

Borna disease virus

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Borna disease virus, a negative-strand RNA virus, infects a wide variety of warm-blooded animals. Depending on the age of the host and the integrity of its immune response, infection may be asymptomatic or cause a broad spectrum of behavioral disorders. Unusual features of Borna disease virus biology include nuclear localization of replication and transcription; diverse strategies for regulation of gene expression; and interaction with signaling pathways resulting in subtle neuropathology. Although the question of human infection remains unresolved, burgeoning interest in this unique pathogen has provided tools for exploring the pharmacology and neurochemistry of neuropsychiatric disorders potentially linked to infection. Analysis of rodent models of infection has yielded insights into mechanisms by which neurotropic agents and/or immune factors may impact developing or mature central nervous system circuitry to effect complex disturbances in movement and behavior. *Journal of NeuroVirology* (2003) 9, 259–273.

Keywords: animal model; Borna disease virus; neuropharmacology; neuropsychiatric disease; RNA virus

Introduction

It is more than a decade since nucleic acids of Borna disease virus (BDV) were cloned (Lipkin *et al*, 1990; VandeWoude *et al*, 1990). The BDV subtractive cloning project, initiated to develop the tools required to assess the role of BDV in human disease, opened up a new field in molecular virology and pathogenesis, but failed in its primary objective. Despite the introduction of diagnostic polymerase chain reaction (PCR) assays, and serologic methods based on recombinant proteins and peptides, the epi-

demology of BDV remains obscure and controversial (Bode *et al*, 2001; Lipkin *et al*, 2001; Staeheli and Lieb, 2001). This review summarizes recent advances in BDV research, with emphasis on molecular biology; virus/host cell interactions; epidemiologic data indicating the occurrence of natural BD outside of endemic Central European areas, and highlighting controversy regarding its role in human neuropsychiatric disease; and experimental models of infection that provide insights into developmental neurobiology.

Molecular biology

Borna disease virus (BDV) is the prototype of a new family Bornaviridae, genus *Bornavirus*, within the nonsegmented negative-strand RNA viruses (order Mononegavirales). Although similar in genomic organization to other nonsegmented negative-strand (NNS) RNA viruses, BDV is distinctive in its nuclear localization of replication and transcription (Briese *et al*, 1992; Carbone *et al*, 1991a; Cubitt and de la Torre, 1994). This feature is shared with plant nucleorhabdoviruses; it is, however, unique amongst NNS RNA animal viruses. The molecular biology of BDV is complex, and includes overlap of open reading frames (ORFs) and transcription units,

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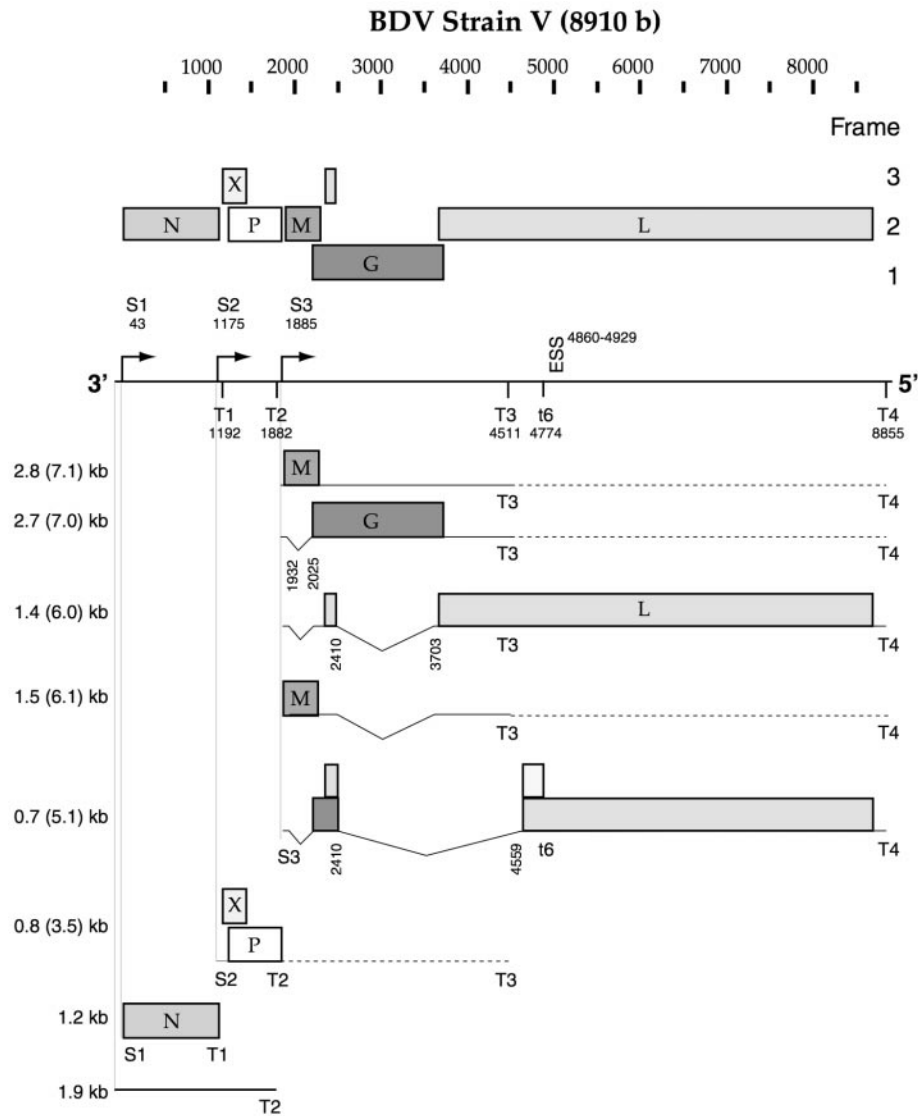


Figure 1 BDV genomic map and transcripts. *Abbreviations:* S1 through S3, initiation sites of transcription; T1 through T4, and t6, termination sites of transcription. Readthrough at termination signals T2 and T3 are indicated by dashed lines; ESS, exon-splicing suppressor.

transcriptional read-through of termination signals, and differential use of initiation codons (Briese *et al.*, 1994; Schneemann *et al.*, 1994, 1995). BDV uses cellular splicing machinery to generate some of its mRNAs (Figure 1) (Cubitt *et al.*, 1994; Schneider *et al.*, 1994b), an aspect consistent with its nuclear localization of transcription and replication. Although splicing is also found in Orthomyxoviridae (segmented, negative-strand RNA viruses), it is unprecedented in Mononegavirales.

