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# Virus-induced neuronal dysfunction and degeneration

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## 1. ABSTRACT

In general, virus infections of the brain are rather rare in the immune competent host. However, neurotropic viruses have developed mechanisms to exploit weaknesses in immunological defense mechanisms that eventually allow them to reach and infect CNS neurons. Once in the CNS, these viruses can induce significant neuronal dysfunction and degeneration of specific neuronal populations, sometimes leading to devastating, life-threatening consequences for the host. Here, we examine viruses with the ability to infect neurons and their resulting pathologies, their modes of entry to the CNS, and the cellular and molecular alterations that these viruses induce in neuronal cells. We also discuss the importance of various pathogenic events associated with viral infection of neurons and elaborate on the implications of recent findings suggesting that neuronal cells affected by viruses undergo a "dying back" pattern of degeneration. Finally, findings of virus-induced alterations in kinase activity are discussed in the context of recent evidence linking abnormalities in kinase signaling to the pathogenesis of major human neurodegenerative conditions.

## 2. PATHOLOGIES OF THE NERVOUS SYSTEM CAUSED BY VIRAL INVASION

Viral invasion can have severely detrimental effects on the nervous system. Each virus that has the capability to invade the nervous system of the immune competent host presents with a distinct pathological manifestation. Further, each virus type can induce varying pathologies among different hosts. These pathologies above can be placed into several different groups based on the typical region of the nervous system that they infect. Table 1 lists the characteristics of neurotropic viruses that cause neurological disease in the immune competent host, including neurological diseases associated with each virus, their mode of entry into the brain, the region of the nervous system involved, and major neuropathological hallmarks associated with each disease. The term "cytolytic virus" refers to those viruses that lyse or kill their host cell after replication.

### 2.1. Brain pathologies

Close to 20,000 cases of acute encephalitis occur every year in the United States (1). This pathology typically

**Table 1.** Characteristics of major neurotropic viruses

| Type of Virus | Area of CNS/PNS involved | Neurological Disease | Neuropathology | Mode of Entry into Brain | References |
|---|---|---|---|---|---|
| **Herpes Simplex Virus** | Asymmetric involvement in temporal and inferior frontal lobes and limbic structures | Encephalitis | Necrotizing, cytolytic virus | Retrograde fast axonal transport | ***2*** ***5*** |
| **Human Immunodeficiency Virus** | Reservoir of macrophages and microglia | Dementia, Mild cognitive and motor impairment, myelopathy, peripheral neuropathy | Diffuse pallor in white matter, multinucleated cells, vacuolar myelopathy, microglial nodules; non-cytolytic virus | Hematological (Trojan Horse) | ***11*** ***13*** ***16*** ***21*** ***54*** ***150*** |
| **Poliovirus** | Preferential involvement of anterior horn cells in gray matter of the spinal cord | Poliomyelitis | Selective degeneration of MNs in anterior horn; cytolytic virus | Hematological, retrograde fast axonal transport | ***23*** |
| **Rabies Virus** | Widespread throughout CNS | Encephalitis, paralysis | Negri bodies, Severe edema; cytolytic virus | Retrograde fast axonal transport | ***7*** ***8*** ***9*** |
| **West Nile Virus** | Predominantly brain stem and deep nuclei of CNS, anterior horn cells | Encephalitis, Meningitis, poliomyelitis | Neuronal loss, perivascular inflammation, microglial nodules, and neuronophagia; cytolytic virus | Remains uncertain | ***26*** |

presents as a medical emergency, and without appropriate treatment patient mortality is high (1) (*2*). Acute encephalitis is a severe and rare consequence of virus infection, and is characterized by severe inflammation and dysfunction of the parenchyma (*3*). Herpes simplex virus (HSV) and rabies virus (RV) will be described in this section as specific examples of viral encephalitis.

It is believed that herpes simplex encephalitis (HSE) occurs after latent reactivation of the virus (*4*). However, only 10% of patients with HSE have a history of herpes. The regions of the CNS predominantly infected by HSV are the temporal and inferior frontal lobes, along with limbic structures (*5*). HSE is characterized by an acute, necrotizing and lytic infection with lateral asymmetry (*5*). In the more affected areas of the brain, the infection can often result in hemorrhages. Inflammatory perivascular infiltrates and acidophilic intranuclear inclusion bodies (Cowdry type A bodies) are present in neurons and glia. Before antiviral treatment for HSE existed, mortality was ≥70%, and surviving patients were left with severe neurological sequelae (*6*). Although mortality and morbidity have been reduced through the use of antiviral therapies, neurological deficits often remain in surviving patients. For example, the most common long-term symptoms after resolved HSE include memory impairment, abnormalities in personality and behavior, epilepsy and dementia (*6*).

Untreated RV infections rapidly spread through the CNS. The majority of cases lead to a type of encephalitis termed "classical rabies", which is almost inevitably fatal. Once RV has traveled from the peripheral nerves to the spinal cord, ascension into the brain occurs within hours (*7*). RV is rapidly and intra-axonally transported in the CNS. As a consequence, infection is characteristically spread throughout the entire brain (*8*). At the microscopic level, RV is characterized by the formation of cytoplasmic inclusions termed Negri bodies. RV-infected brains show marked neuronal degeneration along with an inflammatory reaction, severe edema and vascular congestion (*9*).

Viral infections of the brain often result in acute and long-term neurological dysfunction. For example, human immunodeficiency virus (HIV) infection of the CNS leads to HIV-associated dementia (HAD), a clinical syndrome commonly characterized by cognitive, behavioral and motor symptoms (*10*). The neuropathology of HAD includes diffuse pallor within the white matter, vacuolar myelopathy and microglial nodules (*11-13*). These pathological hallmarks are found in 80-90% of brains from AIDS patients (*11-13*). The cellular basis of these symptoms remains unclear. While brain infection of monocytic and endothelial cells by HIV is well documented, categorical evidence of neuronal infection by HIV is lacking (*14*).With the advent of highly active anti-retroviral therapy (HAART), HAD incidence has dramatically decreased (*15*); however, HAD is still a major cause of morbidity and mortality among HIV patients (*16*) and it has not decreased to the extent of other AIDS-related illnesses (*17*). This may be due to the fact that HAART drugs do not penetrate the BBB well (*15*). It has been demonstrated that HIV can infect the brain during the initial phase of viremia (virus invasion into the bloodstream), possibly within the first couple of weeks of

infection (*18, 19*). Because it can take many years to progress to HAD, there is controversy on the status of HIV within the brain before HAD symptoms manifest. Specifically, a debate exists on the activity of the HIV virus in the CNS during the asymptomatic phase, and on whether HIV infection is maintained as a reservoir while it remains within the CNS during this time (*20, 21*). HIV-infected patients indeed harbor low levels of HIV-derived DNA within their brains during this asymptomatic phase, notably in microglia, endothelial cells and astrocytes (*20*). However, viral replication is not detected in the brain during the asymptomatic HIV phase, suggesting little viral infection during the asymptomatic phase (*21*). Other studies reported signs of neuronal injury in the brain early in the course of HIV (*22*), suggesting that HAD may be a chronic syndrome that slowly develops over years.

**2.2. Spinal cord pathologies**

Poliomyelitis is an acute viral infectious disease caused by 1-2% of all poliovirus (PV) infections (*23*) being characterized by permanent flaccid muscle paralysis, muscle wasting and hyporeflexia (diminished reflexes). These symptoms result from the degeneration of motor neurons within the spinal cord, brain stem, or motor cortex. This leads to the development of paralytic poliomyelitis, the various forms of which (spinal, bulbar, and bulbospinal) vary only with the amount of neuronal damage and inflammation that occurs, and the region of the CNS that is affected (*23*). In acute cases, perivascular cuffs of mononuclear cells and neuronophagia of anterior horn cells are present. However, other viruses can also cause flaccid paralysis when they infect the anterior horn of the spinal cord, so the definition of poliomyelitis has been expanded (*24*). As Sabin states, "paralytic poliomyelitis can now be regarded as a clinical-pathologic syndrome that is caused by enteroviruses, consisting of the three types of polioviruses and probably 19 other enteroviruses" (*24*). More recently, West Nile Virus (WNV) has been discovered to cause poliomyelitis in addition to encephalitis (*25*) (26).

