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Review

Borna disease virus interference with neuronal plasticity

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Abstract

Viruses able to infect the central nervous system (CNS) are increasingly being recognized as important factors that can cause mental diseases by interfering with neuronal plasticity. The mechanisms whereby such infections disturb brain functions are beginning to emerge. Borna disease virus (BDV), which causes a persistent infection of neurons without direct cytolysis in several mammalian hosts, has recently gained interest as a unique model to study the mechanisms of viral interference with neuronal plasticity. This review will summarize several hypotheses that have been put forward to explain possible levels of BDV interference with brain function.

Keywords: Borna disease virus; Neuronal plasticity; Central nervous system

Contents

1. Introduction

Experimental infection by disease-inducing neurotropic viruses is a powerful tool for investigating basic mechanisms of brain functions and how they can be altered during disease.

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Many possible outcomes to a viral infection in the CNS exist (Ahmed et al., 1996; Oldstone, 1991). In some instances, viruses can persist in the absence of inflammatory infiltration and lysis of virally infected cells, which are the classic hallmarks of virus infection. Such viral infections can remain unnoticed because they are not associated with easily identifiable manifestations of acute infections. Nonetheless, a persistent infection may affect the infected cells by interfering with several cellular functions. Damage associated with viral persistence can sometimes be very specific and target a defined type of neuron, such as herpesvirus persistence in sensory neurons or poliovirus infection of motoneurons (Mims and White, 1984; Storey et al., 2002). Alternatively, the infection can trigger the production of soluble factors, such as cytokines, chemokines or neurotransmitters, which in turn may have neurotoxic effects. Besides genetic and environmental factors, viruses are also suspected to contribute to the etiology of human mental disorders (Lipkin and Hornig, 2004; Yolken and Torrey, 1995). Thus, deciphering the bases of neuronal dysfunction caused by viral persistence using animal models and in vitro systems may provide clues for studying disease pathogenesis of neurobehavioral disorders in humans. The exquisite neurotropism of Borna disease virus (BDV) and the pattern of BDV-associated changes in neuronal physiology and behavior makes it a unique model for this type of investigation.

In this review, we will summarize our current understanding on the interference of Borna disease virus with brain function. We decided to focus in particular on possible interference with neuronal plasticity and remodeling, as well as on the underlying possible molecular mechanisms.

1.1. Borna disease virus

Natural infections with BDV were initially described in horses and sheep, while experimental infections have been established in a wide variety of vertebrates (Dürrwald and Ludwig, 1997; Ludwig et al., 1988; Staeheli et al., 2000). Depending on the age and immune status of the host, BDV infection may present as immune-mediated disease with fatal outcome (Borna disease) or subtle behavioral alterations without overt inflammation (Dürrwald and Ludwig, 1997; Ludwig et al., 1988; Staeheli et al., 2000). Intrigued by the behavioral abnormalities observed in BDV-infected animals such as in rats (Narayan et al., 1983) or in the lower primate *Tupaia glis* or tree shrews (Sprankel et al., 1978), studies initiated in the 1980s tried to clarify whether BDV infection is linked to psychiatric diseases (Amsterdam et al., 1985; Rott et al., 1985). These studies identified BDV-specific antibodies in sera of psychiatric patients with a higher prevalence than in control cohorts, suggesting that human BDV infection may be linked to psychiatric diseases. However, attempts to confirm human BDV infection by non-serological methods, including detection of viral nucleic acid by nested RT-PCR or virus isolation have revealed inconsistent results (Bode and Ludwig, 2003; Carbone, 2001; Ikuta et al., 2002; Schwemmle, 2001) and, therefore, this issue is still controversial. Multicenter studies using standardized detection techniques may clarify this controversy in the future.

BDV is a non-segmented, negative-strand RNA virus (Briese et al., 1992; Cubitt et al., 1994a) that persistently infects the central nervous system (CNS) of a broad range of animals (Gosztonyi and Ludwig, 1995). It is non-cytolytic and replicates almost exclusively in neurons (Fig. 1). However, infection of astrocytes and glial cells also occur at later stages of infection (Carbone et al., 1991; Gosztonyi and Ludwig, 1995). Although BDV is highly neuronotropic, it can be adapted to persistently infect a broad range of non-neuronal cells lines (Ludwig et al., 1988; Staeheli et al., 2000). BDV encodes for at least six proteins: the nucleoprotein (N), the phosphoprotein (P), the protein (X), the matrix protein (M), the glycoprotein (G) and the polymerase (L) (Briese et al., 1995; Kishi et al., 2002; Schneider, 2005). Unlike the replication of other *Mononegavirales*, BDV replication and tran-

