Neuroteratology and Animal Modeling of Brain Disorders

Trevor Archer and Richard M. Kostrzewa

Abstract Over the past 60 years, a large number of selective neurotoxins were discovered and developed, making it possible to animal-model a broad range of human neuropsychiatric and neurodevelopmental disorders. In this paper, we highlight those neurotoxins that are most commonly used as neuroteratologic agents, to either produce lifelong destruction of neurons of a particular phenotype, or a group of neurons linked by a specific class of transporter proteins (i.e., dopamine transporter) or body of receptors for a specific neurotransmitter (i.e., NMDA class of glutamate receptors). Actions of a range of neurotoxins are described: 6-hydroxydopamine (6-OHDA), 6-hydroxydopa, DSP-4, MPTP, methamphetamine, IgG-saporin, domoate, NMDA receptor antagonists, and valproate. Their neuroteratologic features are outlined, as well as those of nerve growth factor, epidermal growth factor, and that of stress. The value of each of these neurotoxins in animal modeling of human neurologic, neurodegenerative, and neuropsychiatric disorders is discussed in terms of the respective value as well as limitations of the derived animal model. Neuroteratologic agents have proven to be of immense importance for understanding how associated neural systems in human neural disorders may be better targeted by new therapeutic agents.

Keywords Neuro-ontogeny · Neurotoxins · Neurotoxicity · Neuroteratology · Epidermal growth factor · Nerve growth factor · 6-Hydroxydopa · 6-Hydroxydopamine · DSP-4 · MPTP · 5,7-DHT · Methamphetamine · NMDA · IgG-saporin · Domoic acid · Quinpirole · Valproate · Parkinson's disease · Schizophrenia · Autism · Lesch–Nyhan disease · Tardive dyskinesia

T. Archer (✉)
Department of Psychology, University of Gothenburg, Box 500,
430 50 Gothenburg, Sweden
e-mail: trevor.archer@psy.gu.se

R.M. Kostrzewa
Department of Biomedical Sciences, Quillen College of Medicine,
East Tennessee State University, PO Box 70577, Johnson City, TN 37614, USA
e-mail: kostrzew@etsu.edu

Curr Topics Behav Neurosci (2016) 29: 1–40
DOI 10.1007/7854_2015_434
Published Online: 09 February 2016

Contents

1 Introduction

The concept posed in this paper is that perinatal insult can influence later-life neural survival or later-life susceptibility to toxic challenge. Also, perinatal insult can alone result in lifelong neural and behavioral abnormalities in humans, able to be modeled by appropriate treatments of animals. The series of topics highlighted here provide support for what was once a concept, but which is now recognized fact, supported by experimental and observational data in animal subjects and humans.

There are an encyclopedic number of studies demonstrating that perinatal exposure of noxious or seemingly innocuous agents alter the pattern of neural ontogenetic development and produce permanent neuroanatomical, neurochemical, and/or behavioral abnormalities. Examples of this are provided for what might be termed selective neurotoxins.

One general and surviving notion has been that the neurodegenerative and, for that matter, even the neurodevelopmental psychiatric disorders are induced by specific agents that degenerate one or more clearly defined population(s) of neurons, circuits, and/or regions, e.g., dopaminergic neurons in parkinsonism. However, the much more prevalent issue of senescence is a wider phenomenon affecting cells throughout the body, including spontaneous dying of neurons, as per pars compacta substantia nigra (SNpc) dopaminergic neurons and onset of Parkinson's disease (PD) (Rodriguez et al. 2015). Neuropsychiatric disorders, such as schizophrenia, attention deficit/hyperactivity disorder (ADHD), autism and depression, and Lesch–Nyhan disease (LND), stem from abnormalities and disruptions, both genetic and environmental, of the normal courses of the developmental cycles (Grados et al. 2014; Groves et al. 2014). For example, exposure to femtomolar concentrations (fM, 10^{-15} mol/dm^3 or 10^{-12} mol/m^3) of fragrances (generally sweet or pleasant smell) results in morphological changes at the light microscopic level in fetal neuroblastoma cell lines pertaining to reduced oxytocin-positive and arginine vasopressin-positive neurons in male but not female neuroblastoma cell lines (Sealey et al. 2015). Stressor exposure during early life has the potential to increase an individual's susceptibility to a number of neuropsychiatric conditions such as mood and anxiety disorders and schizophrenia in adulthood. Epigenetic processes exert cellular/tissue-specific changes in regulating expression of genes, providing potential biomarkers for examining the developmental trajectory of early stress-induced susceptibility to adult neuropsychiatric and/or neurologic disorders (Ibi and González-Maeso 2015; Marco et al. 2016). With the proliferation of gene-based models and etiology-based models for studying brain disorders (Bezard et al. 2013), the predictability of human and animal in vivo outcomes for neurotoxicity and retardation of developmental trajectories proceeds apace.

Under conditions of chronic inflammation, "mediator" molecules like cytokines may be disadvantageous to organism development over prolonged or exaggerated periods. Neuroprotective or neurotoxic outcomes evolving from interactions between cytokines and/or metabolites of tryptophan catabolism, the neuroactive kynurenines, partly influenced by corticosteroid action, contribute to the fate of several signaling pathways, e.g., serotonergic, dopaminergic, and glutamatergic transmissions, and receptor functions such as *N*-methyl-D-aspartate receptor (NMDA-R) or α_7-nicotinic acetylcholine receptor (Myint 2013). For instance, altered kynurenine metabolism is implicated in the pathogenesis of Alzheimer's disease (AD), PD, and Huntington's disease (HD), whereas the metabolites and key enzymes, analogs of the metabolites, and small-molecule enzyme inhibitors, preventing the formation of neurotoxic compounds, confer both neuroprotective and therapeutic properties (Tan et al. 2012). Inflammatory mediators activate the kynurenine metabolic pathway and immobilize the production of neuroactive metabolites, thereby initiating a pathogenic cascade with neuropsychiatric consequences (Allison and Ditor 2015; Brundin et al. 2015; Meier et al. 2015). According to the (genetic) Vulnerability-stress-inflammation developmental notion of schizophrenia, stress generates immune alterations (proinflammatory cytokines)

that influence dopaminergic, serotonergic, noradrenergic, and glutamatergic neurotransmission through the activation of the enzyme indoleamine 2,3-dioxygenase (IDO) of tryptophan/kynurenine metabolites, leading to kynurenic acid, with the concomitant activation of microglia, a veritable cascade of neuroinflammatory events (Müller et al. 2015).

1.1 Developmental Inflammatory Processes

Immune activation through prenatal or early postnatal exposure to viruses or bacterial products (e.g., lipopolysaccharide (LPS)) consistently impairs brain development and influences behavioral, emotional, and cognitive functional domains (Kirsten et al. 2013; Xia et al. 2014; Zhu et al. 2014a, b) with consequences for the pathogenesis of neuropsychiatric conditions (Delany et al. 2015; Kelly et al. 2015; Mossakowski et al. 2015; Pariante 2015). Maternal inflammation is similarly reflected in neuroinflammatory events resulting in structural and functional disturbances to the developing offspring brain.

Prenatal LPS-induced reorganization of the dendritic architecture was found in both L2PC-A and L2PC-B types, predominantly in the L2PC-A type in mouse offspring (Gao et al. 2015); there was also a differential alteration of intrinsic electrophysiological properties of the two L2PC types. As the resting membrane potential of L2PC-A neurons became hyperpolarized, these neurons were less excitable, whereas the resting membrane potential of L2PC-B neurons was partially depolarized and more excitable. Thus, morphological and electrophysiological abnormalities were linked to pyramidal neuron dysfunction stemming from inflammatory events during pregnancy. Parental microglia-induced neuroinflammation, triggered by bacterial or viral infections, may induce features of neuropsychiatric/neurologic disorders, such as ADHD, schizophrenia, and autism in offspring (Byrnes et al. 2009). In mice exposed prenatally to LPS at gestational days 15 and 17, there was downregulation of peripheral benzodiazepine receptors (PBRs), mediated by the activation of mGluR5 in astrocytes (Arsenault et al. 2015). In addition, the mGluR5–PBR interaction in a mouse model of schizophrenia (Basta-Kaim et al. 2015; Wischhof et al. 2015) was applicable to brain disorder pathophysiology. Thus, LPS-driven ontogenetic effects at mGluR5 have implications in later-life onset of neuropsychiatric disorders.

Inflammatory cytokines are able to affect neuronal ontogeny indirectly by acting at glia and subverting their imbued neuroprotective action to one that is adverse for neurons. By this means, gestational inflammation can indirectly affect neural function—and thereby pose a risk for later age development of neurological or psychiatric disorders (Fukushima et al. 2015; Jo et al. 2015; Steardo et al. 2015). A number of mechanisms may come into play: (i) stimulation of the phagocyte NADPH oxidase (PHOX) to produce superoxide and derivative oxidants, (ii) expression of inducible nitric oxide synthase (iNOS) that produces NO and derivative oxidants, (iii) release of glutamate and glutaminase, (iv) release of tumor necrosis

factor alpha (TNF-α), (v) release of cathepsin B, (vi) phagocytosis of stressed neurons, and finally, (vii) decreased release of nutritive brain-derived neurotrophic factor (BDNF) and insulin-like growth factor-1 (IGF-1) (Brown and Vilalta 2015).