While the vast majority of RV infections manifest themselves as encephalitis, approximately 20% of RV infection cases result in a slow progression of paralysis. This clinical disease is termed paralytic rabies, and the paralysis progresses from the region of the animal bite to the rest of the body. Primary features of this disease include motor weakness of all limbs and respiratory muscles (27). Vascular changes, inflammation and inclusion bodies are most severe in the spinal cord and brain stem (28). Spinal and peripheral nerves show signs of damage including axonal loss, Wallerian degeneration, and segmental demyelination and remyelination (28).

**2.3. Pathologies of the peripheral nervous system**

Peripheral neuropathy is the most common neurological complication of HIV; over 30% of HIV patients present with peripheral neuropathy (29). Intriguingly, the prevalence of HIV-associated neuropathies reportedly increased since HAART therapy was introduced (30), (31). The most common type of neuropathy is HIV-associated distal sensory polyneuropathy (DSP), which is associated with late stages of HIV and can cause excruciating pain on the soles of the feet, as well as parasthesias, gait instability and autonomic dysfunction (32). The cellular basis of HIV-DSP remains uncertain. HIV-DSP tends to affect the distal lower extremities more commonly than the distal upper extremities (31). Even though the number of myelinated fibers is reduced, unmyelinated nociceptive fibers are predominantly lost. Peripheral nerves are also infiltrated by lymphocytes and macrophages (32). HIV-associated DSP is primarily an axonal neuropathy, characterized by a "dying back" pattern of degeneration (29, 32). As described below, this pattern of neuronal degeneration is characterized by early defects in synaptic function, distal axonal degeneration, and eventually neuronal cell death.

**2.4. Acute viral infections and chronic neuronal dysfunction**

It is well established that viruses can enter the nervous system and sustain a chronic infection. A well-documented example is given by HSV, which chronically (and mostly asymptomatically) infects dorsal root ganglion (DRG) neurons. Another example is the lymphocytic choriomeningitis virus (LCMV), which can also establish a chronic infection in the brains of mouse fetuses. LCMV infection leads to a life-long carrier state with neurological sequelae (33). Specifically, LCMV carrier mice show impairments in learning and memory, as well as various neurochemical abnormalities (33). No significant inflammation or necrosis is observed in LCMV carrier mice, suggesting that the pathological events above result from LCMV infection itself, rather than the host's immune response (33). Thus, LCMV infection establishes a precedent for an acute viral infection leading to a chronic neurological dysfunction in the carrier state. Likely, this is a characteristic of LCMV that is shared by other neurotropic viruses. Supporting this idea, compelling epidemiological data showed a significant incidence of postencephalic parkinsonism in patients that survived the 1918 influenza epidemic in Europe (34). This precedent suggests that chronic, slowly progressive degenerative disease syndromes can manifest long after viral infection.

Although highly controversial, a significant body of literature exists suggesting that viral infections could trigger the development of major late-onset human neurodegenerative diseases (35) including amyotrophic lateral sclerosis (ALS), Parkinson's Disease (PD), Alzheimer's disease (AD) and multiple sclerosis (MS). Serological studies led to suggest a potential role of enteroviruses (EV) and HSV in the etiology of ALS, a fatal neurodegenerative disease selectively affecting motor neurons (36). The striking similarity of PD clinical symptoms and those elicited by Japanese encephalitis virus infection also led to propose a viral origin of PD (37). Circumstantial evidence also exists suggesting the involvement of virus infections in the development of AD and MS. In the case of AD, it has been proposed that the presence of HSV in the brain represents a risk factor (38). Supporting this view, HSV-infected neurons showed increased accumulation of ABeta, a major component of extracellular plaques characteristic of AD. In the case of

MS, a viral etiology has long ago been proposed, because there is a greater incidence of MS in temperate climates (39). Several studies established positive correlations between the development of MS and various viruses including measles virus, human herpes virus-6, canine distemper virus, parainfluenza virus, and Epstein-Barr Virus (40) (41). Despite the correlations above, conclusive evidence demonstrating a role of viruses in the etiology of ALS, PD and AD is lacking (35). Moreover, the existence of genetic, inheritable forms of these neurodegenerative disorders above appears difficult to conciliate with such possibility.

### 2.5. Non-pathogenic viral infections of the CNS

Notably, there are examples of viral infections of neurons that do not result in neuropathologies. Adeno-associated viruses (AAV) are single-stranded, non-enveloped DNA viruses that are capable of infecting neurons with minimal disruption of cell function (42). AAV serotypes have been isolated from a wide range of normal human tissues including brain (43). In humans, AAV infection occurs so commonly that >50% of normal healthy humans have a detectable level of anti-AAV antibodies in circulation (44-46). In fact, the lack of pathogenic effects during CNS infection by AAV account for their clinical development as gene transfer vectors (47). Following intracranial delivery, AAV capsids are capable of entering neurons at or near synaptic terminals followed by retrograde transport to the neuronal cell body in remote locations of the brain (48) (49) (50) (51). Several serotypes of AAV preferentially infect neurons in the brain (52) (51). The non-pathogenic nature of AAV infection is an important observation since it demonstrates that other viral pathologies may be a consequence of the specific protein or genetic complement of a virus, rather than a general response to the presence of exogenous proteins and/or genes in the CNS.

## 3. MODES OF VIRUS ENTRY INTO THE BRAIN

### 3.1. Hematological route

The BBB is highly successful at regulating the ingress of molecular components into the brain. In the immune competent host with a fully functional BBB, very few viruses have the capability of infecting the brain through the blood. However, when the BBB is compromised in the case of disease states or immune suppression, many viruses are capable of entering the brain through the bloodstream. Lentiviruses, PVs and WNVs are examples of viruses capable to bypass the functional BBB using related, but unique mechanisms.

The lentivirus family of viruses (of which HIV is a member), uses a mechanism termed “Trojan Horse” to cross the BBB (53) (54). Lentiviruses first infect leukocytes, which then traffic into the brain through the bloodstream. Since the virus can persist inside the leukocytes, it evades recognition and thus can pass unimpeded through the BBB (54). Providing support to this idea, gene sequences coding for the HIV protein gp160 in the brain most phylogenetically match HIV gp160 gene sequences in the bone marrow, compared to other tissues; this suggests that cells originating in the bone marrow traffic the HIV virus into the brain (55, 56). In a more recent study using the animal model of Simian Immunodeficiency Virus (SIV), the movement of fluorescein-labeled leukocytes was tracked into the perivascular space and choroid plexus of the brain within two weeks of infection (57). Further, the primary cells in the brain that are infected by HIV are of mesodermal lineage (i.e. perivascular macrophages and parenchymal microglia). Although there is some debate over whether the macrophages or the microglia have a more substantial role as a reservoir of HIV in the brain, it is generally accepted that cells derived from the reticuloendothelial lineage are the main cell type infected by HIV in the CNS (58).

PV can enter the body via the oral route, first infecting the cells in the pharynx and later cells in the intestinal mucosa, where they divide for about a week. PV later spreads to the follicular dendritic cells in the tonsils, the intestinal lymphoid tissue, and the cervical and mesenteric lymph nodes, where multiplies abundantly (*23*). PV is subsequently absorbed into the bloodstream. By studying the tissue distribution volume of PV-inoculated mice, it was found that the rate of accumulation of poliovirus in the CNS was too rapid to be explained by axonal transport alone. Rather, it was postulated that the main route through which PV enters the CNS is hematological (59). More recently, a study examined PV internalization *in vitro* using cultured human brain microvascular endothelial cells (HBMEC) as an experimental model for the study of PV interactions with the BBB (60). It was found that PV enters HBMEC cells by a mechanism involving binding to CD155 (the PV receptor) and internalization through dynamin-dependent caveolar endocytosis (60). Based on these findings, it appears that PV bypasses the BBB by entering the endothelial cells comprising the BBB.

