

# Rabies virus infection: An update

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**There are still many unanswered questions in the pathogenesis of rabies, but recent progress has been made. During most of the long incubation period of rabies, the virus likely remains close the site of viral entry. Centripetal spread to the central nervous system and spread within the central nervous system occur by fast axonal transport. Neuronal dysfunction, rather than neuronal death, is responsible for the clinical features and fatal outcome in natural rabies. Recent work has changed our perspective on the ecology of rabies virus under particular circumstances in certain species. Hopefully, advances in our understanding of rabies pathogenesis will lead to advances in the treatment of this dreaded disease.** *Journal of NeuroVirology* (2003) **9**, 253–258.

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## Introduction

Rabies is normally a rapidly fatal neurological disease and to date therapeutic efforts in humans have proved futile except in rare cases in which rabies vaccine was administered prior to the onset of clinical disease (Jackson, 2002a; Jackson *et al*, 2003). A better understanding of rabies pathogenesis may be helpful in making future advances in therapy. In this review, selected topics in the pathogenesis of rabies, including the events at the site of viral entry, transport of rabies virus to the central nervous system (CNS), neuronal dysfunction and death, and nonfatal outcome of infection will be discussed. A comprehensive review on rabies pathogenesis has recently been published (Jackson, 2002b).

## Events at the site of viral entry

There is a long and variable incubation period in human and animal rabies, usually lasting 20 to 90 days, but sometimes it lasts longer than 1 year (Smith *et al*,

1991). Although there is uncertainty about the precise events during this incubation period, a delay in the movement of rabies virus likely occurs at the site of viral entry or inoculation. The best experimental animal studies to date, examining the events that take place during the incubation period, were performed in striped skunks using a Canadian isolate of street rabies virus obtained from skunk salivary glands (Charlton *et al*, 1997). Studies performed using reverse transcriptase–polymerase chain reaction (RT-PCR) amplification showed that viral genomic RNA was frequently present in the inoculated muscle (found in four of nine skunks), but not in either spinal ganglia or the spinal cord, when skunks were sacrificed 62 to 64 days post inoculation. Immunohistochemical studies performed prior to the development of clinical disease showed evidence of infection of extrafusal muscle fibers and occasional fibrocytes at the site of inoculation. Although it is unclear, the infection of muscle fibers may be a critical pathogenetic step for the virus to gain access to the peripheral nervous system. Rabies virus binds to nicotinic acetylcholine receptors at the neuromuscular junction (Lentz *et al*, 1982), and recent studies using nerve-muscle cocultures indicate that the neuromuscular junction is the major site of entry into neurons (Lewis *et al*, 2000). Two additional putative rabies virus receptors have recently been reported: the neural cell adhesion molecule (Thoulouze *et al*,

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1998) and the p75 neurotrophic receptor (Tuffereau *et al*, 1998). The neural cell adhesion molecule is expressed in three major isoforms and expression occurs in adult muscle and at the neuromuscular junction (Moscoso *et al*, 1998; Polo-Parada *et al*, 2001).

Studies in rodent models with fixed rabies virus strains indicate that rabies virus is capable of direct entry into peripheral nerves without a replicative cycle in extraneural cells, which is associated with a short incubation period (Shankar *et al*, 1991; Jackson, 2002b). This mechanism of viral entry may rarely occur under natural conditions, such as after multiple bites to the head and neck, associated with very short incubation periods. Studies in the highly susceptible suckling hamster model also showed early infection in neuromuscular and neurotendinal spindles (Murphy *et al*, 1973), but involvement of these structures has not been demonstrated in more natural models with long incubation periods.