Despite all the evidence that neuroinflammation and reactive gliosis feature prominently in most brain and CNS disorders, the notion of glial cells as passive responders to neuronal damage rather than drivers of synaptic dysfunction is changing. Glia have active signaling activity with neurons and influence synaptic development, transmission, and plasticity by mobilizing a plethora of secreted and contact-dependent signals (Chung et al. 2015). Reactive astrogliosis, a feature of AD, presents a continuum of neuropathological processes with accompanying morphological, functional, genetic, and epigenetic events (Jain et al. 2015; Pekny et al. 2014; Steardo et al. 2015; Verkhratsky et al. 2015). Calcium, proteoglycan, TGF-β, NFκB, and complement mediate the neuron–glia interactions under physiological and neurodegenerative states (Lian and Zheng 2015). Although the influences of astrocytes on the aging process are more suspected than implicated, they appear to adopt different functions dependent on disease progression and the extent of accompanying parenchymal inflammation. Astrocytes enable clearance of Aβ and restrict the spread of inflammation in brain, yet astrocytes promote neurodegeneration in AD by releasing neurotoxins and negating crucial metabolic roles (Birch 2014). Using an experimental model of small subcortical infarcts in mice for studying pathophysiological changes in the corticospinal tract and assessing long-term neurologic outcomes and behavioral performance, Uchida et al. (2015) administered the vasoconstrictor peptide, endothlin-1 (ET-1), and the NOS inhibitor *N*(G)-nitro-L-arginine methyl ester (L-NAME), into the internal capsule of mice. At two months, they observed a loss of axons and myelin surrounded by reactive gliosis in the region of the injection and severe neurological deficits.

1.2 Perinatal Insult and Neurologic Neurodegenerative Disorders

The Latent Early-life Associated Regulation (LEARn) model poses environmental exposures as "hits," which, when sufficient in strength and/or number as a fetal insult, leads to altered neural development and later-life disorder or susceptibility to disorder (Lahiri et al. 2009)—giving support to the "developmental origins of health and disease" (DOHaD) hypothesis (Barker 2007). This topic has been recently reviewed, in reference to perinatal insult and the ultimate development of neurodegenerative disorders (Tartaglione et al. 2016).

For example, perinatal exposure of mice or monkeys to lead (Pb) results in later-life cognitive deficits accompanied by the upregulation of amyloid precursor protein (APP), Aβ deposits, and phosphorylated tau in brain—features of **Alzheimer's disease (AD)** (Bihaqi and Zawia 2013; Bihaqi et al. 2014). Similarly, perinatal exposure of rats to lead (Pb) leads to a similar pattern of deficits along

with an increase in the brain level of 8-hydroxy-2′-deoxyguanosine (oxo8dG), a major DNA oxidation metabolite reflecting oxidative stress (Bolin et al. 2006). Other heavy metals (arsenic, cadmium) and pesticide exposure during perinatal development produce similar dysfunctions in animals (Baldi et al. 2011; Ashok et al. 2015). This series of examples supports the contention that early-life insults can have permanent effects in brain and behavior.

In an analogous manner, perinatal exposure or treatment with iron leads to behavioral indices of **PD** in mice (Fredriksson et al. 1999, 2000) and rats (Dal-Pizzol et al. 2001), with effects thought to be associated with observed oxidative stress in brain. Manganese (Mn) had a direct effect but also increased the susceptibility of brain to later-life toxic insult (Cordova et al. 2012).

These examples give credence to the likelihood that there are multiple kinds of perinatal insults that produce lifelong neural dysfunctions, some of which lead to a greater incidence of neurological, neurodegenerative, and psychiatric disorders in humans.

1.3 Neurotrophins and Neuronal Development

In a long series of studies beginning in the first half of the twentieth century, R. Levi-Montalcini discovered that there were proteins termed neurotrophins that were essential for the development of the nervous system. One of these neurotrophins, nerve growth factor (NGF), was shown to promote the growth and development of the sympathetic nervous system during ontogeny, now known to act by regulating the expression of genes associated with axonal growth and synaptogenesis (Miller and Kaplan 2001). NGF likewise has a prominent effect on the maintenance and development of cholinergic nerves in basal forebrain (Niewiadomska et al. 2009). Impaired cleavage of proNGF to NGF has been suggested as one of the possible causes of degeneration of basal forebrain cholinergic nuclei in AD (Tuszynski and Blesch 2004). Reduced neuronal responding to NGF is another of many other possibilities related to the loss of cholinergic nerves in AD (Cooper et al. 1994). The multifactorial effect of NGF on the nervous system and on the immune system development has been recently reviewed (Bracci-Laudiero and De Stefano 2016).

Synthesis of NGF in brain cells and in the peripheral nervous system is upregulated by the catecholamines (Barra et al. 2014; Hasan and Smith 2014; Sygnecka et al. 2015), which is in keeping with the physiological relation between the level of NGF mRNA and the density of innervation in the peripheral sympathetic nervous systems (Furukawa 2015). NGF is essential for the survival and functional maintenance of forebrain cholinergic neurons projecting mainly to the cortex and hippocampus (Hohsfield et al. 2014; Iulita and Cuella 2014; Perez et al. 2015), with particular importance for the relative levels of pro-NGF and mature

NGF. Thus, for example, diabetic encephalography has been characterized by deteriorations in the maturation of NGF (Soligo et al. 2015). NGF increases low-density lipoprotein receptor levels in PC6.3 cells and in cultured septal neurons from embryonic rat brain (Do et al. 2015), indicating that NGF and simvastatin, which is used to decrease unhealthy lipid levels, stimulates lipoprotein uptake by neurons with a positive effect on neurite outgrowth. Increases in low-density lipoprotein receptors and lipoprotein particles in neurons may exert a functional role during the brain development, as well as in neuroregenerative processes and following traumatic brain injuries. Although aging is a normal physiological process accompanied, more often than not, by deteriorations in certain cognitive domains, alterations in the levels of neurotrophic factors NGF, BDNF, and GDNF (glia-derived neurotrophic factor) are implicated in this decline, which implicates lowered neurotrophic levels in the pathogenesis of AD and other age-related disorders (Budni et al. 2015).

2 Actions and Mechanisms of Selective Neurotoxins

2.1 6-Hydroxydopamine

6-Hydroxydopamine (6-OHDA), the first selective neurotoxin to come into common use, was discovered in the late 1960s by H Thoenen and JP Tranzer during their search for norepinephrine (NE) analogs that might provide dark osmophilic "staining" of noradrenergic nerves during the electron microscopic observation (Thoenen and Tranzer 1968a, b). 5-Hydroxydopamine (5-OHDA) fulfilled that criterion, but 6-OHDA to their surprise produced overt destruction of noradrenergic nerves and its action was selective, leaving surrounding tissues and other nerves intact. 6-OHDA was eventually found to produce its neurotoxicity by generating intraneuronal oxidative stress and by an action on mitochondrial cytochromes, thereby blocking ATP formation and energy depletion of neurons (Cohen and Heikkila 1974). Later, 6-OHDA neurotoxicity was extended to dopaminergic nerves, as well (Ungerstedt 1968, 1971).

6-OHDA has found extensive use in neuroscience research, being cited (as "6-hydroxydopamine OR 6-OHDA") in ~12,000 papers in PubMed. 6-OHDA is a useful agent for uncovering effects of noradrenergic and dopaminergic nerves and for studying neurotoxic processes and mechanisms and reactive neuroprotective strategic mechanisms of these nerves. As a neurotoxin, 6-OHDA destruction of pars compacta SNpc in adult species (rodents, non-human primates) is of value for producing animal modeling of PD. As a neuroteratogen—6-OHDA administration during ontogeny—6-OHDA has effectively modeled several neural disorders including PD, ADHD, and LND, each of which is described subsequently.

2.2 6-Hydroxydopa

Following the discovery of 6-OHDA as a neurotoxin, 6-hydroxydopa (6-OHDOPA) was developed with the rationale that (1) 6-OHDOPA would be able to cross the blood–brain barrier (6-OHDA does not), (2) to be decarboxylated to 6-OHDA in brain; thus, 6-OHDOPA would actually be a protoxin, and (3) 6-OHDOPA-derived 6-OHDA would then destroy noradrenergic and/or dopaminergic nerves deep in brain, (4) while obviating unintentional damage to other nerves which would otherwise occur during injection of 6-OHDA per se into brain (Ong et al. 1969; Berkowitz et al. 1970). Subsequently, 6-OHDOPA was confirmed as a neurotoxin, able to produce destruction to noradrenergic sympathetic nerves (Kostrzewa and Jacobowitz 1972; Sachs and Jonsson 1972a, b) and noradrenergic nerves in brain (Jacobowitz and Kostrzewa 1971; Kostrzewa and Jacobowitz 1973; Zieher and Jaim-Etcheverry 1973, 1975a, b). 6-OHDOPA also proved to be a unique neuroteratologic agent, able to destroy noradrenergic nerves in brain (Kostrzewa and Harper 1974)—with preference for locus coeruleus nuclei (Kostrzewa and Harper 1974; Tohyama et al. 1974a, b; Clark et al. 1979) and the dorsal bundle providing noradrenergic innervation to dorsal brain (Kostrzewa and Garey 1976, 1977)—while leaving dopaminergic innervation to rodent striatum virtually intact (Kostrzewa et al. 1988). This specificity of 6-OHDOPA for noradrenergic nerves provided a unique advantage in mapping noradrenergic nerves in brain in the 1970s (Jacobowitz and Kostrzewa 1971; Sachs et al. 1973).

6-OHDOPA, however, had specifically low potency and also lethality at high dose (Kostrzewa and Garey 1976). Part of the lethal effect may reside in additional agonist action of 6-OHDOPA at non-NMDA glutamatergic receptors (Rosenberg et al. 1991). At the time of its discovery 35 years ago, 6-OHDOPA was useful as a selective noradrenergic neurotoxin. Important discoveries were made by the use of this neurotoxin on noradrenergic systems in brain, including mapping of the dorsal noradrenergic bundle to forebrain, cerebellum, and spinal cord. 6-OHDOPA likewise was useful in uncovering the labile nature of locus coeruleus neurons. At this time, the inherent limitations of 6-OHDOPA relegate it to secondary status; tagged antibodies for marker enzymes (e.g., immunotoxin for dopamine-β-hydroxylase) also provide a more advantageous means to assess noradrenergic nerves. 6-OHDOPA mechanisms and actions were recently reviewed (Kostrzewa 2016).

