Potential Role
of Viruses in Neurodegeneration

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ABSTRACT

Viruses have the capacity to induce alterations and degenerations of neurons by different direct and indirect mechanisms. In the review, we have focused on some examples that may provide new avenues for treatment or altering the course of infections, i.e., antibodies to fusogenic virus membrane proteins, drugs that interfere with lipid metabolism, calcium channel blockers, immunoregulatory molecules, and, and inhibitors of excitotoxic amino acids. Owing to their selectivity in attack on regions of nervous tissue, governed by viral factors and by routes of invasion, viral receptors or metabolic machineries of infected cells, certain viral infections show similarities in distribution of their resulting lesions in the nervous system to that of the common human neurodegenerative diseases (namely, motor neurons disease, Parkinson's disease, and Alzheimer's disease). However, it should be emphasized that no infectious agent has as yet provided a complete animal model for any of these diseases, nor has any infectious agent been linked to them from observations on clinical or postmortem materials.

Index Entries: Virus; nervous system; neurodegenerative diseases; ALS; Alzheimer's disease; Parkinson's disease; Creutzfeldt-Jakob's disease; Gerstmann-Sträussler-Scheinker syndrome; motor neuron disease; virus; prion; protein synthesis; membranes; cytoskeleton; immunologic tolerance; glutamate; lipids; calcium; excitotoxic amino acids.

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INTRODUCTION

Common neurodegenerative disorders, such as motor neuron disease, Parkinson's disease, and Alzheimer's disease, are still of unknown etiology and there is as yet no animal model that reproduces all the characteristic structural changes in any of them. This contrasts the situation for the rare sporadic Creutzfeldt-Jakob's disease and the genetic Gerstmann-Sträussler-Scheinker (GSS) syndrome, in which prions have been demonstrated (Prusiner, 1989), and, recently, many of the features of the GSS syndrome have been reproduced in transgenic mice containing a single amino acid substitution similar to that observed in the human prion protein in this disease (Hsiao et al., 1990). This review will focus on some of the direct and indirect mechanisms by which viruses can cause nerve cell degeneration or death. Then, the question of whether viruses can cause changes with a distribution pattern in the nervous system similar to that of the more common neurodegenerative diseases will be addressed.

VIRUS-INDUCED NERVE CELL DEGENERATION

Direct Effects

With few exceptions viruses produce no primarily toxic factors. They are obligate intracellular parasites that use a cell's metabolic and transport machineries for their synthesis and assembly. As a consequence of interferences with these, viruses may exert effects on the host cell's morphology, leading to cell degeneration and ultimately cell death.

Host-Cell RNA and Protein Synthesis Shutoff

Some viruses, like picorna, herpes, and vesicular stomatitis virus, can cause an early and complete shutoff of the host-cell protein synthesis that ultimately may lead to cell death (Knipe, 1990). Other viruses, like paramyxo-, arena- and retroviruses, cause a less-efficient, gradual, or late host-cell metabolism shutoff, and some viruses induce no shutdown at all. It is not known whether a limited shutoff of the host cell's metabolism can cause long-term degenerative changes or altered neuronal viability.

Membrane and Lipid Metabolism

Structural proteins of paramyxoviruses consist of internal proteins associated with the nucleic acids and of envelope proteins. The envelope proteins of mumps virus (a paramyxovirus) include a hemagglutinin protein, which attaches the virus to cell-surface receptors and a fusion protein, which fuses viral membranes with cellular membranes. After synthesis, the different viral proteins are assembled at the plasma membane from which the newly formed viruses bud. Treatment with antibodies to hemag-

glutinin neutralizes mumps virus and limits the infection, whereas treatment with nonneutralizing antibodies to the fusion protein does not eliminate the virus infection from the brain. However, it prevents or delays neural destruction (Andersson et al., 1988; Löve et al., 1986). This indicates that expression of the fusion protein is one important pathogenetic factor for virus-induced neuronal cell death.