BDV encodes at least six proteins. Five proteins correspond to the nucleoprotein (N, p40), phosphoprotein (P, p23), matrix protein (M, p16), glycoprotein (G, p57), and L-polymerase (L, p190) found in other Mononegavirales. The sixth, p10 (X protein), does not have a clear homologue in other NNS RNA viral systems. Data on alternative splicing indicate that the

repertoire of BDV proteins may be larger still. Alternative splicing is a cardinal feature of BDV molecular biology. Splicing to remove approximately 100 bp of M ORF sequence (intron I; Cubitt *et al.*, 1994; Schneider *et al.*, 1994b) from some mRNAs allows expression of the surface glycoprotein G by leaky ribosomal scanning (Schneider *et al.*, 1997b); splicing to remove approximately 1.3 kb of G ORF sequence allows fusion of a small upstream ORF with the large, last ORF (intron II; Cubitt *et al.*, 1994; Schneider *et al.*, 1994b), to generate the full-length L-polymerase protein (Walker *et al.*, 2000). Recently, an additional splice acceptor site (nucleotide [nt] 4559) has been characterized that may allow translation of two additional viral proteins (see Figure 1; Cubitt *et al.*, 2001; Tomonaga *et al.*, 2000). However, because this splice acceptor site is not conserved in the BDV No/98

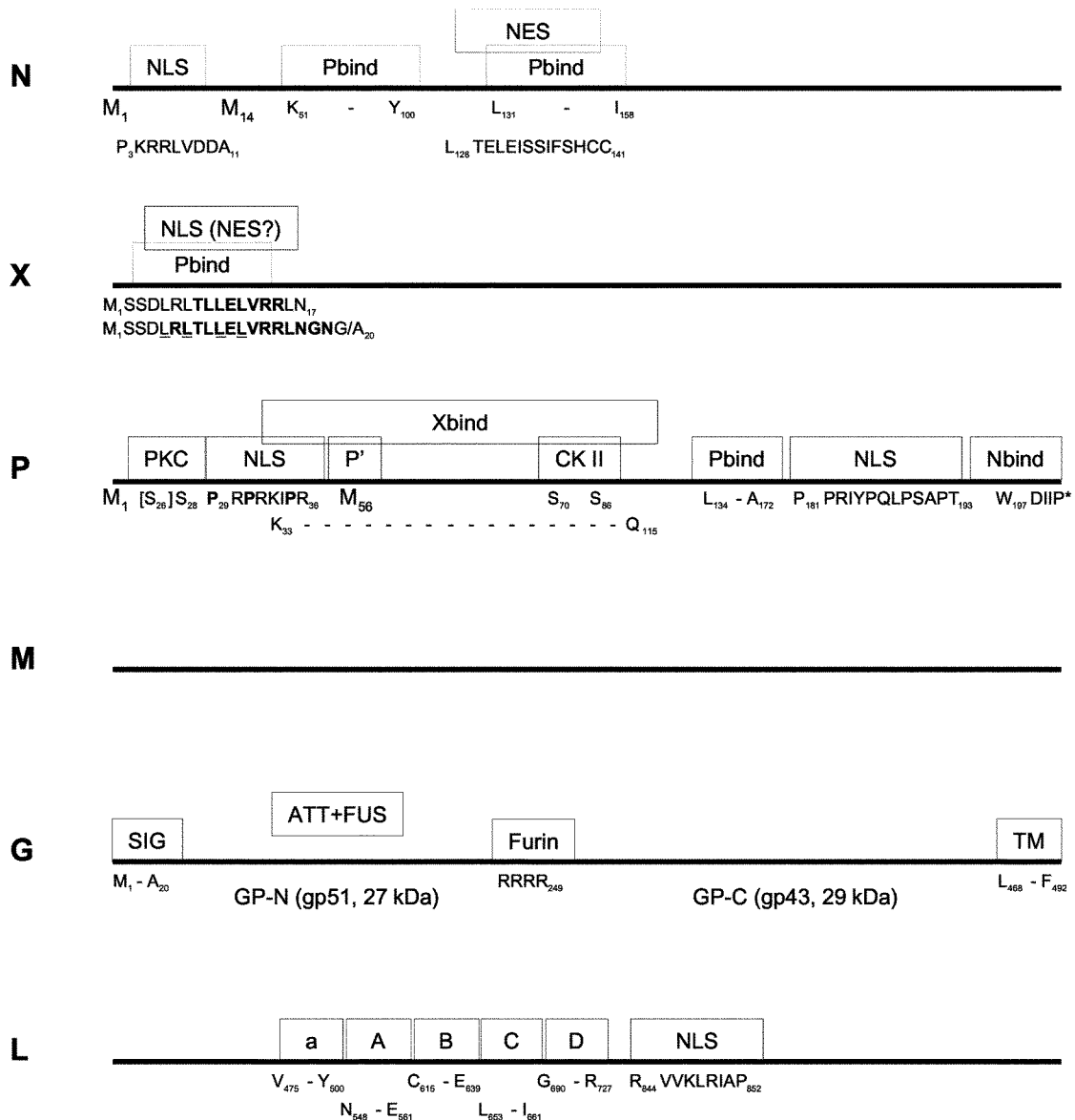


Figure 2 Functional motifs identified in BDV proteins. *Abbreviations:* M1 and M14 in N, and M1 and M56 in P, represent start sites of p40 and p38, and P or P' respectively; NLS, nuclear localization signal; NES, nuclear export signal; Pbind, P binding site; Xbind, X binding site; Nbind, N binding site; PKC, PKC ϵ phosphorylation site; CKII, casein kinase phosphorylation site; SIG, signal peptide; TM, transmembrane domain; ATT + FUS, attachment and fusion domain; Furin, furin cleavage site; a, A, B, C, D, conserved L-polymerase motifs.

isolate, the function of these proteins is unlikely to be essential in the basic life cycle of BDV (Pleschka *et al*, 2001).