In a mouse model, it was discovered that the double stranded RNA of WNV binds to the toll-like receptor-3, which activates tumor necrosis factor-alpha (TNF$\alpha$) (61). This may initiate a chain of inflammatory events leading to increased BBB permeability, which would enable the WNV to enter the brain (61).

### 3.2. Peripheral nerve route

Another major mechanism by which viruses infect neurons involves the entry through peripheral nerve endings located in the skin and mucosa. This process is followed by retrograde axonal transport of viruses from the cell periphery to the neuronal cell body (62). Remarkably, axons of the peripheral nervous system can attain lengths of $\geq$1 meter, imposing a major challenge for the migration of viruses to the neuronal cell body. It would not be possible for viruses to enter the brain through the peripheral nerve route solely by diffusion, as it has been calculated that it would take anywhere from 61 to 647 years (depending on the virus) to move 1 cm in the cytoplasm by diffusion alone (62). Thus, in order for viruses to reach the brain within a reasonable time, they must take advantage of an endogenous neuronal mechanism known as retrograde axonal transport (62). HSV, PV, and RV are all examples of viruses that utilize unique mechanisms to enter the brain

by differentially hijacking retrograde axonal transport (see section 4 below).

HSV-1 infects the oral and nasal mucosa and is then retrogradely transported to the trigeminal ganglion and olfactory bulb, respectively, where it becomes latent (63, 64). The prevailing view on HSV-1 infection of the CNS is that it is caused by reactivation of the latent HSV-1, more so in the olfactory bulb than in the trigeminal ganglion, causing herpes simplex encephalitis (63, 64). PV can enter the brain in approximately 1% of all infections. It has been demonstrated that PV inoculated into muscle travels to the neuromuscular junction (NMJ), where it is endocytosed into the peripheral nerves in a poliovirus receptor (PVR/CD155) dependent manner (65). Ohka and colleagues inoculated the hindlimbs of PV-sensitive Tg21 mice, and evaluated hind limb paralysis and transport of PV along the sciatic nerve at different time points (65). This study calculated that PV travels at velocities of $\geq$ 12 cm/day, a velocity consistent with rates reported for retrograde axonal transport (65). As for RV, it is typically transmitted by animal bites into the intramuscular region of the host. Within 60 hours, RV invades both sensory and motor neurons, and then is retrogradely transported to the CNS (66).

## 4. FAST AXONAL TRANSPORT MECHANISMS FACILITATE THE BIDIRECTIONAL TRAFFIC OF VIRUSES ALONG AXONS

Neuronal cells are the largest and most exquisitely polarized cells in the human body, with some neuronal cell types (i.e., motor neurons) reaching more than a meter in length. This unique cellular architecture imposes significant challenges to neurotropic viruses, which need to complete various aspects of their replication cycle in specific cellular compartments. For example, in certain viruses genomic replication needs to take place in the nuclear compartment, which is typically distant from the original site of viral entry in the neuronal host cell. In addition, viral spreading and emergence from the infected host cell often requires transport of viral components from the site of DNA synthesis and packaging at the neuronal cell body towards the axon endings. Rather than utilizing simple diffusion, viruses highjack the endogenous transport machinery of the neuronal host cell to facilitate their own transport along axons (62) (67). For this reason, interactions among viral proteins and proteins in the axon are of great importance. Below we describe some well-established properties and molecular components of axonal transport, and provide examples of interactions among viral protein constituents and proteins involved in axonal transport.

### 4.1 Fast axonal transport: basic mechanisms and regulation

The process of translocation of membrane proteins and lipid components along axons of neuronal cells is collectively known as fast axonal transport (FAT) (reviewed in (68)). This process is absolutely dependent on the integrity of axonal microtubules (69), and the mechanochemical forces generated from ATP hydrolysis by microtubule-based molecular motor proteins (70). Significantly, a large body of pharmacological experiments indicates that the transport of viruses along axons depends upon the integrity of axonal microtubules, consistent with a role of FAT in this process (62, 71). For example, the movement of both adenoviruses (72) and parvoviruses (PaV) (73) towards the nucleus can be blocked by treatment of infected cells with both nocodazole and vinblastine, well-characterized drugs that promote microtubule destabilization. In axons, microtubules are organized in such way that their plus ends point towards the periphery, whereas the minus ends points towards the cell body (74). This unique spatial organization allows for the bidirectional transport of molecular components along axons. Depending on the direction of movement, FAT can be divided in anterograde and retrograde FAT (75) (76). Anterograde FAT involves the transport of materials from their sites of synthesis in the neuronal cell body towards the cell periphery, at rates of 200-400 mm/day (77). On the other hand, retrograde FAT constitutes the movement of materials from the cell periphery towards the neuronal cell body, proceeding at an average pace of 100-250 mm/day (78). Significantly, viruses can move in either direction of FAT. HSV for example, first uses retrograde FAT to reach the neuronal cell body from its site of entry at the nerve endings (79). After latency is established, HSV can become reactivated and transported by anterograde FAT to the nerve endings, where it infects the mucosa to complete their cycle (80, 81).

Anterograde FAT provides newly synthesized components required for neuronal membrane function and maintenance, and is mainly carried out by microtubule-dependent molecular motors of the kinesin superfamily (70). Electron microscopic and biochemical studies indicate that the material moving in anterograde FAT includes various membrane-bouded organelles (MBOs), including synaptic vesicle and axolemma precursors, tubulovesicular structures, mitochondria and dense core vesicles (82). MBOs moving in anterograde FAT are needed for supply and turnover of intracellular membrane compartments, as well as the maintenance of axonal metabolism. Using video-enhanced differential interference contrast microscopy in isolated squid axoplasm, conventional kinesin was first discovered (83) and found to represent the most abundant microtubule-dependent molecular motor protein in mature neurons (84). Accumulative evidence indicates that conventional kinesin is involved in the anterograde FAT of mitochondria, synaptic vesicles and coated vesicles (85). Conventional kinesin is a heterotetrameric protein complex composed of a long, coiled-coil rod that incorporates two kinesin heavy chains (kinesin-1s, KHCs) on one end, and two kinesin light chains (KLCs), which form a fan-like structure (86) (Figure 1). Recent studies indicate that conventional kinesin holoenzymes are formed of KHC and KLC homodimers (87). KHCs are responsible for the mechanochemical properties of the conventional kinesin holoenzyme, containing both microtubule-binding and ATPase domains at their amino terminus (86). KLCs on the other hand, play a role in the binding (88) and targeting (89) of conventional kinesin to selected MBOs, through interactions involving