The vast majority of human rabies cases that occur without a history of an exposure are thought to be due to unrecognized or forgotten bites, and molecular characterization of the rabies virus variants has indicated that in the United States they are most frequently from bats, particularly silver-haired bats and eastern pipistrelle bats (Noah *et al*, 1998). Experimental studies on the silver-haired bat virus indicate that the virus replicates well at lower than normal body temperatures (34°C) and is associated with higher infectivity in cell types present in the dermis, including fibroblasts and epithelial cells, than with coyote street virus (Morimoto *et al*, 1996). Hence, the silver-haired bat virus may be adapted for efficient local replication in the dermis, which could explain the success of this variant. However, after superficial exposures it is unclear how or at precisely what sites the virus invades peripheral nerves in the skin or subcutaneous tissues.

### Transport of rabies virus to the CNS

Colchicine, a microtubule-disrupting agent active for tubulin-containing cytoskeletal structures, is an effective inhibitor of fast axonal transport. Colchicine was applied locally to the sciatic nerve in rats using elastomer cuffs in order to obtain high local concentrations of the drug and avoid adverse systemic effects, and the propagation of rabies virus was prevented, providing strong evidence that rabies virus spreads from sites of peripheral inoculation to the CNS by fast axonal transport (Tsiang, 1979). Rabies virus spreads in peripheral nerves and in the CNS within axons by fast axonal transport at a rate of 12 to 100 mm per day (Kucera *et al*, 1985; Lycke and Tsiang, 1987; Tsiang *et al*, 1991). Rabies virus has been used as a neuroanatomical tracer in order to define circuits of synaptically linked neurons in rodents and primates, and these *in vivo* studies have provided evidence that axonal transport of rabies virus occurs ex-

clusively in the retrograde direction (Tang *et al*, 1999; Kelly and Strick, 2000). Two recent reports have provided evidence that the rabies virus phosphoprotein, particularly involving amino acid residues at positions 143 and 147 (Poisson *et al*, 2001), interacts strongly with the 10-kDa cytoplasmic dynein light chain (LC8) (Jacob *et al*, 2000; Raux *et al*, 2000). LC8 is a component of both cytoplasmic dynein and myosin V and is important in both microtubule-directed organelle transport and in actin-based vesicle transport in axons. However, the role of the interaction of the rabies virus phosphoprotein and dynein for axonal transport of the ribonucleocapsid complex has not yet been demonstrated. Mutants with a deletion in amino acid residues of the phosphoprotein encompassing a conserved LC8-interacting motif and simultaneous substitution of the arginine at position 333 of the glycoprotein showed neuroattenuation in mice (Mebatsion, 2001). Interestingly, mutants with deletions in the LC8 binding region of the phosphoprotein remained as pathogenic as their parent virus after intramuscular inoculation of suckling mice, indicating that LC8 is actually dispensable in young mice for the spread of pathogenic rabies virus from a peripheral site to the CNS (Mebatsion, 2001).

In studies using a rabies virus glycoprotein-deficient recombinant rabies virus, Etesami *et al* (2000) recently demonstrated that the glycoprotein is important for the transsynaptic spread of rabies virus between neurons. Yan *et al* (2002) examined the role of the rabies virus glycoprotein in determining the topographic distribution of rabies virus infection 7 days after stereotaxic inoculation of virus into the hippocampus of rats using a variety of rabies virus strains and recombinant viruses, including a rabies virus recombinant constructed using the vesicular stomatitis virus glycoprotein. With all of the recombinant viruses, the viral distribution was similar to that of parental viruses from which the glycoprotein was derived. Hence, further evidence is provided that the rabies virus glycoprotein exerts a very important influence on the distribution of rabies virus infection in the nervous system. Mazarakis *et al* (2001) have also recently demonstrated that rabies virus glycoprotein-pseudotyped lentivirus (equine infectious anemia virus)-based vectors enhance gene transfer to neurons by facilitating retrograde axonal transport. Hence, a variety of studies emphasize the importance of the rabies virus glycoprotein in the uptake, transport, transsynaptic spread, and topographic distribution of the infection in the nervous system.