Although most attention has been paid to the interactions between viral replication, and the host-cell RNA and protein synthesis, viruses may also induce profound disturbances in the metabolism of lipids in a cell's membrane (Farooqui et al., 1987). Herpesviruses may cause changes in neutral lipid composition of a cell (Jerkofsky and de Siewo, 1986) and human immunodeficiency virus can depress phospholipid synthesis in T-cell lines (Lynn et al., 1988). A neurotropic picorna virus, like mengovirus, may instread cause increased synthesis of phospholipids and stimulate an extensive proliferation of smooth endoplasmic reticulum in an infected cell (Schimmel and Traub, 1987). Inhibitors of lipid biosynthesis can block growth of poliovirus (Guinea and Carrasco, 1990) and syncytia formation in cells infected with measles virus (Malvoisin and Wild, 1990). Wild et al. (1986) have suggested that virus-induced modifications in host-lipid metabolism may persist even after the virus infection has been eliminated. The lipid composition of a cell's membrane can also regulate virus-induced membrane fusion, which suggests a role for lipids in the pathogenesis of virus infections. Furthermore, increasing a cell's content of saturated fatty acids can be associated with increased production of infectious viruses (Roos et al., 1990). Virus-induced hemolysis or cytolysis and cell fusion is also much subjected to the influence of the lipid composition of the viral envelope membrane (Huang and Uslu, 1986). As viruses acquire their envelope lipids from the infected host cell, it is of interest to evaluate how the unique lipid composition of the membranes in the brain may influence the lytic activity and virulence of a virus replicating in the nervous system.

Cytoskeletal Elements

A cardinal feature of the common neurodegenerative diseases are alterations in the cytoskeletal elements, involving neurofibrillary changes in Alzheimer's disease, Lewy bodies in Parkinson's disease, and different types of filamentous inclusion bodies in motor neuron disease. It may therefore be of interest to focus on the profound changes in the cytoskeletal network of a cell that viruses may cause (Luftig, 1982). For instance, measles, cytomegalo-, and vesicular stomatitis virus can cause a depletion of actin filaments (Bohn et al., 1986; Fagraeus et al., 1978; Jones et al., 1986; Simon et al., 1990). Reoviruses can cause disruption of intermediate filaments and certain strains of these viruses bind to microtubules by a specific protein (Sharpe et al., 1982). Other viruses cause an extensive reorganization of all cytoskeletal elements (Carvalho et al., 1988; Murti

and Goorha, 1983; Murti et al., 1988; Norrild et al., 1986). The early small t antigen of Simian virus 40 binds to tubulin (Murphy et al., 1986), blue-tongue virus associates with the vimentin intermediate filaments (Eaton et al., 1987), and the matrix protein of certain paramyxoviruses interacts with actin (Giuffre et al., 1982). Recently, a direct role for the vesicular stomatitis virus matrix protein in the cytopathological alterations in cellular shape has been implicated (Blondel et al., 1990). In cultured spinal cord and root ganglia neurons, Sendai virus nucleocapsid proteins show an asymmetric distribution in dendrites vs axons similar to that of the microtubule-associated protein MAP_2 (Weclewicz et al., 1990). The effects of interactions between viruses and the cytoskeleton on the function and survival of neurons have not been explored. Neurofibrillary tangles similar to those in Alzheimer's disease are found in brains from patients with postencephalitic parkinsonism and subacute sclerosing panencephalitis.

Calcium Regulation

The permanent neuron provides an ideal harbor for a persistent virus. By suppressing the expression of its envelope components, the virus may avoid direct host-cell destruction or elimination by circulating virus antibodies. Noncomplete, noninfectious viruses may then be present for extended periods of time in the brain, which also has been observed for several enveloped RNA viruses, like paramyxoviruses, arena viruses, and retroviruses (Kristensson and Norrby, 1986). For instance, neurons in cerebral cortex, containing nucleocapsid antigen of the parainfluenza virus (Sendai virus) are still seen 250 days after infection of newborn mice. In such neurons the expression of viral envelope proteins is suppressed (Kristensson et al., 1984).

The effects of a persistent virus infection on a nerve cell's function can be studied in tissue culture. Cultured spinal ganglia neurons were infected with two different paramyxoviruses—Sendai, which causes cell death after about six days, and mumps, which causes a persistent infection with survival of about 60% of the neurons. All Sendai virus proteins were detected, but the mumps virus-infected neurons expressed only the internal viral nucleocapsid proteins (Löve et al., 1987). Neurophysiological examinations showed that membrane potential, action potential amplitude, and input-resistance were not affected in such persistently infected neurons. However, when recorded two days after infection the maximum rate of rise of the calcium spike, recorded in sodium-free Tris solution containing tetraethylammonium, was reduced at a time when there was no apparent change in input resistance, indicating specific effects of the virus on Ca^{2+} channel activation. These functional changes were later normalized. Also, in Sendai-infected neurons, there was an early reduced influx of Ca^{2+} during the action potential, but later these neurons also showed a reduced action potential amplitude and input resistance, and finally, some