2.3 DSP-4

DSP-4 [*N*-(2-chloroethyl)-*N*-ethyl-2-bromobenzylamine] is another neurotoxin discovered by S Ross and colleagues in the early 1970s during their search for bretylium-related compounds (Ross et al. 1973; Ross and Renyi 1976). DSP-4 was initially found to cross the blood–brain barrier and cyclize to a reactive aziridinium targeted to the NE transporter (NET) and taken up primarily by locus coeruleus

noradrenergic nerves, leading to NE depletion (Jonsson et al. 1981, 1982) and overt destruction (Lyons et al. 1989). DSP-4 was recently reviewed (Bortel 2014; Nowak 2016; Ross and Stenfors 2015).

As a neuroteratogen, DSP-4 has relatively selective action on locus coeruleus projections to neocortex, hippocampus, cerebellum, and spinal cord, while leaving peripheral sympathetic nerves relatively unaffected (Zieher and Jaim-Etcheverry 1975a). Typically, reactive sprouting of noradrenergic innervation to hindbrain and cerebellum occurs consequent to relative inactivation or destruction of locus coeruleus-derived innervation to neocortex, hippocampus and spinal cord (Jonsson et al. 1981, 1982; Dabrowska et al. 2007; Bortel et al. 2008; Sanders et al. 2011). Effects are lifelong. DSP-4 has been used to study the neurotoxic and neuroprotective mechanisms of noradrenergic neurons and to determine the association between early loss of noradrenergic innervation and brain and behavioral outcomes.

2.4 *Co-administration of DSP-4 and MPTP*

When noradrenergic nerves are lesioned with DSP-4 prior to MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treatment of C57/Bl6 mice, dopaminergic lesioning is enhanced (Fornai et al. 1997). Prenatal iron (Fe^{2+}, 7.5 mg/kg, on postnatal days 19–12) further exacerbates the effects on dopaminergic neurons and extent of movement disordering produced by the combination of DSP-4 and MPTP (Archer and Fredriksson 2006). Noradrenergic neuronal dysfunction is considered to add to the motor dysfunction in PD, as indicated by enhanced dysfunction of the subthalamic nucleus following the combination of DSP4 and 6-OHDA (Wang et al. 2014). This topic was recently reviewed (Archer 2016b).

2.5 *Methamphetamine*

The AMPH analog methamphetamine (METH) replicates many of the effects of AMPH. METH (like AMPH), with high affinity for the NET, DAT (dopamine transporter), and the serotonin (5-HT) transporter SERT, is accumulated by these nerves to evoke non-exocytotic release of NE, DA, and 5-HT (Sitte and Freissmuth 2010). Acute effects reflect sympathomimetic and serotoninergic actions at their respective receptor sites (de la Torre et al. 2000). Chronic METH is associated with neurotoxicity (Seiden et al. 1976), being related to acute METH-induced hyperthermia, promotion of reactive oxygen species (ROS), and excitotoxicity (Krasnova and Cadet 2009). Neuroteratologic effects of METH are expressed in large part by a spectrum of behavioral alterations, as outlined later in this paper.

2.6 Domoic Acid

Domoic acid, an agonist at AMPA/kainate-R, is an excitotoxin in high dose (Verdoorn et al. 1994; Tasker et al. 1996), producing neuronal loss and astrocytosis in hippocampus and amygdala, as well as prefrontal cortex and thalamus (Teitelbaum 1990). In both humans and laboratory rodents, neuropathological disturbances are characterized also by reactive gliosis and loss of neurons detected from 24 h onward and most severely after a week or two (Ananth et al. 2001, 2003). Immunohistochemical and histopathologic evidence of chronic inflammation from rats treated with domoic acid indicated severe neuronal degeneration, astrocytosis, microgliosis, universal NOS expression, and dystrophic calcification from 5 days to 54 days after administration (Vieira et al. 2015).

When administered to perinatal rats, domoic acid produces head tremor with vacuous chewing, "wet-dog shakes," circling, forelimb tremor, hindlimb hyperextension, and hind-paw biting. At very high dose myoclonic jerks and clonic-tonic convulsions (Xi et al. 1997; Doucette et al. 2000).

When administered in low dose during the second week of postnatal ontogeny, these rats in adulthood displayed prominent cell loss in hippocampal CA1 and CA3 regions (Doucette et al. 2004; Bernard et al. 2007), a reduction in GABA neurons (Gill et al. 2010) with prominent mossy fiber sprouting (Holmes et al. 1999), and behaviorally, these rats, as adults, had stage 2/3 seizure (Racine 1972) induced by a novel/stressful environment (Doucette et al. 2004). Other behavioral deficits have been noted (Pérez-Gómez and Tasker 2014). The neurotoxic and behavioral outcome of perinatal domoic acid was recently reviewed (Pérez-Gómez and Tasker 2014; Doucette and Tasker 2016).

2.7 192 IgG-Saporin

The immunotoxin 192 IgG-saporin consists of the monoclonal antibody 192 IgG conjugated to the ribosome-inactivating protein (RIP) saporin. In perinatal rats, 192 IgG targets the low-affinity rat NGF receptor ($p75^{NGF}$), which is expressed solely on cholinergic neurons in the nucleus basalis magnocellularis (NBM) and diagonal band of Broca (DBBh) in rat basal forebrain. Saporin, being then internalized by receptor-mediated endocytosis, travels by retrograde axonal transport to the neuronal perikaryon and inactivates ribosomes to inhibit protein synthesis, leading to neuronal cell death (Wenk et al. 1994; Leanza et al. 1995; Pappas et al. 1996; Robertson et al. 1998). Perinatal IgG-saporin selectively destroys 70–75 % of cholinergic in NBM/DBBh (Leanza et al. 1996), leading to $\sim$70 % cholinergic denervation of hippocampus. In contrast to 192 IgG-saporin treatment of adult rats, which also destroys cerebellar Purkinje cells (Leanza et al. 1995; Waite et al. 1995; De Bartolo et al. 2009, 2010), perinatal 192 IgG-saporin spares Purkinje cells which have a lower expression of $p75^{NGF}$.

192 IgG-saporin reduces ultrasonic vocalization (Kehoe et al. 2001; Ricceri et al. 2007) and impairs passive avoidance learning in rat pups (Ricceri et al. 2002). In adulthood, 192 IgG-saporin-lesioned rats spent less time exploring a novel environment (Ricceri et al. 1997; Scattoni et al. 2003), but otherwise there was limited impairment in learning and memory (Leanza et al. 1996; Pappas et al. 1996) except at 22 months (Pappas et al. 2005). The perinatal effects of IgG-saporin were recently reviewed (Petrosini et al. 2014, 2016).

2.8 Quinpirole

Acute administration of the DA D_2-R agonist quinpirole produces several short-lived behavioral effects, the most prominent being yawning with penile erection in male rats (Kostrzewa and Brus 1991). However, when administered to rats once a day for several days during postnatal ontogeny, quinpirole produces DA D_2-R supersensitization that is manifested as enhanced yawning, locomotor activity, altered pain threshold, and vertical jumping with paw treading (Kostrzewa et al. 1991, 1993a, b; Kostrzewa 1995; Kostrzewa and Kostrzewa 2012). DA D_2-R supersensitivity persists for the duration of the life span (Oswiecimska et al. 2000) and is associated with enhanced AMPH-induced release of DA in rat striatum (Nowak et al. 2001; Cope et al. 2010).

Rats that had been quinpirole-primed during the first week or more of postnatal life have cognitive impairment (Brown et al. 2002) and deficits in prepulse inhibition (Maple et al. 2015). These behavioral effects are accompanied by a reduced brain level of BDNF (Brown et al. 2008; Thacker et al. 2006) and reduced expression level of the regulator of G-protein-signaling (RGS) RGS 9 gene which functions to terminate D_2-R agonist action. Because these effects are largely attenuated by olanzapine (Thacker et al. 2006), rats with permanent D_2-R supersensitivity have been posited as an animal of schizophrenia (Brown et al. 2012; Brown and Peterson 2016; Kostrzewa et al. 2016c; Maple et al. 2015).

3 Animal Modeling with Neuroteratologic Agents

3.1 Rodent Model of PD Produced by Perinatal 6-OHDA Treatment

Perinatal intracerebral (icv) treatment of rats with 6-OHDA (134 μg, half on each side) produces near-total lesioning of SNpc and lifelong near-total dopaminergic denervation of striatum. Acutely there is no discernible behavioral effect, and rats develop into adulthood with no motor deficit. Permanent serotoninergic

hyperinnervation of striatum occurs as rats develop into adulthood (Berger et al. 1985; Snyder et al. 1986). Repeated DA D_1 agonist treatments in adulthood prime DA D_1-R, which remain supersensitized for the remainder of life, while DA D_2-R are less affected (Breese et al. 1984a, 1985a, b, 1987; Criswell et al. 1989; Hamdi and Kostrzewa 1991; Kostrzewa and Gong 1991; Gong et al. 1992, 1993a, 1994; see Kostrzewa 1995; Kostrzewa et al. 1998). The perinatal 6-OHDA-lesioned rats represents a suitable animal model of severe PD (Kostrzewa et al. 2006; Kostrzewa et al. 2016b).

An alternative animal model of PD is produced by administering 6-OHDA unilaterally in adult rats to lesion the SNpc; effectiveness of known and putative anti-parkinsonian agents can be assessed by counting the numbers of rotations produced by those treatments (Ungerstedt 1971). Bilateral 6-OHDA adulthood treatment would produce aphasia, adipsia, lack of grooming, and immobility—with consequent death in a matter of day, except with prolonged special care. Still, these rats remain fragile.

