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Rabies virus receptors

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Rabies virus (RABV) is a pathogen well adapted to the mammalian nervous system (NS) where it infects the neurons, causing an acute myelo-encephalitis fatal in most mammalian species, and humans in particular. RABV is transmitted by saliva of an infected animal through bites or scratches or by unfortunate transplantation of organs originated from unsuspected rabid donors. RABV enters the NS via a motor neuron through the neuromuscular junction (NMJ), or a sensory nerve through nerve spindles. It then travels from one neuron to the next, along the spinal cord to the brain and the salivary glands where virions are excreted in the saliva. The envelope G protein trimer is responsible for the attachment of the virus to target cells and enable the virus to be transported to the NS via the retrograde pathway. There is convincing evidence that the muscular form of the nicotinic acetylcholine receptor (nAChR), the neuronal cell adhesion molecule (NCAM) and the p75 neurotrophin receptor (p75NTR) bind RABV and/or facilitate RABV entry into cells. Other components of the cell membrane, such as gangliosides, may also participate in the entry of RABV. According to the localization of the three molecules, their role in entry and propagation of the virus could be as follows: RABV particles from saliva are transferred by bites to the vicinity of NMJs and sensory terminations. At the NMJs, free RABV particles bind to nAChR located on the top of junctional folds, in area where nerves and muscles are in close contact. This concentrates virus particles in front of the NMJs and improves the probability of RABV being taken up by the nerve terminal. RABV particles bind to NCAM present at the presynaptic membrane. The presence of gangliosides in this membrane concentrates NCAM into "lipid raft" microdomains, thereby allowing the simultaneous binding of G proteins and improving the membrane fusion process or allowing the detachment of RABV from nAChR. After crossing the NMJ, RABV is internalised by neutral and acidic vesicles, which may trigger the fusion of the virus envelope and the release of nucleocapsids. Alternatively, intact RABV remain in vesicles and travel along the nerve endings to the neuronal soma where replication can occur. Possibly in sensory endings or at subsequent steps of the RABV journey, but probably not at the NMJs where P75NTR is not detected, the binding of RABV to p75NTR may enable RABV to follow caveolae transcytosis, allowing the axonal retrograde transport of RABV particles.