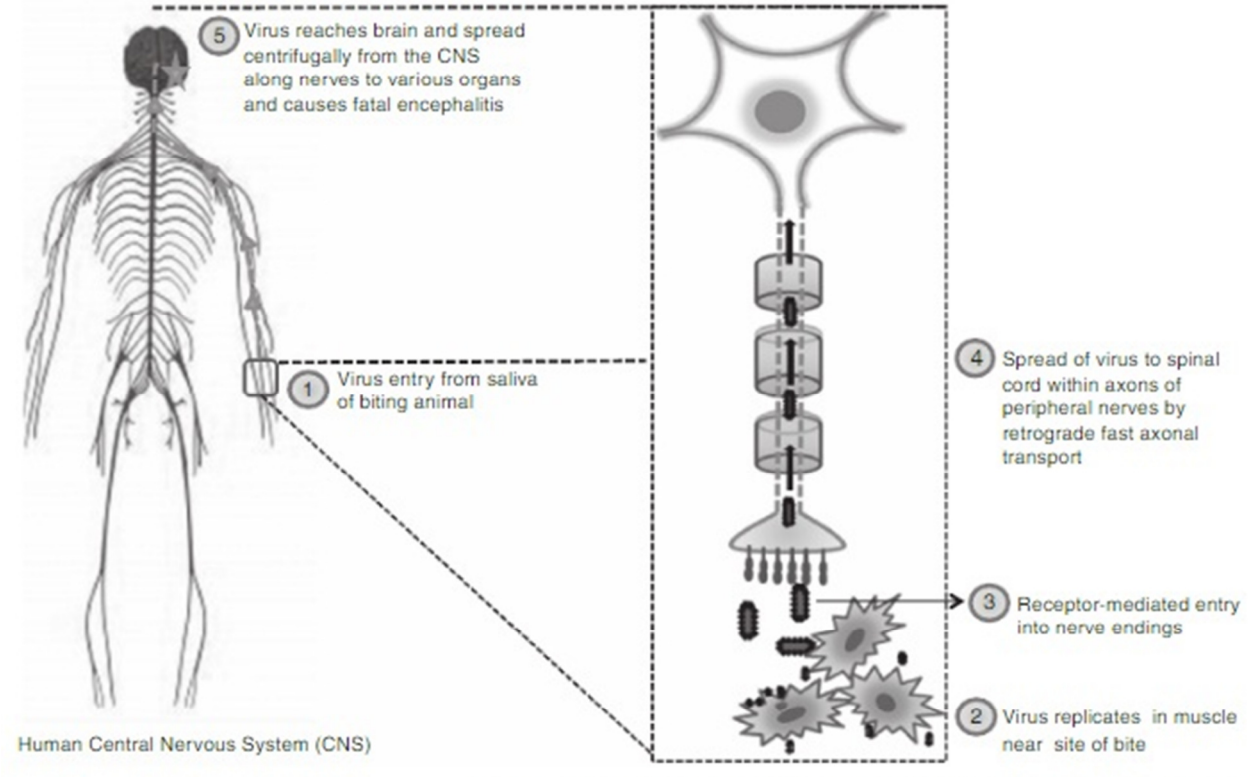
RABIES VIRUS

Rabies is a major zoonotic disease in the world caused by rabies virus. It is resulting from deleterious effect exerted by rabies viruses to the central nervous system (CNS) of human and warm-blooded animals. It is transmitted from animal to animal and from animal to human through saliva. Rabid animal bites e.g. infected dog bites introduce the virus into muscle and nerve ending-rich tissues from which it penetrates into nerve cells where it replicates and progressively travels through the spinal cord to the brain requiring weeks or even months depending upon the distance from the site of the bite to the brain. It is recognized for centuries by its peculiar pathogenic outcome that is hydrophobia, hallucinations, aggressive behavior, and paralysis, eventually leading to coma and death.

The word rabies is derived from the Latin word **rabere**, which means to be mad, to rage, or to rave , The first written description of rabies in the literature is cited in the Babylon Codex. Dog owners in the Babylonian city of Eshnunna were fined heavily for deaths caused by their dogs biting the people. Democritus, a Greek philosopher, recorded a case of canine rabies in 500 BC. In 400 BC, Aristotle wrote that 'dogs suffer from the madness. This causes them to become very irritable and all animals they bite become diseased. In 1885, Louis Pasteur obtained his first success against rabies through postexposure vaccination, but even more than 125 years later, the disease still continues to affect mankind, especially in developing countries in Africa, Asia, and Latin America.