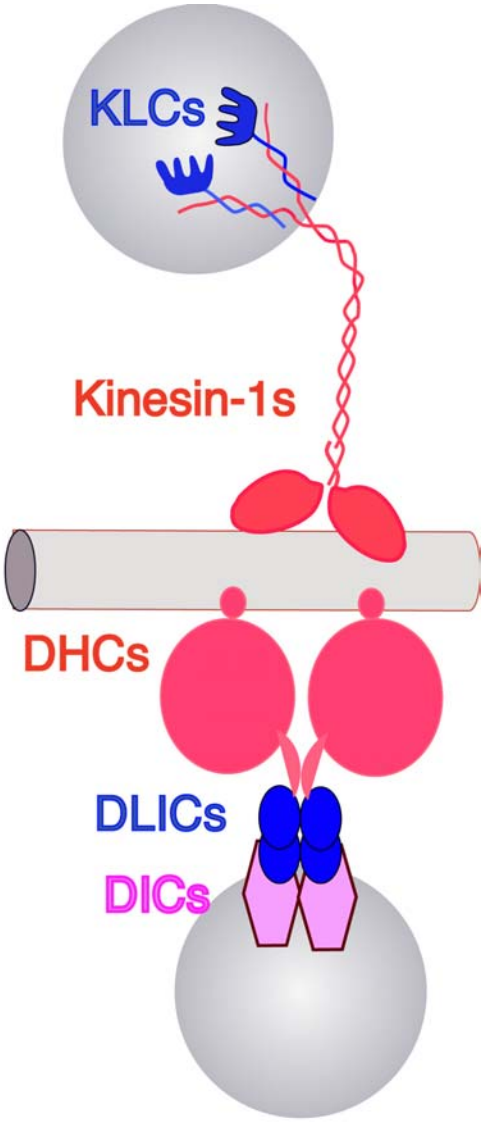


**Figure 1**. Subunit organization of major microtubule-based motors. Conventional kinesin (top) is a heterotetrameric motor molecule composed of heavy chains (kinesin-1, in red) and light chains (KLCs, in blue) homodimers. Kinesin-1s translocate along microtubules (MT) using energy derived from ATP hydrolysis. KLCs interact with the C-termini of kinesin-1s, and play a critical role in the binding of conventional kinesin to transported membrane-bounded organelle cargoes. Cytoplasmic dynein (bottom) exists as a protein complex formed by at least two heavy chains (DHCs, in red), two intermediate chains (DICs, in pink), four light intermediate chains (LICs, in blue), and several light chains (LCs, not shown). DHCs contain are motor domain responsible the ATPase and microtubule-binding activities of CDyn (92), whereas DICs have been involved in the binding of the CDyn complex to various membrane-bounded organelle cargos (95, 97).

their tandem repeat domain (88) and their alternatively spliced carboxy terminus (90), respectively.

Appropriate neuronal survival and maintenance also requires signaling complexes (i.e, activated neurotrophin receptors) and MBOs containing degradation products (i.e., lysosomes and multivesicular bodies) to be transported in the retrograde direction from synaptic terminals and axons to the neuronal cell body (91). The execution of retrograde FAT is carried out by the minus end-directed microtubule-based molecular motor cytoplasmic dynein (CDyn) (92-94) (Figure 1). *In vivo*, CDyn exists as a large (1.2 MD), multisubunit protein complex formed by at least two heavy chains of 500 kDa (DHCs), two 74 kDa intermediate chains (DICs), four 53-59 kDa light intermediate chains (LICs), and several light chains (LCs) (95). A protein complex termed dynactin also appears associated with a small fraction of total CDyn in cells (96). DHCs contain a motor protein domain and are responsible for the ATPase and microtubule-binding activities of CDyn (94). Biochemically heterogeneous CDyn variants containing different DIC isoforms are bound to specific MBO cargos (95, 97).

Basic neuronal functions including synaptic transmission and survival all depend upon the localized delivery of selected MBOs at specific neuronal and axonal subdomains. For example, neurotransmitter-bearing synaptic vesicles are delivered in a regulated fashion to presynaptic terminals, whereas vesicles carrying selected types of sodium channels are exclusively delivered at nodes of Ranvier (98). These observations imply the existence of molecular mechanisms that allow for the regulation of MBO delivery to specific axonal domains (98). What is the molecular basis of FAT regulation *in vivo*? In recent years, it has become apparent that phosphorylation of molecular motors represents a major mechanism for the regulation of FAT (99, 100). Many of these findings stemmed from the use of the squid axoplasm, a unique experimental model for the study of axon-specific events (101). Biochemical, pharmacological, and cell biological experiments identified multiple kinases and phosphatases that differentially affect conventional kinesin (98, 100, 102-105) or CDyn (106-109) function. These kinases can directly or indirectly modify specific subunits of molecular motors, and regulate certain aspects of their functionality (98, 100, 103, 105), thus providing a molecular basis for the regulation of FAT *in vivo*.

Discrete functional activities of conventional kinesin include enzymatic (i.e. binding to microtubules and ATPase activity) and non-enzymatic activities (i.e. attachment to the transported cargos). It was found that the interaction of conventional kinesin with both cargos and microtubules is subject to regulation by specific protein kinases. Conventional kinesin detachment from MBOs was found to be a process that involved the activities of chaperones and several protein kinases (98, 100, 110). Because different cargos need be delivered to specific axonal compartments, a prediction was made that multiple pathways exist to mediate delivery of functional subsets of MBOs (98). An example of such a pathway for removing conventional kinesin from MBOs involves the activity of the protein kinase Glycogen Synthase Kinase 3 (GSK-3) (100). GSK-3 selectively phosphorylates KLC subunits and

promotes detachment of conventional kinesin from the transported cargo (100, 111). Both KHCs and KLCs can be phosphorylated by Casein Kinase 2 (CK2) (98) (105), and this kinase inhibits both anterograde and retrograde FAT when introduced into isolated squid axoplasm (98). Kinesin heavy chains (KHC) are also targeted by regulatory protein kinases. For example, dephosphorylation of KHCs by the protein phosphatase Calcineurin is required for mobilization of secretory granules (105). On the other hand, phosphorylation of KHCs interferes with their binding to microtubules, and thus with the overall processivity of conventional kinesin (112). Additional work has also helped delineating novel signaling pathways that lead to localized activation of these kinases above (104, 113). For example, it was found that activation of axonal GSK-3 is subject to regulation by a pathway involving the activity of Cyclin-Dependent Protein Kinase 5 and Phosphatase 1 activities (104). Based on these findings above, it was suggested that the local activation of specific kinase pathways in axons allows for the delivery of specific cargos to selected axonal subcompartments (87, 104). Conventional kinesin-mediated cargo delivery thus depends upon precise tuning of kinase activities in specific axonal subdomains.

Following the discovery of CDyn, it was found that differentially phosphorylated pools of this molecular motor complex travel along axons. All CDyn subunits appear to be phosphorylated *in vivo* (109). Metabolic labeling experiments *in vivo* showed that DHCs moving in the anterograde direction are less phosphorylated than DHCs in cytoplasmic pools (108). Since anterogradely moving CDyn is likely in an inactive form, it was hypothesized that phosphorylation of DICs might play a role in the regulation of CDyn activity (108). Supporting this idea, neurotrophin-induced stimulation of Trk receptors in cultured neurons induces phosphorylation of DICs (114) and activation of CDyn-dependent retrograde transport (97). Moreover, kinase-deficient forms of Trk fail to be retrogradely transported, again suggesting that Trk-induced kinase activity regulates CDyn function (115). Although the identity of kinases regulating CDyn *in vivo* is uncertain, experiments in both isolated squid axoplasm and the squid giant synapse indicate that Protein Kinase C (PKC) activation increases CDyn-dependent retrograde FAT (106).