Motifs are characterized on some BDV proteins, including nuclear localization signals (NLSs) on N (Kobayashi *et al*, 1998; Pyper and Gartner, 1997), P (Schwemmler *et al*, 1999b; Shoya *et al*, 1998), L (Walker and Lipkin, 2002), and presumably X (Wolff *et al*, 2002), as well as a nuclear export sequence (NES) on N (Kobayashi *et al*, 2001) (see Figure 2). Sites of interaction between N, P, and X (Berg *et al*, 1998; Kobayashi *et al*, 2001; Schwemmler *et al*, 1998), and the phosphorylation sites of P (Schwemmler *et al*,

1997) have been mapped. Further, the viral G protein has recently been analyzed in more detail. Nonetheless, the proposed functions of BDV proteins are still hypothetical and based primarily on analogy to other NNS RNA viruses.

The BDV G protein is a type I glycoprotein of 94 kDa (Kiermayer *et al*, 2002; Richt *et al*, 1998; Schneider *et al*, 1997a). Proteolytic processing by the cellular protease furin (Richt *et al*, 1998) yields two fragments, GP-N and GP-C (Kiermayer *et al*, 2002; Richt *et al*, 1998) (Figure 2). The 94-kDa precursor accumulates in the endoplasmic reticulum, whereas the GP-C cleavage product is transferred to the cell

membrane. However, both the glycosylated 94-kDa precursor and glycosylated GP-C (gp43) are found associated with infectious particles (Gonzalez-Dunia *et al.*, 1997). The second cleavage product, glycosylated GP-N (gp51), was elusive until recently, when it was shown to be present in infected cells and infectious particles by enzymatic deglycosylation on blot (Kiermayer *et al.*, 2002).

BDV enters the host cell by receptor-mediated endocytosis, and membrane fusion occurs in the acidic environment of the endosome (Gonzalez-Dunia *et al.*, 1998). Cleavage of the 94-kDa precursor is essential for virus infectivity, and it has been speculated that proteolytic processing might activate a sequence reminiscent of fusion peptides of other viruses located close to the N-terminus of gp43 (Richt *et al.*, 1998). Recent analyses by pseudotyping, however, indicate that the N-terminal portion of G alone is sufficient to mediate virus attachment and entry into the cell (Perez *et al.*, 2001).

BDV is still the sole known example of the family Bornaviridae. Reported sequences have less than 6% divergence at the nt level, a remarkable degree of conservation for an RNA virus (Kilbourne, 1991; Schneider *et al.*, 1994a). The extent to which this represents selective pressure or fidelity of the BDV RNA-dependent RNA polymerase is unclear. Resolution of this question awaits establishment of *in vitro* transcription and/or reverse genetic systems. Interestingly, BDV replication and spread were recently found to be inhibited by Ara-C (1- β -D-arabinofuranosylcytosine), a nucleoside analogue that specifically inhibits DNA polymerase enzymes. The mechanism of action remains unclear, but is postulated to be direct inhibition of the viral polymerase rather than an indirect effect mediated by host cell factors (Bajramovic *et al.*, 2002).

Epidemiology

Natural BD has been well known as a fatal behavioral and movement disorder of horses and sheep in endemic areas of Central Europe for more than a century (Ludwig *et al.*, 1988). Outbreaks of severe disease are infrequent and remain restricted to this region; however, recent studies suggest a larger host as well as geographic range of BDV infection (Bahmani *et al.*, 1996; Caplazi *et al.*, 1994; Dauphin *et al.*, 2001; Galabru *et al.*, 2000; Hagiwara *et al.*, 1996, 1997a, 1997b, 2001; Helps *et al.*, 2001; Horii *et al.*, 2001; Kao *et al.*, 1993; Lundgren *et al.*, 1993; Malkinson *et al.*, 1993; Nakamura *et al.*, 1995, 1996; Reeves *et al.*, 1998; Yilmaz *et al.*, 2002). Enhanced case ascertainment due to surging interest in BDV and the introduction of sensitive serologic and nucleic acid-based diagnostic assays for infection almost certainly contribute to these findings; however, dissemination of the virus has not been excluded comparing archived materials to more recently collected specimens. With

a few notable exceptions, including reports of disease in Japan in horses (Hagiwara *et al.*, 2000); domestic cats (Nakamura *et al.*, 1999); and dogs (Okamoto *et al.*, 2002); and in Austria and France in dogs (Weissenbock *et al.*, 1998) and lynxes (Degiorgis *et al.*, 2000), investigators reporting infection in new regions or host species do not typically pursue studies of virus isolation, experimental infection, or detailed neuropathology. This is unfortunate as the credibility of BDV epidemiology would be enhanced by more comprehensive analyses.

Neither the reservoir nor the mode for transmission of natural infection is known. An olfactory route for transmission has been proposed because intranasal infection is efficient and the olfactory bulbs of naturally infected horses show inflammation and edema early in the course of disease (Ludwig *et al.*, 1988). Reports of BDV nucleic acid and proteins in peripheral blood mononuclear cells also indicate the possibility of hematogenous transmission (Rubin *et al.*, 1995; Sierra-Honigmann *et al.*, 1993). There is one report suggesting potential for vertical transmission (Hagiwara *et al.*, 2000). Rodents are proposed as a candidate for BDV reservoirs because experimental infection of neonatal rats results in virus persistence and is associated with the presence of virus in saliva, urine, and feces (Sierra-Honigmann *et al.*, 1993). The one reported study examining natural infection of wild rodents has not supported this hypothesis (Tsujiura *et al.*, 1999). BDV has been reported in bird excrement, suggesting the possibility of an avian reservoir (Berg *et al.*, 2001). Rigorous epidemiologic investigation of the global distribution and ecology of BDV should be emphasized in future research.

