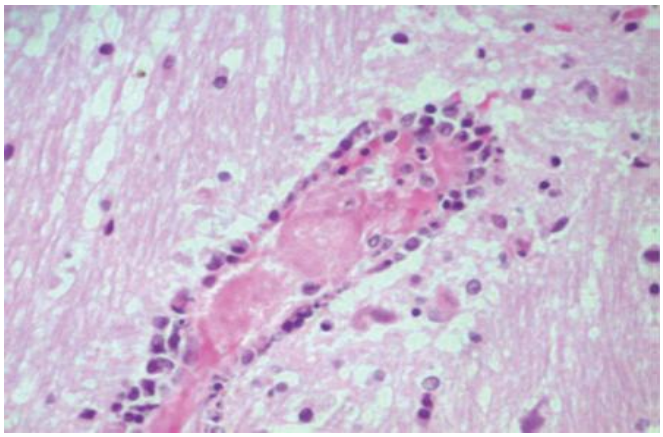

Fig. 1.1:-Vasculitis and associated intravascular thrombosisin human brain necrosis, and peripheral multinucleatedgiant cell formation (70)

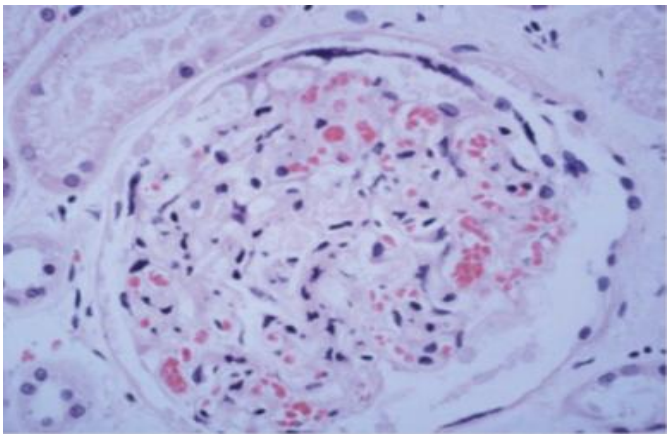

Fig. 1.2:-Glomerulus in human Nipah infection with thrombosis (70)

Vaccine Development:-

Vaccines effectively control other well-known paramyxovirus infection infections e.g. Measles and Mumps in human beings and Rinderpest infection in cattle (57,58,59). New vaccination strategy is based on the use of recombinant vectors derived from adeno-associated virus (AAV)(60) . Now days AAV vectors are considered to be powerful tools for in vivo gene transfer and gene therapy (61). In fact, these vectors are able to transfer genetic material in a wide variety of tissues in vivo,this leads to a strong and sustained expression of the transgene (62). AAV vectors have the ability to express the nipah virus G protein to induce a protective immune response(63).

The majority of paramyxo viruses enter the host cell via two surface glycoprotein's : one is Class I fusion (F) glycoprotein and theother is an attachment glycoprotein, which may be a hemagglutinin–neuraminidase (HN), hemagglutinin(H) (64), or in case for henipavirusesit may be a G glycoprotein (65), therefore effective resistance to paramyxovirus infection through vaccination is generally mediated by an acquired immune response to viral surface protein or glycoprotein's generally for infections associated with viraemic phase (66).Recent studies for the development of vaccines against henipa virus focused on viral envelope F and G glycoprotein's which are either expressed as a recombinant immunogen subunit or in a recombinant virus (67). The vaccination strategies against henipa virus infection generally based on regular repeated injections of high doses of Hendra virus G proteins mixed with some adjuvant to induce a protective humoral response (68,69).

Conclusion and future aspects:-

In light of the potential ecological availability of Hendra Virus and Nipah Virus, as they are highly pathogenic and able to infect a broad range of mammalian hosts, the development of effective therapeutic measuresis the major area of research to be focus. The use of structure glycoproteins (F & G) in vaccine preparation induces a protective humoral immune response.

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