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-

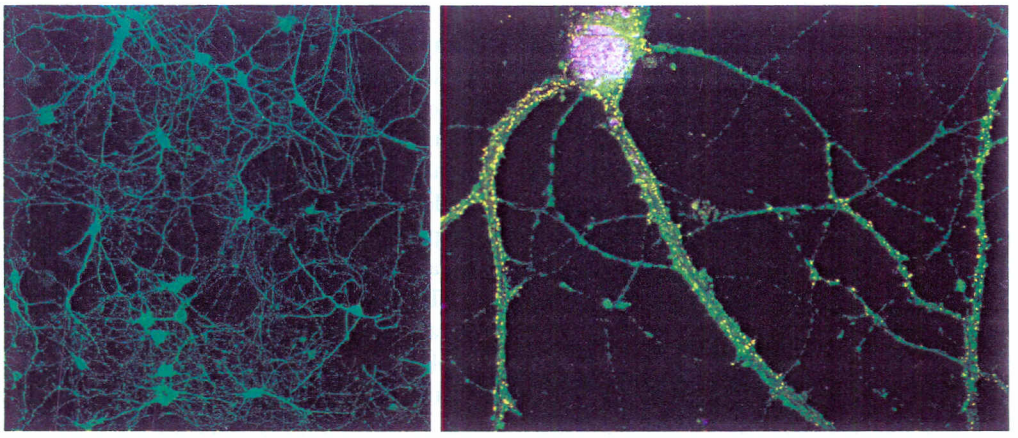

Fig. 1. BDV replicates at high levels in neurons without overt cytopathic effect or impaired cell survival. Representative low and high magnification views (left and right panels, respectively) of primary cultures of rat neurons infected with BDV. Left: immunofluorescence staining for BDV-N, showing 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.