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

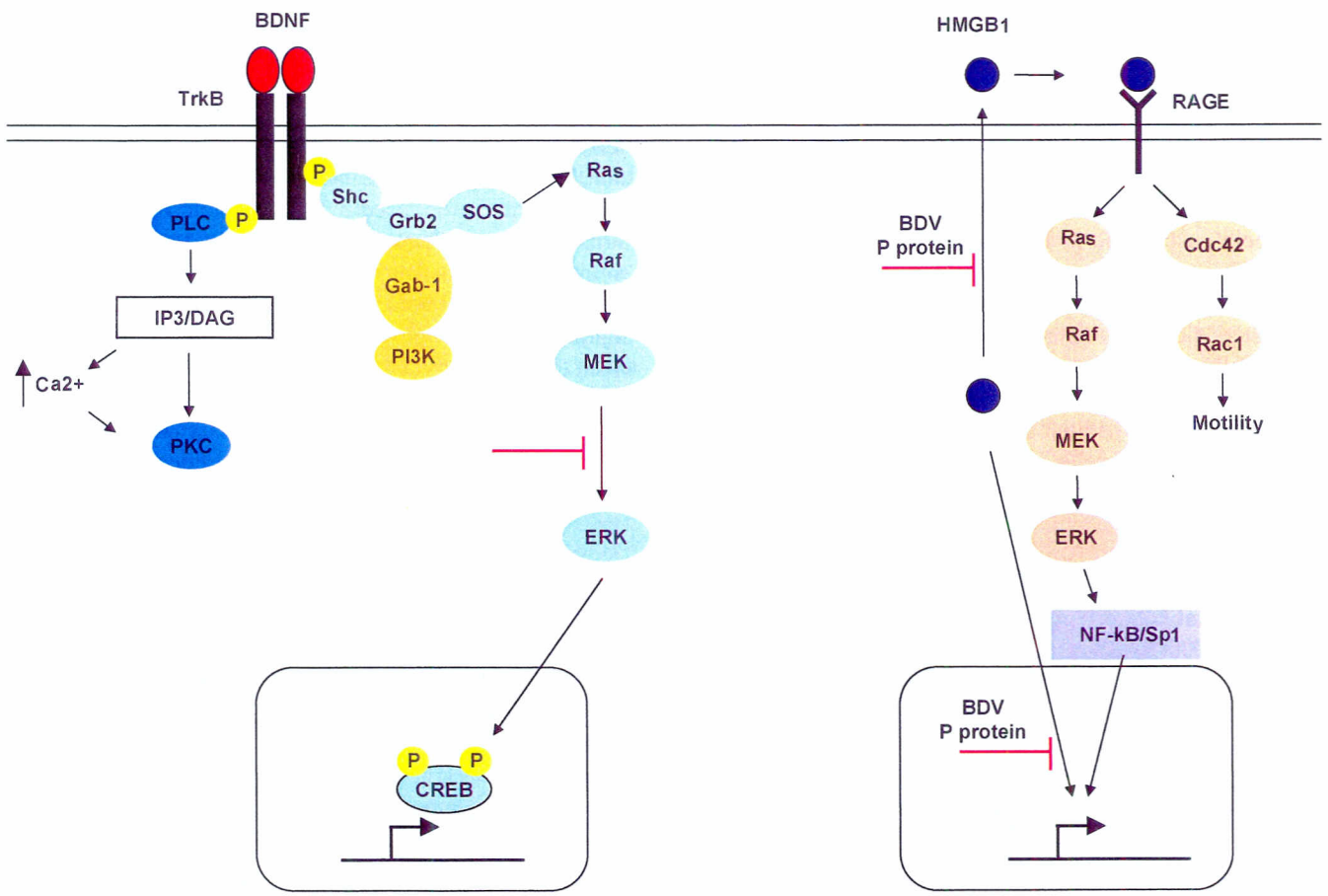

Fig. 2. Overview of signaling pathways induced by neurotrophins (with the example of BDNF binding to its TrkB receptor, left panel) and by amphoterin (HMGB1) binding to RAGE (right panel). The possible levels of interference mediated by BDV in these signaling pathways are indicated (see text for details). 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.