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Short Communication

Rabies: Pharmacotherapy

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Abstract

Rabies glycoprotein outer content of rabies viral cell wall downgrade virion infected cellular apoptosis. Cellular apoptosis inversely related to virulence of virus. Beta bungarotoxin of krait (*Bungarus Caeruleus*) venom molecular structure similar to the glycoprotein of the rabies virus. The antibodies or immunoglobulin against the krait venom (beta-bungarotoxin) para- specially inhibit the viral glycoprotein and upgrade the apoptosis of infected neuron, accompanied with a virulence of rabies virus, may arrest the progression disease in the brain.

Introduction

Rabies is most fatal disease Irrespective of advanced intensive care management, irrespective of combination of specific therapy including the rabies vaccine, immunoglobulin, monoclonal antibodies, ribavirin, interferon alpha and ketamine [1]. In the 21st century, rabies remains as one of the most feared and important threats to public health. There are probably 75000 human deaths per year worldwide from rabies. Our knowledge and understanding regarding why humans suffer from rabies is incomplete. However a recent study on the viral structure, including its glycoprotein and the corresponding affected human receptors showed that Pharmacological agonists and antagonists can be used to overcome the adverse effect of the virus on various nervous system receptors which might give hope to alleviate the misery, prolong the survival and give us a ray of hope for recovery. Rabies virus is a single-strand RNA virus. Virions are bullet-shaped particles containing a ribonucleoprotein, nucleocapside core, surrounded by a lipid-bilayer envelop. The virus encodes five structural proteins; nucleoprotein, phosphoprotein and transcriptase are associated with genome RNA in ribonucleoprotein, matrix protein and glycoprotein. The Glycoprotein projects from the outer layer and is a primary target for neutralizing antibodies. The Negri bodies represent accumulation of viral particles. The Rabies virus replicates in muscles and nerve endings from the site of bite of canines. Within 24 hours of the bite, the virus reaches the neuromuscular and neurotendinal spindles, this entry of virus represent deep site into the nervous system. It binds to the nicotinic acetyl choline receptor at the neuromuscular junction [2]. Virus from the infected brain descends through the afferent sensory nerves to the salivary glands, lacrimial glands and to densely innervated tissues including the heart. The Virus causes neuronal dysfunction followed subsequently by apoptosis. The Virus localizes in the brain stem, thalamus, basal ganglion and the spinal cord. Hydrophobia has been reported as a symptom because the pharyngeal and laryngeal (bulbar) spasms have been incorrectly interpreted as fear of drinking water. Even a similar response to air blowing across the face has been incorrectly interpreted as aerophobia. Autonomic instability characterized by hypertension or hypotension, excessive sweating, salivation, piloerection, priapism, neurogenic pulmonary edema, sinus tachycardia, respiratory failure, tachycardia, heart failure, arrhythmias, coronary sinus rhythm, diabetes insipidus and spontaneous ejaculation are also important sequel. Once the virus enters the central nervous system, it is not exposed to the immune system and therefore cannot be cleared by antibodies.

There is considerable evidence that the specific attachment component of the enveloped virus is the glycoprotein, and removal of the virus spike glycoprotein enzymatically or genetically, renders some negative stranded virus non infectious [3]. The glycoprotein involved in the attachment of the virus to the cell surface has been identified. In the rabies virus, a single amino acid substitution, i.e. replacing arginine at position 333 of the glycoprotein molecule renders the virus non-pathogenic [4]. From the neuromuscular and neurotendinal spindles, the virus reaches the spinal cord by retrograde transport within the axon, since disruption of the axon or blockade of axoplasmic flow prevents the centripetal spread of the virus. In the central nervous system, the virus is disseminated by direct transfer of the virus from neuron to neuron, at synapses. The Rabies virus infects specialized surface patches which contain a high density of AChR. The highest density of AChR occurs at the tip of the junctional folds of the neuromuscular junction. Similarly, the binding to AChR at central synapses may be responsible for the transfer and spread of virus from neuron to neuron by concentrating the virus at the postsynaptic sites in proximity to the presynaptic axon terminals.