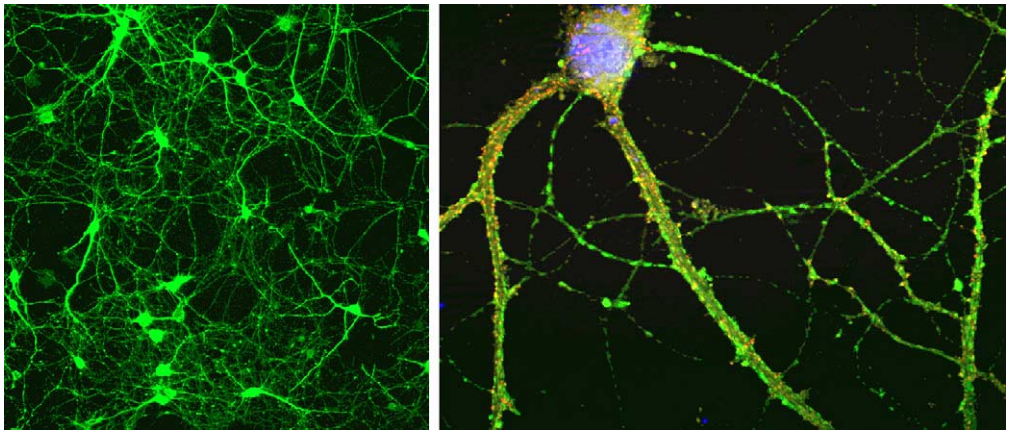

Fig. 1. BDV replicates at high levels in neurons without overt cytopathic effect or impaired cell survival. Representative low and high magnification views (left and right panels, respectively) of primary cultures of rat neurons infected with BDV. Left: immunofluorescence staining for BDV-N, showing that nearly 100% of the neurons in the culture are infected by day 11 post-infection. Right: double immunofluorescence staining for BDV-N (green) and the synaptic marker synapsin 1 (red). Nuclei are stained blue with DAPI. Note that BDV infection does not lead to impaired morphology or survival of the neurons.

scription occurs in the cell nucleus (Briese et al., 1992; Cubitt and de la Torre, 1994), where alternative splicing of viral transcripts regulates the expression levels of M, G and L (Cubitt et al., 1994b; Schneemann et al., 1995; Schneider, 2005). Whereas M and G remain cytoplasmic, P, N, L and X contain nuclear import sequences and are, therefore, targeted to the nucleus, where the polymerase complex is built (Briese et al., 1995; Kishi et al., 2002; Schneider, 2005; Schwemmle et al., 1998). BDV N additionally contains a nuclear export sequence and may, therefore, be involved in the nuclear export of the viral ribonucleoprotein complexes (RNPs) (Kobayashi et al., 2001). Similar to the glycoproteins of other negative-strand RNA viruses, the BDV glycoprotein is post-translationally glycosylated and undergoes cleavage by the cellular protease furin (Gonzalez-Dunia et al., 1997, 1998). The budding process involves the coordinated assembly of the viral RNPs into viral particles by M and the two cleavage products of G (Gonzalez-Dunia et al., 1997, 1998). Despite the pronounced viral transcription and replication activity of this virus, only few infectious particles reside in one cell and almost no free virus is released (Pauli and Ludwig, 1985). Thus, it is assumed that viral dissemination occurs predominantly by cell-to-cell spread, including the infection of neurons by the anterograde and retrograde route (Morales et al., 1988). However, production of viral particles is necessary for viral spread, since the expression and correct processing of BDV G are required for efficient viral dissemination in neurons (Bajramovic et al., 2003).

Until now, detailed studies of BDV at the molecular level were greatly impaired by the lack of a suitable system for manipulating this virus at the genetic level. However, two laboratories have recently established functional polymerase assays based on artificial minigenomes and have confirmed that N, P and L form the active functional polymerase complex (Perez et al., 2003; Schneider et al., 2003). As described elsewhere in this issue, the successful rescue of infectious BDV has also been recently achieved (Schneider, 2005). These new reverse genetic tools will hopefully reveal insights into pathogenesis as well as the molecular biology of BDV.

1.2. Neuronal plasticity

BDV persistence can occur without overt inflammation and yet still cause behavioral abnormalities and neurodevelopmental damage (Pletnikov et al., 2002). This phenomenon has been observed in adolescent or newborn animals (such as in the rat), representing infection at a time when the brain is subjected to extensive tuning and shaping of neuronal connections. Since non-cytolytic replication is a hallmark of BDV, it has been proposed that BDV-linked CNS damage could be caused in part by viral interference with neuronal plasticity (Gonzalez-Dunia et al., 2000) at least in the early phases following BDV infection. The term ‘neuronal plasticity’ refers to the ability of neurons to adapt their functional and morphological characteristics to environmental influences. Learning and neuronal survival and development, therefore, depends on the plasticity of certain neuronal circuits in the CNS. Although it is often related to changes in the efficacy of synaptic transmission, neuronal plasticity is also accompanied by morphological changes, such as the formation of new synapses (synaptogenesis) and an increase of dendritic arborization and postsynaptic spines (Engert and Bonhoeffer, 1999). These morphological changes can be evaluated by changes in the expression profiles of pre- and postsynaptic marker proteins (i.e. synaptophysin, synaptobrevin, PSD-95, etc.) and other neuronal proteins (such as the growth-associated protein GAP-43). As discussed below, some of these markers have demonstrated apparent changes in synaptic density following BDV infection in neonatal rats or in BDV-P transgenic mice (Gonzalez-Dunia et al., 2000; Kamitani et al., 2003).

