Neurobiology of Borna disease virus

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Borna disease virus (BDV), the prototype of a newly recognized virus family (Bornaviridae) within the nonsegmented negative-strand RNA viruses (Mononegavirales), infects a broad range of warmblooded animals to cause neurologic dysfunction (de la Torre, 1994; Lipkin et al., 1995; Ludwig et al., 1988; Schneemann et al., 1995). This unusual agent is not lytic, replicates at low levels, and may persist in the nervous system despite a vigorous immune response (Carbone et al., 1987; de la Torre, 1994; Lipkin et al., 1995; Ludwig et al., 1988; Narayan et al., 1983; Richt et al., 1992; Rott and Becht, 1995; Schneemann et al., 1995). The issue of human infection remains to be resolved; however, there is accumulating data to suggest that BDV may be associated with selected diseases of the human central nervous system (CNS) (Amsterdam et al., 1985; Bode et al., 1988, 1992, 1996; Bode 1995; de la Torre et al., 1996a; Fu et al., 1993, Kishi et al., 1995; Kishi et al., 1996; Nakaya et al., 1996; Rott et al., 1985; Waltrup II et al., 1995; Sauder et al., 1996).

The molecular biology of BDV includes such intriguing features as a nuclear localization for replication and transcription (Briere et al., 1992; Cubitt and de la Torre, 1994), overlap of open reading frames and transcription units (Briere et al., 1994; Schneemann et al., 1994), posttranscriptional modification of subgenomic RNAs by splicing (Briere et al., 1994; Cubitt et al., 1994; Schneider et al., 1994b) and differential use of initiation codons (Schneemann et al., 1995). In concert, these features provide a multi-level strategy for tight control of BDV gene expression and are likely to contribute to neurotropism and persistence.

Cells of many different lineages and species can be infected in vitro with BDV; however, virus production is more efficient in neural than nonneural cells (Carbone et al., 1993; Mayr and Danner, 1972; Pauli and Ludwig, 1985). BDV is also neurotropic in vivo, with a particular predilection for neurons of the limbic system. Cells initially targeted in infection of horses and rats include neurons of the hippocampus and amygdala (Gosztonyi and Ludwig, 1995; Lipkin et al., 1988; Ludwig et al., 1988; Solbrig et al., 1994). The virus later spreads throughout the CNS to infect astrocytes, Schwann cells and ependymal cells (Carbone et al., 1991; Carbone et al., 1989; Gosztonyi and Ludwig, 1995; Ludwig et al., 1988). Natural infection is thought to occur by the olfactory route; however, because BDV proteins and nucleic acids have also been found in PBMCs of infected rodents (Sierra-Honigmann et al., 1993) and horses (Bode et al., 1994), the possibility of hematogenous transmission cannot be excluded. Viral transport is presumably axonal and trans-synaptic. Following intranasal infection, viral antigen is detected sequentially in olfactory receptor cells, olfactory nerve fibers, cells of the olfactory bulb, and olfactory cortex (Morales et al., 1988). In hippocampus, viral antigen is localized in axon terminals which form synaptic contacts with CA1 pyramidal cell dendrites prior to appearing in pyramidal cell bodies (Gosztonyi and Ludwig, 1995). Similar to rabies virus, it is likely that the spread of BDV infection within the CNS is mediated primarily by ribonucleoprotein particles rather than enveloped virions (Gosztonyi et al., 1993).

Clinical signs of BD may be dramatic, subtle or apparently absent depending on the integrity and intensity of the host immune response to viral gene products (Stitz et al., 1995). In adult immunocompetent animals (e.g., experimentally infected rats), BDV causes an immune-mediated multi-phasic syndrome (Borna disease, BD) which may include stereotyped motor behaviors, dyskinesias, dystonias, ataxia and paresis (Narayan et al., 1983; Solbrig et al., 1994, 1995, 1996a, b). These rats have distinct disturbances in brain levels of monoamine neurotransmitters, heightened sensitivity to dopamine agonists, and altered levels of the dopamine D2 and D3 receptors in striatum, prefrontal cortex and nucleus accumbens (Solbrig et al., 1994, 1996a, b). Furthermore, the administration of psychotropic drugs active in dopamine circuits suppresses some behavioural disturbances in these animals (e.g., hyperactivity, self-mutilation). In contrast to the robust disease observed in adult-infected rats, rats

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infected as neonates do not mount a cellular immune response to the virus and have a different syndrome which presumably represents direct viral effects. This syndrome is characterized by stunted growth, hyperactivity, subtle learning disturbances and altered taste preferences (Bautista et al., 1994; Dittrich et al., 1989). Neonatal infection is associated with abnormal architecture in cerebellum (Bautista et al., 1995) and hippocampus (Carbone et al., 1991), and alterations in tissue factor expression (Gonzalez-Dumia et al., 1996); its neuropharmacology has not yet been defined.

The potential for BDV to induce complex behavioral changes in experimentally infected animals suggests that if BDV can be implicated as a human pathogen it is likely to be associated with neuropsychiatric disease. Several reports suggest an association between BDV infection and neuropsychiatric disorders including schizophrenia, affective disorders and chronic fatigue syndrome. Initial support for human infection emerged from studies demonstrating the presence of serum antibodies reactive with BDV proteins; the prevalence of these antibodies is higher in neuropsychiatric patients than in control groups (Amsterdam et al., 1985; Bode et al., 1988, 1992; Fu et al., 1993; Rott et al., 1985; Waltrip II et al., 1995). Furthermore, BDV nucleic acids, proteins and virus have been detected in PBMCs from neuropsychiatric patients (Bode et al., 1995, 1996; de la Torre et al., 1996a; Kishi et al., 1995, 1996; Nakaya et al., 1996; Sauder et al., 1996). Even more recently, BDV nucleic acids and proteins have been reported in postmortem brain tissues of patients with hippocampal sclerosis and schizophrenia (Salvatore et al., unpublished data; de la Torre et al., 1996b). Many of these studies remain controversial because they are based on methods sensitive to low levels of contamination such as nested RT-PCR or cocultivation. In addition, the observation that putative human isolates are similar in sequence to known animal and tissue culture isolates has been used as evidence to argue they represent contaminants. However, the finding of sequence conservation is consistent with previous analyses of well-characterized isolates disparate by host species and geography (Binz et al., 1994; Schneider et al., 1994a).

To address the significance of BDV as a potential human pathogen, multicenter projects have been established to investigate the prevalence of BDV infection in patients with neuropsychiatric diseases using standardized methods for serology and epidemiology. In the event that such efforts indicate an association between BDV infection and human disease several issues will be raised with respect to its apparently unique pathogenesis in our species. (1) Viral gene products are readily detected in CNS of other natural and experimental hosts without recourse to methods as sensitive as nested RT-PCR. What is the basis for restricted BDV gene expression in humans? (2) There is no evidence to suggest that BDV in humans causes the syndrome of full-blown disease observed in other immunocompetent hosts. Does this reflect low level expression of viral gene products or immunomodulation? (3) Some data suggest that clinical disease and virus load may vary over time (Bode, 1995; Bode et al., 1993, 1994, 1995). Do environmental factors trigger or exacerbate disease? (4) Little is known about the epidemiology of BDV. What are its reservoirs for BDV in urban and rural settings and how is it transmitted to humans?

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References


