Available online at www.sciencedirect.com
SCIENCE DIRECT®
Pharmacology, Biochemistry and Behavior 74 (2003) 777–787
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Review article

Neuropharmacological sequelae of persistent CNS viral infections: lessons from Borna Disease Virus

Marylou V. Solbrig[a,*], George F. Koob[b]

[a]Department of Neurology and Pharmacology, University of California at Irvine, 3107 Gillespie Neuroscience Research Building, Irvine, CA 92697-4292, USA
[b]Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA, USA

Received 20 September 2002; received in revised form 8 January 2003; accepted 13 January 2003

Abstract

Borna Disease Virus (BDV) is a neurotropic RNA virus that is worldwide in distribution, causing movement and behavior disorders in a wide range of animal species. BDV has also been reported to be associated with neuropsychiatric diseases of humans by serologic study and by recovery of nucleic acid or virus from blood or brain. Natural infections of horses and sheep produce encephalitis with erratic excited behaviors, hyperkinetic movement or gait abnormalities; naturally infected cats have ataxic "staggering disease." Experimentally infected primates develop hyperactivity, aggression, disinhibition, then apathy; prosimians (lower primates) have hyperactivity, circadian disruption, abnormal social and dominance behaviors, and postural disorders. However, the neuropharmacological determinants of BD phenotypes in laboratory and natural hosts are incompletely understood. Here we review how experimentally infected rodents have provided models for examining behavioral, pharmacologic, and biochemical responses to viral challenge, and how rodents experimentally infected as neonates or as adolescents are providing models for examining age-specific neuropharmacological adaptations to viral injury.

Keywords: Borna Disease; Virus; Encephalitis; Dopamine; Serotonin; Rat; Mouse

1. Introduction

In these days of increasing pressure to understand transmissible agents, renewed recognition of infectious causation of both acute and chronic diseases is occuring. Viruses are causes or cofactors in degenerative, inflammatory, and malignant diseases of the nervous system by virtue of their existence as parasites, antigens, or genetic elements. However, viruses also can mimic the effects of drugs, with postlesion compensatory changes in surviving structures, or direct effects on cell signaling and metabolism.

Borna Disease (BD) was a sporadic, epidemic encephalitis of horses and sheep in 18th and 19th century Central Europe (Zwick, 1939). In 1985, Borna Disease Virus (BDV) was proposed as an etiologic agent of bipolar affective disorder, based on finding BDV antibodies by indirect immunofluorescence assay in 1.6% (16/979) of psychiatric patients tested (Rott et al., 1985). Because BDV was associated with psychiatric diseases of man, diseases with no underlying histopathology (by the standard techniques of the 1980s), inquiries into whether viral infection itself could cause central nervous system (CNS) pharmacological and neurochemical changes began. The recognition that experimental infection of rodents (Hirano et al., 1983; Narayan et al., 1983a; Dittrich et al., 1989; Solbrig et al., 1994; Gosztonyi and Ludwig, 1995) and primate species (Sprankel et al., 1978; Stitz et al., 1981) caused robust movement, behavior, or cognitive disorders led to the study of these syndromes in the context of neurotransmitter-specific behavioral paradigms. The widening knowledge of the anatomy and neuropharmacology of motor, reward, prefrontal, limbic, and memory circuits during the 1980s and 1990s supported this line of investigation. The result has been the establishment of a pharmacology of persistent viral infection, generalizable beyond the Borna system, and applicable to understanding the mechanisms of neural injury and adaptation.

* Corresponding author. Tel.: +1-949-824-6270; fax: +1-949-824-6305.
E-mail address: msolbrig@uci.edu (M.V. Solbrig).

0091-3057/03/$ – see front matter © 2003 Elsevier Science Inc. All rights reserved.
doi:10.1016/S0091-3057(03)00019-4

2. The agent

BDV, the prototype of the family Bornaviridae and genus *Bornavirus* within the nonsegmented negative-strand RNA viruses, infects the CNS of warm-blooded animals (birds and mammals), causing acute, subacute, or chronic persistent infections (Ludwig and Bode, 2000; Ludwig et al., 1988; Gosztonyi and Ludwig, 1995; Stitz et al., 1995; Solbrig et al., 1995; De la Torre, 2001; Ikuta et al., 2002). Disease expression depends on host species, strain, age, and immune status. Natural infection has been confirmed worldwide in horses, sheep, cattle, cats, dogs, and birds (Ludwig and Thein, 1977; Ludwig et al., 1988; Waelchli et al., 1985; Lundgren et al., 1993; Malkinson et al., 1993; Bode et al., 1994; Caplazi et al., 1994; Hagiwara et al., 1996; Weissenbock et al., 1998). An olfactory route of transmission has been proposed because Bornaviruses are neurotropic, intranasal infection is effective in experimental animals, and the olfactory bulbs of naturally infected horses show inflammation and edema early in disease. Reports of BDV nucleic acid and proteins in the peripheral blood of horses (Bode et al., 2001) are consistent with the possibility of a hematogenous spread as well. Estimates of worldwide veterinary disease burden have been difficult for lack of universally applied detection reagents or methods, low index of suspicion in mild cases, and limited herd surveillance to evaluate the extent of subclinical carrier states (Ludwig and Bode, 2000).

3. BDV and human disease

The probability and extent to which BDV has entered human populations has been addressed in case reports and case–control studies. BDV has been reported to be associated with schizophrenia, affective disorders, intravenous drug abuse, neuropsychiatric disorders with dopamine or monoamine substrates by serologic tests, by detection of BD sequences in peripheral blood mononuclear cells (PBMCs), granulocytes, and brain, or by recovery of virus from PBMCs, peripheral granulocytes, and brain (Rott et al., 1985; Bode et al., 1988, reviewed by Bode, 1995; Bode and Ludwig, 2001; Planz et al., 1999; Lipkin et al., 2001). Published estimates of BDV seroprevalence by immunofluorescence, Western blot, immunoprecipitation, or ELISA technique range from 1.6% (16/979) (Rott et al., 1985) to 38% (53/138) (Fu et al., 1993a) of psychiatric patients, from 0% to 20% (Waltrip et al., 1995) of disease-free subjects, and 3.8% (4/106) of drug abuse patients (Bode et al., 1988). Variability in detection has been attributed to differential reagent or assay performance (Lieb and Staeheli, 2001), and to temporal fluctuations in concentration equilibrium among BDV-specific circulating immune complexes (CICs), free antibody, and plasma antigens (Bode et al., 2001). Using a new enzyme immunoassay technique that combines antibody, antigen, and BDV–CIC detection, positive results were reported in 100% (56/56) of affective disorder patients, with high CIC levels considered predictive of depressive symptoms, but also in 30% (22/65) of healthy subjects (Bode et al., 2001). BDV sequences were found in PBMCs of 37% (22/60) (Kishi et al., 1995) to 67% (4/6) (Bode et al., 1995) of psychiatric patients, and live virus in 10% (3/33) of PBMCs of psychiatric inpatients (two with depression, one with obsessive–compulsive disorder; Bode et al., 1996; De la Torre et al., 1996a). Blood granulocyte cell fractions of 100% (3/3) of psychiatric patients have been shown to contain BDV sequences, with live virus very similar to a laboratory strain reported recovered from 33% (or 1/3) of these specimens (Planz et al., 1999). Brains of 80% (4/5) of patients with hippocampal sclerosis (De la Torre et al., 1996b) and 16% (1/6) with Parkinson's disease (Haga et al., 1997) had viral sequence or antigen, detected by PCR, in situ hybridization, or immunohistochemical techniques. Using co-cultivation procedures, infectious virus was reported to be isolated from the postmortem brain of one recent-onset schizophrenic when a total of four schizophrenic and two healthy control brain autopsy specimens were tested (Nakamura et al., 2000).