Most of our current knowledge about neuronal plasticity was inspired by the pioneering work of D. Hebb, who postulated that if two interconnected neurons were adequately stimulated, the synapses between them would be strengthened (Hebb, 1949). Later, the discovery of long-term potentiation (LTP) provided the first mechanism supporting Hebb’s hypothesis, by showing that specific patterns of neuronal stimulation would give rise to long-lasting increase in the efficacy of neuronal transmission (Bliss and Lomo, 1973; Lomo and Bliss, 2003). Alternative patterns of stimulation can also result in a decrease in the efficacy of transmission, a phenomenon designated as long-term depression (LTD). Both LTP and LTD are believed to play essential roles in learning and on the storage of new information. Although neuronal plasticity occurs in several areas of the CNS, the most studied system is the hippocampus. The hippocampus plays an important role in the establishment of memory (in particular in acquiring orientation in a new environment, also called spatial learning). Some neuronal connections in the hippocampus have been used as the main anatomical substrate for the demonstration of LTP (Rosenzweig and Barnes, 2003). The “trisynaptic loop” of the hippocampus connects dentate granule cells (which receive a major input from the entorhinal cortex) to the pyramidal neurons of the CA3 region of the hippocampus proper, which are in turn connected to neurons of the CA1 region. Interestingly, BDV has a predominant tropism for neurons of the hippocampus and limbic cortex (Gosztonyi et al., 1993; Gosztonyi and Ludwig, 1984). In addition, neonatal infection of rats leads to selective loss of dentate granule cells, thus disrupting the above-mentioned loop. Viral persistence, therefore, likely interferes with neuronal plasticity processes in the hippocampus.

The molecular and cellular mechanisms underlying neuronal plasticity are the subject of intense investigations. Molecules such as calcium, neurotransmitters (in particular glutamate and serotonin, or 5-HT), neurotrophic growth factors (or neurotrophins) and nitric oxide are some of the signals that mediate neuronal plasticity (Mattson et al., 2004). They activate many intracellular signaling pathways (reviewed in detail by Malenka and Bear, 2004; Thomas and Huganir, 2004), including protein kinase A (PKA), PKC, CaM kinase

II, MAP kinases and tyrosine kinase SRC, which will then lead to the phosphorylation of molecules that are involved in synaptic transmission. Here, we will specifically address the role of neurotrophins (McAllister et al., 1999) because BDV is putatively linked to neurotrophin system dysregulation. Neurotrophins (as well as their specific receptors) are expressed at high levels in areas of the brain subjected to intense plasticity and several neurotrophins are secreted in an activity-dependent manner.

The neurotrophins comprise a family of at least four structurally related proteins: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin-4/5 (NT-4/5). Their corresponding receptors are tyrosine kinase receptors (Trk receptors) and p75 (McAllister et al., 1999). Binding of the neurotrophins to their cognate Trk receptor initiates signaling cascades (see Fig. 2, left panel) by phosphorylation of tyrosine residues on the cytoplasmic domains of the receptors. This phosphorylation induces docking of adapter proteins to phosphotyrosine-binding or src-homology-2 motifs. These adapter proteins couple the receptors to intracellular signaling cascades, which include the phosphatidylinositol-3-kinase/Akt kinase pathway, phospholipase Cγ and the Ras/MEK/ERK kinase pathway that ultimately leads to gene expression, neuronal survival and neurite outgrowth.

In summary, neuronal plasticity is a key process involved in learning, memory and neuronal survival. Any interference with molecular pathways involved in the regulation of neuronal plasticity (such as the synthesis of or the response to neurotrophic factors) will likely have important consequences on brain development and function.

2. Current models used to study BDV-induced behavioral changes

2.1. Infection of tree shrews

BDV infection in tree shrews (*Tupaia glis*) is a unique example of BDV-induced behavioral abnormalities in a species