days later, a reduction in membrane potentials before the cells disintegrated (Maehlen et al., 1991). Altering Ca^{2+} concentration in the medium affected survival of mumps-infected neurons and treatment with nifedipine, which is a blocker of the L-type of voltage-dependent Ca^{2+} channels, could almost completely reduce neuronal death (Andersson et al., 1991a). A disturbance of a neuron's regulation on intracellular Ca^{2+} therefore seems to be an important pathogenetic factor for direct viral-induced neuronal degeneration. The role of viral envelope components in neurodegeneration was recently emphasized by Dreyer and coworkers (1990), who reported that the highly purified recombinant gp 120 envelope protein from human immunodeficiency virus type 1 can increase intracellular free Ca^{2+} in rodent retinal and hippocampal neurons in culture and that the Ca^{2+} channel antagonist nimodipine abrogated this and reduced neuronal death. In our study of replicating viruses, however, we observed a pathogenetic role for Ca^{2+} also in neurons that did not express detectable viral envelope proteins, indicating that factors not related to insertion of viral envelope proteins into the plasmalemma can be involved in disturbing a neuron's Ca^{2+} regulation during infection. Why some neuronal virus infections are complete with formation of envelopes while others are abortive, may be determined both by viral and by neuronal factors. A striking example of the latter may be the recently by Ljungdahl et al. (1989) described neuronal gamma-interferon (IFN-γ)-like molecule present in a subpopulation of sensory neurons. In tissue culture systems, these neurons seem to have an altered susceptibility to certain virus infections and, when infected, they are more prone to survive than to degenerate (Eneroth et al., 1991). It is interesting to note that sensory ganglia in many host animals, including man, may harbor several persistent viral infections, most notably herpes simplex virus (Dobson et al., 1990).

Indirect Effects

The nervous system can also be affected by indirect mechanisms. Molecular mimicry between a virus protein and a host protein may give rise to autoimmunity if the immunologic tolerance is broken, but only exceptionally will this cause pathological alterations (Oldstone, 1987). Here, we will discuss the possibility that long-distance neurodegenerative effects may be elicited by induction of major histocompatibility complex (MHC) antigens and release of excitotoxic amino acids.

MHC Induction

Even if the virus does not cause a direct nerve cell death or the expression of viral envelope protein is suppressed, the neuron may still be destroyed in the host animal by an action executed by cytotoxic T-cells (CD8+). These T-cells can recognize even fragments of internal, nucleocapsid viral proteins expressed in context with MHC class I at the cell

surface. The normal brain contains little or no MHC class I, but this molecule is induced during certain viral infections, which may facilitate virus elimination. For instance, when cytotoxic T-cells are depleted in measles-infected rats, persistence of virus in neurons of the brain is promoted (Maehlen et al., 1989). The MHC class I induction in such infected rats is seen not only in the infected neurons, but also diffusely at wide distances in uninfected neurons and other cell types.

MHC induction in the nervous system may follow neuroanatomical tracts, since lesion of a peripheral nerve branch can induce MHC class I antigen in the corresponding motor neurons in the CNS, in which case, MHC class II antigen and the HIV receptor CD4 molecule are also expressed in surrounding microglial cells (Maehlen et al., 1988). Interestingly, an IFN-γ-like molecule is induced in such axotomized motor neurons (Olsson et al., 1989). Signals to induce these molecules, which regulate immune responses, may therefore travel by axonal transport. A long-term expression of such molecules may potentially cause neurodegeneration, since in other systems, like β-cells in pancreatic islands, aberrant expressions of IFN-γ and MHC antigens can cause a slowly progressive cell degeneration (Allison et al., 1988; Sarvetnick et al., 1988). Hypothetically, a virus may therefore send signals from one site within or without the nervous system, by itself or by polypeptides released from infected cells, to other areas to induce these immunoregulatory molecules that, if they persist, may lead to ultimate nerve cell death.