Experimental Study

In the rat brain, the binding of quinucidinyl benzylate, an antagonist of the muscarinic AChR, is markedly decreased with the onset of symptoms of rabies. When cultured myotubes were exposed to rabies virus, antigen distributed in patches on the cell surface in a pattern similar to that observed following staining with rhodamine-labeled alpha-bungarotoxin. Alpha bungarotoxin is a polypeptide isolated from elapid snake venom which binds specifically and nearly irreversibly to the nicotinic AChR [5]. Pretreatment of myotubules with alpha-bungarotoxin and another ligand for the AChR, d-tubocurarine, dramatically reduced the number of myotubes that became infected. Both of these ligands bind to the 40000 dalton alpha subunit which contains the acetyl choline binding site of the AChR. There has been recent speculation that NMDA receptor may be one of the rabies virus receptors [6]. Identification of the virus receptor has

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practical significance in providing a basis for preventing infection by blocking the attachment step. In rabies disease, this could be useful because the host defense mechanism fails to prevent the disease. Delaying the infection may give -an opportunity to normal immune response by active of passive immunization. In rabies immune response is the potential to harm from potentiated immune response. In rabies, the brain blood flow may be preserved in association with brain death.

Human immunoglobulin has a limited ability to cross an intact blood brain barrier. There is no scientific rationale for the use of therapeutic coma in human rabies [7], though therapeutic coma (midazolan and Phenobarbital), ketamine and antiviral therapies (dubbed the "Milwaukee protocol") have been tried. There are 20 documented reports of failure of The Milwaukee protocol [5,7] . Autonomic complications may occur in rabies and may lead to death. The Release of inflammatory markers such as interleukins 1 alpha beta, 6 and 10 tumor necrosis factor, interferon and nitric oxide c modifies the hippocampus and other limbic system functions.

An Indian Vaidya (a doctor who know details of Ayurveda), reported in ancient literature of Ayurveda that *Datura* seeds extract (atropine) improves the survival in rabies mad animals [8,9]. Thus atropine may alleviate the salivary and bronchial secretion. Two neurotransmitter receptors in the central nervous system, for N-methyl-D-aspartate subtype R1 and GABA, have been suggested as possible receptors for rabies.

Magnesium sulphate block ligand-gated calcium channels, resulting in reduced acetyl choline release from presynaptic terminals, and reduced CNS over stimulation mediated *via* NMDA receptor activation. This also prevent the virus transmission [1,9]. It inhibits the NMDA receptor which is also a virus carrier and a neuroexcitator. Zolpidem a GABA agonist accelerates the CNS inhibition.

The Virus colocalises with nicotinic acetyl choline receptors. Binding at this postsynaptic site is competitive with cholinergic ligands including the snake venom neurotoxin alpha-bungarotoxin, which shows sequence homology with the envelop glycoprotein of rabies virus (Figure 1).

The Rabies virus virulence is influenced by its glycoprotein envelop. This envelop is responsible for the absence of apoptosis until a terminal stage (Figure panel B). The viral glycoprotein may bind to nicotinic acetyl choline receptor on the muscle. Apoptosis is the most important defense mechanism against rabies virus infection. The extent of apoptosis correlates with the amount of expression of rabies-virus glycoprotein in the infected neuron (Figure panel B). The Down regulation of glycoprotein expression in neuronal cells contributes to pathogenesis by preventing apoptosis [2,3].

Antibodies against virus glycoprotein will evoke antigen antibody reaction with liberation of cytokines and inflammatory markers which are injurious to CNS. A agonist derived from alpha-bungarotoxin will target the virus glycoprotein, it inhibits or prevents the releases of virus glycoprotein in infected neuron, as result of this, the apoptosis of infected neuron is upgraded, resulting in rapid death of the infected neuron and the intra neuronal virus fails to mature and multiply. The released virus from the upgraded apoptotic neuron is immature, and dies as soon as liberated, thereby fails to infect the surrounding neuron. This results into an auto-suicide of virus and cure or arrest of progression of the CNS disease (Figure Panel A). As opposed to in an untreated neuron, apoptosis is down regulated by the glycoprotein liberated from the rabies virus. Before the neuron dies, enough time is available for the virus to consume the cellular content, multiply and attend maturity. The released mature virus is competent to infect the surrounding neurons till the patient dies [10] (Figure Panel B).