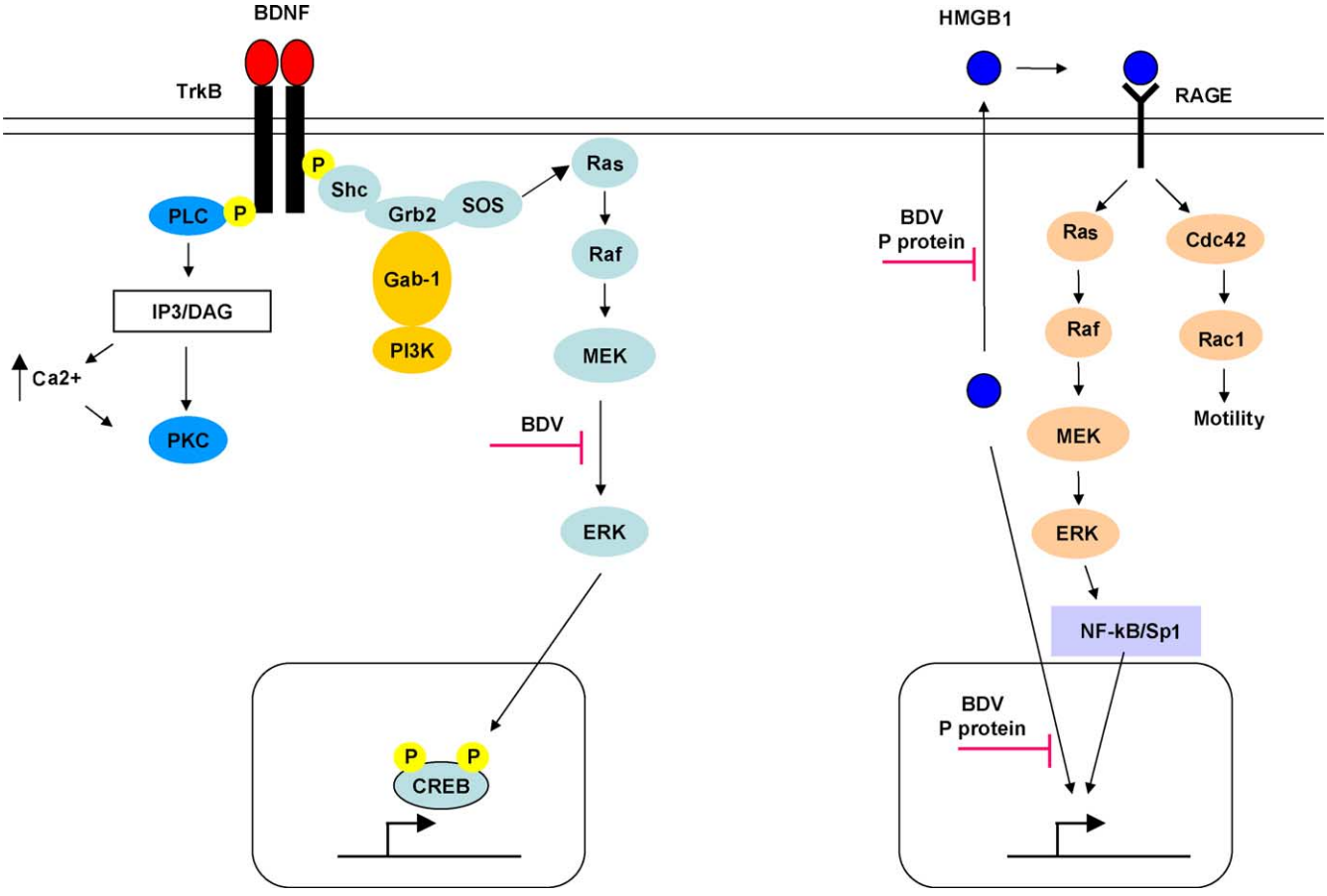

Fig. 2. Overview of signaling pathways induced by neurotrophins (with the example of BDNF binding to its TrkB receptor, left panel) and by amphoterin (HMGB1) binding to RAGE (right panel). The possible levels of interference mediated by BDV in these signaling pathways are indicated (see text for details). Abbreviations used in the figure: BDNF, brain-derived neurotrophic factor; TrkB, neurotrophin receptor B; PLC, phospholipase C; IP3, inositol 1,4,5 trisphosphate; DAG, diacylglycerol; PKC, protein kinase C; PI3K, phosphoinositide 3-kinase; Grb2, growth factor receptor-bound protein 2; Gab1, Grb2-associated binder-1; SOS, son of sevenless; MEK, MAP kinase kinase; ERK, extracellular signal-regulated protein kinase; CREB, cyclic AMP response element-binding protein; HMGB1, high mobility group B1 protein; RAGE, receptor for advanced glycation endproducts; Cdc42, cell division cycle 42; Rac1, ras-related C3 botulinum toxin substrate 1 and NF-κB, nuclear factor kappa B.

that exhibits complex social organization and behavioral repertoire (Sprankel et al., 1978). BDV infection of tree shrews leads to an inflammatory reaction in the CNS with no extensive neuronal damage. The clinical manifestations of the behavioral disease in these animals were largely shown to be dependent on the housing conditions; different disease outcomes were observed between socially isolated and group-housed animals (Sprankel et al., 1978). Socially isolated BDV-infected females exhibited a phase of exaggerated spontaneous locomotor activity, followed by a phase of clinical neurological symptoms characterized by spatial and temporal disorientation, and alterations in behavior. In contrast, BDV-infected tree shrews kept in pairs exhibited a significant increase in all components of social behavior and there was a reversal of social roles in the initiation of sexual interaction. While the pathogenetic mechanisms of abnormal social activities remains obscure, it has been suggested that the disinhibition towards the environmental stimuli observed in infected animals could be due to BDV-induced damage to the limbic system, which has been implicated in the regulation of social interaction (Sprankel et al., 1978). It is unclear whether this damage results from an inflammatory reaction or directly from BDV interference with neuronal plasticity.

2.2. Infection of gerbils

In 1999, the group of K. Ikuta in Japan reported that the Mongolian gerbil (*Meriones unguiculatus*) was found to be extremely susceptible to BDV infection (Nakamura et al., 1999). This group has recently established that gerbils exhibit a prominent neurological disease upon BDV infection associated with high mortality (Watanabe et al., 2001, 2003). Specifically, neonatally infected gerbils develop a fatal neurological disease without neuronal destruction. Remarkably, infection develops without signs of inflammation or activation of resident CNS cells. In particular, there is no activation of astrocytes (astrocytosis) associated with high replication of BDV in the brain. Intriguingly, elevated levels of cytokines, in particular of IL1β, have been observed in the brains of BDV-infected gerbils (Watanabe et al., 2003). Since IL1β has considerable effects when expressed in the CNS (Neveu and Liege, 2000), elevated levels of this cytokine may contribute to the neuronal pathology observed in BDV-infected gerbils. In conclusion, the gerbil model may offer an alternative system for examining the mechanisms underlying BDV interference with neuronal function, although no impairment in neuronal plasticity has yet been documented in this model.