Excitotoxic Amino Acids

Another indirect mechanism by which neurons at a long distance from the infected ones may be destroyed is illustrated in a model where BALB/C mice were infected with a hamster neuroadopted strain of measles virus. Clusters of cortical neurons are infected, but it is an abortive virus replication with suppressed formation of virus envelope proteins. It is non-cytolytic, attracts no inflammatory cells, and the cerebral neocortex is histologically normal. However, the mice develop a severe state of hyper-excitation, leading to necrosis of sectors in the uninfected pyramidal band of the hippocampus. There is also a pronounced astroglial proliferation. Since excitation is such a remarkable feature of this infection, mice were treated with the NMDA receptor antagonist MK 801, which is a noncompetitive blocker of excitotoxic amino acids that can pass the blood–brain barrier. This treatment could prevent the neurodegeneration in the pryamidal bands, but the degree of astrogliosis was the same, which indicates that this response is not only secondary to the nerve cell damage (Andersson et al., 1991b). Since the hippocampal neurons were not infected, it is suggested that their degeneration is caused by virus-induced release of excitotoxic amino acids, which may explain why hyperexcitation completely dominates the clinical picture; an excitatory virus.

TOPOGRAPHICAL DISTRIBUTION
OF VIRUS INFECTIONS
IN THE NERVOUS SYSTEM

Motor Neuron Infection

There are several examples that viruses, for instance, poliomyelitis virus and certain rhabdoviruses, can selectively attack motor neurons by retrograde axonal transport from the periphery.

The receptor for poliomyelitis virus has recently been identified as a member of the immunoglobulin superfamily (Mendelsohn et al., 1989). Patients with old poliomyelitis may develop neuromuscular symptoms, which may remain relatively stable or undergo a very slowly progressive course, suggesting a benign form of motor neuron disease (Dalakas, 1986). It is presently unknown whether this reflects an activation of a persistent viral infection, aging effect, or something else. All attempts to detect virus antigens in human material have so far been negative. Some patients have developed motor neuron disease after being affected by encephalitis lethargica (Brait et al., 1973), and some cases of chronic progressive myelopathy are associated with the retrovirus human T-lymphotropic virus type 1 (Kawanischi et al., 1989).

Since the original description that wild-mouse ectropic murine leukemia virus can cause a spontaneous lower motor neuron disease in aging mice (*see* Gardner, 1985), much attention has been paid to the interaction of motor neurons and retroviruses. The wild mice are infected congenitally or as newborns, maintain a lifelong persistent infection with viremia, show immunologic tolerance to the virus, and develop hindleg paralysis at a frequency of about 10%. Although it has been questioned whether or not retroviruses can infect the nondividing neurons (Bilello et al., 1986), Sharpe et al. (1990) have recently described that the neurotropic retrovirus (strain Cas-Br-E) shows an abortive replication in large motor neurons of the spinal cord. The viral envelope protein is not formed, and consequently the virus cannot be detected with conventional methods. Such mice develop a slowly progressive spongy degeneration in the spinal cord and astrogliosis. Inflammatory cells are generally absent. Endogenous retroviruses show a widespread presence in the genome of mammals. Cartag and Plagemann (1989) observed that RNA levels of the nonpathogenic endogenous ecotropic murine leukemia virus increased selectively in motor neurons of the mouse spinal cord during aging, and after exposure to X-rays or cyclophosphamide. Lactate dehydrogenase-elevating virus (LDV), which is a nonpathogenic togavirus, injected into such mice caused a slowly progressive degeneration of motor neurons in the spinal cord. This observation shows that two nonpathogenic viruses can interact to produce a neurodegenerative disease, and that this disease

is influenced by the age of the host animal and by environmental factors. Furthermore, the long-terminal repeat region of the genome of these retroviruses seems to be responsible for the topographical localization of the viral infection in the nervous system, and a few modifications in this region alter the distribution pattern of disease (Paquette et al., 1990). All attempts to link human motor neuron disease to any known infectious agent have so far been unsuccessful (Sillevis Smitt and de Jong, 1989).

Substantia Nigra Infection

Like certain drugs and toxic agents, viruses can also rather selectively attack the substantia nigra and cause parkinsonism. Well-known examples of this are postencephalic parkinsonism, after von Economo's encephalitis, and transient parkinsonism, after Coxsackie B virus infections. There is also an experimental model described by Fishman et al. (1985) with a rather selective attack on the substantia nigra and the subthalamic nucleus by a strain of mouse hepatitis virus, which belongs to the corona virus class. However, no virus has so far produced a Parkinson-like disease with formation of the characteristic Lewy bodies nor been isolated from patients with Parkinson's disease, and serological studies trying to link known viruses to this disease have been negative (Duvoisin, 1986).