In contrast to adulthood 6-OHDA-lesioned rats, the perinatally 6-OHDA-lesioned rats provide immense advantages for assessing anti-parkinsonian agents. Because perinatally 6-OHDA-lesioned rats are able to eat, drink, groom, and ambulate—as per intact controls, even in the relative absence of SNpc dopaminergic neurons, this neurochemical/neuroanatomical model of PD is behaviorally robust and demonstrates ambulatory enhancement when treated with anti-parkinsonian agents; motor dyskinesia produced by high-dose L-DOPA is able to be discerned (Kostrzewa et al. 2006; Kostrzewa et al. 2016b). These rats have been used to assess the elevation of tissue levels of striatal DA after acute L-DOPA treatment (Kostrzewa et al. 2002, 2005); also the effect of acute AMPH on striatal exocytosis (Nowak et al. 2005); and the effect of acute L-DOPA on striatal levels of ROS (Kostrzewa et al. 2000, 2002; Nowak et al. 2010). The perinatal 6-OHDA-lesioned rat, as a modeling of PD, is described in detail in a recent paper (Kostrzewa et al. 2016b).

3.2 Exercise Effectiveness in Improving Behavioral Deficits in a Rodent Model of PD

Physical exercise has proven to be effective and is a recommended alternative for ameliorating, even reversing motor and behavioral dysfunctions in neurodegenerative disorders (Archer 2011, 2012, 2014; Archer et al. 2014a, b; Archer and Garcia 2015; Archer and Kostrzewa 2012; Archer et al. 2011a, b, 2014a, b). In a rodent model of PD, exercise produced profound ameliorative effects (Archer and Fredriksson 2010, 2012, 2013; Archer et al. 2011a, b, 2014a, b; Fredriksson et al. 2011). Exercise is a particularly useful intervention in PD patients in sedentary occupations. The several links between exercise and quality of life, disorder

progression and staging, risk factors, and symptom biomarkers in PD all endow a promise for improved prognosis. Nutrition provides a strong determinant for disorder vulnerability and prognosis, with fish oils and vegetables with a Mediterranean diet offering both protection and resistance, whereas exercise increases synaptic strength and influences neurotransmission. Nevertheless, the heterogeneity of exercise/activity programs, including stretching, muscle strengthening, balance, postural exercises, occupational therapy, cueing, and/or treadmill training, remains an issue and consensus concerning the optimal approach (Abbruzzese et al. 2015; but see also Uhrbrand et al. 2015). Three factors determining the effects of exercise on disorder severity of patients may be presented: (i) exercise effects on motor impairment, gait, posture, and balance; (ii) exercise reduction of oxidative stress, stimulation of mitochondrial biogenesis, and upregulation of autophagy; and (iii) exercise stimulation of dopaminergic neurochemistry and trophic factors.

Running-wheel performance, as measured by distance run by control and parkinsonian-modeled mice from different treatment groups, was related to dopaminergic system integrity, indexed by striatal DA levels (Archer and Kostrzewa 2016). Support for these notions (regarding the almost finite advantages to be gleaned from exercise) continues to emerge. Exercise triggers plasticity-related events in the human PD brain, such as corticomotor excitation, increases in gray matter volume, and an elevation in BDNF levels (Hirsch et al. 2015). Finally, both nutrition and exercise may facilitate positive epigenetic outcomes, such as lowering the dosage of L-DOPA required for a therapeutic effect. Exercise, as a potent epigenetic regulator, implies a potential to counteract pathophysiological processes and alterations, notwithstanding a paucity of understanding in the underlying molecular mechanisms and dose–response relationships (Archer 2015).

3.3 *Rodent Model of ADHD Produced by Perinatal 6-OHDA with Adulthood 5,7-DHT Lesions*

In the 1970s, B Shaywitz and colleagues produced an animal of "minimal brain dysfunction," akin to today's nomenclature for ADHD, by 6-OHDA lesioning of perinatal rats. These rats demonstrate attentional deficits with spontaneous hyperlocomotor activity, each of which is attenuated by acute AMPH treatment (Shaywitz et al. 1976a, b). Over the past 40 years, this has remained the gold standard for rodent modeling of ADHD.

A variation of this model consists of perinatal 6-OHDA lesioning (134 μg, half on each side), followed by adulthood (10 weeks of age) lesioning with 5,7-dihydroxytryptamine (5,7-DHT, 75 μg icv). Treatment of 6-OHDA-lesioned rats with 5,7-DHT had the effect of reducing striatal serotoninergic hyperinnervation by 30 % and suppressing D_1-R supersensitivity while enhancing 5-HT_{2C}-R sensitivity. Behaviorally, these rats displayed enhanced hyperlocomotor activity (vs rats lesioned solely with 6-OHDA), and this activity was attenuated by AMPH (Kostrzewa et al. 1994). Moreover, this animal model of ADHD was able to discern

the ability of m-chlorophenylpiperazine (mCPP), a 5-HT agonist, to suppress the hyperlocomotor activity and thereby indicate a new approach toward ADHD treatment (Brus et al. 2004). In vivo microdialysis study indicates that the activity-suppressant effects of AMPH and mCPP are unrelated to exocytosis of striatal DA and 5-HT (Nowak et al. 2007). The higher level of hyperlocomotor activity in rats with the dual 6-OHDA + 5,7-DHT lesions represents a more robust model of ADHD in testing agents with the potential for ADHD treatment (Paterak and Stefański 2014; Kostrzewa et al. 2008). This animal model for ADHD was recently reviewed (Kostrzewa et al. 2016a). A non-pharmacological approach toward abating features of ADHD has been demonstrated (Archer and Kostrzewa 2012).

3.4 ADHD and NMDA-R Systems

An imbalance between central inhibitory/excitatory neurotransmitters and relative activity/connectivity between brain regions, with concomitant disturbances of higher cognitive function, is considered to reflect the pathogenesis of ADHD (He et al. 2015; Mohl et al. 2015; Monden et al. 2015; Roman-Urrestarazu et al. 2015).

Dysfunction of the default-mode network in ADHD patients is considered together with some of the animal models used to examine the neurobiological aspects of ADHD. Much evidence indicates that compounds/interventions that antagonize/block glutamate receptors and/or block glutamate signaling during the "brain growth spurt" (or in the adult animal model) may induce functional and biomarker deficits. Mice treated with glutamate receptor antagonist (MK-801, dizocilpine; ketamine) during the "brain growth spurt" fail to display exploratory activity when placed in a novel environment (the test cages) and later fail to adapt to the environment with locomotor suppression, implying a cognitive dysfunction. A disturbance of glutamate signaling during a critical stage of neural ontogeny may contribute to the ADHD pathophysiology. In a functional magnetic resonance imaging (fMRI) study of executive functioning in ADHD adults and matched controls, it was observed that in people with ADHD, there was a failure of deactivation of the medial prefrontal cortex (Salavert et al. 2015). In another study of ADHD adults, using a rest-to-take switching task, there was a disturbed reinitiation of a rest state.

"Hot" and "cool" cognitive functions present a dichotomy within executive function whereby the former refers to affective domains and the latter to cognitive domains (Doebel and Zelazo 2013; Hongwanishkul et al. 2006; Zelazo et al. 2003, 2004). Top-down processes that operate in more affectively neutral contexts have been termed "cool" executive functioning, whereas those operating in motivationally and emotionally significant situations are referred to as "hot" (Zelazo and Carlson 2012). ADHD children exhibited "cool" executive function deficits which appeared to be unrelated to comorbid oppositional defiant disorder (Antonini et al. 2015). Finally, Babenko et al. (2015) have highlighted the intricate interplay

between prenatal stress exposure, associated changes in miRNA expression, and DNA methylation in placenta and brain with possible links to greater risks for incidence of ADHD later in life. The association of studies with NMDA-R antagonists and ADHD has been reviewed recently (Archer 2016a; Archer and Garcia 2016).

3.5 *Rodent Model of Lesch–Nyhan Disease Produced by Perinatal 6-OHDA Treatment*

Lesch–Nyhan disease (LND), a relatively rare neuroteratologic disorder attributable to a mutation in the HPRT 1 gene, is characterized by deficiency in hypoxanthine–guanine phosphoribosyltransferase (HGPRT). Abnormality in purine recycling leads to high serum levels of uric acid, the end product of purine metabolism, and gout—deposition of uric acid crystals in joints and soft tissue. Neurological symptoms represent a range of stages from mild to severe, but often being associated with self-biting and self-mutilation (Abel et al. 2014; Fu et al. 2015; Schroeder et al. 2001). In five different strains of mice with an HPRT gene knockout—characterized by one of two different HPRT gene mutations (Jinnah et al. 1999)—the nigrostriatal dopaminergic tract was found to be incompletely developed and the striatum had both reduced DA content and increased oxidative stress (Visser et al. 2001). While the HPRT-deficient mouse represents a viable model for the enzymatic deficiency in LND, the behavioral counterpart representing self-mutilation, however, is better modeled in rats that were perinatally lesioned with 6-OHDA (Breese et al. 1984b, 1986, 1989, 1990a, b; 1994; 2005). In these rats, DA D_1-R are overtly supersensitive (for some behaviors) (Kostrzewa and Gong 1991; Kostrzewa et al. 1992; Gong et al. 1993a, b; 1994) and are further able to be supersensitized by repeated treatments with L-DOPA or a D_1-R agonist—a priming process (Breese et al. 1984a, 1985a, b, 1987). When perinatal 6-OHDA-lesioned rats are acutely treated as adults with L-DOPA or with a DA D_1-R agonist, there is prominent self-biting and self-mutilation that can be counteracted with a DA D_1-R antagonist (see Wong et al. 1996; Papadeas and Breese 2014). Curiously, LND individuals have a DA deficiency in basal ganglia (as per 6-OHDA rats), and this apparently accrues from inadequate development of dopaminergic innervation (Göttle et al. 2014). The perinatal 6-OHDA-lesioned rat as a model of LND has recently been reviewed (Knapp and Breese 2016).