In world yearly 70000 patients dies due to rabies. There are no advance attempts for treatment of rabies. Hence more emphasis to be given to prevention by active and passive immunization. Thus in rabies prevention is a mother of cure.

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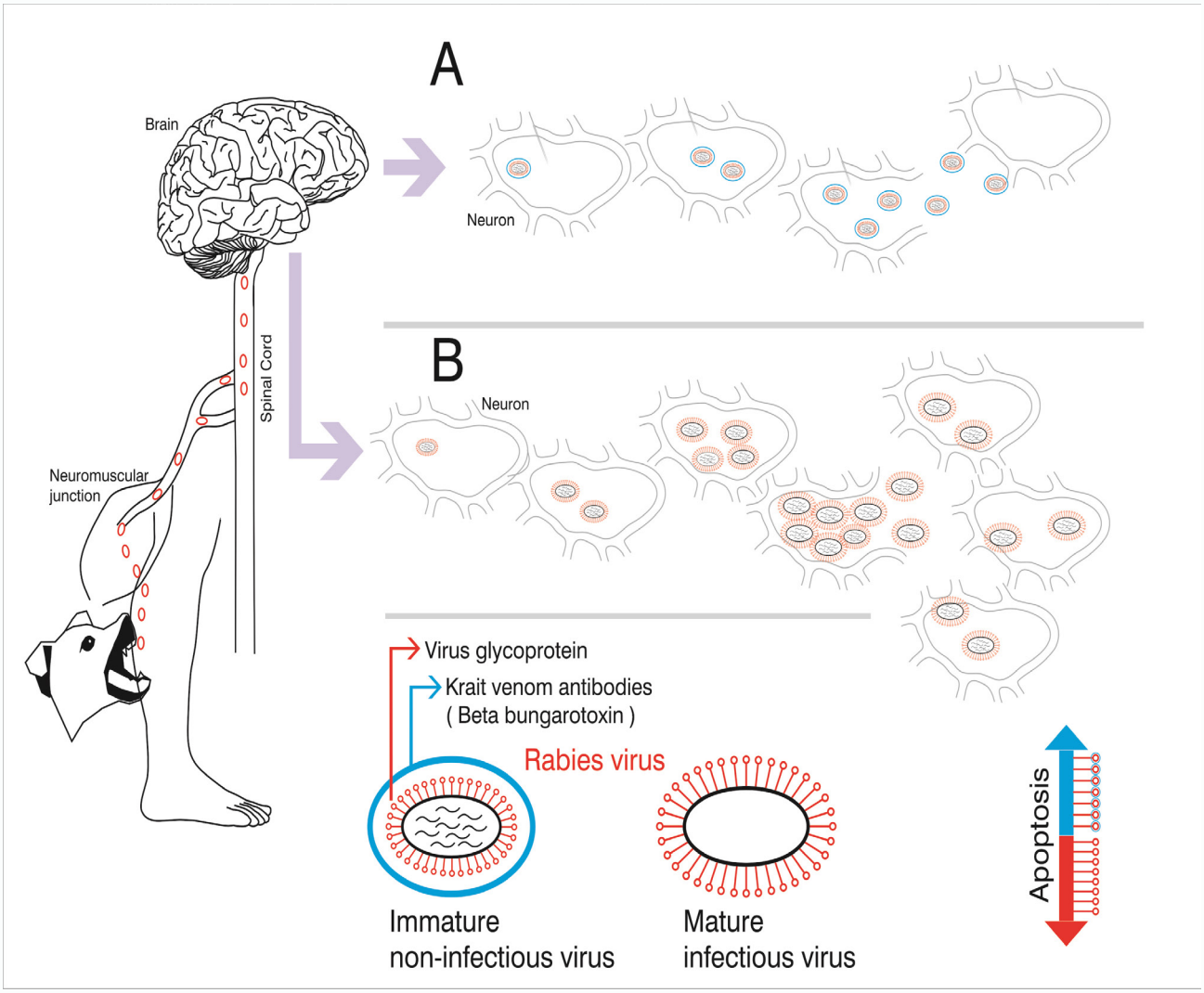

Figure 1: Sequence homology with the envelop glycoprotein of rabies virus.