Reticular Core Neuron Infection

In the brain, certain subcortical nuclei have widespread connections and may serve to modulate the function of the cerebral cortex or basal ganglia. These constitute the reticular core neurons, which include serotonergic neurons in the raphe nuclei, noradrenergic neurons in the locus ceruleus, dopaminergic neurons in the substantia nigra and ventral tegmental area, and cholinergic neurons in the basal nucleus of Meynert, the diagonal band and the septal nuclei. With the exception of the substantia nigra neurons, which have been dealt with in the preceding section, these nuclei are the site for severe degenerative changes with formation of neurofibrillary tangles in Alzheimer's disease. Some of the nuclei project directly to the olfactory bulbs. As pathological changes have been observed in olfactory neurons in patients with Alzheimer's disease, it has in fact been suggested that a disease-provoking agent may gain access to the brain along olfactory pathways (Pearson and Powell, 1989; Talamo et al., 1989). Vesicular stomatitis virus (VSV), which is a rhabdovirus, can in the nasal cavity selectively attack the olfactory epithelium, spread to the brain along olfactory pathways, and kill the animal (Lundh et al., 1987). By using a slowly replicating temperature-sensitive strain of VSV and suckling 11-d-old rats, the spread in the brain can be limited to olfactory pathways and certain reticular core neurons. The rats survive and the virus antigen disappears after about 10 days. The serotonergic midline raphe neurons seem to be more vulnerable to this ''hit and run'' effect of the virus than

the cholinergic and noradrenergic neurons, although all three systems are infected. Infection of cholinergic neurons, however, did not include those in the basal nucleus of Meynert, which do not project directly to the olfactory bulbs. When tested at up to 18 mo of age, these rats showed persistent behavioral changes and learning disabilities (Mohammed et al., 1990). There is a marked depletion in serotonin and its metabolite, whereas other neurotransmitters, including those of the cholinergic system, which is markedly affected in Alzheimer's disease, are relatively unaffected. Histologically, there are no Alzheimer-like changes in the hippocampus or cerebral cortex. Thus, there is no model available that reproduces completely the biochemical or histological alterations of Alzheimer's disease. Although an infectious agent has been suggested as an essential element in the multifactorial disorder of Alzheimer's disease (Mozar et al., 1987), no evidence for the occurrence of any of the common viruses has been obtained in this disease (Gautrin and Gauthier, 1989; Friedland et al., 1990; Pogo et al., 1987).

CONCLUDING REMARKS

Viruses have the capacity to induce alterations and degeneration of neurons by differrent direct and indirect mechanisms. In this review, we have focused on some examples that may provide new avenues for treatment or altering the course of infection, i.e., antibodies to fusogenic virus membrane proteins, drugs that interfere with lipid metabolism, calcium channel blockers, immunoregulatory molecules, and inhibitors of excitotoxic amino acids. Owing to their selectivity in attack on regions of nervous tissue, governed by viral factors and by routes of invasion, viral receptors or metabolic machineries of infected cells, certain viral infections show similarities in distribution of their resulting lesions in the nervous system to that of the common human neurodegenerative diseases (viz, motor neuron disease, Parkinson's disease, and Alzheimer's disease). However, it should be emphasized that no infectious agent has as yet provided a complete animal model for any of these diseases, nor has any infectious agent been linked to them from observations on clinical or postmortem materials. The recent developments in studies of retrovirus and prion infections of the nervous system have provided new and important insights into how certain neurodegenerative diseases may be expressed as acquired, sporadic, familial, or autosomal dominant, and how aging may influence neuronal expression of disease-provoking genes (Hsiao and Prusiner, 1990; Ridley et al., 1986). The recent observation of a family with the inherited prion disease GSS, which displays neurofibrillary tangles and plaques similar to Alzheimer's disease, may indicate a linkage between these disease processes (Ghetti et al., 1989). The difficulties encountered in trying to link an infectious agent as a cause to human neuro-

degenerative diseases are that, it may be hidden, be at a wrong place, or at a wrong time, may be even back in infancy. Also, the agent may be restricted to humans and to their nervous systems, and may therefore not pass species' barriers to be transmissible to animals or to nonnervous tissue. As evident from studies of endogenous retroviruses, a neurodegenerative disease may even result from the combined effect of an ubiquitous virus and another nonpathogenic virus, and the course may be modified by factors in the environment. From the studies of prion diseases, the question may be raised whether novel, nonviral infectious agents are to be discovered also in the common human neurodegenerative diseases.

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