Most studies of BDV and human disease have focused on affective disorders and schizophrenia; yet, there have been additional findings of BDV antibodies in patients with HIV or AIDS encephalopathy (7.8%, 36/460), chronic fatigue syndrome (0–24%, 6/25), multiple sclerosis (13%, 15/114), glioblastoma (1), schistosomiasis, and malaria (6.9%, 10/145 adults; 18.8%, 9/48 children) (reviewed by Bode, 1995; Lipkin et al., 2001; Ikuta et al., 2002)—patients for whom immune dysfunction is expected. Weak immunoreactivity or cross-reactivity possibly is distributed across the human population, reaching detectable levels when there is simultaneous immune dysregulation or suppression, induced, for example, by stress (Dietrich et al., 1998), nutritional status, or concurrent infection. Longitudinal data for a full assessment of public health risk or pattern of spread in the human population is needed.

4. BD in animals

The origin, original host, and natural history of BDV remain mysterious. Direct spread among herd members is assumed. In its hosts, BDV may have manifested transmissibility and may have avoided immunologic detection by olfactory entry and residence in the brain, an immunoprivileged site. Intermediate vectors such as insects have not been identified. Vector-borne diseases are often transmitted among hosts that are stationary, dormant, or senescent, in contrast to BD, spread between host animals that are highly mobile.

Clinical features of natural and experimental diseases of animals include hyperactivity (ungulates, rodents, primates),

movement and posture disorders (ungulates, rodents, felines, primates), stereotypic or perseverative behaviors (ungulates, rodents, felines), abnormal social behaviors (rodents, primates), and impaired cognitive function (rodents) (summarized in Ludwig and Bode, 2000; Ludwig et al., 1988; Solbrig et al., 1995).

BDV pathogenesis has been extensively studied in rodent models. In rats, two diseases have been defined based on host developmental factors: (1) infection of adolescent or adult immunocompetent rats (an immune-mediated syndrome characterized by dramatic disturbances in movement and behavior; Nitzschke, 1963; Hirano et al., 1983; Narayan et al., 1983a,b; Ludwig et al., 1988; Solbrig et al., 1994, 1995, 1996a,b,c, 1998); and (2) infection of neonatal rats—a distinct syndrome characterized by cerebellar and hippocampal dysgenesis, hyperactivity, learning disturbances (Hirano et al., 1983; Narayan et al., 1983b; Dittrich et al., 1989; Bautista et al., 1994, 1995; Hornig et al., 1999, Rubin et al., 1999), and transient cellular immune reaction and "endogenous" brain inflammatory response (Hornig et al., 1999; Sauder and De la Torre, 1999). Viral distribution is the same, regardless of age of acquisition of infection, and direct CNS host cell lysis by the virus does not occur. Disease outcome relates to developmental maturity of the nervous and immune systems at the time of viral exposure. Early life programs of neural structure maturation are disrupted by neonatal infection. The hippocampus is poorly formed as neurons fail to migrate to form the dentate gyrus, and the cerebellum is hypoplastic, diminished by loss of parenchymal volume, foliation, and Purkinje cells. In adolescent infection, neurochemical changes occur in systems still capable of plasticity at that age, such as reward and prefrontal circuits. The vigorous $CD8^+$ T-cell immune response of adolescent or adult-infected animals accompany neuronal cell loss (Planz and Stitz, 1999; Planz et al., 1993; Bilzer and Stitz, 1994), particularly in dopaminergic and cholinergic/hippocampal circuits (Gies et al., 2001; Stitz et al., 2002).

In mice of all strains, virus replicates to similar titers in the brain, but susceptibility to BDV neurologic disease is strain-specific (Rubin et al., 1993) and related to $CD8^+$ T-cell activation (Hallensleben et al., 1998). Disease ranges from persistent, asymptomatic infection to fatal meningoencephalitis, with low disease susceptibility attributed to immunologic ignorance on the T-cell level towards a decisive viral target (Hausmann et al., 1999). Spatial learning impairments are linked to an elevated CNS chemokine (Sauder et al., 2001).

5. Adolescent rat infection: a viral model of movement and behavior disorders

Hyperactivity, dyskinesias, stereotypies, and excitability (stimulus sensitivity) are the characteristics of BD in rats intracerebrally infected at adolescence, at 4 weeks of age (Solbrig et al., 1994). Infection at this stage falls within the window of opportunity for the induction of changes in systems capable of considerable plasticity until the start of the early adult period, such as the monoaminergic systems (Tarazi et al., 1998; Benes et al., 2000). These are the same systems important in the pathophysiology and treatment of mental and neurological disorders of adolescence and early adulthood.

The neuropharmacological basis for behavioral disturbances has emerged through the use of pharmacological and neurotransmitter-specific probes. Infected animals have behavioral supersensitivity to the psychostimulants D-amphetamine (Solbrig et al., 1994), cocaine (Solbrig et al., 1998), and nicotine (Solbrig, unpublished data) (Table 1). This supensitivity has been attributed to partial DA deafferentation and compensatory hyperactivity in surviving striatal (CP and NAc) terminals (Solbrig et al., 1994)

Table 1
Pharmacological responses of ad-BD rats

Drug	Behavioral response
DA (Dopamine)	
Agonists	
D-amphetamine	↑ Locomotion + stereotypies
Apomorphine	Sedation at low (autoreceptor) doses; dyskinesias at high doses
Cocaine	↑ Locomotion, stereotypies, seizures
Antagonists	
SCH23390 (D1 antagonist)	↓ Self-mutilation + sedation
Haloperidol	No response
Raclopride	No response
Clozapine	Sedation
Alpha-methyl-*para*-tyrosine (AMPT)	No response
Opiates	
Agonists	
U50488 (kappa opioid agonist)	EPS (bradykinetic extrapyramidal syndrome)
Antagonists	
Naloxone	Seizures
Cholinergics	
Nicotinic agonist	
Nicotine	Seizures
Muscarinic agonist	
Pilocarpine	↓ Dyskinesias
Physostigmine	↓ Dyskinesias
Muscarinic antagonist	
Scopolamine	↑ Dyskinesias + stereotypies
Cannabinoids	
Agonist	
AM404 (anandamide transport blocker)	Sedation
Antagonist	
SR141716A (CB1 antagonist)	Seizures

All animals were male Lewis rats intracerebrally infected at 4 weeks of age, tested as adults 6 weeks after infection.

(Table 2), tyrosine hydroxylase (TH) hyperphosphorylation and hyperactivity in nigrostriatal projections (Solbrig et al., 2000), metabolic hyperactivity in the prefrontal cortex (PFC) DA circuit (Solbrig et al., 1996a), and reduced dopamine D2 and D3 receptors but preserved D1 receptor numbers in the striatum (Solbrig et al., 1994, 1996b). The reduced D2 striatal receptors and the reduced indirect striatal pathway throughput that result are primary pathologies also of Huntington's disease, the choreic syndrome of man.

In rats, BDV actually has wide distribution beyond the DA system, and is found in all monoamine nuclei and circuits (limbic circuits, cortical circuits, and brainstem motor nuclei; Solbrig et al., 1994). Hyperactivity in serotonin (5-HT) and norepinephrine (NE) circuits was inferred from increases in the primary metabolites of 5-HT and NE in the striatum and PFC, respectively (Table 2), and from syndrome improvement with the atypical neuroleptic clozapine (a drug with anti-DA, anti-5-HT, and anti-adrenergic actions). Multitransmitter effects of BD in rats raise the possibility of the linkage of BDV with certain treatment-resistant or -refractory schizophrenias. Extreme stereotypic and self-injurious behaviors of BD rats were not blocked by haloperidol, a conventional antipsychotic, nor by the pure D2 antagonist raclopride (Solbrig et al., 1994) (Table 1).

Psychostimulant sensitivity of BD rats can be a function of the preservation of D1 pathway signaling, as D1 receptors are important in mediating behavioral effects of cocaine (Nestler, 1997; Zhang et al., 1998), and can arise from recruitment of other transmitter or signaling systems. In BD rats, pre- and postsynaptic striatal lesions trigger a reactive neurotrophin expression pattern, with increased transcripts of neurotrophin-3 and brain-derived neurotrophic factor (Solbrig et al., 2000)—growth factors contributing to biochemical, structural, and behavioral changes of repeated psychostimulant exposure (Horger et al., 1999; Pierce et al., 1999). Growth factor stimulation can bias a cell toward kinase activation and reactions, including cyclic adenosine monophosphate (cAMP), and, therefore, cAMP-dependent protein kinase A (PKA) reactions (Cai et al., 1999) (see Fig. 1). The result for BD rats would be an increased phosphorylation of TH (the rate-limiting enzyme in DA synthesis) (Solbrig et al., 2000), increased phospho cAMP response–element binding (CREB) protein proportions in the striatum (Solbrig, unpublished data), a location that would support psychostimulant sensitivity (Fig. 1), and increased CREB target gene transcription (Solbrig et al., 2002).