Basic neuronal functions including growth, information processing and survival all depend upon exquisite compartmentalization and transport of membrane proteins, which is achieved by FAT. Supporting this idea, several loss-of-function mutations in conventional kinesin (116) and CDyn subunits (117, 118) have been found to cause inherited human neuropathologies, such as Hereditary Spastic Paraplegia and various forms of motor neuron diseases. Interestingly, these diseases proceed following a dying back pattern of neurodegeneration (119-121). Thus, genetic evidence demonstrates that even modest decrements in FAT can suffice to produce degeneration of specific neuronal populations (122). Additionally, alterations in regulatory mechanisms of FAT have also been implicated in neurodegeneration. Highlighting the importance of FAT regulation for neuronal function, recent experimental evidence indicates that alterations in kinase-dependent regulatory pathways for FAT can lead to neuronal degeneration (123, 124) (103, 111, 125). Abnormal patterns of protein phosphorylation have long been recognized in most human neurodegenerative diseases, and specific alterations in kinase and phosphatase activities have been reported in several animal models of these diseases. However, no specific pathogenic target has been identified and the relationship of changes in kinase activity and disease pathogenesis has been uncertain. Given the critical role of FAT in neuronal function, the information above suggests that abnormalities in the activity of kinases regulating FAT could represent an important pathogenic event in various human neurodegenerative diseases (123, 124) (106, 126, 127). Based on this notion, the term "dysferopathies" was proposed to describe neurodegenerative diseases exhibiting dysfunction of vesicle transport and associated loss of synaptic function (106, 128). Various human neurodegenerative conditions fall in this category. For example, abnormal activation of JNK by pathogenic, polyglutamine-expanded forms of huntingtin and androgen receptor polypeptides results in increased phosphorylation of kinesin-1, and inhibition of anterograde FAT (103, 129). Similarly, neurons expressing familial AD-linked mutations in presenilin-1 showed increased activation of GSK-3, and a concomitant reduction in conventional kinesin-based motility (111). Supporting these later findings, nerve ligation studies showed reductions in anterograde FAT in mice expressing FAD-linked PS1 mutations, and this reduction correlated with motor neuron deficits (125). Alterations in retrograde FAT have also been found in association with toxin-induced forms of PD. Specifically, abnormal regulation of CDyn-mediated motility has been proposed to underlie the toxic effects of the parkinsonian drug MPP+ (106). Further, the effects of MPP+ on retrograde FAT depended upon abnormal activation of axonal and synaptic PKC (106, 128). These findings above provide a mechanistic explanation for the early degeneration of axons and synaptic dysfunction observed in these neurodegenerative diseases.

### 4.2 Interactions between viruses and fast axonal transport components

Different viruses appear to utilize unique strategies to hijack the intracellular FAT machinery and be transported to the appropriate intracellular compartment (67). Early observations of bidirectional transport of HSV along axons suggested interactions of this virus with molecular components involved in anterograde and retrograde FAT (130). Accordingly, experimental evidence has emerged demonstrating that HSV can directly interact with specific subunits of molecular motor proteins (131, 132), and this appears to be a recurring theme among neurotropic viruses. HSV is composed of an inner core, a capsid, a tegument, and an outer envelope. The outer envelope is not transported along with the rest of the virus (79), so the tegument was proposed as an interaction site between HSV and motor proteins. By labeling the tegument protein VP16 with green fluorescent protein and then visualizing HSV transport in the giant squid axon, it

was found that HSV undergoes retrograde transport at rates consistent with FAT (79). In addition, studies involving quantitative immunoelectron microscopy and immunofluorescence showed colocalization between HSV-1 capsids and different CDyn subunits, including DHCs, DIC and p150Glued, a major subunit of the dynactin complex (133). However, it is still unknown exactly how HSV-1 interacts with CDyn. A study using *in vitro* pull down assays reported an interaction between the capsid protein VP26 and the DLC subunits RP3 and Tctex1, suggesting that this interaction might be critical for retrograde transport of HSV (131). However, deletion of VP26 from the HSV capsid did not affect trafficking of HSV capsids to the nucleus, suggesting that the binding of HSV to CDyn does not rely exclusively on VP26 (134). Similar studies revealed a role of various HSV proteins in the anterograde transport of HSV. Specifically, deletion of the HSV tegument proteins Us9 (80) and UL36p (135) dramatically attenuated anterograde transport of HSV. Consistent with the anterograde FAT of HSV, a screening of HSV proteins that might bind to KHCs revealed a direct interaction between the HSV protein Us11 and KHCs (132).

Retrograde transport of adenoviruses has been well documented (67). Shortly after being taken up into the cell, adenoviruses enter the endosome, which is then lysed. Endosome lysis allows the escape of adenoviruses, which later undergo retrograde trafficking to the nucleus of their host cell (136). Adenoviruses can move in alternating plus and minus directions of the microtubule, and movement towards the nucleus is prevented by treating infected cells with antibodies recognizing specific subunits of the CDyn complex (137). Overexpression of dynamitin, which is thought to disrupt dynactin-dynein interactions, decreases the retrograde transport of adenoviruses towards the nucleus, and concomitantly increases its motility in the anterograde direction (72). Coimmunoprecipitation experiments and microtubule binding assays have shown an interaction of adenovirus with CDyn (138).

RVs, PVs, and PaVs have also been reported to interact with the CDyn complex. Yeast two-hybrid screening and co-immunoprecipitation studies showed an interaction between the RV phosphoprotein P and LC8, a DLC subunit, suggesting a role for this polypeptide in the retrograde transport of RV(139, 140). Consistent with this notion above, mutations that abolish the binding of P protein to LC8 significantly reduced RV spreading from the neuronal cell periphery (141). Similar approaches as those applied to RVs identified an interaction between CD155, the PV receptor, and Tctex-1, a DLC (142). Moreover, the movement of canine parvovirus capsids to nuclei was reportedly reduced by microinjection of an antibody against DIC into the cytoplasm of infected cells (143). Immunoprecipitation experiments also revealed an interaction of canine parvovirus capsids with CDyn (143).

Microscopic experiments using green fluorescent protein-tagged HIV proteins allowed the visualization of axonal HIV trafficking to the nucleus (144). These experiments indicated that HIV virions could move intracellularly following curvilinear paths, finally accumulating in perinuclear regions. Pharmacological experiments suggest that, unlike other viruses (i.e, HSVs and PVs), HIV trafficking might depend upon both microtubules and the actin cystoskeleton (144). Significantly, antibody-mediated disruption of CDyn's activity resulted in accumulation of green fluorescent protein-tagged HIV virions at the periphery of infected cells, suggesting that the activity of CDyn is required for HIV transport to the nucleus (144). In addition, the HIV proteins Tat (145) and gp120 (146), which are overproduced and shed by infected cells, have been shown to be internalized and transported along axons in the rat brain.

Understanding the detailed mechanism of viral protein interaction with the host cell cytoskeleton will ultimately help clarify whether the host cells sees a virus as "cargo" or "garbage" (67). The evidence cited above for both anterograde and retrograde viral transport presupposes the existence of specific interactions between viral and host cell proteins. An alternative hypothesis holds that viral engagement in retrograde FAT does not necessarily depend on specific protein-protein interactions. Rather, recruitment of viruses in retrograde FAT might result from one or more less specific viral particle characteristics, such as hydrophobicity, size and/or charge, that are not necessarily reflected in specific peptide sequences (67). In fact, these mechanisms are not mutually exclusive. Viral nucleocapsids may engage in retrograde and anterograde FAT using different strategies. Whereas anterograde transport might reflect a positive selection requiring specific peptide signals, retrograde transport might be more accurately modeled as a default process that collects organelle-sized particles that lack anterograde signals. Therefore, transport of the HSV nucleocapsid during initial infection may not require any one specific protein to interact with CDyn whereas transport of newly formed nucleocapsids toward the plasma membrane may require specific peptide interaction with conventional kinesin.

## 5. PATHOGENIC EVENTS AND MECHANISMS UNDERLYING VIRUS-INDUCED NEURONAL DYSFUNCTION AND DEGENERATION

As discussed in Section 2 above, infection of neuronal cells by viruses can lead to deleterious effects on their survival and functionality. In some cases (i.e., HIV), it is unclear whether the neuronal defects associated with viral infection result from the incorporation of viral proteins after infection, or the production of viral proteins after delivery of the reverse transcribed genome to the nucleus. Regardless, an understanding of the molecular mechanisms leading to disease may thus aid in designing novel strategies for disease prevention and for the development of novel therapeutic approaches. Major questions on this topic relate to mechanisms underlying the neuronal dysfunction and degeneration induced by neurotropic viruses. The eventual induction of apoptotic cell death appears to be a common consequence of neurotropic viral infection (reviewed in (147)). However, recent electrophysiological, microscopic and cell biological

evidence suggests that neurons targeted by neurotropic viruses can degenerate following a "dying back" pattern. Interestingly, this pattern of neuronal degeneration represents a major hallmark of dysferopathies, which are characterized by alterations in synaptic and axonal function preceding neuronal cell death (119-121). Below we discuss experimental evidence suggesting that, besides the eventual activation of apoptotic pathways, neurotropic viruses can differentially affect axonal and synaptic function.

