Current Scenario of Antiviral Drugs for Japanese Encephalitis

Shailendra K. Saxena1*, Parth T. Agrawal1 and Madhavan P.N. Nair2

1CSIR-Centre for Cellular and Molecular Biology (CCMB), Uppal Road, Hyderabad, India
2College of Medicine, Florida International University, USA

*Corresponding Author: Shailendra K Saxena, Senior Scientist (Infectious Diseases), CSIR-Centre for Cellular and Molecular Biology, Uppal Road, Hyderabad 500 007 (AP), India, Tel: +914027192630; Fax: +914027160591; 2716 0311; E-mail: shailen@cccmb.res.in; shailen1@gmail.com

Current Scenario

Japanese Encephalitis (JE) is caused by neurotropic Japanese Encephalitis Virus (JEV) which belongs to flaviviridae family and is the most important encephalitis causing virus in Asia. JEV is reported to cause 35-50 thousand cases and 10-15 thousand deaths annually [1]. Viruses belonging to the flaviviridae primarily spread through arthropod vectors, and is the major cause of one of the most fatal disease around the globe. Flaviviruses are small RNA viruses transmitted by mosquitoes and ticks. Upon entering the host, they take over host cell machinery in order to propagate and flourish. JEV generally affects small children (<15 yrs) and elderly people (>65 yrs) who have weak immune system and hence are vulnerable [2]. JEV generally affects small children (<15 yrs) and elderly people (>65 yrs) who have weak immune system and hence are vulnerable [2]. JEV infection was initially reported in Southeast Asia but now it is affecting populations worldwide [3]. JEV leads to major outbreaks in tropical regions of Asia with China, Japan, Korea, Philippines, Southeastern Asia and India [4]. JE's mortality rate is almost 25-30%. Though intensive care and support help to lower the death rate, patients still continue to suffer from JE for longer period of time. Some effects such as learning difficulties and behavioral problems can remain masked for several years. From total JE infected patients, nearly one-third die without any vaccination and the number of unvaccinated individuals is continuously increasing. Viruses have evolved various mechanisms to disrupt the host immune system. One important amongst them is preventing the infected cells from sending out chemotactic signals to activate the adaptive immune response. Subsequently, there is a burning need for the development of novel therapeutic drugs against JE.

There are many promising candidates against JE infection which need further assessment and increased availability to the needful. Nitazoxanide (NTZ) is a thiazolide anti-infective which is validated to have antiviral properties [6,7] and is used for the treatment of parasitic gastroenteritis. Combination of N-methylisatin-β-thiosemicarbazone derivative (SCH16) with ribavirin and mycophenolic acid demonstrates the antiviral activity of SCH16 against JE in vitro [8]. Griffithsin (GRFT) is a broad spectrum antiviral protein that is effective against several glycosylated viruses which may be used for therapeutic development against JEV or other flaviviruses [9]. Bispidine, an amino acid conjugate of 3,7-diazabicyclo[3.3.1]nonane acts as a molecular scaffold for the development of potent antivirals against encephalitis viruses [10]. Tilapia hepcidin (TH) 1-3, an antimicrobial peptide can control JEV viral infection and could be a promising antiviral candidate [11]. Mycophenolic acid is reported to inhibit the replication of JEV in mouse model experiments, therefore could be used against JEV infection [12]. Minocycline acts as neuroprotective agent in various animal studies of a number of acute CNS injuries, neurodegenerative disorders and CNS infection. It is reported to reduce the neuronal damage by JEV in cell culture models by inhibiting oxidative stress [13]. Studies have shown that pentoxifylline acts as antiviral against several RNA and DNA viruses. In vivo studies have shown that pentoxifylline at a concentration of 100mg/kg body weight can protect mice introduced to LD (50) of JEV [14]. Rosmarinic acid is reported to reduce mice mortality infected with JEV [15]. Short interfering RNA (siRNA) can be used as a broad spectrum antiviral agent for treating encephalitis caused by multiple flaviviruses like JEV, West Nile virus, tick-borne encephalitis virus [16]. Dehydroepiandrosterone (DHEA) is an adrenal derived steroid which involves in protection against neurotoxicity and viral induced encephalitis, resulting in a better survival rate of the animals [17]. A low molecular weight dithiol, Diethyldithiocarbamate (DDTC) is an immunomodulator and modifier of different biological actions in animal and human models. It is also effective in several disease conditions. Many experiments have shown that DDTC have a possible therapeutic role during JEV infection [18]. It has been studied that macrophage derived neutrophil chemotactic factor (MDF) induces production of nitric oxide (NO) during JEV infection, which has an antiviral effect. NO may play a crucial role in the innate immunity of the host to restrict the initial stage of JEV infection in the central nervous system [19, 20]. Several kinds of furanonaphthoquinone (FNQ) derivatives have antiviral activity against JEV. FNQ3 inhibits JEV replication through attacking viral RNA and protein synthesis [21].

Isatis indigotica is a herb which grows in China and is traditionally used for the clinical treatment of viral diseases like encephalitis, hepatitis and influenza. Pretreatment of Isiduntigotica extracts, indirubin and indigo significantly inhibit JEV replication in vitro. They obstruct JEV attachment and hence have potent antiviral activity [22]. Rheum palmatum is another Chinese traditional herb which exhibits a great variety of anticancer and anti-viruses properties. Methanol extract of R.palmatum and chrysophanol may have high therapeutic index as antiviral against JEV [23]. Pokeweed antiviral protein (PAP) is a plant derived N-glycosidase ribosomal inactivating protein isolated from Phytolacca americana. PAP possesses antiviral activity against JEV infection making it promising antiviral agent [24]. Aloe-emodin is a potential interferon inducer produced from Chinese herbal medicines and is reported for antiviral activity against JE [25]. Kaempferol is a natural flavonol which acts as antiviral agent as it inactivates virus by binding with JEV frame shift site RNA (fsRNA) [26]. Lactoferrin is a natural anti-microbial protein which attaches to cell surface expressed heparan sulfate, one potential receptor for JEV, and has anti-JEV activity [27]. Astragal Radix extracts (AE) has protective effect by intraperitoneal injection against JEV infection. The studies of the mice model experiment show that the protective effect of AE is dependent on a non-specific mechanism during the early stage of infection.
before it moves to antibody production and peritoneal exudate cell (PEC) plays an important role [28].

Another promising field is nanotherapeutics. Nanomaterials have the characteristic of high surface-to-volume ratio and have been discovered for their antiviral activities. Success in synthesizing surfactant-modified nanoscale silicate platelet (NSP) with antiviral activity may open doors towards future antiviral developments, for example, Nanoscale silicate platelet modified with sodium dodecyl sulfate (NSQC), functions as a potent and safe antiviral nonhydrolysis against many viruses [29].

Efforts for flaviviral drug research and development are growing at fast pace. Drug designing against the NS2B and NS3 nonstructural proteins of flaviviruses are being attempted. This design focuses on vital physiochemical and biochemical properties of proteases by using crystallography based models of NS3 substrate interaction compounds. Efforts are being employed to target the capping enzyme and E and NS5 proteins of flaviviruses. Crystal structure of enzymatically active domains of these nonstructural protein inhibitors has been interpreted by research to understand its sub cellular and support for this work. We thank Ms. Sneham Tiwari for critical reading of the manuscript. SKS and MPN are also supported by NIH Awards (R37DA025576; R01MH085259).

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