Sequence conservation amongst isolates is a major confounding factor in BDV epidemiology. Infection is frequently diagnosed by detecting BDV transcripts in clinical materials such as peripheral blood mononuclear cells or tissues following amplification by nested reverse transcriptase-polymerase chain reaction (nRT-PCR). This method, although sensitive, is prone to artifact due to inadvertent introduction of template from laboratory isolates or cross contamination of samples (Schwemmle *et al.*, 1999a). In most viral systems, specific signatures readily facilitate determination of provenance; however, in BDV, similarities in sequence between putative new isolates and confirmed isolates cannot be used to exclude the former as artifacts.

Unique sequence variations specific for a particular host species, time point of isolation, or geographic origin are not yet defined (Binz *et al.*, 1994; Schneider *et al.*, 1994a; Zimmermann *et al.*, 1994). One isolate from a horse in Austria was found to have a higher level of divergence at the nt level than others (strain No/98; Nowotny *et al.*, 2000; Pleschka *et al.*, 2001). Protein sequence was highly conserved (93% to 96% over the entire genome). Biological characterization of this isolate is pending; it remains to be determined whether phenotypic features warrant

classification of this isolate as a new strain of BDV. Laboratory isolates may differ in virulence in animal models depending on their passage history (Hirano *et al*, 1983; Kao *et al*, 1984); however, the first evidence to indicate a molecular basis for such differences was reported only recently when enhanced neurovirulence was associated with two amino acid changes each in the G protein and the polymerase genes (Nishino *et al*, 2002). Another phenotypic difference, sensitivity to amantadine sulfate, is reported for some human isolates (Bode *et al*, 1997; Dietrich *et al*, 2000; Ferszt *et al*, 1999). Other isolates appear to be resistant to amantadine sulfate *in vitro* and *in vivo* (Cubitt and de la Torre, 1997; Hallensleben *et al*, 1997; Stitz *et al*, 1998b). It is unclear whether sensitivity to this drug is specific to the isolates studied by Bode and coworkers. The authors are not aware of similar data for other human isolates (Nakamura *et al*, 2000; Planz *et al*, 1999). The epidemiology of human disease is unresolved (Tables 1 and 2) (Bode *et al*, 2001; Lipkin *et al*, 2001; Schwemmler, 2001). Reports of international collaborative studies based on standardized diagnostic instruments and molecular and serological assays are anticipated in 2003.

Animal and tissue culture models of pathogenesis

Once inside the host cell, mechanisms for BDV pathogenicity remain poorly defined. Virus infection is noncytopathic and persistent. Mechanisms of pathogenicity in the brain may include direct interaction with intracellular signaling and function, or interference with intercellular communication essential to brain function, probably through soluble factors such as cytokines, neurotrophins, and/or neurotransmitters (Gosztonyi and Ludwig, 2001; Hornig *et al*, 2001). The best studied systems are the adult- and the neonatally-infected Lewis rat models.

Infection of adult Lewis rats produces a prominent neurobehavioral disorder and is characterized by pronounced immunopathology. In the acute phase (4 to 8 weeks post infection), cellular infiltrates (CD4⁺ and CD8⁺ T cells, natural killer [NK] cells, macrophages) and Th₁-type cytokines are prominent in perivascular and parenchymal regions of the central nervous system (CNS); in the chronic phase (15 weeks post infection and beyond), a decline in infiltrates is accompanied by an increase in Th₂-type cytokines and a shift to a humoral immune response (Hatalski *et al*, 1998). CD8⁺ T cells mediate destruction of virus-infected cells in the CNS, whereas CD4⁺ T cells promote production of antiviral antibodies. Although antibodies to N and P generated during the acute phase of disease are non-neutralizing (Furrer *et al*, 2001), antibodies with neutralizing capacity increase dramatically after the acute phase (Hatalski *et al*, 1995) and likely participate in restriction of

virus to neural tissues (Stitz *et al*, 1998a). Mechanisms contributing to viral persistence are as yet uncertain. Altered viral gene expression is an unlikely explanation as there is little substantive change in the CNS over the course of disease in viral titers (Carbone *et al*, 1987; Narayan *et al*, 1983), transcripts coding for BDV proteins, or levels of BDV N and P proteins (Hatalski, 1996). Modulation of immune responses as BD progresses to the chronic phase may exert some influence on BDV persistence. BDV-specific Th₁ tolerance appears to be induced; as rats progress to the chronic stage of infection, the capacity of lymphocytes isolated from acute phase CNS to lyse BDV-specific target cells is lost (Sobbe *et al*, 1997). These changes in BDV-specific tolerance during chronic infection may result from presentation of BDV antigens in brain without essential costimulatory signals (Karpas *et al*, 1994; Houry *et al*, 1995; Schwartz, 1992), allowing Th₁ cells to become anergic or undergo apoptosis. Indeed, apoptosis of perivascular inflammatory cells is most apparent at 5-6 weeks post infection, coincident with the onset of the chronic phase and the decline in encephalitis (Hatalski *et al*, 1997).

The distinct clinical and behavioral features of the immune-mediated adult rat model closely parallel the CNS pathology of the acute and chronic phases. In the acute phase, coinciding with monocyte infiltration in CNS regions of early viral burden, such as hippocampus, amygdala, and other limbic structures (Carbone *et al*, 1987), animals demonstrate exaggerated startle responses and hyperactivity. As animals enter the chronic phase of infection, high-grade stereotyped motor behaviors (continuous repetition of behavioral elements, including sniffing, chewing, scratching, grooming, and self-biting), dyskinesias, dystonias, and flexed seated postures appear (Solbrig *et al*, 1994), in parallel with the spread of virus throughout limbic and prefrontal circuits. Up to 10% of animals become obese, achieving body weights up to 300% of normal (Ludwig *et al*, 1988).