3.6 *Permanent Animal Model of Tardive Dyskinesia*

Tardive dyskinesia (TD) is a movement disorder produced in primates and other mammalian species by repeated treatments, over a period of months, with a DA D_2-

R antagonist. In humans, the D_2-R antagonist is a common feature of antipsychotic agents used to treat schizophrenia. TD presents as involuntary repetitive purposeless movements, most often of the lower face—resembling someone chewing gum and sometimes also with tongue thrusting (Casey 1987; Jeste and Caligiuri 1993). In rats, TD is most reasonably produced by including haloperidol or other D_2-R antagonist in the drinking water (Waddington et al. 1983; Waddington 1990). After a period of ~3 months, these rats, behaviorally, display spontaneous purposeless (vacuous) chewing movements (VCMs) which persist for as long as the D_2-R antagonist is present in the drinking water. After withdrawal of the D_2-R antagonist from drinking water, VCMs gradually disappear over a period of 4 to 6 weeks. This latter feature in rats—relating to the regression of TD upon D_2-R antagonist withdrawal—contrasts with human TD, in which the TD persists and is often permanent even after the D_2-R antagonist withdrawal.

In an attempt to produce a permanent model of TD, rats were first lesioned as perinates with 6-OHDA (134 μg, half on each side). When these rats (and controls) reached adulthood, haloperidol was added to the drinking water for a period of nearly one year. While intact control rats developed TD (i.e., increased number of VCMs) after ~3 months, 6-OHDA-lesioned rats developed TD only after 2 months. Moreover, the number of VCMs in haloperidol/6-OHDA rats was 2-fold greater than the number of VCMs in haloperidol/intact control rats. Significantly, after the removal of haloperidol from drinking water (i.e., haloperidol withdrawn stage), VCMs gradually disappeared in haloperidol/intact rat over a period of ~2 months, while VCMs persisted in 6-OHDA-lesioned rats, at the same elevated level and until the experiment ended 8 months later. At that time, it was determined that the D_2-R number (i.e., V_{max}) had been increased during the haloperidol phase and that D_2-R number had reverted to normal by 8 months—signifying that numbers of VCMs were unrelated to numbers of strital D_2-R (Huang et al. 1997).

The advantage of persistent VCMs in the withdrawal phase is that it becomes possible to test agents that might have the ability to suppress VCMs. To this end, it was found that agonists and antagonist at both the D_2-R and D_1-R had no effect, nor did agonists or antagonists at a number of other types of receptors. Only antagonists at 5-HT-R attenuated VCMs in rats in the withdrawal phase, and the common feature of each of these antagonists was that they have affinity for the 5-HT_{2C}-R, a likely site that can be targeted to reduce TD in humans during the antipsychotic withdrawal phase (Kostrzewa et al. 2007). This animal model of TD is described in detail in a recent paper (Kostrzewa and Brus 2016).

3.7 Valproate Modeling of Autism Spectrum Disorder

Prenatal/postnatal/perinatal etiologies, ranging from exposures involving drugs to infections, as well as genetic factors, are complicit in autism spectrum disorder

(ASD) that affects roughly 1–2 % of all children, according to the current analyses (Pelly et al. 2015). Several maternal diseases during pregnancy are linked to ASD, pregestationally and/or gestationally, including diabetes mellitus, maternal infections (i.e., rubella, cytomegalovirus), prolonged fever, and maternal inflammation, inducing changes in a variety of inflammatory cytokines (Ornoy et al. 2015); among external agents affecting ASD outcome are drugs such as valproic acid (VPA), the anticonvulsant agent and mood stabilizer, and antiepileptic compounds (Kulaga et al. 2011; Jacobsen et al. 2014). VPA is associated with poorer longer-term child developmental outcomes (Galbally et al. 2010).

Several aspects of animal models, generally and specifically pertaining to ASD, are scrutinized and surveyed, including construct validity, face validity, ASD-like behavioral and neurochemical alterations, histone deacetylase inhibition which elevates ROS, oxidative stress, and the status of experimental models and mitigating factors. These above processes relate to an altered epigenetic landscape in ASDs via altered methylation/hydroxymethylation patterns, local histone modification patterns, and chromatin remodeling (Banerjee et al. 2014; Grayson and Guidotti 2015; Siniscalco 2015).

ASD is characterized by deficits in social interaction and restricted or repetitive behaviors, but often accompanied by other behavioral (e.g., aggression), intellectual (e.g., lower IQ), neurological (e.g., epilepsy), or psychiatric (e.g., anxiety, depression) symptoms (Levy et al. 2009). The antiepileptic drug valproate (VPA), when used clinically to treat epilepsy and bipolar disorder in pregnant women (Lloyd 2013), is associated with a 4 % risk for offspring to develop ASD (Christianson et al. 1994; Christensen et al. 2013), with the incidence being 4–5 times greater in males (Wingate et al. 2014). Several types of animal models of ASD have been produced, but the most common model is produced by VPA treatment of perinatal rats (Rodier et al. 1997; Ranger and Ellenbroek 2016).

When pregnant rats are treated with VPA on gestation day 12, the time of fetal neural tube closure (Kim et al. 2011), the brain of offspring has notable abnormalities, including increased neocortical thickness with a higher number of cortical neurons (Sabers et al. 2015), reduced spine density in the hippocampus (Takuma et al. 2014), hyperserotonemia (Narita et al. 2002), and other defects. Behaviorally in rats and mice, there is hyperactivity, repetitive behaviors, and social deficits (Kim et al. 2014), resembling the behavioral spectrum in humans with ASD.

VPA is thought to act by inhibiting histone deacetylase (Phiel et al. 2001), resulting in hyperacetylated histones and associated increased transcriptional activity of multiple genes (Lloyd 2013), which is thought to account for the neuroteratologic effects. Secondarily, VPA increases the production of ROS in brain (Winn and Wells 1999), which may be detrimental to DNA integrity.

Animal modeling of ASD by VPA has been reviewed recently (Roullet et al. 2013; Ranger and Ellenbroek 2016).

4 Perinatal Insults that Model Psychosis Schizophrenia

There are a plethora of agents that, when administered to animals during ontogenetic development, model features of schizophrenia in the adulthood stage. Some of the more common agents having such an effect include epidermal growth factor (EGF) and its homologue neuregulin (NRG-1), METH, phencyclidine (PCP), and quinpirole. Details regarding these substances and their respective roles in animal modeling of psychosis and schizophrenia are described in the following section.

4.1 Epidermal Growth Factor and Schizophrenia Modeling

When administered to perinatal rats and mice, both EGF and NRG-1 produce adulthood effects that mirror some of the features common in schizophrenia: PPI deficit, altered sensorimotor gating and social interaction, exploratory suppression, cognitive deficit, sensitization to psychostimulants (METH; MK-801, dizocilpine), and other behavioral effects (Sotoyama et al. 2011, 2013; Sakai et al. 2014). Most deficits are reversed by atypical antipsychotics such as clozapine and risperidone but not by typical antipsychotics such as haloperidol (Sotoyama et al. 2013). Yet, in the EGF and NRG-1 models, learning is not compromised, as demonstrated by testing for context fear learning and passive avoidance learning (Futamura et al. 2003; Tohmi et al. 2005).

EGF is thought to exert its major effect on dopaminergic neurons in the SN, increasing dopaminergic activity in the globus pallidum (Sotoyama et al. 2011), while NRG-1 is more selective for dopaminergic neurons in the VTA (Abe et al. 2009; Iwakura et al. 2011a, b), producing enhanced dopaminergic activity in the prefrontal cortex (Kato et al. 2011). ROS formation is considered as a primary process in mediating these effects, as antioxidants suppress some of the adulthood behavioral deficits (Mizuno et al. 2008, 2010). This topic has been reviewed recently (Nagano et al. 2016).

4.2 Phencyclidine and Schizophrenia Modeling

In rodents, prolonged non-competitive NMDA-R antagonism by ketamine or PCP evokes a change in biomarkers in brain accompanied by a spectrum of behavioral activities that model schizophrenia—with non-classical antipsychotics acutely reversing many of the deficits (Barnes et al. 2015; Pyndt Jørgensen et al. 2015). Acute and subchronic treatments with PCP affect differentially the neuronal activity of different brain regions: basal DA, but not serotonin. Output in the medial prefrontal cortex is markedly reduced, and tyrosine hydroxylase expression in the ventral tegmental area is decreased, thereby accounting in part for concomitant

behavioral alterations expressed through locomotor sensitization and cognitive deficits (Castañé et al. 2015).

Perinatal administration of the NMDA-R antagonist PCP to rodents produces a spectrum of neuropathological and behavioral effects that model some of the features of schizophrenia. Disruption of glutamate signaling during ontogeny by PCP is thought to impede development of the GABAergic system in brain (Ben-Ari et al. 1997; Le Magueresse and Monyer 2013), resulting in an overall imbalance in neuronal excitation and inhibition in brain in adulthood (Hoftman and Lewis 2011). In perinatal PCP-treated rats and mice, there is an adulthood reduction in fast-spiking GABAergic interneurons in medial prefrontal cortex, nucleus accumbens, and hippocampus (Nakatani-Pawlak et al. 2009; Kaalund et al. 2013; Radonjic et al. 2013; Kjaerby et al. 2014), mimicking reduced GABAergic interneuronal activity in the brain of schizophrenic patients (Reynolds et al. 2004). In the nucleus accumbens, there is also a prominent reduction in dendritic spine density of spiny neurons (Nakatani-Pawlak et al. 2009). Anatomic and neurochemical changes in PCP rodents include a decrease in the number of parvalbumin-positive cells and spine density in the frontal cortex, nucleus accumbens, and hippocampus (Nakatani-Pawlak et al. 2009). Also in brain, glutathione and antioxidant defenses are reduced (Radonjic et al. 2010; Stojkovic et al. 2012).