**5.1 Activation of apoptotic cell death pathways**

A wide variety of neurotropic viruses from different families can cause apoptosis in the cells that they infect (147). Although apoptosis generally helps to remove the virus through subsequent phagocytosis, it may also have detrimental consequences to the host (147). HIV, PV and HSV are well-established examples of viruses inducing apoptosis in the nervous system as a pathogenic response.

A significant body of experimental evidence indicates that HIV infection induces apoptosis (148) and neuronal loss in both the CNS and the PNS (149) (150). The molecular basis of HIV-induced apoptosis is not completely understood, but it is thought to occur through several different mechanisms caused by multiple HIV proteins, including the envelope proteins gp120 and Tat. When expressed in transgenic mice, gp120 alone can induce neuronal cell death in the CNS, mimicking the cell death seen in HAD (151). However, controversy exists on whether gp120 can induce neuronal death directly or indirectly. A line of evidence suggests that gp120 first infects macrophages and lymphocytes, which then infiltrate the DRG (32). These infected cells would release inflammatory and neurotoxic factors such as IL-6, ultimately damaging DRG neurons and causing peripheral neuropathy (152). However, others have demonstrated that gp120 can directly bind to DRG neurons to cause neurotoxicity (153). Supporting this latter idea, DRG neurons express both CXCR4 and CCR5 chemokine receptors, which serve as co-receptors for gp120 (154). Both acute and chronic treatment of DRG neuronal cultures with gp120 induced apoptosis (155) (156), which was prevented by either the natural ligand for CXCR4 SDF1 (157), anti-CXCR4 antibodies (158), or by the CXCR4 antagonist AMD 3100 (159). As a purely neuronal culture was used, it was demonstrated that gp120 can cause apoptosis independently from interactions with other cell types; gp120-induced apoptosis appears dependent on its interaction with host cell CXCR4 (160). In fact, HIV strains that specifically utilize CXCR4 were demonstrated to cause more apoptosis than other strains that bind to CCR5 instead (158), suggesting that apoptosis is induced more readily through specific receptor interactions. Tat is another HIV protein with neurotoxic properties, which is released by infected macrophages and microglia. Tat can be internalized and induce apoptosis in a variety of neuronal cultures, including human fetal neurons (161) and neuroblastoma cells (162). Moreover, a basic domain comprising the amino acids 49-57 in Tat appears to be critical to elicit its neurotoxic effects (163).

Induction of apoptotic pathways appears to be the major molecular event underlying the symptoms of poliomyelitis. Animal models of poliomyelitis showed that motor neurons infected in the spinal cord undergo apoptosis in direct correlation with viral load and at the same time points that paralysis begins (164). Significantly, the pattern of neuronal degeneration associated with PV infection differs significantly with that seen in dying back neuropathies. Specifically, the proximal segments of axons degenerate first after PV infection, and then axonal degeneration progresses distally (165). At the molecular level, it was found that binding of PV to its receptor CD155 results in activation of JNK and the pro-apoptotic protein Bax (166). Recently, it was also found that in HSE, neuronal apoptosis relates directly to HSV-1 viral load (167). Apoptosis occurs during acute HSV-1 infection, but not during later sequelae, even if inflammation is still present (167). Also, HSV-1-infected hippocampal neurons show an increase in apoptotic markers, which was dependent on the activity of JNK (168).

**5.2 Alterations in synaptic function**

Viral infection of the nervous system can lead to severe defects in synaptic transmission. A well-documented example corresponds to neuronal infection by the borna disease virus (BDV). Evidence exists that humans possess antibodies to BDV, but it is controversial whether BDV may cause neurological symptoms in humans (169). BDV causes a wide range of neurological illnesses in animals, mainly livestock in central Europe (169). BDV has been shown to block synaptic potentiation by a mechanism involving reductions in PKC-mediated phosphorylation of the synaptic proteins MARCKS and Munc18-1, which are involved in synaptic vesicle recycling (170). A recent work examined how networks of neurons respond to BDV infection using neurons cultured on multielectrode arrays, which allow for the evaluation of electrical activity in real-time (171). It was found that while BDV did not impair spontaneous neuronal activity, it did block activity-dependent enhancement of synaptic transmission, suggesting that BDV may induce impairments in synaptic plasticity (171).

A major consequence of HIV infection is the loss of synaptic connections in the CNS, and HAD pathology correlates well with changes in synapse activity and synaptic loss (172). For example, in mild HIV neurocognitive disorders, synaptic density is reduced in the frontal cortex, and this reduction can be correlated with cognitive impairment (173). Abnormal amounts of both presynaptic and postsynaptic dopaminergic proteins have also been found in the striatum of HAD patients (174). Animal models of HAD similarly confirmed pathological observations above, and demonstrated that synaptic dysfunction appears earlier in the progression of HAD pathology than neuronal apoptosis. Mice with transgenic expression of the HIV protein gp120 in astrocytes under an astrocyte-specific promoter show reductions in the number of presynaptic terminals and dendrites in the CNS (151), whereas transgenic mice selectively expressing gp160 (consisting of gp120 and gp41) in neurons display alterations in synaptic function (175). Mouse models of HIV-1 encephalitis (HIVE) similarly display impairments in synaptic function, as demonstrated by attenuated responses to paired pulse facilitation and long-term

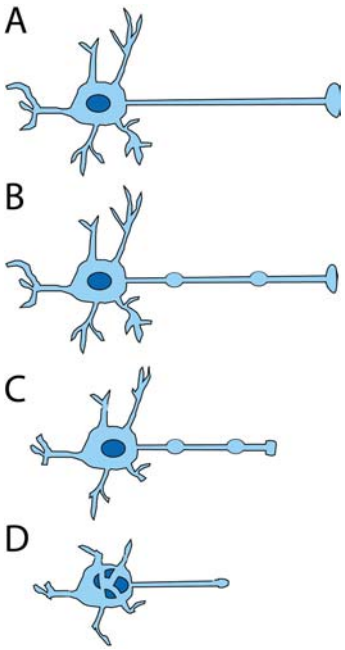


**Figure 2.** gp120-induced dying back neuropathy. In the initial stages of HIV infection, neurons of the PNS and CNS remain healthy (A). As the disease progresses, neurons of both the CNS and PNS begin to exhibit signs of synaptic and axonal dysfunction (156, 172, 175) (B), which underlie the neurological defects observed with HAD in the CNS and DSP in the PNS. In the PNS, a prominent degeneration of unmyelinated nociceptive C fibers is seen, which progresses as a "dying-back neuropathy". This pattern of neuronal degeneration is marked by early synaptic loss (or nerve end degeneration in the case of DRGs) and distal axon degeneration that gradually progresses in the retrograde direction (towards the cell body) (C). Neurons fail to sustain proper synaptic connections with their target cell, gradually losing their trophic support. The sequence of events above (B to C) ultimately results in neuronal cell death, typically by activation of apoptotic pathways (147, 209) (D).

potentiation (176). The HIV protein Tat has also been shown to inhibit the induction of long-term potentiation in the CA1 region of hippocampal slices (177), while gp120 actually enhances giant depolarizing potentials in neonatal rat hippocampal slices (178). The observations cited above indicate that HIV infection is directly linked to synaptic damage; experimental evidence suggests that the HIV proteins gp120 and Tat play critical roles in HAD pathology.