Disorders of movement and behavior in adult-infected rats are associated with dysfunction in dopamine (DA) circuits (Solbrig *et al*, 1994, 1995, 1996a, 1996b, 1998), as seen in many neuropsychiatric disorders (Anderson, 1994; Cooper *et al*, 1991; Ernst *et al*, 1997; Hamner and Diamond, 1996; Kane and Marder, 1993; Kelsoe *et al*, 1996; Partonen, 1996), and may be further linked to serotonin (5HT) abnormalities (Solbrig *et al*, 1995). Enhanced sensitivity of central DA systems of adult-infected BD animals to DA agonists, antagonists, and DA reuptake inhibitors is observed. Administration of the mixed-acting DA agonist, dextroamphetamine (Solbrig *et al*, 1994), or of cocaine, a DA reuptake inhibitor, to adult-infected rats elicits increased locomotor and stereotypic behavior, indicating dose-dependent potentiation of DA neurotransmission (Solbrig *et al*, 1998). Low, presynaptic, autoreceptor doses of the direct DA agonist, apomorphine, reduce hyperactivity, whereas

Table 1 Serum immunoreactivity to BDV in subjects with various diseases

Disease	Prevalence		Assay	Reference
	Disease	Control		
Psychiatric (various)	0.6% (4/694)	0% (0/200)	IFA	Rott <i>et al</i> , 1985
	2% (13/642)	2% (11/540)	IFA	Bode <i>et al</i> , 1988
	4%–7% (200/5000–350/5000)	1% (10/1000)	WB/IFA	Rott <i>et al</i> , 1991
	12% (6/49)		IFA	Bode <i>et al</i> , 1993
	30% (18/60)		WB	Kishi <i>et al</i> , 1995b
	14% (18/132)	1.5% (3/203)	WB	Sauder <i>et al</i> , 1996
	24% (13/55)	11% (4/36)	IFA	Igata-Yi <i>et al</i> , 1996
	0% (0/44)	0% (0/70)	IFA/WB	Kubo <i>et al</i> , 1997
	2.8% (35/1260)	1.1% (10/917)	ECLIA	Yamaguchi <i>et al</i> , 1999
	9.8% (4/41)		IFA	Bachmann <i>et al</i> , 1999
	14.8% (4/27)	0% (0/13)	IFA	Vahlenkamp <i>et al</i> , 2000
	0% (0/89)	0% (0/210)	IFA/WB	Tsuji <i>et al</i> , 2000
	1.1%–5.5% (1/90 or 5/90)	0% (0/45)	WB (N or P)	Fukuda <i>et al</i> , 2001
	2.1% (17/816)		ECLIA	Rybakowski <i>et al</i> , 2001a
	2.4% (23/946)	1.0% (4/412)	ECLIA	Rybakowski <i>et al</i> , 2001b, 2002
Affective disorders	12.6% (11/87)	15.5% (45/290)	IFA	Lebain <i>et al</i> , 2002
	4.5% (12/265)	0% (0/105)	IFA	Amsterdam <i>et al</i> , 1985
	4% (12/285)	0% (0/200)	IFA	Rott <i>et al</i> , 1985
	38% or 12% (53/138 or 17/138)	16% or 4% (19/117 or 5/117)	WB (N or P)	Fu <i>et al</i> , 1993a
	37% (10/27)		IFA	Bode <i>et al</i> , 1993
	12% (6/52)	1.5% (3/203)	WB	Sauder <i>et al</i> , 1996
	0%–0.8% (0/122–1/122)	0% (0/70)	IFA/WB	Kubo <i>et al</i> , 1997
	2% (1/45)	0% (0/45)	WB	Fukuda <i>et al</i> , 2001
	92.6% (26/28)	32.3% (21/65)	CIC	Bode <i>et al</i> , 2001
	25% (1/4)		IFA	Bode <i>et al</i> , 1993
Schizophrenia	9%–28% (8/90 or 25/90)	0%–20% (0/20 or 4/20)	WB (N or P)	Waltrip <i>et al</i> , 1995
	17% (15/90)	15% (3/20)	IFA	Waltrip <i>et al</i> , 1995
	14% (16/114)	1.5% (3/203)	WB	Sauder <i>et al</i> , 1996
	20% (2/10)		WB	Richt <i>et al</i> , 1997
	0%–1% (0/167–2/167)	0% (0/70)	IFA/WB	Kubo <i>et al</i> , 1997
	14% (9/64)	0% (0/20)	WB	Waltrip <i>et al</i> , 1997
	17.9% or 35.8% (12/67 or 24/67)	0% (0/26)	WB (N or P)	Iwahashi <i>et al</i> , 1997
	12.1% (38/276)		WB	Chen <i>et al</i> , 1999b
	10.3% (3/29)	23.1% (6/26)	IFA	Selten <i>et al</i> , 2000
	9% (4/45)	0% (0/45)	WB	Fukuda <i>et al</i> , 2001
	12.6% (11/87)	15.5% (45/290)	IFA	Lebain <i>et al</i> , 2002
	24% (6/25)		WB	Nakaya <i>et al</i> , 1996
CFS	34% (30/89)		WB	Kitani <i>et al</i> , 1996; Nakaya <i>et al</i> , 1997
	0% (0/69)	0% (0/62)	WB	Evengard <i>et al</i> , 1999
	100% (7/7)	33% (1/3)	WB	Nakaya <i>et al</i> , 1999
MS	13% (15/114)	2.3% (11/483)	IP/IFA	Bode <i>et al</i> , 1992
	0% (0/50)		IFA	Kitze <i>et al</i> , 1996
Mental health care workers	9.8% (8/82)	2.9% (8/277)	WB	Chen <i>et al</i> , 1999b
Family of schizophrenic patients	12.1% (16/132)	2.9% (8/277)	WB	Chen <i>et al</i> , 1999b
Live near horse farms	2.6%–14.8% (2/78–16/108)	1% (1/100)	ELISA	Takahashi <i>et al</i> , 1997
Ostrich exposure	46% (19/41)	10% (4/41)	ELISA	Weisman <i>et al</i> , 1994

