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

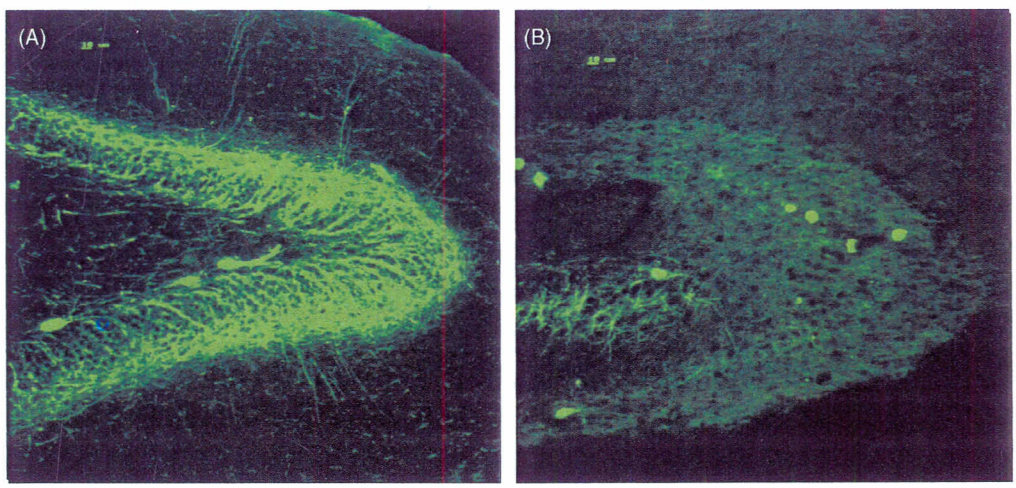

Fig. 3. BDV infection of the newborn rat causes a reduction in axonal arborization of parvalbumin-positive cells in the dentate gyrus. Brain sections from control (panel A) and newborn-infected rat (panel B) were prepared and immunolabelled at postnatal day 35 with an antibody specific for parvalbumin, 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.