### Neuronal dysfunction and death

Natural rabies is normally characterized by severe neurologic signs and fatal outcome with relatively mild neuropathologic changes in the CNS, supporting the idea that neuronal dysfunction, rather than

neuronal cell death, must play an important role in producing the disease (Jackson, 1997; Iwasaki and Tobita, 2002; Jackson, 2002b). A variety of experimental studies in rabies virus infection have investigated possible abnormalities in neurotransmission involving acetylcholine (Tsiang, 1982; Jackson, 1993; Dumrongphol *et al*, 1996), serotonin (Bouzamondo *et al*, 1993; Ceccaldi *et al*, 1993), and  $\gamma$ -amino-n-butyric acid (GABA) (Ladogana *et al*, 1994). Abnormalities of uncertain significance were found, but no fundamental defect was demonstrated that explains neuronal dysfunction in rabies. Dysfunction of ion channels has been shown in rabies virus-infected cultured mouse neuroblastoma NA cells with the whole-cell patch-clamp technique (Iwata *et al*, 1999). The infection reduced the functional expression of voltage-dependent sodium channels and inward rectifier potassium channels, and there was a decreased resting membrane potential reflecting membrane depolarization. There was no change in the expression of delayed rectifier potassium channels, indicating that nonselective dysfunction of ion channels had not occurred. The reduction in sodium channels and inward rectifier potassium channels could prevent infected neurons from firing action potentials and generating synaptic potentials, resulting in functional impairment. Koprowski and coworkers (1993) have hypothesized that nitric oxide neurotoxicity may mediate neuronal dysfunction in rabies. Induction of inducible nitric oxide synthase mRNA (Koprowski *et al*, 1993) and increased brain levels of nitric oxide (Hooper *et al*, 1995) have been demonstrated in rabies virus-infected rodents, but the significance of these findings is uncertain. The role of nitric oxide in rabies pathogenesis needs further study.

*In vivo* studies by Prośniak *et al* (2001) in mice have shown that infection with fixed rabies virus resulted in down-regulation of about 90% of genes in the normal brain, at more than four-fold lower levels by using subtraction hybridization. Only about 1.4% of genes became up-regulated, including genes involved in regulation of cell metabolism, protein synthesis, and growth and differentiation. Determining whether any of these changes have important biologic significance will be very challenging.

Neurotropic viruses may cause cell death by either apoptosis or necrosis (Griffin and Hardwick, 1999; Allsopp and Fazakerley, 2000; Fazakerley and Allsopp, 2001). Apoptosis depends on synthesis of macromolecules and requires energy, whereas necrosis is associated with energy failure. Each of these forms of cell death is associated with typical morphologic features. The challenge virus strain (CVS) of fixed rabies virus has been observed to induce apoptotic cell death in rat prostatic adenocarcinoma cells (Jackson and Rossiter, 1997), mouse neuroblastoma cells (Theerasurakarn and Ubol, 1998), and in mouse embryonic hippocampal neurons (Morimoto *et al*, 1999). Morimoto and coworkers have observed that variants that are more neurovirulent in adult mice