Abbreviations: ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; WB, Western immunoblot; IP, immunoprecipitation; CIC, circulating immune complexes; CFS, chronic fatigue syndrome; MS, multiple sclerosis; N, nucleoprotein; P, phosphoprotein.

higher doses increase locomotion. Both pre- and postsynaptic sites of the DA transmitter system appear to be damaged in striatum: DA reuptake sites, as measured by mazindol binding, are reduced in caudate-putamen (Solbrig *et al*, 1998) and nucleus accumbens (Solbrig *et al*, 1996b); and postsynaptic D2, but not D1, receptor binding is markedly reduced in caudate-putamen whereas D2 and D3 receptor binding are reduced in nucleus accumbens (Solbrig *et al*,

1994, 1996a, 1996b). In contrast, postsynaptic DA receptors (D1, D2) remain intact in prefrontal cortex (Solbrig *et al*, 1996a). Further support for D2-selective losses and resultant D1 hypersensitivity as mediators of neurobehavioral disturbances in adult BD is found in the ability to reverse locomotor hyperactivity through administration of D1 receptor-blocking agents, such as the D1 antagonist, SCH23390, or clozapine, an atypical antipsychotic with mixed D1,

Table 2 BDV RNA, virus or protein in subjects with various diseases

Disease	Tissue	Prevalence		Divergence*	Reference
		Disease	Controls		
Psychiatric (various)	PBMC	67% (4/6)	0% (0/10)	0%–3.6% 0%–4.0% 0.07%–0.83% 0%–5.1% [Protein]	Bode <i>et al</i> , 1995
	PBMC	37% (22/60)			Kishi <i>et al</i> , 1995b
	PBMC	42% (5/12)	0% (0/23)		Sauder <i>et al</i> , 1996
	PBMC-coculture	9% (3/33)	0% (0/5)		Bode <i>et al</i> , 1996; de la Torre <i>et al</i> , 1996
	PBMC	2% (2/106)	0% (0/12)		Kubo <i>et al</i> , 1997
	PBMC	0% (0/24)	0% (0/4)		Richt <i>et al</i> , 1997
	PBMC	0% (0/159)			Lieb <i>et al</i> , 1997
	Blood	(1/1)			Planz <i>et al</i> , 1998
	PBMC	4% (5/126)	2.4% (2/84)		Iwata <i>et al</i> , 1998
	PBMC	20% (3/15)	0% (0/3)		Planz <i>et al</i> , 1999
	PBMC	0% (0/81)			Kim <i>et al</i> , 1999
	PBMC	0% (0/27)			Bachmann <i>et al</i> , 1999
	CSF	0% (0/27)			Bachmann <i>et al</i> , 1999
	PBMC	1.8% (1/56)	0.6% (1/173)		Tsuji <i>et al</i> , 2000
	Affective disorders	PBMC	37% (10/27)		15.4% (2/13)
PBMC		1.1% (1/90)	0% (0/45)	Fukuda <i>et al</i> , 2001	
PBMC		33% (1/3)	0% (0/23)	Sauder <i>et al</i> , 1996	
PBMC		17% (1/6)	0% (0/36)	Igata-Yi <i>et al</i> , 1996	
Brain		40% (2/5)	0% (0/10)	Salvatore <i>et al</i> , 1997	
PBMC		4% (2/49)	2% (2/84)	Iwata <i>et al</i> , 1998	
CSF		5% (3/65)	0% (0/69)	Deuschle <i>et al</i> , 1998	
PBMC		2% (1/45)	0% (0/45)	Fukuda <i>et al</i> , 2001	
Schizophrenia		Brain	0% (0/3)	0% (0/3)	Sierra-Honigmann <i>et al</i> , 1995
		CSF	0% (0/8)	0% (0/8)	Sierra-Honigmann <i>et al</i> , 1995
	PBMC	0% (0/7)	0% (0/7)	Sierra-Honigmann <i>et al</i> , 1995	
	PBMC	64% (7/11)	0% (0/23)	Sauder <i>et al</i> , 1996	
	PBMC	10% (5/49)	0% (0/36)	Igata-Yi <i>et al</i> , 1996	
	PBMC	100% (3/3)		Kishi <i>et al</i> , 1996	
	PBMC	0% (0/10)	0% (0/10)	Richt <i>et al</i> , 1997	
	Brain	53% (9/17)	0% (0/10)	Salvatore <i>et al</i> , 1997	
	PBMC	9.8% (6/61)	0% (0/26)	Iwahashi <i>et al</i> , 1997	
	PBMC	4% (3/77)	2% (2/84)	Iwata <i>et al</i> , 1998	
	PBMC	14% (10/74)	1.4% (1/69)	Chen <i>et al</i> , 1999a	
	Brain	25% (1/4)		Nakamura <i>et al</i> , 2000	
	PBMC	13.8% (4/29)	34.6% (9/26)	Selten <i>et al</i> , 2000	
	PBMC	0% (0/45)	0% (0/45)	Fukuda <i>et al</i> , 2001	
	FMS	PBMC	12% (3/25)		Nakaya <i>et al</i> , 1996
PBMC		12% (7/57)	4.9% (8/172)	Kitani <i>et al</i> , 1996; Nakaya <i>et al</i> , 1997	
PBMC		0% (0/18)		Evengard <i>et al</i> , 1999	
CSF		0% (0/18)	0% (0/6)	Wittrup <i>et al</i> , 2000	
Hippocampal sclerosis		Brain	80% (4/5)		de la Torre <i>et al</i> , 1996
		Brain	15% (3/20)	0% (0/85)	Czygan <i>et al</i> , 1999
MS		CSF	11% (2/19)	0% (0/69)	Deuschle <i>et al</i> , 1998
		PBMC	0% (0/34)	0% (0/40)	Haase <i>et al</i> , 2001
Mental health care workers		PBMC	15% (7/45)	1.4% (1/69)	Chen <i>et al</i> , 1999a
Normal controls		PBMC		5% (8/172)	Kishi <i>et al</i> , 1995a
	Brain		6.7% (2/30)	Haga <i>et al</i> , 1997	