2.3. Infection of mice

Despite pronounced virus replication in the brain, it was originally thought that the mouse was resistant to BDV-induced disease (Kao et al., 1984; Rubin et al., 1993). However, subsequent investigations demonstrated that certain mouse strains, such as MRL mice, become severely diseased upon BDV infection (Hallensleben et al., 1998). The neurological symptoms and behavioral abnormalities result mainly from immunopathological processes mediated by MHC class I-restricted cytotoxic CD8 T cells, which require help from CD4 T cells (Hausmann et al., 1999). However, BDV-infected mice that lack functional $CD8^+$ T cells and, thus do not develop an immunopathology, exhibited defects in their spatial learning abilities, these mice presented slightly impaired escape performance, while their exploratory behavior in an open field test was indistinguishable from uninfected control mice (Sauder et al., 2001). Intriguingly, the learning deficits correlated with elevated levels of expression of the chemokine IP-10.

2.4. Studies in transgenic models

In 2003, Kamitani and colleagues generated transgenic mice expressing BDV P in the CNS, specifically in astrocytes using the GFAP promoter (Kamitani et al., 2003). This selective glial expression of P in mice led to behavioral and neurological abnormalities, such as enhanced inter-male aggressiveness, hyperactivity and spatial reference memory deficits. Analysis by immunocytochemistry revealed a marked decrease in synaptic density, assessed by staining for synaptophysin, without reactive astrocytosis. In addition, brains of transgenic mice displayed significant reductions in brain-derived neurotrophic factor and serotonin receptor expression. This study raised the intriguing possibility that selective glial dysfunction induced by the P protein of BDV may, in turn, be responsible for neuronal deficits seen in transgenic animals. Although BDV-P transgenic mice may provide a new animal model for studying behavioral abnormalities, the significance for the physiopathology of BDV infection is unclear, since neurons and not astrocytes are the primary site of BDV replication. Recently, another group has generated mice transgenic for BDV N, expressed in either neurons or astrocytes. However, no behavioral abnormalities were reported in this case (Rauer et al., 2004).

2.5. Infection of rats

The model of rat infection with BDV has been the most widely used for behavioral studies (Hornig et al., 2003; Pletnikov et al., 2002, 2003). The spectrum of BDV-caused diseases in rats ranges from progressive, immune-mediated meningoencephalitis to subtle behavioral abnormalities, depending on several factors, in particular on the age of the rat at infection (Bautista et al., 1994; Dittrich et al., 1989; Hornig et al., 2003; Pletnikov et al., 2002, 2003).

2.5.1. Infection of adult rats

In adult immunocompetent rats, BDV causes a biphasic disease first characterized by a classical immune-mediated CNS disorder, associated with massive neuronal destruction and behavioral disturbances. The near-resolution of inflammatory infiltrates, viral persistence and signs of chronic neurological disease follows this first phase. The massive

neuronal destruction caused by the immune reaction readily explains the chronic nature of the neurological disease (Schwemmle et al., 1999). This model of virus-induced inflammation in the brain has spawned numerous studies, which have addressed the immune effectors implicated in the pathology of CNS disease and highlighted the interest in this experimental model for studying the immunopathological role of T cells in such diseases (Bilzer and Stitz, 1994; Planz et al., 1993; Stitz et al., 2002).

Most of the behavioral disturbances observed following infection of adult rats with BDV have been associated with the prominent inflammatory reaction that takes place in the CNS. The hyperactive-aggressive early phase after BDV infection correlates well with the peak of inflammation in the brain parenchyma and is rather common in encephalitic reactions to viral infections, such as rabies or picornavirus infections (Johnson, 1998). The tropism of BDV for biogenic amine and limbic systems means these brain regions are primary targets for virus-induced specific immune responses, which may explain the hyperactivity and frenzied behavior observed in infected rats (Solbrig and Koob, 2003; Solbrig et al., 1994).

The immune-mediated destruction of the brain parenchyma of the extrapyramidal motor and limbic systems gives rise to a multitransmitter CNS disease that can be revealed with several pharmacological probes and offers an attractive model for investigating the impact of infection on several neuromediators. The pharmacological disturbances are dominated by alterations in the dopamine system, which present with enhanced susceptibility to dopamine agonists such as D-amphetamine and cocaine (Solbrig and Koob (2003)). These disturbances are linked to changes in the expression pattern of dopamine receptors, together with increased tyrosine hydroxylase activity (the rate-limiting enzyme in dopamine synthesis). In addition to the dopaminergic system, alterations in serotonin and norepinephrine circuits were also reported. Furthermore, striatal lesions (likely a consequence of the destruction of brain cells by the anti-BDV immune response) were accompanied by a reactive enhanced expression of neurotrophic factors (Solbrig and Koob, 2003; Solbrig et al., 2000). While the devastating effect of the antiviral immune response in these animals makes it difficult to assess possible direct effects of BDV on neuronal plasticity, compensatory changes at the neural systems level are still revealed by this model.