Behaviorally, there are cognitive deficits in the adulthood rodents that were treated perinatally with PCP, as demonstrated by impaired working memory (Morris water maze testing (Sircar 2003) and rate of learning (delayed spontaneous alternation task) (Wang et al. 2001), sensorimotor dysfunction (deficit in prepulse inhibition) (Anastasio and Johnson 2008; Broberg et al. 2010, 2013; Chen et al. 2011; Kjaerby et al. 2013), social withdrawal (White et al. 2009), reduced attention in a social novelty discrimination paradigm (Terranova et al. 2005), and executive function (attentional set-shifting task for executive function) (Broberg et al. 2008). Many of the behavioral deficits are reversed by atypical antipsychotics. This topic was recently reviewed (Neill et al. 2014; Grayson et al. 2016).

4.3 Methamphetamine and Schizophrenia Modeling

METH, used and abused illicitly as an aphrodisiac and euphoriant, produces elevated mood, increased alertness and concentration, "energy" in fatigued individuals, and reduced appetite and promotes (initial) weight loss at lower doses, whereas at higher doses the drug induces psychosis, affective disorders, and rhabdomyolysis (Ago et al. 2006; De Carolis et al. 2015; Harro 2015; Mouton et al. 2015). METH use by pregnant women is associated with cognitive, attentional, and mood dysfunctions in offspring (Hrebíčková et al. 2014; McDonell-Dowling and Kelly 2015; Smith et al. 2015).

Ontogenetic effects of METH are diverse and heavily reliant on gestational age in terms of long-lived alterations in behavior, epigenetic expression, neuronal

organization, and overall neurotransmission and receptor parameters (Roos et al. 2015; Vrajová et al. 2014). The prenatal effects on cognitive and emotional behavior provide evidence of drastic disruptions of normal behavioral patterns (Fialová et al. 2015; Malinová-Ševčíková et al. 2014; Šlamberová et al. 2014, 2015). Long-term behavioral alterations induced by chronic METH use imply alterations in gene and protein expression within specific brain subregions involved in the reward circuitry and accompanied by major epigenetic modifications—histone acetylation and methylation (Desplats et al. 2014; Godino et al. 2015). Although epigenetic changes have not as yet been detected following prenatal METH exposures, these findings are awaited (Cadet 2014; Cadet and Jayanthi 2013).

Perinatal METH treatment has a range of effects on adulthood behaviors in rodents, depending upon whether METH is pre- and/or postnatal (Graham et al. 2013; Jablonski et al. 2016). Postnatal METH treatment in the range of birth through the postweaning period has the most pronounced effects, generally suppressing adulthood spontaneous locomotor activity and increasing acoustic startle reactivity (Vorhees et al. 2009). Given at the critical postnatal period, METH produces learning impairment and spatial memory impairment (Vorhees et al. 1994a, b, 2009).

Perinatal METH produces a persistent reduction in brain levels of DA and 5-HT, inhibiting tyrosine hydroxylase activity (Ricaurte et al. 1982; Bowyer et al. 1998), also 5-HT transporters (Kokoshka et al. 1998), and also other neurotransmitter systems. This topic was recently reviewed (Bisagno and Cadet 2014; Jablonski et al. 2016).

4.4 Quinpirole and Schizophrenia Modeling

Repeated daily postnatal quinpirole treatments of rats produce permanent DA D_2-R supersensitivity (Kostrzewa 1995; Kostrzewa et al. 2003, 2004, 2008, 2011, 2016c). In adulthood, these rats display enhanced D_2-R agonist-evoked behaviors and a spectrum of behavioral alterations. Rats exhibit improved active avoidance responding (Brus et al. 1998b), learning and memory deficits (Brus et al. 1998a) in the Morris water maze task, on place, and on match-to-place versions of this task (Brown et al. 2002, 2004a, 2005), and a deficit in prepulse inhibition (PPI) to acute startle (Maple et al. 2007). In the hippocampus on these rats, BDNF and NGF were reduced (Thacker et al. 2006; Maple et al. 2007), while in the striatum, nucleus accumbens, and frontal cortex expression of RGS9, a transcript regulating G-protein coupling to the D_2-R was reduced (Maple et al. 2007). Long-term olanzapine treatment reversed the cognitive deficits, reversed the PPI deficit, and normalized otherwise reduced BDNF and NGF levels in hippocampus (Thacker et al. 2006; Maple et al. 2007) and RGS9 expression (Maple et al. 2007). Because nicotine likewise reverses D_2-R supersensitization, drugs acting on α_7 nAChRs (e.g., nicotine) have been suggested for the treatment of schizophrenia (Tizabi et al. 1999;

Brown et al. 2004b, 2006; Perna and Brown 2013). Quinpirole modeling of schizophrenia was recently reviewed (Kostrzewa et al. 2016a, b, 2016c; Brown and Peterson 2016).

4.5 Stress and Neuropsychiatric Disorders

Prenatal restraint stress (PRS) during the last week of gestation is associated with postweaned offspring displaying attentional deficits, increased anxiety, impaired spatial learning (Lemaire et al. 2000) and deficit in working memory (Maccari et al. 2003), reduction in social play behavior, increased latency in approaching a novel object (Laviola et al. 2004), and a syndrome complex resembling features of ASD (see Weinstock 2008). Clearly, glucocorticoids are implicated in these outcomes. Disruption in the circadian rhythm also has analogous effects to PRS, as each is posed as a means to model psychiatric disorders (Marco et al. 2016).

4.6 Genetic Model of Alzheimer's Disease

In the laboratory mouse model for AD, APPswe/PS1dE9, with mutant transgenes of APP and presenilin-1 (PS1), chronic inflammation provokes amyloid plaque formation as early as 4 months of age, with numbers of plaques increasing with aging (Ruan et al. 2009). CD11b-positive microglia clusters appeared in hippocampus and neocortex at the same period of development and these also proliferated with age. Clustered glial fibrillary acidic protein (GFAP)-positive astrocytes were observed in hippocampus and cortex after six months of age and became more numerous with aging. Astrocytes appear to be central to AD pathophysiology since the β-amyloid peptide Aβ suppresses cholinergic innervation and synaptic function, subsequent to astrocytic glutamate gliotransmission. Further, Aβ causes neuronal hyperexcitability (Hertz et al. 2015). Other developmental animal models of AD are expected to be introduced and to become more commonplace.

5 Conclusion

Neurotoxins have become paramount in exploring neuronal function in relation to neuroscience research and, in particular, in animal modeling of neurological, psychiatric, and behavioral dysfunctional states. This concise review highlights the mechanisms and action of the most commonly used neurotoxins and reviews the use of individual neurotoxins in animal modeling of PD, ADHD, LND, autism, TD, and psychotic and schizophrenic states. The influence of neurotrophins, EGF in particular, on ontogenetic is outlined, and the influence of perinatal stress as well as

disrupted circadian cycling on neuronal ontogeny is described. Animal modeling of human disorders is likely to be used to an ever greater extent and through use of neurotoxins yet to be discovered.

References

Abbruzzese G, Marchese R, Avanzino L, Pelosin E (2015) Rehabilitation for Parkinson's disease: Current outlook and future challenges. Parkinsonism Relat Disord pii:S1353-8020(15)00380-6

Abe Y, Namba H, Zheng Y, Nawa H (2009) In situ hybridization reveals developmental regulation of ErbB1-4 mRNA expression in mouse midbrain: implication of ErbB receptors for dopaminergic neurons. Neuroscience 161(1):95–110

Abel TJ, Dalm BD, Grossbach AJ, Jackson AW, Thomsen T, Greenlee JD (2014) Lateralized effect of pallidal stimulation on self-mutilation in Lesch-Nyhan disease. J Neurosurg Pediatr 14(6):594–597

Ago M, Ago K, Hara K, Kashimura S, Ogata M (2006) Toxicological and histopathological analysis of a patient who died nine days after a single intravenous dose of methamphetamine: a case report. Leg Med (Tokyo) 8(4):235–239

Allison DJ, Ditor DS (2015) Targeting inflammation to influence mood following spinal cord injury: a randomized clinical trial. J Neuroinflammation 12(1):204

Ananth C, Thameem Dheen S, Gopalakrishnakone P, Kaur C (2001) Domoic acid-induced neuronal damage in the rat hippocampus: changes in apoptosis related genes (bcl-2, bax, caspase-3) and microglial response. J Neurosci Res 66(2):177–190

Ananth C, Gopalakrishnakone P, Kaur C (2003) Induction of inducible nitric oxide synthase expression in activated microglia following domoic acid (DA)-induced neurotoxicity in the rat hippocampus. Neurosci Lett 338(1):49–52

Anastasio NC, Johnson KM (2008) Atypical anti-schizophrenic drugs prevent changes in cortical *N*-methyl-D-aspartate receptors and behavior following sub-chronic phencyclidine administration in developing rat pups. Pharmacol Biochem Behav 90(4):569–577

Antonini TN, Becker SP, Tamm L, Epstein JN (2015) Hot and cool executive functions in children with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder. J Int Neuropsychol Soc 21(8):584–595

Archer T (2011) Physical exercise alleviates debilities of normal aging and Alzheimer's disease. Acta Neurol Scand 123:221–238

Archer T (2012) Influence of physical exercise on traumatic brain injury deficits: scaffolding effect. Neurotox Res 21(4):418–434

Archer T (2014) Health benefits of physical exercise for children and adolescents. J Novel PysioTher 4:203

Archer T (2015) Physical exercise as an epigenetic factor determining behavioral outcomes. Clin Exp Psychol 1:1