Table 2
Neurotransmitter effects of BDV infection of adolescent rats

Brain region	Neurotransmitter			
	DA	NE	5-HT	DYN (mRNA)
Cortex				
Ad-BD	– ↑ DOPAC/DA	– ↑ MHPG/NE	– – 5-HIAA/5-HT	nd
Hippocampus				
Ad-BD	nd	nd	nd	↓
Striatum				
Ad-BD	↓ ↑ DOPAC/DA	– – MHPG/NE	– ↑ 5-HIAA/5-HT	–

Ad-BD, rats infected with BDV at 4 weeks of age.
(–) No statistically significant changes.
nd, Not determined.

BDV enhancement of phosphorylating kinase reactions also has been demonstrated in vitro (Hans et al., 2001; Planz et al., 2001), where kinases are hypothesized to facilitate viral replication and infectivity (Planz et al., 2001) (Fig. 1). The Raf/MEK/ERK signaling pathway is activated by infection of guinea pig CRL 1405 cells, rat fetal glial C6 cells, Vero, and human embryonal kidney 293T cells, as shown by immune complex kinase assays (Planz et al., 2001). Mitogen-activated phosphorylating (MAP) kinases usually function as linkers of stimuli from the cell surface to cellular events involved in proliferation, differentiation, or survival by phospholipid messengers, transcription, or translation. For BDV, though, MAPK pathway stimulation by virus is thought to be independent of cell surface stimulation by binding and uptake (Planz et al., 2001). Since there has been no direct evidence that BDV proteins are phosphorylated by MAPK, the mechanism of activation is not yet known. Conceivably, kinase activations may improve BD viral life cycle efficiency by regulating other cellular enzymes associated with BDV. Alternatively, kinase activations may alter cell cycle progression, and cause or contribute to host cell de-differentiation to create a cell environment conducive to persistent infection. For example, in PC12 cells, BDV causes constitutive activation of the extracellular signal-regulated kinase (ERK) 1/2 pathway. Limited translocation to the nucleus of activated products and limited transcriptional activation result in persistent infection of less specialized (de-differentiated) cells (Hans et al., 2001).

The ability to regulate phosphorylating kinases is known for several viruses: HIV (Popik et al., 1998; Yang and Gabuzda, 1999), SIV (Popik and Pitha, 1998), human CMV (Rodems and Spector, 1998), adenovirus (Bruder and Kovesdi, 1997), and hepatitis B (Benn et al., 1996). For HIV, kinase activation is a mechanism of coupling viral replication to cell cycle progression or mitosis (Yang and Gabuzda, 1999). For other viruses, phosphorylating reactions have been related to immune regulation (Schneider-Schaulies et al., 2002) or cell transformation (DiMaio and Mattoon, 2001). For BDV, use of probes for phosphorylating kinases to evaluate viral biology, the potential and extent of biological overlap or convergence of BD intracellular signals with neurotransmitter or neurotrophin signals, can be revealed. In vivo, the wide but nonhomogeneous neuraxis distribution of BDV underscores the importance of both cellular and system changes in multiple transmitter systems, providing insight into disease expression.

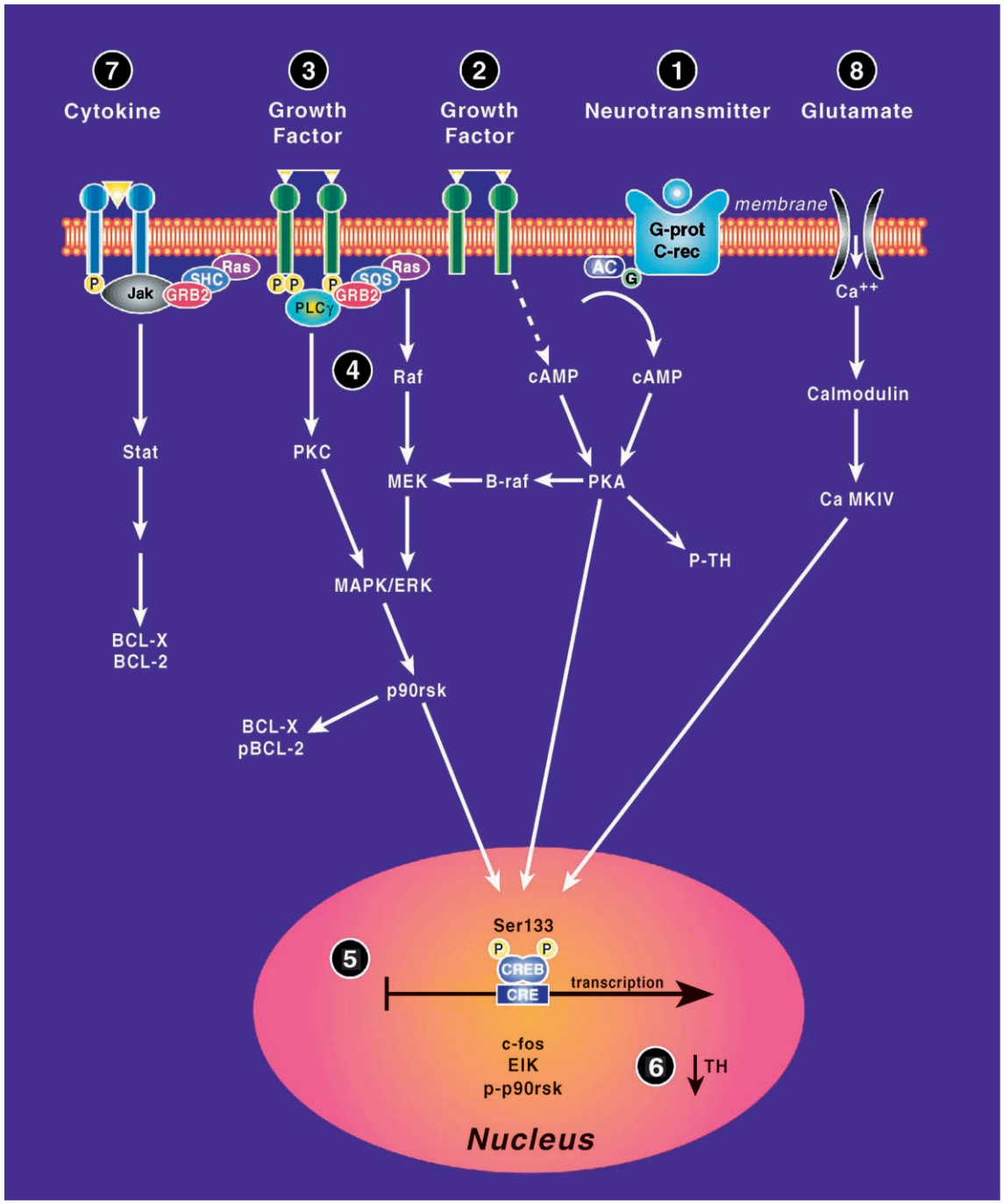

Fig. 1. BDV has pharmacological effects, upregulating cAMP pathways, certain kinase pathways, and selectively activating transcription factors and gene expression. While the receptor systems depicted in the figure may not coexist in the same cell, this schematic cell illustrates a number of cellular convergent points for effects of virus, neurotransmitters, and neurotrophins. (1) Hyperactive catecholamine systems such as DA (Solbrig et al., 1994) stimulate G protein-coupled receptors, increasing second messengers such as cAMP, in turn increasing the activity of PKA and its phosphorylated substrates. (2) Upregulated neurotrophins, also through a cAMP-dependent mechanism (Cai et al., 1999), may increase the activity of PKA and phosphorylated targets such as TH (Solbrig et al., 2000). (3) Neurotrophin binding to the *trk* family of receptors induces receptor dimerization, phosphorylation, recruitment of protein complexes, and initiation of signals through the MAPK cascade. ERK 1/2 and PKC activate P-p90RSK, which activates CREB and other transcription factors. (4) BDV increases Raf, MEK, and ERK activities in vitro (Hans et al., 2001; Planz et al., 2001), and activated products are translocated to the nucleus. Effects of infection on transcription factors and transcripts vary. (5) Elk and PElk increase and P-p90RSK, PCREB, and c-*fos* decrease (Hans et al., 2001). (6) Transcripts of many genes, including TH, decrease (Hans et al., 2001). (7) Cytokines as well as growth factors induce antiapoptotic proteins of the BCL-2 family, sustaining a cell during infection. (8) Decreased glutamate uptake by infected astrocytes, increasing extracellular glutamate, would mediate neural injury (Billaud et al., 2000). BDV = Borna Disease Virus; DA = dopamine; cAMP = cyclic adenosine monophosphate; PKA = cAMP-dependent protein kinase A; TH = tyrosine hydroxylase; MAPK = mitogen-activated phosphorylating kinase; ERK = extracellular signal-regulated kinase; PKC = protein kinase C; CREB = cAMP response–element–binding protein; MEK = mitogen-activated protein kinase kinase; PCREB = phosphorylated CREB.