Gnanadurai, Clement & Lyon, David & Jackson, Alan & Fu, Zhen. (2013). Rabies Virus.

Pathways for rabies virus spread from bite site to CNS

Rabies virus is susceptible to 1% sodium hypochloride, 2% gluteraldehyde, 70% ethanol, formaldehyde, and quaternary ammonium compounds. They are inactivated on exposure to

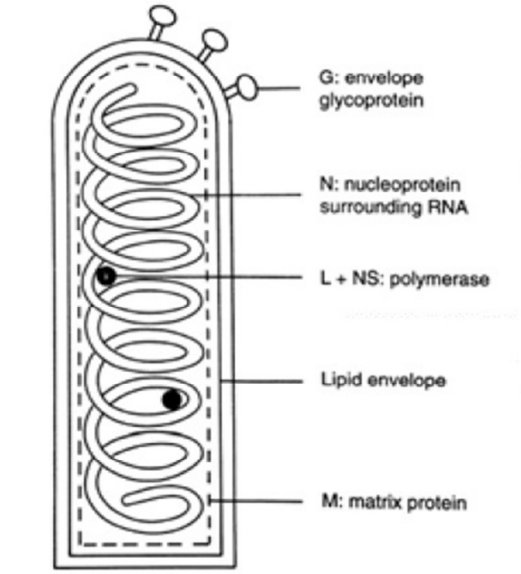
ultraviolet radiation, by heat (1 hour at 50°C), and by lipid solvents. They are rapidly inactivated in sunlight and does not survive for long periods out of the host unless protected in a cool, dark area.

Classification of Rabies virus

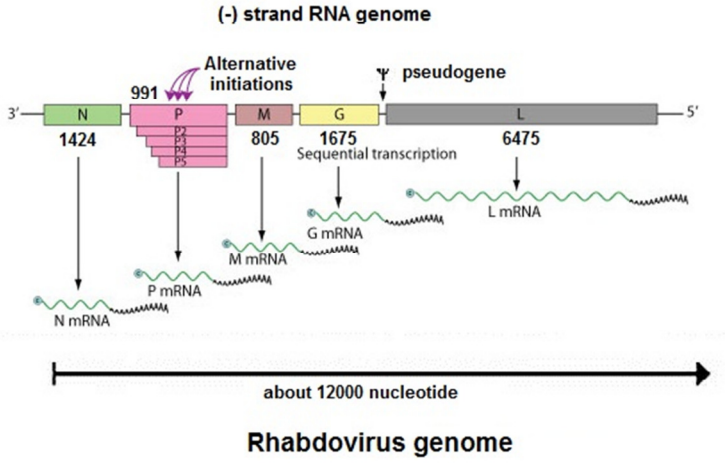
Rabies virus is a enveloped single stranded RNA virus of genera *Lyssavirus* in a family *Rhabdoviridae* of order *Mononegavirales*.

Structure of Rabies virus

Rabies virions are bullet-shaped virus with 10 nm spike-like glycoprotein peplomers (small proteins spikes) covering the surface. It has 45 – 100 nm diameter, 100 – 430 nm in length with single stranded, linear, and negative sense RNA genome of ~11.9 kb in length. The RNA genome of the virus encodes five genes whose order is highly conserved. These genes encodes five types of proteins that are nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and a viral RNA polymerase (L). All rahbdoviruses have two major structural components; helical ribonucleoprotein core (RNP) and surrounding envelops. The two proteins, P (phosphoprotein) and L (RNA polymerase) are associated with RNP. The glycoprotein forms approximately 400 trimeric spikes, which are tightly arranged on the surface of the virus. The virus nucleoprotein (N) plays critical role in replication and transcription. Both viral transcription and replication are reduced, if the nucleoprotein is not phosphorylated.



Structure of Rabies virion



Rhabdovirus genome

G (surface) proteins: It is the surface glycoprotein spike and exist as trimmers. There are about 1200 G proteins (400 trimers) per virus particle. It is a transmembrane protein with an N-terminal signal sequence which binds to cellular receptors and is the target of neutralizing antibodies. There are three sugar chains that are N-glycosidically attached. Entry of the virus into the cytoplasm adopts endocytic pathway and not at the plasma membrane. This is because the G protein trimer undergoes a change in conformation at pH 6.1 which stabilizes the trimer and probably allows a hydrophobic region of the molecule to become exposed and to embed in the membrane of the cell to be infected.

M (matrix) protein: It is a peripheral membrane protein (originally M stood for membrane) that appears to line the inner surface of the viral membrane. It may act as a bridge between the membrane or G protein and the nucleocapsid.