Archer T (2016a) NMDA-R blockers and ADHD modeling, In: Kostrzewa RM, Archer T (eds.) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Archer T (2016b) Noradrenergic-dopaminergic interactions due to DSP4—MPTP neurotoxin treatments: iron connection. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Archer T, Fredriksson A (2006) Influence of noradrenaline denervation on MPTP-induced deficits in mice. J Neural Transm (Vienna) 113(9):1119–1129

Archer T, Fredriksson A (2010) Physical exercise attenuates MPTP-induced deficits in mice. Neurotox Res 18(3–4):313–327

Archer T, Fredriksson A (2012) Delayed exercise-induced functional and neurochemical partial restoration following MPTP. Neurotox Res 21(2):210–221

Archer T, Fredriksson A (2013) The yeast product Milmed enhances the effect of physical exercise on motor performance and dopamine neurochemistry recovery in MPTP-lesioned mice. Neurotox Res 24(3):393–406

Archer T, Garcia D (2015) Exercise and dietary restriction for promotion of neurohealth benefits. Health 7:136–152

Archer T, Garcia D (2016) Attention-deficit/hyperactive disorder: focus upon aberrant *N*-methyl-D-aspartate receptor systems. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Archer T, Kostrzewa RM (2012) Physical exercise alleviates ADHD symptoms: regional deficits and development trajectory. Neurotox Res 21(2):195–209

Archer T, Kostrzewa RM (2016) Exercise and nutritional benefits in PD: rodent models and clinical settings. In: Kostrzewa RM, Archer T (eds) Neurotoxin Modeling of Brain Disorders-Lifelong Outcomes in Behavioral Teratology. Springer, New York

Archer T, Fredriksson A, Johansson B (2011a) Exercise alleviates Parkinsonism: clinical and laboratory evidence. Acta Neurol Scand 123(2):73–84

Archer T, Fredriksson A, Schütz E, Kostrzewa RM (2011b) Influence of physical exercise on neuroimmunological functioning and health: aging and stress. Neurotox Res 20(1):69–83

Archer T, Garcia D, Fredriksson A (2014a) Restoration of MPTP-induced deficits by exercise and Milmed(®) co-treatment. PeerJ 2:e531

Archer T, Josefsson T, Lindwall M (2014b) Effects of physical exercise on depressive symptoms and biomarkers in depression. CNS Neurol Disord: Drug Targets 13(10):1640–1653

Arsenault D, Coulombe K, Zhu A, Gong C, Kil KE, Choi JK, Poutiainen P, Brownell AL (2015) Loss of metabotropic glutamate receptor 5 function on peripheral benzodiazepine receptor in mice prenatally exposed to LPS. PLoS One 10(11):e0142093

Ashok A, Rai NK, Tripathi S, Bandyopadhyay S (2015) Exposure to As-, Cd-, and Pb-mixture induces Aβ, amyloidogenic APP processing and cognitive impairments via oxidative stress-dependent neuroinflammation in young rats. Toxicol Sci 143(1):64–80

Babenko O, Kovalchuk I, Metz GA (2015) Stress-induced perinatal and transgenerational epigenetic programming of brain development and mental health. Neurosci Biobehav Rev 48:70–91

Baldi I, Gruber A, Rondeau V, Lebailly P, Brochard P, Fabrigoule C (2011) Neurobehavioral effects of long-term exposure to pesticides: results from the 4-year follow-up of the PHYTONER study. Occup Environ Med 68(2):108–115

Banerjee S, Riordan M, Bhat MA (2014) Genetic aspects of autism spectrum disorders: insights from animal models. Front Cell Neurosci 8:58

Barker DJ (2007) The origins of the developmental origins theory. J Intern Med 261(5):412–417. Review

Barnes SA, Sawiak SJ, Caprioli D, Jupp B, Buonincontri G, Mar AC, Harte MK, Fletcher PC, Robbins TW, Neill JC, Dalley JW (2015) Impaired limbic cortico-striatal structure and sustained visual attention in a rodent model of schizophrenia. Int J Neuropsychopharmacol 18 (2). pii: pyu010. doi: 10.1093/ijnp/pyu010

Barra R, Cruz G, Mayerhofer A, Paredes A, Lara HE (2014) Maternal sympathetic stress impairs follicular development and puberty of the offspring. Reproduction 148(2):137–145

Basta-Kaim A, Fijał K, Ślusarczyk J, Trojan E, Głombik K, Budziszewska B, Leśkiewicz M, Regulska M, Kubera M, Lasoń W, Wędzony K (2015) Prenatal administration of liposaccharide induces sex-dependent changes in glutamic acid decarboxylase and parvalbumin in the adult rat brain. Neuroscience 287:78–92

Ben-Ari Y, Khazipov R, Leinekugel X, Caillard O, Gaiarsa JL (1997) $GABA_A$, NMDA and AMPA receptors: a developmentally regulated 'ménage à trois'. Trends Neurosci 20(11):523–529. Review

Berger TW, Kaul S, Stricker EM, Zigmond MJ (1985) Hyperinnervation of the striatum by dorsal raphe afferents after dopamine-depleting brain lesions in neonatal rats. Brain Res 336(2):354–358

Berkowitz BA, Spector S, Brossi A, Focella A, Teitel S (1970) Preparation and biological properties of (-) and (+)-6-hydroxydopa. Experientia 26(9):982–983

Bernard PB, MacDonald DS, Gill DA, Ryan CL, Tasker RA (2007) Hippocampal mossy fiber sprouting and elevated trkB receptor expression following systemic administration of low dose domoic acid during neonatal development. Hippocampus 17:1121–1133

Bezard E, Yue Z, Kirik D, Spillantini MG (2013) Animal models of Parkinson's disease: limits and relevance to neuroprotection studies. 28(1):61–70

Bihaqi SW, Zawia NH (2013) Enhanced taupathy and AD-like pathology in aged primate brains decades after infantile exposure to lead (Pb). Neurotoxicology 39:95–101

Bihaqi SW, Bahmani A, Adem A, Zawia NH (2014) Infantile postnatal exposure to lead (Pb) enhances tau expression in the cerebral cortex of aged mice: relevance to AD. Neurotoxicology 44:114–120

Birch AM (2014) The contribution of astrocytes to Alzheimer's disease. Biochem Soc Trans 42(5):1316–1320

Bisagno V, Cadet JL (2014) Methamphetamine and MDMA neurotoxicity: biochemical and molecular mechanisms. In: Kostrzewa RM (ed) Handbook of neurotoxicity. Springer New York, pp 219–236. ISBN 978-1-4614-5835-7 (print); ISBN 978-1-4614-5836-4 (eBook); ISBN 978-1-4614-7458-6 (print and electronic bundle). doi:10.1007/978-1-4614-5836-4_75

Bolin CM, Basha R, Cox D, Zawia NH, Maloney B, Lahiri DK, Cardozo-Pelaez F (2006) Exposure to lead and the developmental origin of oxidative DNA damage in the aging brain. FASEB J 20(6):788–790

Bortel A (2014) Nature of DSP-4 neurotoxicity. In: Kostrzewa RM (ed) Handbook of neurotoxicity. Springer, New York, pp 347–363. ISBN 978-1-4614-5835-7 (print); ISBN 978-1-4614-5836-4 (eBook); ISBN 978-1-4614-7458-6 (print and electronic bundle). doi:10.1007/978-1-4614-5836-4_80

Bortel A, Słomian L, Nitka D, Swierszcz M, Jaksz M, Adamus-Sitkiewicz B, Nowak P, Jośko J, Kostrzewa RM, Brus R (2008) Neonatal N-(-2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) treatment modifies the vulnerability to phenobarbital- and ethanol-evoked sedative-hypnotic effects in adult rats. Pharmacol Rep 60:331–338

Bowyer JF, Frame LT, Clausing P, Nagamoto-Combs K, Osterhout CA, Sterling CR, Tank AW (1998) Long-term effects of amphetamine neurotoxicity on tyrosine hydroxylase mRNA and protein in aged rats. J Pharmacol Exp Ther 286(2):1074–1085

Bracci-Laudiero L, De Stefano ME (2016) NGF in early embryogenesis, differentiation and pathology in the nervous and immune systems. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Breese GR, Baumeister AA, McCown TJ, Emerick SG, Frye GD, Mueller RA (1984a) Neonatal-6-hydroxydopamine treatment: model of susceptibility for self-mutilation in the Lesch-Nyhan syndrome. Pharmacol Biochem Behav 21(3):459–461

Breese GR, Baumeister AA, McCown TJ, Emerick SG, Frye GD, Crotty K, Mueller RA (1984b) Behavioral differences between neonatal and adult 6-hydroxydopamine-treated rats to dopamine agonists: relevance to neurological symptoms in clinical syndromes with reduced brain dopamine. J Pharmacol Exp Ther 231(2):343–354

Breese GR, Baumeister A, Napier TC, Frye GD, Mueller RA (1985a) Evidence that D-1 dopamine receptors contribute to the supersensitive behavioral responses induced by L-dihydroxyphenylalanine in rats treated neonatally with 6-hydroxydopamine. J Pharmacol Exp Ther 235(2):287–295

Breese GR, Napier TC, Mueller RA (1985b) Dopamine agonist-induced locomotor activity in rats treated with 6-hydroxydopamine at differing ages: functional supersensitivity of D-1 dopamine receptors in neonatally lesioned rats. J Pharmacol Exp Ther 234(2):447–455

Breese GR, Mueller RA, Napier TC, Duncan GE (1986) Neurobiology of D_1 dopamine receptors after neonatal-6-OHDA treatment: relevance to Lesch-Nyhan disease. Adv Exp Med Biol 204:197–215

Breese GR, Duncan GE, Napier TC, Bondy SC, Iorio LC, Mueller RA (1987) 6-hydroxydopamine treatments enhance behavioral responses to intracerebral microinjection of D_1- and D_2-dopamine agonists into nucleus accumbens and striatum without changing dopamine antagonist binding. J Pharmacol Exp Ther 240(1):167–176