2.5.2. *Infection of newborn rats*

In contrast to the model described above, neonatal infection of Lewis rats with BDV proceeds to lifelong behavioral abnormalities without overt inflammation (Pletnikov et al., 2002). Infection of neonatal rats, thus offers a unique model for studying BDV-induced structural and functional CNS alterations. Although these animals appear normal to the casual observer, they do display behavioral abnormalities (Bautista et al., 1994; Dittrich et al., 1989; Pletnikov et al., 1999a,b). In particular, they exhibit hyperactivity, cognitive defects, social behavior (play) abnormalities and chronic anxiety (Hornig et al., 1999; Pletnikov et al., 2002). Following neonatal infection, BDV will preferentially damage CNS areas that experience an extensive postnatal differentiation (Bautista et al., 1995; Eisenman et al., 1999; Pletnikov et al., 2003). One such area is the dentate gyrus of the hippocampal formation, where granule cells progressively degenerate following BDV infection (Fig. 3). These cells are the principle neurons of the dentate gyrus; at birth, only about 15% of them have been generated (Bayer, 1980a), with the majority of the cell population being generated during the first 2 weeks postnatally (Bayer, 1980a,b). Recent observations have provided evidence for neurogenesis of granule cell throughout life (Kempermann et al., 1997; Song et al., 2002), suggesting that

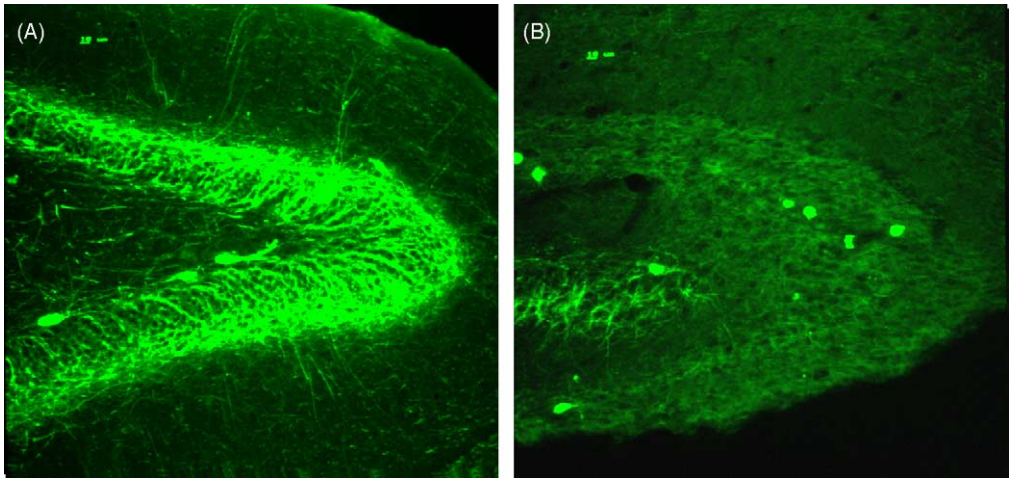

Fig. 3. BDV infection of the newborn rat causes a reduction in axonal arborization of parvalbumin-positive cells in the dentate gyrus. Brain sections from control (panel A) and newborn-infected rat (panel B) were prepared and immunolabelled at postnatal day 35 with an antibody specific for parvalbumin, a calcium-binding protein that is highly expressed in a specific subset of neurons of the dentate gyrus. At this time point, BDV-infected dentate granule cells are already damaged. As a possible consequence, parvalbumin-positive cells fail to innervate granule cells, resulting in axonal retraction. Note the almost normal somatic staining in panel A, in contrast to the disappearance of the axonal immunoreactivity in panel B.

the dentate gyrus is an area designated for neuronal plasticity. In other brain areas, a specific dropout of neurons has been reported, in particular a loss of foliation and death of Purkinje cells in the cerebellum (Bautista et al., 1995; Eisenman et al., 1999). Late in infection, cortical shrinkage has been demonstrated, accompanied with reduced levels of synaptophysin and GAP-43 (Gonzalez-Dunia et al., 2000; Pletnikov et al., 2002). As a result of the BDV-induced neurodevelopmental damage, a prominent activation of glial cells (astrocytes and microglia) occurs, together with increased levels of proinflammatory cytokines and chemokines in the CNS of these animals (Hornig et al., 1999; Plata-Salaman et al., 1999; Sauder and de la Torre, 1999; Weissenbock et al., 2000; Zocher et al., 2000). This prominent activation of soluble factors is likely to contribute to neuronal defects observed in this model in the later stages of infection. Neonatal infection also leads to monoaminergic dysfunction, revealed by changes in the levels of tissue serotonin and norepinephrin, in particular a strong increase in serotonin in the limbic system of BDV-infected rats (Dietz et al., 2004; Pletnikov et al., 2000).