Adolescent stage insults influence the development of the brain, and also how the brain ages. As adults, BDV-infected rats develop spontaneous seizures and accelerated senescence with loss of cholinergic markers: choline acetyltransferase (from cortex, hippocampus, amygdala), acetylcholesterase (from cortex, hippocampus diagonal band), and vesicular cholinergic transporter (from cortex and hippocampus) (Gies et al., 2001). Additional pharmacologic, neurochemical, neuroanatomic, and molecular studies have established the scope of cholinergic, opioid, and other transmitter disturbances of infected animals (Table 1) (Lipkin et al., 1988; Fu et al., 1993b; Solbrig et al., 1995, 1996c, 1999, 2002) and have assessed contributions of virus-specific T-cell immune response and chronic inflammation to convulsive and degenerative phenomena (summarized in Stitz et al., 2002).

6. Neonatal rat infection: a viral model of neurodevelopmental disorders

Early life BD, with its limited inflammatory reactions, is distinct from the meningoencephalitic syndrome of infection acquired during adolescence. Exposure by intracerebral inoculation to BDV on Day 1 of life confers a degree of tolerance to infection that largely limits inflammatory reaction to resident (CNS) cells of the brain immune system. Neonatal BDV infection of rats has been studied as a model of viral-induced neurodevelopmental disorders to elucidate mechanisms of early life viral insult, and may be relevant to pervasive development disorders, including the autistic spectrum disorders of children. The distribution of virus in both neonatal and adolescent infections is similar at comparable times postinfection. Unlike adult infection, the neonatal syndrome is not dopamine-dominated. Instead, the neonatal BD syndrome features 5-HT and NE dysfunction, abnormal social behavior, abnormal motor behaviors, delayed developmental milestones, and cerebellar and hippocampal dysgenesis (Carbone et al., 2001).

Changes in 5-HT can be mediators of developmental events. For example, 5-HT influences neurogenesis and/or neuronal removal, dendritic refinement, synaptic remodeling, maintenance, and cell migration (Whitaker-Azmitia, 2001). Pharmacological manipulations, such as cocaine (Akbari et al., 1994; Cabrera-Vera et al., 2000) or monoamine oxidase inhibitor (Whitaker-Azmitia et al., 1994) administration, result in increased levels of synaptic 5-HT in developing animals but lead to loss of 5-HT terminals in the adult animal.

As in these toxic and other rodent hyperserotonergic models of autism (Whitaker-Azmitia, 2001), 5-HT is increased in the cortex and hippocampus of neonatally infected BD rats at Postnatal Day (PND) 21 (Pletnikov et al., 2000). Animals are hyperresponsive to sound, freeze in response to a novel environment at 4 weeks of age, are hyperactive in open field tests, and show stereotypic movements, delayed ontogeny of motor reflexes, and abnormal vocalizations (Pletnikov et al., 1999a,b; Hornig et al., 1999, 2001). In neonatally infected rats, 5-HT remains increased in the cortex and hippocampus throughout adult life, and is increased in the cerebellum of rats as adults. NE is increased in the cortex and cerebellum of adult rats, and DA is unchanged in the cortex, striatum, and hypothalamus (Pletnikov et al., 2000) (Table 3). If 5-HT does set its own terminal density, lower numbers of 5-HT receptors may be predicted for areas with high 5-HT.

BDV infection also causes lifelong changes in food intake and body weight. Neonatally infected rats (by 1 month of age) have increased mRNA levels of the orexigenic neuropeptide Y (NPY) and reduced levels of the anorexic proopiomelanocortin (POMC) transcripts in the hypothalamus (Plata-Salaman et al., 1999)—a profile that might anticipate leptin deficiency and a stimulatory effect on feeding. However, leptin receptor mRNA levels are normal; young animals are hyperphagic but growth-retarded (Plata-Salaman et al., 1999). Throughout life, the majority of BD rats are small for age, but a few are huge (800–1000 g). Some neonatal (Solbrig, unpublished data) and adolescent-infected rats (Gosztonyi and Ludwig, 1995) become obese with age, suggesting that secondary adaptations during chronic infection alter energy homeostasis.

NPY, also an anxiolytic peptide mediating stress and cognitive effects, is increased in the cortex and hippocampus of neonatally infected rats at 1 month of age (Plata-Salaman et al., 1999). Animals tested at 4 months of age show low-anxiety responses (e.g., locomotor hyperactivity and absence of freezing behavior in brightly lit open field testing; Dittrich et al., 1989). Yet contextual and cued fear conditioning of autonomic responses also were increased despite motor and thigmotaxic (wall-seeking) behaviors consistent with reduced anxiety (Pletnikov et al., 1999a). The dissociation of behavioral and endocrine stress responses implies viral effects on reflex or integration

Table 3
Neurotransmitter effects of BDV infection of neonatal rats

Brain region	Neurotransmitter			
	DA	NE	5-HT	DYN (mRNA)
Cortex				
Neo-BD	–	↑	↑	–
	– DOPAC/DA		– 5-HIAA/5-HT	
Hippocampus				
Neo-BD	nd	–	↑	–
			– 5-HIAA/5-HT	
Striatum				
Neo-BD	–	nd	nd	nd
	– DOPAC/DA			

Neo-BD, rats infected with BDV at 1 day of life.
(–) No statistically significant changes.
nd, not determined.

circuits beyond NPY, or incomplete buffering effects by NPY on stress-promoting signals.

The learning and memory impairments of neonatally infected rats on tests of spatial or aversive learning (Dittrich et al., 1989) may be pharmacologic, structural, or both. NPY, associated with spatial learning deficits when overexpressed in the hippocampus of transgenic rats (Thorsell et al., 2000), is increased in neonatally infected rat hippocampus (Plata-Salaman et al., 1999). Reductions in synaptic growth-associated protein GAP-43, depressor of acquisition learning (De la Torre et al., 1996c; Brot et al., 1997), are among several neurodegenerative markers displayed by neonatally infected rats as they age. Reductions in GAP-43 and synaptophysin in the hippocampus and cortex, cerebral volume loss, loss of cortical large pyramidal and parvalbumin positive GABA neurons, and irregular synaptophysin staining consistent with axonal transport defects have been found (Gonzalez-Dunia et al., 2000). Inhibition of function of the neurite outgrowth promoter, amphoterin/HMG-1, by binding of the BDV p24 phosphoprotein (Kamitani et al., 2001) may likewise affect synapse and circuit maintenance throughout the brain.