**5.3 Axonal damage and degeneration**

Given the lack of protein synthesis machinery in mature axons, the functionality and maintenance of this major neuronal compartment is tightly associated with appropriate function and regulation of FAT. It thus appears conceivable that neurotropic viruses can induce neuronal dysfunction not simply by activating cell death-related pathways in the cell body, but also by inducing alterations in regulatory pathways for FAT. Correct synaptic function also depends upon the regulated delivery and turnover of selected MBOs (i.e., synaptic vesicles and mitochondria). Accordingly, alterations in axonal transport and turnover of synaptic vesicles trafficking can cause profound effects in synaptic functionality (106, 128). Therefore, axonal pathology may be instrumental in the development of neuronal damage in response to viral infection.

Signs of axonal damage have been shown in the case of HSV-2-induced HSE. Unlike HSV-1, HSV-2 infection causes axonal degeneration in mainly myelinated fibers of the sensory roots in the lower thoracic and lumbosacral spinal cord (179). Additionally, another member of the herpesvirus family, the pseudorabies virus, induces the formation of axonal varicosities in peripheral sensory neurons (180). Evidence suggests that these varicosities are formed to allow viral egress from the axons (180), and it is conceivable that the abnormal formation of varicosities on axons of sensory neuron axons may interfere with usual axonal function.

Axonal alterations have also been observed in classical and paralytic rabies. While classical rabies shows signs of anterior horn cell pathology, paralytic rabies is primarily associated with peripheral nerve damage (27). Significantly, RV infection results in axonal loss and Wallerian degeneration (28). Wallerian degeneration refers to a process that results when part of the axon degenerates in isolation of changes in the neuronal cell body. Minguetti and colleagues reported axonal degeneration and demyelination in both peripheral and cranial nerves of rodents inoculated with RV (181, 182). Examination of mouse sciatic nerves inoculated with RV revealed that axonal degeneration mainly occurred in myelinated axons (183). In another study, a detailed analysis of brain pathology in RV-infected mice found fragmentation, beading and vacuolation of axons along with little or no signs of apoptosis, suggesting that axonal dysfunction might play a large role in the development of rabies (184). The overall data points to axonal degeneration, as opposed to cell death, as the primary cause of pathology in neurons infected with RV.

Axonal damage exists in both the PNS and CNS in response to HIV infection. HIV-DSP causes a minimal loss of neurons, suggesting that axonal degeneration is the predominant neuronal pathology (32). Further, in a mouse model of HAD in which transgenic mice selectively overexpressed gp160 in neurons, axonal damage and swelling was apparent (175). Dorsal root ganglion (DRG) neurons exposed to supernatants from macrophages infected with HIV exhibited neurite retraction and segmentation, without apoptosis (185). The HIV proteins Tat and gp120 appear to be instrumental in causing axonal degeneration. In fetal DRG neurons, both Tat and gp120 treatment caused neurite retraction (186). Additionally a study using compartmentalized chambers demonstrated that gp120 caused axon degeneration by directly acting on axons through a separate mechanism than the one involved in induction of apoptosis (156). Taken together, the data above suggest that axonal degeneration represents an early and critical pathological event underlying HIV-DSP (Figure 2).

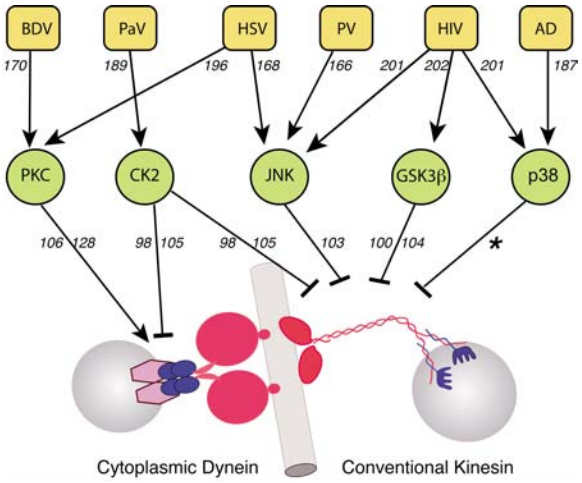


**Figure 3.** Overview of protein kinases involved in the regulation of fast axonal transport (FAT), and their relationship to neurotropic viruses. Several protein kinases have been identified (green circles), which phosphorylate and regulate the activity of conventional kinesin and cytoplasmic dynein (CDyn), major microtubule-dependent motor proteins responsible for FAT in neuronal cells. These kinases phosphorylate specific subunits of molecular motor protein complexes, and regulate specific aspects of their activities. In healthy neurons, the activity of these kinases is tightly regulated and allows for the selective delivery of membrane-bouded cargos to specific subcellular compartments. Highlighting the importance of this process, abnormalities in the activity of kinases and aberrant phosphorylation of molecular motors have been shown in relationship to dysferopathies, neurodegenerative diseases characterized by a "dying-back" pattern of degeneration. By affecting the activity of selected regulatory kinases of FAT, neurotropic viruses (yellow squares) might differentially interfere with FAT, eventually leading to alterations in synaptic and axonal function, and ultimately to neuronal pathology. Inhibitory events are indicated by T-shaped lines; arrowheads indicate activation. References are indicated by numbers in italics. An asterisk indicate unpublished data (Morfini and Brady).

### 5.4. Pathogenic mechanisms underlying virus-induced neuropathologies

Various types of proteins are encoded in viral genomes, including those involved in its replication and packaging. In addition, the genomes of most viruses code for proteins that modify the normal functioning of endogenous proteins in the host cell, and that facilitate the various needs associated with different cycle stages of the virus. For example, the genome of the oncogenic Rous sarcoma virus codes for v-src, a constitutively active version of the normal host cellular kinase c-src. Expression of v-src in the host cell results in sustained and abnormal phosphorylation of c-src substrates, eventually promoting a proliferative-like state in the host cell that facilitates the replication of RSVs. As discussed above, many neurotropic viruses need to be transported over long distances along axons before they can reach the neuronal cell body. The reliance of neurotropic viruses on FAT, and the regulation of this cellular process by phosphorylation-dependent mechanisms suggest that viruses could promote their own transport along axons by modulating signaling pathways involved in FAT regulation. Given the close relationship between abnormal phosphorylation of molecular motors and neuronal degeneration (123, 124) (106, 126, 127), it is also conceivable that virus-induced alterations in neuronal function result from sustained or acute activation of protein kinases and phosphatases involved in FAT regulation. Supporting this idea, a large body of experimental evidence indicates that viruses can affect specific signaling pathways in neuronal cells. Moreover, various connections between viruses and kinases known to affect FAT have been established. Some specific examples are presented in Figure 3, and further discussed below.

HSV, PV and adenovirus have been shown to activate various stress-activated protein kinases (SAPKs) in their host cells. For example, HSV-1 infection of hippocampal neurons in culture resulted in increased activation of JNK (168). Further, increased phosphorylation and activation of JNK have also been found in brains of HSE patients, suggesting that abnormal JNK activation might play a role in HSE pathogenesis (168). Similarly, PV infection of the neuroblastoma cell line IMR5 resulted in rapid activation of JNK (166), whereas adenoviruses have also been shown to activate the SAPK p38 (187). Significantly, inhibition of FAT resulting from increased activation of axonal JNK and p38 kinases has been linked to the pathogenesis of polyglutamine-expansions diseases (103), and ALS (Morfini and Brady, unpublished). Both JNK and p38 kinases can directly phosphorylate KHCs, and this event reduces conventional kinesin processivity by interfering with conventional kinesin binding to axonal microtubules (103)

Some experimental evidence suggests a role for virus-encoded kinases in the regulation of viral replication and transport. For example, the pseudorabies virus kinases US3 and UL13 appear to be important for regulating anterograde delivery of the pseudorabies virus to the distal axon (188). In an experiment mutating viruses to delete US3 and UL13, newly formed viruses had an increase of retrograde movement coupled with a decreased amount of the viral membrane marker (188). Although the exact targets of US3 and UL13 remain elusive, the activity of these viral kinases may be necessary for anterograde transport of pseudorabies viruses (188).