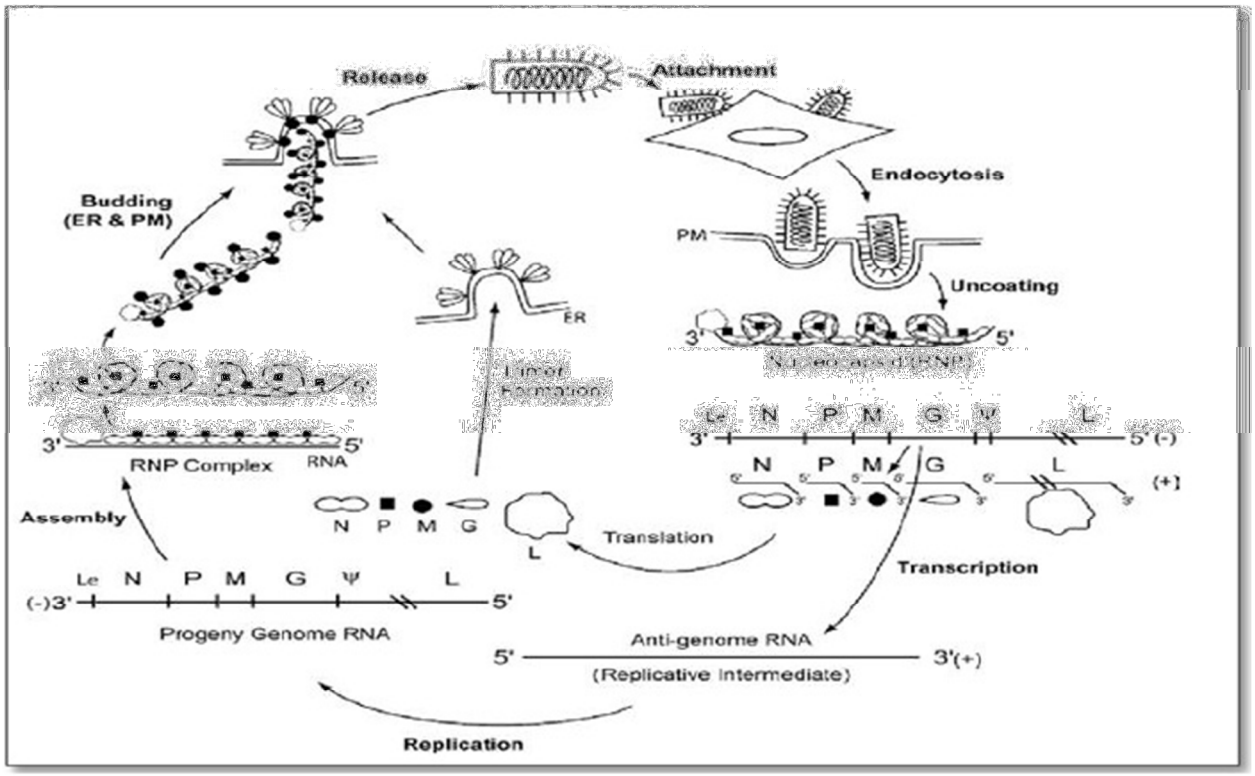
Nucleocapsid: It is the infectious ribonucleoprotein core of the virus. It is a helical structure with striated appearance that lies within the membrane.

N (nucleoprotein) protein: It is the major structural protein and covers the RNA genome. It protects the genome from nucleases and holds it in a conformation that allows transcription

L (Large) protein and NS (nonstructural, otherwise known as P (phospho)): These proteins together form the RNA-dependent RNA polymerase or transcriptase. The L protein has a molecular weight of 240 kDa and its gene takes up 60% of the genome.

Replication of Rabies virus

Like other viruses, the replication of rabies viruses starts with the attachment of appropriate host cells i.e. motor neuron cells, penetration, uncoating transcription and translation, and assembly and release. Firstly, rabies viruses get access to the cytoplasm of host cell by interacting through coated pits (viropexis) or by interaction of glycoprotein (G) with cell surface receptor such as nicotinic acetylcholine receptor (nAChR) (pre-treatment with antagonist α-bungarotoxin may result in decline in infection), neural cell adhesion molecule (NCAM; localized in presynaptic membrane that can be blocked by heparin sulfate), and low affinity p75 neurotrophin receptor (p75NTR) resulting in the internalization or endocytosis of viral particle. It is evident that carbohydrate moieties, phospholipid, highly sialylated gangliosides and other membrane-associated proteins might all contribute to the cellular membrane receptor structure for rabies viruses.