A role for excitotoxicity in the CNS injury of infected rats has been suggested based on colocalization and presumed interference of BD antigen with excitatory terminals and kainate-1 receptors in hippocampus (Gosztonyi and Ludwig, 1995, 2001); experimental evidence that BD also infects astrocytes (Carbone et al., 1989, 1991); in vitro demonstration of BDV infection of feline primary cortical astrocytes inhibiting glutamate uptake (Billaud et al., 2000); and a preliminary report of neuroprotection by the cysteine precursor, *N*-acetylcysteine, to replenish intracellular glutathione and to protect cells from AMPA receptor-mediated toxicity (Gosztonyi and Ludwig, 2001). Neonatal rat time course experiments provide further support. Tumor necrosis factor-alpha (TNF-α) is a cytokine thought to rapidly increase in neurons and signal surrounding microglia following excitotoxic events at the synapse (Bruce-Keller, 1999). In neonatally infected rats, TNF-α expression is elevated in hippocampus and cerebellum at PND 7 (Plata-Salaman et al., 1999). By PND 8, transcripts for early response cytokines produced by the microglia (IL-1β, TNF-α, and IL-6) are detected (Plata-Salaman et al., 1999; Sauder and de la Torre, 1999)—a sequence consistent with microglia recognizing excitotoxic injury and initiating an inflammatory cascade.

Although activated microglia express an array of proinflammatory cytokines that could contribute to the activation and polarization of T cells, T-cell recruitment is limited and nonescalating. Neurodevelopmental injury proceeds despite a brief T-cell response restricted to the neocortex (Weissenbock et al., 2000) and absent direct cell lysis by virus.

Time course experiments are establishing the influence of cytokine and neurotrophin signals on immune, neurodevelopmental, and lesion hierarchies in neonatally infected rats (Hornig et al., 1999; Plata-Salaman et al., 1999; Sauder and de la Torre, 1999; Zocher et al., 2000, summarized in Carbone et al., 2001). Failure of normal age-related increases in neurotrophin BDNF and NT3 transcripts (in the hippocampus and cerebellum) between 4 and 12 weeks of age coincides with increases in mRNA for inflammatory cytokines interleukin-1 (IL-1) and TNF-α (in hippocampus, cerebellum, and cortex) at 4 weeks. Generalized expression of proapoptotic factor transcripts and downregulation of antiapoptotic factor mRNA in the hippocampus and cerebellum at 4 weeks accompany apoptotic cell loss (in hippocampus) at 4–6 weeks and architectural changes in hippocampus, cerebellum, and cortex (Hornig et al., 1999, summarized in Carbone et al., 2001; Pletnikov et al., 2002).

Simultaneous increases in 5-HT and NE in hippocampus, cerebellum, and cortex (Pletnikov et al., 2000) may signify a reactive monoaminergic pattern, compensatory changes in the face of anatomic injury. Alternatively, the monoaminergic changes may be the consequence of activity in other transmitter circuits—circuits that triggered the microglial inflammatory reaction. For example, microglia, possessing potassium channels (Kettenmann et al., 1990), respond to neuronal depolarization and concurrent potassium release. Microglia also can respond to purine transmitters by proliferation (Gebicke-Haerter et al., 1996) and release of IL-1β (Ferrari et al., 1996). Adenosine and ATP are ubiquitous neurotransmitters, with receptors in hippocampus (Shen et al., 2002), cortex (Marchi et al., 2002), cerebellum (DeSanty and Dar, 2001; El Yacoubi et al., 2001), and striatum (Blum et al., 2002; Toda et al., 2002), such that regional 5-HT and NE changes could conceivably reflect purine or potassium signals that drive the inflammatory cascade.

7. Mouse infection: viral models of genetic–neural–immune interactions

Mice have been used to evaluate the genetic and immune determinants of disease (Hausmann et al., 1999). Mice, as rats, could be readily infected with BDV by intracerebral inoculation once natural BDV isolates were mouse-adapted by serial passages in rat brain (Kao et al., 1984). Most laboratory strains of mice develop persistent but clinically and histologically inapparent illness. MRL strain mice are the exception. Adolescent MRL mice, when infected, develop meningoencephalitic BD with hyperactive, disinhibited, aggressive behaviors (Rubin et al., 1993) similar to those produced by experimental infection of adolescent rats. As in rats, severe clinical disease is mediated by MHC class I-restricted cytotoxic T cells (Hallensleben et al., 1998). Even neonatally infected wild-type MRL mice develop symptomatic immune ($CD8^+$ T cell)-mediated BD, while β2 microglobulin knockout MRL mice lacking $CD8^+$ T cells do not (Hallensleben et al., 1998). In another β2 microglobulin-deficient strain, C57BL/10J, also lacking $CD8^+$ T cells, BDV mice develop persistent noncytolytic

infection and infection of most hippocampal neurons. Because CNS infection occurs without hippocampal neuronal loss or dysplasia (distinguishing neonatal mice from rat infections) can follow examination of cognitive effects of persistent viral infection of an otherwise apparently intact hippocampus by gross examination. Only mice with high transcript levels of interferon-gamma (IFN-γ) inducible protein IP-10, a CXC chemokine inflammatory cell recruiter with possible pathophysiologic effects on neurons and glia (Bacon and Harrison, 2000), show poor water maze performance (Sauder et al., 2001). The significance of BDV chemokine activation will be more fully appreciated once there is a greater understanding of the role of chemokines in neurodevelopmental integrity, synaptic function, and signal transduction.

8. Conclusion

Bornaviral disease acquired by adolescent rats is a meningoencephalitic illness. It takes the form of diseases with DA substrates: hyperkinesias, stereotypies, and behavioral sensitivity to psychostimulants. Yet, it is not exclusively a dopaminergic disease; degeneration of multiple transmitter systems occurs. Neonatal rat BD is a global developmental disorder, showing how wide the repertoire of disease consequences of early life viral insult may be. Psychomotor and emotional abnormalities, developmental delay, and cognitive decline are manifestations of the effects of neonatal BDV on highly plastic structures (hippocampus and cerebellum), neuropeptides, and monoamines (transmitters with broad homeostatic or neuromodulatory functions). Considering neonatal and adolescent disease together, the significance of an age-specific effect of CNS viral insult may be established, from which a developmental perspective on disease follows, where individual–environmental interactions across time form a causal pathway to disease.

As in adolescent rat infection, models of neonatal infection of rats and mice have been used to identify syndromes accessible to pharmacological manipulation that can be measured in established paradigms. In addition, mice offer well-characterized genetic backgrounds or engineered traits for evaluating disease expression and severity. Results from animal models and in vitro viral studies (summarized in Fig. 1) together have generated testable hypotheses of viral mechanisms of disease.

Recently, there has been progress in elucidating cellular and neural system consequences of BDV infection, but many gaps remain in understanding virus–host interactions and region-specific pathology. BDV causes persistent CNS infection with discrete phenotypes, which are dependent on the maturational stage of the experimental animal at the time of acquisition of infection. BDV in rodents presents the investigator with viral models of aspects of autism, schizophrenia, movement disorders, cognitive decline, and drug abuse vulnerability. Adolescent-infected rats show immune-mediated multisystem atrophic disease characterized by dramatic disturbances in movement and behavior. Neonatally infected rats show cerebellar and hippocampal dysgenesis, hyperactivity, learning disturbances, and global developmental delays. With these models, pharmacologic, inflammatory, and lesion paths to disease can be dissected. Linkage of viral and neuropharmacological studies has value for examining the pathophysiology of disease and vulnerability to disease by a history of viral insult.

Acknowledgements

This work was supported by National Institutes of Health grants DA00376 (M.V.S.) and DA13332 (M.V.S. virology project; F. Leslie, Center Director) from the National Institute on Drug Abuse. This is publication 15158-NP from The Scripps Research Institute. The authors would like to thank Dr. Michael Buchmeier for his comments on the manuscript and Mr. Mike Arends for his editorial assistance.

References

Akbari HM, Whitaker-Azmitia PM, Azmitia EC. Prenatal cocaine decreases the trophic factor s-100B and induced microcephaly: reversal by postnatal 5-HT1a agonist. Neurosci Lett 1994;170:141–4.

Bacon KB, Harrison JK. Chemokines and their receptors in neurobiology: perspectives in physiology and homeostasis. J Neuroimmunol 2000; 104:92–7.

Bautista JR, Schwartz GJ, de la Torre JC, Moran TH, Carbone KM. Early and persistent abnormalities in rats with neonatally acquired Borna disease virus infection. Brain Res Bull 1994;34:31–40.

Bautista JR, Rubin SA, Moran TH, Schwartz GJ, Carbone KM. Developmental injury to the cerebellum following perinatal Borna disease virus infection. Brain Res Dev Brain Res 1995;90:45–53.