3. Molecular mechanisms that might lead to disturbances in neuronal plasticity by BDV

Behavioral abnormalities have been demonstrated in all animal models of BDV infection. Resulting from the strong tropism of BDV for neurons, these abnormalities are linked in many cases to the damage caused by the prominent antiviral immune response in the CNS. However, models of infection of newborn rats and of transgenic animals expressing BDV proteins in the CNS, strongly suggest that BDV per se also has a direct impact on brain performance. It is sometimes difficult to isolate the contribution of the virus itself to the pathogenesis of BDV infection in the available animal models, owing to its interdependence with the immune response. Nonetheless, infection of the newborn rat has helped to gain insight into the possible direct effects of the virus on neuronal physiology. Studies of the early phases of newborn rat infection has led to the hypothesis that BDV interferes with neuronal communication and plasticity processes, which play essential roles in postnatal brain development. This interference may lead to the degeneration of the dentate gyrus and cerebellar dysgenesis which are observed in this model. Interestingly, BDV-associated cerebellar neurodevelopmental damage is not observed in rats infected after postnatal day 14, suggesting that possible BDV interference with neuronal plasticity has different consequences depending on the CNS maturation stage at the time of infection (Rubin et al., 1999). In the late stages of BDV infection of newborn rats, it again becomes difficult to dissociate the direct effects of BDV on brain cells, since neurodevelopmental damage will trigger the activation of resident glial cells, which in turn produce soluble factors (proinflammatory cytokines, chemokines, etc.) with demonstrated neurotoxic properties (Hornig et al., 1999; Plata-Salaman et al., 1999; Sauder and de la Torre, 1999; Weissenbock et al., 2000; Zocher et al., 2000). Below, we discuss possible mechanisms of BDV direct interference with neuronal function.

3.1. Interference with trophic support from astrocytes to neurons

Results from in vivo studies and cultured glial cells have revealed that infection with BDV impairs astrocytic function. Astrocytes are supporting cells in the CNS and play essential roles in maintaining brain homeostasis. Recent data suggest that they are also important regulators of neuronal activity and synapse stabilization (Newman, 2003; Slezak and Pfrieger, 2003). Thus, it is plausible that the disruption of their normal activities by BDV infection could contribute to impaired brain function. For example, it has been shown that BDV infection of the astrocyte-derived cell line C6 leads to an upregulation of the molecule tissue factor (TF), which is also seen in astrocytes of rats infected with BDV as neonates (Gonzalez-Dunia et al., 1996). This upregulation is due to increased transcriptional activity of the TF promoter together with a stabilization of TF mRNA. This finding may be important, given the possible role of molecules of the TF family in the regulation of brain function. In particular, activation of the coagulation protease cascades by TF results in the generation of the protease thrombin, which plays a role in neural development and plasticity as well as in the regulation of neurite outgrowth and astrocyte morphology (Cunningham, 1992). In another series of experiments, BDV infection induced an inhibition of glutamate uptake in primary cultures of feline astrocytes, suggesting that BDV could affect an astrocyte function that is required to prevent neuronal excitotoxicity (Billaud et al., 2000). In addition, specific expression of BDV P protein in astrocytes led to behavioral abnormalities and impaired neuronal plasticity, further supporting the hypothesis that impaired trophic support of astrocytes to neurons may underlie the neuronal dysfunction associated with BDV persistence (Kamitani et al., 2003). Finally, the activation of CNS glial cells (astrocytes and microglia), a phenomenon observed in the late stages of newborn rat infection with BDV, triggers the production of proinflammatory cytokines, thus further enhancing brain insult (Hornig et al., 1999; Plata-Salaman et al., 1999; Sauder and de la Torre, 1999; Weissenbock et al., 2000; Zocher et al., 2000). However, it should be repeated that BDV has a predominant and early tropism for neurons and that few to no astrocytes contain BDV markers in the first 2 weeks following infection (Bautista et al., 1994; Gosztonyi et al., 1993; Gosztonyi and Ludwig, 1984, 1995). Therefore, the link between impaired astrocytic function and BDV impact on neuronal plasticity awaits confirmation from further studies.

3.2. Interference with amphoterin signaling

Amphoterin, or high mobility group B1 (HMGB1) protein, was recently identified as a protein which interacts with

BDV P (Kamitani et al., 2001). To date, it remains one of the few cellular proteins which have been formally shown to interact with BDV components, along with the demonstration of the interaction between BDV N and the Cdc2–cyclin B1 complex (Planz et al., 2003). HMGB1 belongs to a family of non-histone proteins that are highly abundant in the nucleus (Bustin, 2002; Degryse and de Virgilio, 2003). HMGB proteins contain two homologous DNA-binding domains and an acidic C-terminal domain and are highly conserved in all mammals. Due to their DNA-binding properties, HMGB proteins have been implicated in the regulation of transcription and in DNA repair and recombination, through the interaction of HMGB with nuclear proteins like RAG1, p53 and Hox, which will increase the capacity of the latter proteins to interact with DNA. HMGB proteins are also involved in differentiation processes and in extracellular signaling, which is in part achieved by secretion of HMGB proteins into the extracellular space. Studies with HMGB1 have revealed a key role in neurite outgrowth and cell migration (Degryse and de Virgilio, 2003; Fages et al., 2000; Taguchi et al., 2000) due to its activation of the extracellular receptor, receptor of advanced glycation end products (RAGE). The activation of RAGE leads to the induction of various signaling pathways, resulting in re-organization of the actin cytoskeleton (Rauvala et al., 2000).