After internalization, the viral G protein mediates low pH - dependent fusion with the endosomal membrane and the virus is uncoated, releasing its helical nucleocapsid (NC) of the

ribonucleoprotein (RNP) core. The five structural genes (N, P, M, G, and L) of the viral genome RNA (vRNA) in the NC are transcribed into five positive (+) strand monocistronic m) RNAs and a full - length (+) strand (anti - genome) replicative intermediate RNA (cRNA), which serves as the template for replication of progeny genome (-) strand vRNA. The proteins (N, P, M, and L) are synthesized from their respective mRNAs on membrane free ribosomes in the cytoplasm and the G is synthesized from the mRNA on membrane-bound ribosomes (rough endoplasmic reticulum). After transcription and translation of viral proteins, the N-P-L complex negative-stranded genomic RNA to for the RNP core, and the M protein form a capsule or matrix around the RNP. The RNP-M complex migrates to an area of the plasma membrane containing glycoprotein inserts, and the M-protein initiates coiling. The M-RNP complex binds with the glycoprotein, and the completed virus buds from the plasma membrane. Within the central nervous system (CNS), there is preferential viral budding from plasma membranes. Conversely, virus in the salivary glands buds primarily from the cell membrane into the acinar lumen to maximize the chances of viral particle dispersal for new host.

Pathogenesis of Rabies virus

Soon after entry to myocytes or other non-nerve local cells (connective tissues, muscle cells, etc.) initially, they multiply locally for a week or month(s) (2 weeks to 6 months in cats and dogs, and can be more than a year in humans) before gain access to presynaptic nerve ending. After entry to motor neuron, they travel to CNS (may take several months depending upon sites of infection) where it rapidly multiply and release in to extracellular environments. However, they are egressed by budding through the plasma membrane. In this time period, there is no sign and symptoms of rabies in the host, and therefore this period is called **rabies incubation period**. The viral particles migrate from the nerve-ending[1] entry point (near the bite site) up the axon (may goes at speeds of 10-400 mm/day) and into the nerve cell itself, where it replicates extensively resulting in injury or death of nerve cell (a sign of early manifestation of rabies infection). This nerve damage can lead to paralysis of a limb or a facial region if the nerve ending are supplying electrical messages to the muscles in order to create movement or if it is supplying facial muscles, host may lose the ability to blink or to swallow. This condition is known as ‘paralytic rabies’ or ‘dumb rabies’. After reaching to CNS, the viruses multiply more rapidly and millions of closely packed brain cells being invaded and destroyed, and therefore symptoms of full blown rabies become apparent. However, immune response against the rabies viruses develops both locally and systemically. In the lymph node, blood and spleen, rabies virus infection triggers the appearance of activated lymphocytes ($CD69^{+}$) secreting cytokines, and expressing collapsin response mediator protein 2 (CRMP2), a marker of cell polarization and migration. Peripheral injection of rabies virus in mice triggers the production of circulating neutralizing antibodies. However, the rabies virus pathogenesis continue to express by breeching these immune response generated in the infected individual.

Treatment of Rabies virus

First of all, rabid animal bite wounds are washed properly with running water and soap, and treated with antibacterial compound. After that the individual is vaccinated. Vaccination of rabies may be of two types such as pre-exposure vaccination and post-exposure vaccination.

[1] The nerve endings that supply the muscles and skin of the limbs and face for allowing the animals to move its muscles or feel sensations such as heat, cold, pain, and pressure are the examples of endings of long nerve fibers.

Pre-exposure vaccination: Pre-exposure vaccination or anti-rabies immunization being done to the people who are working under high risk of rabies exposure such as veterinarians, animal handlers, etc. People whose activities bring them into frequent contact with rabies virus or with possibly rabid animals and International travelers who are likely to come in contact with animals in parts of the world where rabies is common need to be given pre-exposure vaccination.

The pre-exposure schedule for rabies vaccination is 3 doses, given at the following times:

- Dose 1: As appropriate
- Dose 2: 7 days after Dose 1
- Dose 3: 21 days or 28 days after Dose 1
- Booster doses if needed, especially to lab workers (periodic testing is recommended).

Post-exposure vaccination: A person who is exposed and has never been vaccinated against rabies should get 4 doses of rabies vaccine - one dose right away, and additional doses on the 3rd, 7th, and 14th days. They should also get another shot called Rabies Immune Globulin at the same time as the first dose.

A person who has been previously vaccinated should get 2 doses of rabies vaccine - one right away and another on the 3rd day. Rabies Immune Globulin is not needed.

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