Benes FM, Taylor JB, Cunningham MC. Convergence and plasticity of monoaminergic systems in the medial prefrontal cortex during the postnatal period: implications for the development of psychopathology. Cereb Cortex 2000;10:1014–27.

Benn J, Su F, Doria M, Schneider RJ. Hepatitis B virus HBx protein induces transcription factor AP-1 by activation of extracellular signal-regulated and c-Jun N-terminal mitogen-activated protein kinases. J Virol 1996;70:4978–85.

Billaud JN, Ly C, Phillips TR, de la Torre JC. Borna disease virus persistence causes inhibition of glutamate uptake by feline primary cortical astrocytes. J Virol 2000;74:10438–46.

Bilzer T, Stitz L. Immune-mediated brain atrophy. $CD8^+$ T cells contribute to tissue destruction during Borna disease. J Immunol 1994;153: 818–23.

Blum D, Gall D, Galas MC, d'Alcantara P, Bantubungi K, Schiffmann SN. The adenosine A1 receptor agonist adenosine amine congener exerts a neuroprotective effect against the development of striatal lesions and motor impairments in the 3-nitropropionic acid model of neurotoxicity. J Neurosci 2002;22:9122–33.

Bode L. Human infections with Borna disease virus and potential pathogenic implications. In: Koprowski H, Lipkin WI, editors. Borna disease. Current topics in microbiology and immunology, vol. 190. Berlin: Springer-Verlag; 1995. p. 103–30.

Bode L, Ludwig H. Borna disease virus—a threat for human mental health? In: Smith GL, Irving WL, McCauley JW, Rowlands DJ, editors. SGM

Symposium 60: New Challenges to Health: The Threat of Virus Infection. Cambridge: Cambridge Univ Press; 2001. p. 269–310.
Bode L, Riegel S, Ludwig H, Amsterdam JD, Lange W, Koprowski H. Borna disease virus-specific antibodies in patients with HIV infection and with mental disorders. Lancet 1988;2:689.
Bode L, Durrwald R, Ludwig H. Borna virus infections in cattle associated with fatal neurological disease. Vet Rec 1994;135:283–4.
Bode L, Zimmermann W, Ferszt R, Steinbach F, Ludwig H. Borna disease virus genome transcribed and expressed in psychiatric patients. Nat Med 1995;1:232–6.
Bode L, Durrwald R, Rantam FA, Ferszt R, Ludwig H. First isolates of infectious human Borna disease virus in patients with mood disorders. Mol Psychiatry 1996;1:200–12.
Bode L, Reckwald P, Severus WE, Stoyloff R, Ferszt R, Dietrich DE, et al. Borna disease virus-specific circulating immune complexes, antigenemia, and free antibodies—the key marker triplet determining infection and prevailing in severe mood disorders. Mol Psychiatry 2001;6:481–91.
Brot MD, Rall GF, Oldstone MB, Koob GF, Gold LH. Deficits in discriminated learning remain despite clearance of long-term persistent viral infection in mice. J Neurovirol 1997;3:265–73.
Bruce-Keller A. Microglial–neuronal interactions in synaptic damage and recovery. J Neurosci Res 1999;58:191–201.
Bruder JT, Kovesdi I. Adenovirus infection stimulates the Raf/MAPK signaling pathway and induces interleukin-8 expression. J Virol 1997;71:398–404.
Cabrera-Vera TM, Garcia F, Pinto X, Battaglia G. Neurochemical changes in brain serotonin neurons in immature and adult offspring prenatally exposed to cocaine. Brain Res 2000;870:1–9.
Cai D, Shen Y, DeBellard ME, Tang S, Filbin MT. Prior exposure to neurotrophins blocks inhibition of axonal regeneration by MAG and myelin via a cAMP-dependent mechanism. Neuron 1999;22:89–101.
Caplazi P, Waldvogel A, Stitz L, Braun U, Ehrensperger F. Borna disease in naturally infected cattle. J Comp Pathol 1994;111:65–72.
Carbone KM, Trapp BD, Griffin JW, Duchala CS, Narayan O. Astrocytes and Schwann cells are virus–host cells in the nervous system of rats with Borna disease. J Neuropathol Exp Neurol 1989;48:631–44.
Carbone KM, Moench TR, Lipkin WI. Borna disease virus replicates in astrocytes, Schwann cells and ependymal cells in persistently infected rats: location of viral genomic and messenger RNAs by in situ hybridization. J Neuropathol Exp Neurol 1991;50:205–14.
Carbone KM, Rubin SA, Nishino Y, Pletnikov MV. Borna disease: virus-induced neurobehavioral disease pathogenesis. Curr Opin Microbiol 2001;4:467–75.
De la Torre JC. Ch. 51: Bornaviridae. In: Knipe DM, Howley PM, editors. 4th ed. Fields virology, vol. 2. Philadelphia: Lippincott, Williams and Wilkins; 2001. p. 1669–77.
De la Torre JC, Bode L, Durrwald R, Cubitt B, Ludwig H. Sequence characterization of human Borna disease virus. Virus Res 1996a;44:33–44.
De la Torre JC, Gonzalez-Dunia D, Cubitt B, Mallory M, Mueller-Lantzsch N, Grasser FA, et al. Detection of Borna disease virus antigen and RNA in human autopsy brain samples from neuropsychiatric patients. Virology 1996b;223:272–82.
De la Torre JC, Mallory M, Brot M, Gold L, Koob G, Oldstone MBA, et al. Viral persistence in neurons alters synaptic plasticity and cognitive functions without destruction of brain cells. Virology 1996c;220:508–15.
DeSanty KP, Dar MS. Involvement of the cerebellar adenosine A(1) receptor in cannabinoid-induced motor incoordination in the acute and tolerant state in mice. Brain Res 2001;905:178–87.
Dietrich DE, Schedlowski M, Bode L, Ludwig H, Emrich HM. A viropsycho-immunological disease-model of a subtype affective disorder. Pharmacopsychiatry 1998;31:77–82.
DiMaio D, Mattoon D. Mechanisms of cell transformation by papillomavirus E5 proteins. Oncogene 2001;20:7866–73.
Dittrich W, Bode L, Ludwig H, Kao M, Schneider K. Learning deficiencies in Borna disease virus-infected but clinically healthy rats. Biol Psychiatry 1989;26:818–28.
El Yacoubi M, Ledent C, Parmentier M, Ongini E, Costentin J, Vaugeois JM. In vivo labelling of the adenosine A2A receptor in mouse brain using the selective antagonist [^{3}H]SCH 58261. Eur J Neurosci 2001;14:1567–70.
Ferrari D, Villalba M, Chioozzi P, Falzoni S, Ricciardi-Castagnoli P, DiVirgilio F. Mouse microglial cells express a plasma membrane pore gated by extracellular ATP. J Immunol 1996;156:1531–9.
Fu ZF, Amsterdam JD, Kao M, Shankar V, Koprowski H, Dietzschold B. Detection of Borna disease virus-reactive antibodies from patients with affective disorders by Western immunoblot technique. J Affect Disord 1993a;27:61–8.
Fu ZF, Weihe E, Zheng YM, Schafer MK, Sheng H, Corisdeo S, et al. Differential effects of rabies and Borna disease viruses in immediate-, early-, and late-response gene expression in brain tissues. J Virol 1993b;67:6674–81.
Gebicke-Haerter PJ, Christoffel F, Timmer J, Northhoff H, Berger M, van Calker D. Both adenosine A1- and A2 receptors are required to stimulate microglial proliferation. Neurochem Int 1996;29:37–42.
Gies U, Gorcs TJ, Mulder J, Planz O, Stitz L, Bilzer T, et al. Cortical cholinergic decline parallels the progression of Borna virus encephalitis. Neuroreport 2001;12:3767–72.
Gonzalez-Dunia D, Watanabe M, Syan S, Mallory M, Masliah E, de la Torre JC. Synaptic pathology in Borna disease virus persistent infection. J Virol 2000;74:3441–8.
Gosztonyi G, Ludwig H. Borna disease—neuropathology and pathogenesis. In: Koprowski H, Lipkin WI, editors. Borna disease. Current topics in microbiology and immunology, vol. 190. Berlin: Springer-Verlag; 1995. p. 39–73.
Gosztonyi G, Ludwig H. Interactions of viral proteins with neurotransmitter receptors. In: Gosztonyi G, editor. The mechanisms of neuronal damage in virus infections of the nervous system. Current topics in microbiology and immunology, vol. 253. Berlin: Springer-Verlag; 2001. p. 121–44.
Haga S, Motoi Y, Ikeda Kthe Japan Bornavirus Study Group. Borna disease virus and neuropsychiatric disorders. Lancet 1997;350:592–3.
Hagiwara K, Nakaya T, Nakamura Y, Asahi S, Takahashi H, Ishihara C, et al. Borna disease virus RNA in peripheral blood mononuclear cells obtained from healthy dairy cattle. Med Microbiol Immunol (Berlin) 1996;185:145–51.
Hallensleben W, Schwemmle M, Hausmann J, Stitz L, Volk B, Pagenstecher A, et al. Borna disease virus-induced neurological disorder in mice: infection of neonates resulting in immunopathology. J Virol 1998;72:4379–86.
Hans A, Syan S, Crosio C, Sassone-Corsi P, Brahic M, Gonzalez-Dunia D. Borna disease virus persistent infection activates mitogen-activated protein kinase and blocks neuronal differentiation of PC12 cells. J Biol Chem 2001;276:7258–65.
Hausmann J, Hallensleben W, de la Torre JC, Pagenstecher A, Zimmermann C, Pircher H, et al. T cell ignorance in mice to Borna disease virus can be overcome by peripheral expression of viral nucleoprotein. Proc Natl Acad Sci USA 1999;96:9769–74.
Hirano N, Kao M, Ludwig H. Persistent tolerant or subacute infection in Borna disease. J Gen Virol 1983;64:1521–30.
Horger BA, Iyasere CA, Berhow MT, Messer CJ, Nestler EJ, Taylor JR. Enhancement of locomotor activity and conditioned reward to cocaine by brain-derived neurotrophic factor. J Neurosci 1999;19:4110–22.
Hornig M, Weissenbock H, Horscroft N, Lipkin WI. An infection-based model of neurodevelopmental damage. Proc Natl Acad Sci U S A 1999;96:12102–7.
Hornig M, Briese T, Lipkin WI. Bornavirus tropism and targeted pathogenesis: virus–host interactions in a neurodevelopmental model. Adv Virus Res 2001;56:557–82.
Ikuta K, Ibrahim MS, Kobayashi T, Tomonaga K. Borna disease virus and infection in humans. Front Biosci 2002;7:470–95.
Kamitani W, Shoya Y, Koayashi T, Watanabe M, Lee B-J, Zhang G, et al.