Abbreviations: PBMC, peripheral blood mononuclear cells; CSF, cerebrospinal fluid; CFS, chronic fatigue syndrome; FMS, fibromyalgia syndrome. *Divergence of P-gene nucleotide sequence from common BDV isolates (strain V and He/80).

D2, D3, and D4 antagonist activity, but not through the administration of D2-selective antagonists (e.g., raclopride) (Solbrig *et al*, 1994).

Neurochemical studies further support a lesion in DA transmission consistent with partial DA deafferentation and compensatory metabolic hyperactivity in nigrostriatal and mesolimbic DA systems. Decreases in DA levels exceed those in dihydroxyphenylacetic acid (DOPAC, the major metabolite of DA) levels in high-performance liquid chromatography (HPLC) analysis of tissues from striatum, nucleus accumbens, and olfactory tubercle (Solbrig *et al*, 1994), whereas in prefrontal cortex marked increases are noted in DOPAC (Solbrig *et al*, 1996a). Depletion of tyrosine hydroxylase (TH)-immunoreactive cells in substantia nigra and ventral tegmental area (Solbrig *et al*, 1994) and in striatum (Solbrig *et al*, 2000), and a decrease in TH protein content in striatum but not in substantia nigra pars compacta, are nonetheless accompanied by an increase in TH functional activity (Solbrig *et al*, 2000). Increased gene expression of neurotrophic factors that

tum, nucleus accumbens, and olfactory tubercle (Solbrig *et al*, 1994), whereas in prefrontal cortex marked increases are noted in DOPAC (Solbrig *et al*, 1996a). Depletion of tyrosine hydroxylase (TH)-immunoreactive cells in substantia nigra and ventral tegmental area (Solbrig *et al*, 1994) and in striatum (Solbrig *et al*, 2000), and a decrease in TH protein content in striatum but not in substantia nigra pars compacta, are nonetheless accompanied by an increase in TH functional activity (Solbrig *et al*, 2000). Increased gene expression of neurotrophic factors that

support growth of DA-producing cells *in vitro*, including brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3, NT-4, and ciliary neurotrophic factor (CNTF), may also contribute to the sensitivity to DA agonist action in adult BD (Solbrig *et al*, 2000).

Additional neuromodulator abnormalities are also noted in the adult model. The expression of genes for neuromodulatory substances and their associated synthesizing enzymes, including somatostatin, cholecystokinin, and glutamic acid decarboxylase, is greatly reduced during the acute phase and recovers toward normal in the chronic phase of adult BD (Lipkin *et al*, 1988). The cholinergic system, a major participant in sensorimotor processing, learning, and memory, is similarly affected, with a decrease in choline acetyltransferase-positive fibers as early as day 6 post infection, progressing to nearly complete loss of these fibers in hippocampus and neocortex by day 15 (Gies *et al*, 1998). Preliminary work on dysregulation of 5HT and norepinephrine (NE) systems suggests metabolic hyperactivity of 5HT, with a modest increase in the metabolite 5-hydroxyindoleacetic acid in striatum, and of NE, as evidenced by a small increase in the NE metabolite, 3-methoxy-4-hydroxyphenethyleneglycol, in prefrontal and anterior cingulate cortex regions (Solbrig *et al*, 1995). These changes may reflect compensatory up-regulation or heterotypic sprouting following partial loss of DA afferents to these brain regions. Selective effects of BDV on 5HT and NE pre- or postsynaptic receptors have not yet been investigated. Pharmacologic and neurotransmitter-specific molecular probes have also been used to characterize endogenous opioid systems in the adult rat model. Infected animals respond abnormally to the opiate antagonist, naloxone, with hyperkinesia and seizures, and also demonstrate increases in striatal preproenkephalin mRNA at 14 and 21 days (Fu *et al*, 1993b), and 6 weeks after BDV infection (Solbrig *et al*, 2002). BDV and met-enkephalin immunoreactivity also coincided in a high percentage of cells (Solbrig *et al*, 2002). Induction of the enkephalin system in adult BD may relate to increased levels of phosphorylated cyclic AMP response element binding (phosphoCREB) protein through activation by BDV of the mitogen-activated protein (MAP) kinase pathway, thus stimulating transcription factors that regulate enkephalin expression in striatum (Konradi *et al*, 1993). However, the mechanisms by which these changes in endogenous opioid systems occur are unclear. The marked CNS inflammation in adult-infected rats confounds the role of direct effects of the virus, virus effects on resident cells of the CNS, and cellular immune responses to viral gene products in production of monoamine, cholinergic, and opiate dysfunction in BD. Thus, our efforts have turned towards the neonatal rat model in an effort to identify the functional and structural consequences of BDV in a system that is linked to more direct interactions of the virus with CNS.