The genome of some non-AAV parvoviruses codes for NS1, a polypeptide known to interact with a wide variety of host cell proteins. Among these, NS1 can interact with the catalytic subunit of CK2 and induce alterations in the phosphorylation of neuronal proteins (189), including tubulin (190) and tubulin-associated protein (191). Interestingly, active CK2 inhibits both anterograde and retrograde FAT (98, 105). This later observation could provide a link between the activation of CK2 by NS1 and the marked degeneration of axons associated with parvovirus infection (192).

The emerging role of PKC in retrograde FAT activation (106, 128) suggests that HSV-1, BDV and RV

infection could affect the normal turnover of membrane components at the synapse. The genome of both RV and BDV code for the phosphoprotein P, a polypeptide subject to phosphorylation and dephosphorylation by host cell kinases (193) (194). After infection, BDV-derived phosphoprotein P acts as a competitive inhibitor of PKC, reducing PKC-mediated phosphorylation of the synaptic proteins MARCKS and Munc18-1, which are involved in synaptic vesicle recycling (170). Through this mechanism, BDV infection results in inhibition of synaptic potentiation. Multiple PKC isoforms can phosphorylate P protein, with PKCgamma being the most effective (193). Interestingly, mutations that increase the activity of PKCgamma cause Spinocerebellar Ataxia X, a neurodegenerative disease characterized by Purkinje cell degeneration (195). HSV-1 on the other hand, has been shown to recruit and activate PKC to the nuclear membrane, an activity proposed to play a role in the budding of nucleocapsids at the inner nuclear membrane (196).

HIV appears to alter multiple host cellular kinase pathways through the three different proteins Nef, Tat and gp120. Nef is an HIV protein that interacts with various cellular kinases. The core of Nef has been shown to interact with the tyrosine kinases Lck, Lyn and Hck (197), (198), as well as Pak2 kinase (199). Further, its N-terminus interacts with the kinase Lck and also the novel PKC family members PKCdelta and PCKtheta (200). Interactions of gp120 with host cellular kinases have also been reported. Treatment of cultured striatal neurons with gp120 has been shown to induce the activation of p38 and JNK (201). Consistent with these findings, a pharmacological inhibitor of Mixed-Lineage Kinases upstream of JNK prevented gp120-induced apoptosis (155). Tat is yet another HIV protein capable of interacting with host kinases. Addition of Tat to a culture of striatal neurons significantly increased phosphorylation of p38 and JNK (201). Further, it appears as though Tat can activate GSK-3beta in neuronal cells (202) (203), which selectively inhibits conventional kinesin-based motility in axons (100). Thus, three different HIV proteins Nef, Tat and gp120 can affect multiple host cellular kinase pathways important for FAT regulation.

### 5.5 Potential therapeutic targets

The observations above suggest that abnormalities in the activities of protein kinases involved in the regulation of FAT might play a role in the pathogenesis of neurotropic virus-induced pathologies. If the toxic effect of neurotropic viral infection indeed derives, at least in part, from such alterations, then the activity of these enzymes could be corrected using pharmacological approaches. Identifying specific kinase activities relevant to FAT in association with each virus will represent a first critical step. After this, novel pharmacological inhibitors could be developed, or already existing ones applied to restore the activity of these kinases to their normal levels, without compromising their basic functions. The development of kinase inhibitors targeting specific pools of a given protein kinase suggests that targeted inhibition of kinases relevant to FAT is not implausible (204). A message of hope is given by the fact that several kinase inhibitors have been already successfully tested *in vivo* in a variety of animal disease models, and some have already entered phase III in human clinical trials, including inhibitors of GSK-3 (205), p38 (206), and JNK kinases (207), among others. One would expect that preventing decrements in FAT would only have a positive outcome for patients.

Recent therapeutic approaches for dying-back neuropathologies based on the sole inhibition of neuronal apoptosis have proven unsuccessful and highlighted the additional need to maintain proper axonal and synaptic connectivity (208). In this context, the application of specific pharmacological compounds targeting abnormalities in kinase activities induced by neurotropic viruses might aid in preventing the axonal and synaptic dysfunction associated with viral infections, ultimately helping neurons maintain their proper connectivity and functionality.

## 6. DISCUSSION

Although the symptoms and pathology of the nervous system after viral infection are well described, little is still known about the molecular mechanisms by which neurotropic viruses induce neuronal dysfunction and degeneration. In recent years, significant evidence has merged highlighting prominent roles for both axonal and synaptic degeneration in the pathogenesis of major human neurodegenerative diseases. Thus, an understanding of the role of synaptic and axonal dysfunction in the pathogenesis of viral infections of the nervous system appears mandatory. Viruses typically utilize intracellular host kinases for their propagation and survival; however, changing host kinase activity or diverting host protein kinases from their proper targets may also lead to abnormalities in the regulation of intracellular signaling pathways critical for neuronal function. Experimental evidence indicating both hijacking of the FAT machinery and modulation of kinase activities by neurotropic viruses suggests that neuronal damage might result from imbalances in the function of critical signaling pathways in the host cell, most notably in synapses and axons. An obvious potential mechanism for neurotoxicity involves the inflammatory response to viral infection. However, given the extreme reliance of neurons on FAT and its regulation by kinase-dependent signaling mechanisms, it seems conceivable that at least some of the neurotoxic effects of viruses are caused by changes in the phosphorylation pattern of axonal and synaptic proteins. The close proximity of neurotropic viruses to critical components of the FAT machinery places them at the optimal subcellular location to interfere with phosphorylation processes regulating FAT. In this regard, a precedent has been established in the case of the pseudorabies virus, where viral kinases themselves can directly regulate FAT dynamics. It is certainly possible that other viruses may directly or indirectly affect FAT through abnormal activation of kinase activities. Alterations in the activity of kinases regulating FAT can have profound consequences, and experimental evidence now supports their involvement in the pathogenesis of various human neurodegenerative

diseases. These ideas above provide a conceptual framework for devising novel therapeutic treatments for neurotropic viral infection. In the future, restoring kinase-dependent signaling pathways that have been altered by neurotropic viruses in the host cell may represent a useful therapeutic strategy. Major progress in the development of kinase inhibitors with accessibility to the nervous system should help achieving a drug-based treatment of the diseased nervous system after viral invasion.

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**Abbreviations:** AAV: adeno-associated viruses, AD: adenovirus, AD: Alzheimer's disease, ALS: Amyotrophic Lateral Sclerosis, BBB: blood-brain barrier, BDV: borna disease virus, CK2: Casein Kinase 2, CNS: central nervous system, DHC: dynein heavy chain, DIC: dynein intermediate chain, DLC: dynein light chain, DRG: dorsal root ganglion, DSP: distal sensory polyneuropathy, GSK-3: Glycogen Synthase Kinase 3, HAART: highly active anti-retroviral therapy, HAD: HIV-associated dementia, HIV: human immunodeficiency virus, HSE: herpes simplex encephalitis, FAT: fast axonal transport, JNK: c-Jun amino terminal kinase, KHC: kinesin heavy chain, KLC: kinesin light chain, LCMV: lymphocytic choriomeningitis virus, MBO: membrane-bounded organelle, MS: multiple sclerosis, PNS: peripheral nervous system, PaV: parvovirus, HSV: herpes simplex virus, PD: Parkinson's disease, PKC: Protein Kinase C, PV: poliovirus, RV: rabies virus, WNV: West Nile virus.

**Key Words:** Virus, Axonal Transport, Neuronal Degeneration, Dying Back, Kinase, Kinesin, Cytoplasmic Dynein, Review

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