Borna disease virus phosphoprotein binds a neurite outgrowth factor, amphoterin/HMG-1. J Virol 2001;75:8742–51.
Kao M, Ludwig H, Gosztonyi G. Adaptation of Borna Disease virus to the mouse. J Gen Virol 1984;65:1845–9.
Kettenmann H, Hoppe D, Gottmann K, Banati R, Kreutzberg GW. Cultured microglia cells have a distinct pattern of membrane channels that differ from peritoneal macrophages. J Neurosci Res 1990;26:278–87.
Kishi M, Nakaya T, Nakamura Y, Kakinuma M, Takahashi TA, Sekiguchi S, et al. Prevalence of Borna disease virus RNA in peripheral blood mononuclear cells from blood donors. Med Microbiol Immunol (Berlin) 1995;184:135–8.
Lieb K, Staeheli P. Borna disease virus—does it infect humans and cause psychiatric disorders? J Clin Virol 2001;21:119–27.
Lipkin WI, Carbone KM, Wilson MC, Duchala CS, Narayan O, Oldstone MBA. Neurotransmitter abnormalities in Borna disease. Brain Res 1988;475:366–70.
Lipkin WI, Hornig M, Briese T. Borna disease virus and neuropsychiatric disease—a reappraisal. Trends Microbiol 2001;9:295–8.
Ludwig H, Bode L. Borna disease virus: new aspects on infection, disease, diagnosis and epidemiology. Rev Sci Tech, Off Int Epiz 2000; 19:259–88.
Ludwig H, Thein P. Demonstration of specific antibodies in the central nervous system of horses naturally infected with Borna disease virus. Med Microbiol Immunol 1977;163:215–26.
Ludwig H, Bode L, Gosztonyi G. Borna disease: a persistent virus infection of the central nervous system. Prog Med Virol 1988;35:107–51.
Lundgren AL, Czech G, Bode L, Ludwig H. Natural Borna disease in domestic animals others than horses and sheep. Zentralbl Veterinarmed, Reihe B 1993;40:298–303.
Malkinson M, Weisman Y, Ashash E, Bode L, Ludwig H. Borna disease in ostriches. Vet Rec 1993;133:304.
Marchi M, Raiteri L, Risso F, Vallarino A, Bonfanti A, Monopoli A, et al. Effect of adenosine A1 and A2A receptor activation on the evoked release of glutamate from rat cerebrocortical synaptosomes. Br J Pharmacol 2002;136:434–40.
Nakamura Y, Takahashi H, Shoya Y, Nakaya T, Watanabe M, Tomonaga K, et al. Isolation of Borna disease virus from human brain tissue. J Virol 2000;74:4601–11.
Narayan O, Herzog S, Frese K, Scheefers H, Rott R. Behavioral disease in rats caused by immunopathological responses to persistent Borna virus in the brain. Science 1983a;220:1401–3.
Narayan O, Herzog S, Frese K, Scheefers H, Rott R. Pathogenesis of Borna disease in rats: immune-mediated viral ophthalmoencephalopathy causing blindness and behavioral abnormalities. J Infect Dis 1983b;148: 305–15.
Nestler EJ. Molecular mechanisms of opiate and cocaine addiction. Curr Opin Neurobiol 1997;7:713–9.
Nitzschke E. Unterschungen uber die experimentelle Bornavirus—Infektion bei der Ratte Zentralbl (Investigation about the experimental Bornavirus—infection in the rat). Vet Med B 1963;10:470–527 [in German].
Pierce RC, Pierce-Bancroft AF, Prasad BM. Neurotrophin-3 contributes to the initiation of behavioral sensitization to cocaine by activating the Ras/mitogen-activated protein kinase signal transduction cascade. J Neurosci 1999;19:8685–95.
Planz O, Stitz L. Borna disease virus nucleoprotein (p40) is a major target for CD8(+) T cell-mediated immune response. J Virol 1999;73:1715–8.
Planz O, Bilzer T, Sobbe M, Stitz L. Lysis of major histocompatibility complex class I-bearing cells in Borna disease virus-induced degenerative encephalopathy. J Exp Med 1993;178:163–74.
Planz O, Rentzch C, Batra A, Winkler T, Buttner M, Rziha H-J, et al. Pathogenesis of Borna Disease virus: granulocyte fractions of psychiatric patients harbor infectious virus in the absence of antiviral antibodies. J Virol 1999;73:6251–6.
Planz O, Pleschka S, Ludwig S. MEK-specific inhibitor U0126 blocks spread of Borna disease virus in cultured cells. J Virol 2001;75: 4871–7.
Plata-Salaman CR, Ilyin SE, Gayle D, Romanovitch A, Carbone KM. Persistent Borna disease virus infection of neonatal rats causes brain regional changes of mRNAs for cytokines, cytokine receptor components and neuropeptides. Brain Res Bull 1999;49:441–51.
Pletnikov MV, Rubin SA, Schwartz GJ, Moran TH, Sobotka TJ, Carbone KM. Persistent neonatal Borna disease virus (BDV) infection of the brain causes chronic emotional abnormalities in adult rats. Physiol Behav 1999a;66:823–31.
Pletnikov MV, Rubin SA, Vasudevan K, Moran TH, Carbone KM. Developmental brain injury associated with abnormal play behavior in neonatally Borna disease virus-infected Lewis rats: a model of autism. Behav Brain Res 1999b;100:43–50.
Pletnikov MV, Rubin SA, Schwartz GJ, Carbone KM, Moran TH. Effects of neonatal rat Borna disease virus (BDV) infection on the postnatal development of the brain monoaminergic systems. Dev Brain Res 2000;119:179–85.
Pletnikov MV, Moran TH, Carbone KM. Borna disease virus infection of the neonatal rat: developmental brain injury model of autism spectrum disorders. Front Biosci 2002;7:d593–607.
Popik W, Pitha PM. Early activation of mitogen-activated protein kinase kinase, extracellular signal-regulated kinase, p38 mitogen-activated protein kinase, and c-Jun N-terminal kinase in response to binding of simian immunodeficiency virus to Jurkat T cells expressing CCR5 receptor. Virology 1998;252:210–7.
Popik W, Hesselgesser JE, Pitha PM. Binding of Human Immunodeficiency Virus Type 1 to CD4 and CXCR4 receptors differentially regulates expression of inflammatory genes and activates the MEK/ERK signaling pathway. J Virol 1998;72:6406–13.
Rodems S, Spector DH. Extracellular signal-regulated kinase activity is sustained early in human cytomegalovirus infection. J Virol 1998;72: 9173–80.
Rott R, Herzog S, Fleischer B, Winokur A, Amsterdam J, Dyson W, et al. Detection of serum antibodies to Borna disease virus in patients with psychiatric disorders. Science 1985;228:755–6.
Rubin SA, Waltrip RW, Bautista JR, Carbone KM. Borna disease virus in mice: host-specific differences in disease expression. J Virol 1993;67: 548–52.
Rubin SA, Bautista JR, Moran TH, Schwartz GJ, Carbone KM. Viral teratogenesis: brain developmental damage associated with maturation state at time of infection. Brain Res Dev Brain Res 1999;112:237–44.
Sauder C, de la Torre JC. Cytokine expression in the rat central nervous system following perinatal Borna disease virus infection. J Neuroimmunol 1999;96:29–45.
Sauder C, Wolfer DP, Lipp H-P, Staeheli P, Hausmann J. Learning deficits in mice with persistent Borna disease virus infection of the CNS associated with elevated chemokine expression. Behav Brain Res 2001;120: 189–201.
Schneider-Schaulies S, Bieback K, Ayota E, Klagge I, ter Meulen V. Regulation of gene expression in lymphocytes and antigen-presenting cells by measles virus: consequences for immunomodulation. J Mol Med 2002;80:73–85.
Shen H, Zhang L, Yuen D, Logan R, Jung BP, Zhang G, et al. Expression and function of A1 adenosine receptors in the rat hippocampus following transient forebrain ischemia. Neuroscience 2002;114:547–56.
Solbrig MV, Koob GF, Fallon JH, Lipkin WI. Tardive dyskinetic syndrome in rats infected with Borna disease virus. Neurobiol Dis 1994;1:111–9.
Solbrig MV, Fallon JH, Lipkin WI. Behavioral disturbances and pharmacology of Borna disease. In: Koprowski H, Lipkin WI, editors. Borna disease. Current topics in microbiology and immunology, vol. 190. Berlin: Springer-Verlag; 1995. p. 93–102.
Solbrig MV, Koob GF, Fallon JH, Reid S, Lipkin WI. Prefrontal cortex dysfunction in Borna disease virus (BDV)-infected rats. Biol. Psychiatry 1996a;40:629–36.
Solbrig MV, Koob GF, Joyce JN, Lipkin WI. A neural substrate of hyperactivity in Borna disease: changes in dopamine receptors. Virology 1996b;222:332–8.