The neonatal rat model does not show overt immunopathology; instead, despite high virus load in the brain and lifelong persistence, animals infected within the first 12 h of life develop a mild behavioral syndrome and restricted neuropathology that may provide a more intriguing model for neuropsychiatric disorders. The cerebellar and hippocampal dysgenesis observed in neonatally infected animals is consistent with the more subtle neurodevelopmental abnormalities reported by some investigators in autism (Kemper and Bauman, 1993), schizophrenia (Altshuler *et al*, 1987; Fish *et al*, 1992), and affective disorders (Soares and Mann, 1997). Neonatally infected animals display a wide range of physiologic and neurobehavioral disturbances. They are smaller than uninfected littermates (Bautista *et al*, 1994; Carbone *et al*, 1991b), without demonstrable alteration of glucose, growth hormone, or insulin-like growth factor-1 (Bautista *et al*, 1994) or amount of food ingested (Bautista *et al*, 1995); display an enhanced preference for salt solutions; and exhibit altered circadian rhythms (Bautista *et al*, 1994). Behavioral and cognitive changes in rats infected in the neonatal period include abnormal early locomotor development (Hornig *et al*, 1999), spatial and aversive learning deficits (Dittrich *et al*, 1989; Rubin *et al*, 1999), increased motor activity (Bautista *et al*, 1994; Hornig *et al*, 1999), abnormal anxiety responses (Dittrich *et al*, 1989; Hornig *et al*, 1999; Pletnikov *et al*, 1999a), stereotypic behaviors (Hornig *et al*, 1999), and reduced initiation of and response to nondominance-related play interactions (Pletnikov *et al*, 1999b). Thus, the neuropathologic, physiologic, and neurobehavioral features of BDV infection of neonates indicate that it not only provides a useful model for exploring the mechanisms by which viral and immune factors may damage developing neurocircuitry, but also has significant links to the range of biologic, neurostructural, locomotor, cognitive, and social deficits observed in a wide range of human neuropsychiatric illnesses, including the neurodevelopmental disorder, autism.

CNS dysfunction in neonatally infected animals has been proposed to be linked to direct viral effects on morphogenesis of the hippocampus and cerebellum, two structures in rodents that continue to mature postnatally. Although overall architecture is maintained, granule cells of dentate gyrus (Carbone *et al*, 1991b; Hornig *et al*, 1999; Rubin *et al*, 1999) and Purkinje cells of cerebellum (Eisenman *et al*, 1999; Hornig *et al*, 1999) are lost through apoptosis (Hornig *et al*, 1999). The extent of neuronal loss in dentate gyrus is correlated with the severity of spatial learning and memory deficiencies in neonatally-infected Lewis rats (Rubin *et al*, 1999). Subtle testing of cerebellar function demonstrates deficits in motor coordination and postural stability (Hornig *et al*, 1999; Pletnikov *et al*, 2001), consistent with Purkinje cell losses. Further studies are needed to evaluate the mechanisms by which early postnatal exposure to

BDV induces apoptotic losses and functional damage in cerebellar and limbic circuitry.

Although cellular inflammatory response to BDV following neonatal infection is restricted, a phenomenon ascribed to the immaturity of rat postnatal immune function, a brief surge in mononuclear cell infiltrates occurs (Hornig *et al*, 1999; Sauder and de la Torre, 1999), along with elevations in expression of proinflammatory cytokine (Hornig *et al*, 1999; Sauder and de la Torre, 1999), chemokine (Sauder *et al*, 2000), and chemokine receptor (Rauer *et al*, 2002) transcripts. However, this transient immune response does not colocalize with sites of neuropathologic damage (Weissenböck *et al*, 2000). Neuropathology instead parallels regions and timecourse of microglial proliferation and expression of major histocompatibility complex (MHC) class I and class II, intercellular adhesion molecule (ICAM), CD4 and CD8 molecules (Weissenböck *et al*, 2000). Humoral immune response to BDV in neonatally infected animals is also curtailed, with anti-BDV antibody titers remaining below 1:10 through 133 days post infection (Carbone *et al*, 1991b).

Although reduced levels of neurotrophic factor mRNAs occur in the neonatal model (Hornig *et al*, 1999; Zocher *et al*, 2000), these changes are restricted to hippocampus and are unlikely to account for losses of Purkinje cells in cerebellum. Alternatively, it is conceivable that abnormal regulation of apoptosis, either failure of normal apoptotic sequences to be curtailed with age or excess activation of apoptotic cell programs, may contribute to abnormal CNS architecture in neonatal infections with BDV or other neurotropic viruses. Excitotoxic stimulation, including activation of glutamatergic circuitry, is one factor that might trigger neuronal apoptosis. Complex alterations in mRNAs for apoptosis mediators, including increased levels of mRNAs for Fas (CD95) and interleukin-1 converting enzyme (ICE, caspase-1),

two promoters of apoptosis, and decreased mRNA for bcl-x, a factor that inhibits apoptosis, have been identified in hippocampus, amygdala, prefrontal cortex, nucleus accumbens, and cerebellum, and are consistent with promotion of apoptosis throughout the brains of rats neonatally infected with BDV (Hornig *et al*, 1999).

Effects of BDV infection at the cellular level are only beginning to be unveiled. Inhibition of cell-to-cell spread of BDV by a MAP kinase/extracellular signal-regulated kinase (ERK) kinase (MEK) inhibitor in cell culture (Planz *et al*, 2001) and analyses of neuronal differentiation of PC12 cells (Hans *et al*, 2001) indicate an interaction of BDV with cellular MAP kinase signaling pathways. Infected PC12 cells demonstrate constitutive phosphorylation of MEK, ERK, and the transcriptional activator, Elk-1 (Hans *et al*, 2001), but fail to differentiate with nerve growth factor (NGF) treatment. Inhibition of neurite outgrowth is also reported in other infected cell lines (Kamitani *et al*, 2001), and has been ascribed to interference by P protein with the normal interaction between the neurite outgrowth factor, amphoterin, and its receptor, RAGE (*Receptor for Advanced Glycation End-products*). BDV-infected cells have altered intracellular distribution of amphoterin, with reduced levels of amphoterin, and of RAGE activation at growth cones of extending cells (Kamitani *et al*, 2001).

Summary

BDV continues to be a fertile system for investigators representing a variety of disciplines. What began for many of us as a tantalizing, if simplistic, potential explanation for the pathogenesis of mental illness has instead become a tool for cellular biology, immunology, and developmental neurobiology.

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