produce less apoptosis over a period of 72 h in primary hippocampal neurons than produced by less neurovirulent variants (Morimoto *et al*, 1999). Prominent apoptotic death of neurons has been observed in the brains of mice of various ages inoculated intracerebrally with the CVS strain of fixed rabies virus, and immunosuppression of adult mice did not reduce the apoptotic process (Jackson and Rossiter, 1997; Jackson and Park, 1998; Theerasurakarn and Ubol, 1998). However, a role of the immune response in the induction of apoptosis cannot be excluded, which was demonstrated in paralyzed mice infected with the attenuated Pasteur strain of rabies virus (Galelli *et al*, 2000). Guigoni and Coulon (2002) observed that primary cultures of CVS-infected purified rat spinal motoneurons did not show major evidence of apoptosis over a period of 7 days, whereas infected neurons did not survive more than 2 days in crude primary spinal cord cultures. This survival was not dependent on the presence of factors in the culture medium. In contrast, cultures of purified hippocampal neurons showed apoptosis in over 90% of neurons within 3 days. These results suggest that different neuronal cell types respond differently to rabies virus infection, and that the presence of glial cells and/or neurons other than motoneurons are essential for apoptosis of spinal motoneurons. Physical contact with glia or synaptic contact with other spinal cord neurons may be necessary for induction of apoptosis in motoneurons, but not for apoptosis of hippocampal neurons. However, apoptosis in infected cultured cells, including embryonic cells, does not closely correspond to what is observed in infected animals. Peripherally inoculated animals with CVS strains do not show the prominent apoptosis that is observed in neurons after intracerebral inoculation (Reid and Jackson, 2001). Conflicting results have been reported by different investigators with respect to the occurrence of neuronal apoptosis after intracerebral inoculation of different street (wild-type) rabies virus variants in mice (Ubol and Kasisith, 2000; Yan *et al*, 2001). Hence, in rabies virus infection, there are complex mechanisms involved in cell death or survival of neurons both *in vitro* and in animal models using different viral strains and routes of inoculation. Nevertheless, neuronal cell death is not prominent in natural rabies, and, hopefully, a greater understanding of the mechanisms involved in neuronal apoptosis in experimental models may provide insights into the pathogenesis of neuronal dysfunction that occurs in natural rabies.

### Nonfatal outcome of rabies virus infections

Although rabies is usually considered a uniformly fatal disease, it has been recognized that animals may sometimes recover from rabies. The fundamental issue is whether a "carrier state" can occur where a rabies vector secretes infectious virus in the saliva and

remains healthy. This was initially reported in vampire bats in the 1930s in Trinidad, but the methods were inadequate (Pawan, 1936). Fekadu reported five dogs that secreted virus for up to 72 months, although these viruses had not caused human disease (Fekadu, 1972, 1975). Serotine bats in Spain were recently observed to have RT-PCR-positive oropharyngeal swabs, and, in many cases, simultaneous brain samples were negative, suggesting viral clearance from the brain but not from extraneural tissues (Echevarria *et al*, 2001).

A recent study of rabies virus infection in spotted hyenas in the Serengeti changes our perspective on naturally occurring variations in rabies pathogenesis (East *et al*, 2001). In this study spotted hyenas were monitored in three social groups for periods of 9 to 13 years. Clinical rabies was never observed. On the basis of rabies virus neutralization antibody (VNA) titers, 37% (37 of 100) were found to be seropositive and repeat studies in six indicated that half of the seropositives became seronegative. High-ranking hyenas had high VNA titers. They also had high oral (open mouths licked by clan members at rates of over twice an hour) and bite contact rates, and they lived to an old age of over 4 years. Although infectious rabies virus was not isolated from saliva, almost half of the seropositive hyenas demonstrated saliva positive for rabies virus RNA by RT-

PCR. Sequence analysis showed sequence divergence with strains found in the Serengeti in African wild dogs, bat-eared foxes, and the white-tailed mongoose, and the sequence more closely resembled that found in dogs in the Middle East and Europe. This excellent report really changes our perspective on the ecology of less virulent viral variants and is an exception to the old dogma that rabies virus kills the great majority of exposed individuals. It is likely that in the future we will learn that under some circumstances the situation is similar in bats and other species.

## Summary

There have been recent important advances in our understanding of how rabies virus spreads and causes disease in its hosts. However, there is no satisfactory explanation for fundamental issues such as the basis for neuronal dysfunction in rabies. More research is needed in good experimental animal models in order for us to better understand the pathogenesis of this ancient disease. Because current approaches to the management of human rabies have proven unsatisfactory (Jackson *et al*, 2003), this knowledge may be important for the development of novel therapies for the treatment of rabies and other viral diseases in the future.

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