Solbrig MV, Koob GF, Lipkin WI. Naloxone-induced seizures in rats infected with Borna disease virus. Neurology 1996c;46:1170–1.

Solbrig MV, Koob GF, Lipkin WI. Cocaine sensitivity in Borna disease virus infected rats. Pharmacol Biochem Behav 1998;59:1047–52.

Solbrig MV, Koob GF, Lipkin WI. Orofacial dyskinesias and dystonia in rats infected with Borna disease virus; a model for tardive dyskinetic syndromes. Mol Psychiatry 1999;4:310–2.

Solbrig MV, Koob GF, Parsons LH, Kadota T, Horscroft N, Briese T, et al. Neurotrophic factor expression following CNS viral injury produces enhanced sensitivity to psychostimulants: potential mechanism for addiction vulnerability. J Neurosci 2000;20(RC104):1–5.

Solbrig MV, Koob GF, Lipkin WI. Key role for enkephalinergic tone in cortico-striatal–thalamic function. Eur J Neurosci 2002;16:1819–22.

Sprankel H, Richarz K, Ludwig H, Rott R. Behavior alterations in tree shrews (*Tupaia glis*, Diard 1820) induced by Borna disease virus. Med Microbiol Immunol (Berlin) 1978;165:1–18.

Stitz L, Krey H, Ludwig H. Borna disease in rhesus monkeys as a model for uveo-cerebral symptoms. J Med Virol 1981;6:333–40.

Stitz L, Dietzschold B, Carbone KM. Immunopathogenesis of Borna Disease. In: Koprowski H, Lipkin WI, editors. Borna disease. Current topics in microbiology and immunology, vol. 190. Berlin: Springer-Verlag; 1995. p. 75–92.

Stitz L, Bilzer T, Planz O. The immunopathogenesis of Borna disease virus infection. Front Biosci 2002;7:D541–55.

Tarazi FI, Tomasini EC, Baldessarini RJ. Postnatal development of dopamine and serotonin transporters in rat caudate–putamen and nucleus accumbens septi. Neurosci Lett 1998;254:21–4.

Thorsell A, Michalkiewicz M, Dumont Y, Quirion R, Caberlotto L, Rimondini R, et al. Behavioral insensitivity to restraint stress, absent fear suppression of behavior and impaired spatial learning in transgenic rats with hippocampal neuropeptide Y overexpression. Proc Natl Acad Sci U S A 2000;97:12852–7.

Toda S, McGinty JF, Kalivas PW. Repeated cocaine administration alters the expression of genes in corticolimbic circuitry after a 3-week withdrawal: a DNA macroarray study. J Neurochem 2002;82:1290–9.

Waelchli RO, Ehrensperger F, Metzler A, Winder C. Borna disease in a sheep. Vet Rec 1985;117:499–500.

Waltrip RW, Buchanan RW, Summerfelt A, Breier A, Carpenter WT, Bryant NL, et al. Borna disease virus and schizophrenia. Psychiatry Res 1995;56:33–44.

Weissenbock H, Nowotny N, Caplazi P, Kolodziejek J, Ehrensperger F. Borna disease in a dog with lethal meningoencephalitis. J Clin Microbiol 1998;36:2127–30.

Weissenbock H, Hornig M, Hickey WF, Lipkin WI. Microglial activation and neuronal apoptosis in Bornavirus infected neonatal Lewis rats. Brain Pathol 2000;10:260–72.

Whitaker-Azmitia PM. Serotonin and brain development: role in human developmental diseases. Brain Res Bull 2001;56:479–85.

Whitaker-Azmitia PM, Zhang X, Raio D. Gestational exposure to monoamine oxidase inhibitors in rats: preliminary behavioral and neurochemical studies. Neuropsychopharmacology 1994;11:125–31.

Yang X, Gabuzda D. Regulation of human immunodeficiency virus type 1 infectivity by the ERK mitogen-activated protein kinase signaling pathway. J Virol 1999;73:3460–6.

Zhang XF, Hu XT, White FJ. Whole-cell plasticity in cocaine withdrawal: reduced sodium currents in nucleus accumbens neurons. J Neurosci 1998;18:488–98.

Zocher M, Czub S, Schulte-Monting J, de la Torre JC, Sauder C. Alterations in neurotrophin and neurotrophin receptor gene expression in the rat central nervous system following perinatal Borna disease virus infection. J Neurovirol 2000;6:462–77.

Zwick W. Borna'sche krankheit und encephalomyelitis der tiere (Borna disease and encephalomyelitis in animals). In: Gildemeister F, Haagen E, Waldmann O, editors. Handbuch der viruskrankheiten (Handbook of viral diseases), vol. 2. Jena, Germany: Fischer; 1939. p. 252–354 [in German].