The impact of the interaction between BDV P and amphoterin on the pathogenesis of BDV is still unclear. It has been shown that the interaction of BDV-P with HMGB1 impairs outgrowth of cell processes of BDV-infected oligodendrocytes and C6 cells and that BDV-infected cells show impaired migration (see Fig. 2, right panel) (Kamitani et al., 2001). This suggests that neuronal outgrowth and neuronal migration, two important prerequisites for connecting neuronal networks in the developing brain, might be affected by BDV infection. However, BDV infection of primary cultures of neurons proceeds without significant morphological damage to neuronal arborization or neurite density (Hans et al., 2004). Given that HMGB1 has been shown to signal to multiple cellular targets and affect several biological pathways (Bustin, 2002), viral interference with HMGB1 function is likely to have consequences on neuronal function. Using the newly established technique of generating BDV entirely from cDNA (Schneider, 2005), it may be possible in the future to test the role of BDV interference with amphoterin by generating BDV mutant viruses that fail to interact with HMGB1, especially since the domain of P responsible for HMGB1 interaction has already been mapped (Kamitani et al., 2001).

3.3. Interference with neurotrophin signaling

The possible interaction between BDV and neurotrophins was first suggested by the observations that neurotrophic factors, such as NGF, could enhance BDV replication in neuronal and glial cell lines (Carbone et al., 1993; Ibrahim et al., 2002). As stated earlier, neurotrophins play key roles in regulating neuronal plasticity and modulating the efficacy of synaptic transmission. Therefore, any interference with the normal response of BDV-infected neurons to neurotrophin stimulation may either affect neuronal morphology during CNS development or the efficacy of synaptic transmission. Thus, the effects of nerve growth factor, the prototypic member of the neurotrophin family, were analyzed on PC12 cells, persistently infected with BDV. The PC12 cell line, a classical model in neurobiology, is a neural crest-derived cell line that exhibits features of neuronal differentiation in response to NGF (Hans et al., 2001). It was shown that persistence of BDV in PC12 cells leads to dramatic changes in cell morphology and impaired expression of the neuroplasticity-related genes GAP-43 and synaptophysin. Moreover, infection with BDV caused a complete block in NGF-induced neurite outgrowth. This block was due in part to the down-regulation of NGF receptors, coupled with changes in the NGF signal transduction cascade, including inhibition of translocation of activated ERK kinases to the nucleus. More recently, it was shown that primary rat hippocampal neurons infected with BDV are also unresponsive to treatment with neurotrophins BDNF and NT-3, not only in terms of ERK phosphorylation but also of the synaptic remodeling which accompanies long-term exposure to neurotrophins (see Fig. 2, left panel) (Hans et al., 2004). In particular, hippocampal neurons infected with BDV displayed defects in the expression of synaptic vesicle proteins and synaptic architecture. As a consequence, synaptogenesis induced by long-term treatment with BDNF was abrogated in BDV-infected hippocampal neurons. These data suggest that the effects of BDV on neurons could be due to viral interference with neurotrophin systems, in particular with neurotrophin-regulated neuronal plasticity (Hans et al., 2004). These studies also revealed that BDV might interfere with signal transduction pathways, specifically the Ras/MEK/ERK cascade, by as yet undefined mechanisms. It was shown that chronic exposure of infected neurons to neurotrophins resulted in increased viral production and, conversely, that inhibitors of the Ras/MEK/ERK pathway (such as the MEK-specific inhibitor U0126) blocked viral spread (Carbone et al., 1993; Hans et al., 2001, 2004; Planz et al., 2001). These findings raised the hypothesis that BDV may divert neurotrophin signaling to enhance viral production. The viral determinants responsible for the interference with the neurotrophin-triggered signaling cascade have yet to be identified. One hypothesis is interference with the phosphorylation of cellular targets by BDV proteins, in particular by the BDV phosphoprotein. Similar to the phosphoproteins, other non-segmented RNA viruses, The P protein of BDV is phosphorylated at several sites by cellular kinases, including by PKCε and CKII (Schwemmle et al., 1997), providing no immediate link with the above-mentioned signaling cascade. Further studies are needed to define better the level of interaction of BDV components with neurotrophin-induced signaling events and to examine the consequences of this interaction on neuronal function. Since neurotrophins and G protein-coupled receptor neurotransmitter signals converge on the MAPK/MEK/ERK pathway, elu-

cidation of viral–neurotrophin interactions will enhance our understanding of behavioral phenotype associated with BDV persistence in the CNS.

4. Conclusion

Studies on animal models of viral infection are instrumental for a better understanding of the biological mechanisms involved in the pathogenesis of many human diseases. They also provide valuable insights into the basic mechanisms of cellular function and factors involved in host defense against pathogens. Some relevant examples are infections with Theiler's virus, which is used as a mouse model for multiple sclerosis, or with LCMV, which has helped to understand the basis of MHC restriction of immune responses (Brahic, 2002; Zinkernagel et al., 1985). In this respect, BDV offers a new and intriguing model because of its unique features, namely its specific neurotropism for neurons of the limbic system (involved in memory and behavior) and its non-cytolytic replication strategy. Studies of BDV biology cover the fields of viral pathogenesis, immunology and neurobiology. Recent advances in the ability to manipulate the BDV genome and the development of novel study systems, such as transgenic mice or the use of ex vivo slice culture systems, open new perspectives for studying the molecular basis of interference with neuronal physiology caused by this persistent virus and may help uncover unrecognized aspects of the basic mechanisms operating in the regulation of neuronal plasticity.

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