Breese GR, Criswell HE, Duncan GE, Mueller RA (1989) Dopamine deficiency in self-injurious behavior. Psychopharmacol Bull 25(3):353–357. Review. Erratum in: Psychopharmacol Bull 1990; 26(3):296

Breese GR, Criswell HE, Duncan GE, Mueller RA (1990a) A dopamine deficiency model of Lesch-Nyhan disease—the neonatal-6-OHDA-lesioned rat. Brain Res Bull 25(3):477–484. Review

Breese GR, Criswell HE, Mueller RA (1990b) Evidence that lack of brain dopamine during development can increase the susceptibility for aggression and self-injurious behavior by influencing D_1-dopamine receptor function. Prog Neuropsychopharmacol Biol Psychiatry 14 (Suppl):S65–S80

Breese GR, Criswell HE, Johnson KB, O'Callaghan JP, Duncan GE, Jensen KF, Simson PE, Mueller RA (1994) Neonatal destruction of dopaminergic neurons. Neurotoxicology 15(1):149–159

Breese GR, Knapp DJ, Criswell HE, Moy SS, Papadeas ST, Blake BL (2005) The neonate-6-hydroxydopamine-lesioned rat: a model for clinical neuroscience and neurobiological principles. Brain Res Brain Res Rev 48(1):57–73

Broberg BV, Dias R, Glenthøj BY, Olsen CK (2008) Evaluation of a neurodevelopmental model of schizophrenia—early postnatal PCP treatment in attentional set-shifting. Behav Brain Res 190(1):160–163

Broberg BV, Oranje B, Glenthøj BY, Fejgin K, Plath N, Bastlund JF (2010) Assessment of auditory sensory processing in a neurodevelopmental animal model of schizophrenia—gating of auditory-evoked potentials and prepulse inhibition. Behav Brain Res 213(2):142–147

Broberg BV, Madsen KH, Plath N, Olsen CK, Glenthøj BY, Paulson OB, Bjelke B, Søgaard LV (2013) A schizophrenia rat model induced by early postnatal phencyclidine treatment and characterized by magnetic resonance imaging. Behav Brain Res 250:1–8

Brown RW, Peterson DJ (2016) Applications of the neonatal quinpirole model to psychosis and convergence upon the dopamine D_2 receptor. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Brown GC, Vilalta A (2015) How microglia kill neurons. Brain Res 1628(Pt B):288–297

Brown RW, Gass JT, Kostrzewa RM (2002) Ontogenetic quinpirole treatments produce spatial memory deficits and enhance skilled reaching in adult rats. Pharmacol Biochem Behav 72(3):591–600

Brown RW, Flanigan TJ, Thompson KN, Thacker SK, Schaefer TL, Williams MT (2004a) Neonatal quinpirole treatment impairs Morris water task performance in early postweanling rats: relationship to increases in corticosterone and decreases in neurotrophic factors. Biol Psychiatry 56(3):161–168

Brown RW, Thompson KD, Thompson KN, Ward JJ, Thacker SK, Williams MT, Kostrzewa RM (2004b) Adulthood nicotine treatment alleviates behavioural impairments in rats neonatally treated with quinpirole: possible roles of acetylcholine function and neurotrophic factor expression. Eur J Neurosci 19(6):1634–1642

Brown RW, Thompson KN, Click IA, Best RA, Thacker SK, Perna MK (2005) The effects of eticlopride on Morris water task performance in male and female rats neonatally treated with quinpirole. Psychopharmacology 180(2):234–240

Brown RW, Perna MK, Schaefer TL, Williams MT (2006) The effects of adulthood nicotine treatment on D_2-mediated behavior and neurotrophins of rats neonatally treated with quinpirole. Synapse 59(5):253–259

Brown RW, Perna MK, Maple AM, Wilson TD, Miller BE (2008) Adulthood olanzapine treatment fails to alleviate decreases of ChAT and BDNF RNA expression in rats quinpirole-primed as neonates. Brain Res 1200:66–77

Brown RW, Maple AM, Perna MK, Sheppard AB, Cope ZA, Kostrzewa RM (2012) Schizophrenia and substance abuse comorbidity: nicotine addiction and theneonatal quinpirole model. Dev Neurosci 34(2–3):140–151

Brundin L, Erhardt S, Bryleva EY, Achtyes ED, Postolache TT (2015) The role of inflammation in suicidal behaviour. Acta Psychiatr Scand 132(3):192–203

Brus R, Szkilnik R, Nowak P, Kasperska A, Oświęcimska J, Kostrzewa RM, Shani J (1998a) Locomotor sensitization of dopamine receptors by their agonists quinpirole and SKF-38393, during maturation and aging in rats. Pharmacol Rev Commun 10:25–30

Brus R, Szkilnik R, Nowak P, Kostrzewa RM, Shani J (1998b) Sensitivity of central dopamine receptors in rats to quinpirole and SKF-38393, administered at their early stages of ontogenicity, evaluated by learning and memorizing a conditioned avoidance reflex. Pharmacol Rev Commun 10:31–36

Brus R, Nowak P, Szkilnik R, Mikolajun U, Kostrzewa RM (2004) Serotoninergics attenuate hyperlocomotor activity in rats. Potential new therapeutic strategy for hyperactivity. Neurotox Res 6(4):317–325

Budni J, Bellettini-Santos T, Mina F, Garcez ML, Zugno AI (2015) The involvement of BDNF, NGF and GDNF in aging and Alzheimer's disease. Aging Dis 6(5):331–341

Byrnes KR, Stoica B, Loane DJ, Riccio A, Davis MI, Faden A (2009) Metabotropic glutamate receptor 5 activation inhibits microglial associated inflammation and neurotoxicity. Glia 57(5):550–560

Cadet JL (2014) Epigenetics of stress, addiction, and resilience: Therapeutic implications. Mol Neurobiol. 53(1):545–560

Cadet JL, Jayanthi S (2013) Epigenetics of methamphetamine-induced changes in glutamate function. Neuropsychopharmacology 38(1):248–249

Casey DE (1987) Tardive dyskinesia. In: Meltzer HY (ed) Psychopharmacology: the third generation of progress. Raven Press, New York, pp 1411–1419

Castañé A, Santana N, Artigas F (2015) PCP-based mice models of schizophrenia: differential behavioral, neurochemical and cellular effects of acute and subchronic treatments. Psychopharmacology 232(21–22):4085–4097

Chen J, Wang Z, Li M (2011) Multiple 'hits' during postnatal and early adulthood periods disrupt the normal development of sensorimotor gating ability in rats. J Psychopharmacol 25(3):379–392

Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, Vestergaard M (2013) Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA 309(16):1696–1703

Christianson AL, Chester N, Kromberg JG (1994) Fetal valproate syndrome: clinical and neuro-developmental features in two sibling pairs. Dev Med Child Neurol 36:361–369

Chung WS, Welsh CA, Barres BA, Stevens B (2015) Do glia drive synaptic and cognitive impairment in disease? Nat Neurosci 18(11):1539–1545

Clark MB, King JC, Kostrzewa RM (1979) Loss of nerve cell bodies in caudal locus coeruleus following treatment of neonates with 6-hydroxydopa. Neurosci Lett 13(3):331–336

Cohen G, Heikkila RE (1974) The generation of hydrogen peroxide, superoxide radical, and hydroxyl radical by 6-hydroxydopamine, dialuric acid, and related cytotoxic agents. J Biol Chem 249(8):2447–2452

Cooper JD, Lindholm D, Sofroniew MV (1994) Reduced transport of ^{125}I-NGF by cholinergic neurons and downregulated TrkA expression in the medial septum of aged rats. Neuroscience 62:625–629

Cope ZA, Huggins KN, Sheppard AB, Noel DM, Roane DS, Brown RW (2010) Neonatal quinpirole treatment enhances locomotor activation and dopamine release in the nucleus accumbens core in response to amphetamine treatment in adulthood. Synapse 64(4):289–300

Cordova FM, Aguiar AS Jr, Peres TV, Lopes MW, Gonçalves FM, Remor AP, Lopes SC, Pilati C, Latini AS, Prediger RD, Erikson KM, Aschner M (2012) Leal RB (2012) In vivo manganese exposure modulates Erk, Akt and Darpp-32 in the striatum of developing rats, and impairs their motor function. PLoS One 7(3):e33057

Criswell H, Mueller RA, Breese GR (1989) Priming of D_1-dopamine receptor responses: long-lasting behavioral supersensitivity to a D_1-dopamine agonist following repeated administration to neonatal 6-OHDA-lesioned rats. J Neurosci 9(1):125–133

Dabrowska J, Nowak P, Brus R (2007) Desensitization of 5-HT(1A) autoreceptors induced by neonatal DSP-4 treatment. Eur Neuropsychopharmacol 17:129–137

Dal-Pizzol F, Klamt F, Frota ML Jr, Andrades ME, Caregnato FF, Vianna MM, Schröder N, Quevedo J, Izquierdo I, Archer T, Moreira JC (2001) Neonatal iron exposure induces oxidative stress in adult Wistar rat. Brain Res Dev Brain Res 130(1):109–114

De Bartolo P, Gelfo F, Mandolesi L, Foti F, Cutuli D, Petrosini L (2009) Effects of chronic donepezil treatment and cholinergic deafferentation on parietal pyramidal neuron morphology. J Alzheimers Dis 17(1):177–191

De Bartolo P, Cutuli D, Ricceri L, Gelfo F, Foti F, Laricchiuta D, Scattoni ML, Calamandrei G, Petrosini L (2010) Does age matter? Behavioral and neuro-anatomical effects of neonatal and adult basal forebrain cholinergic lesions. J Alzheimers Dis 20(1):207–227

de la Torre R, Farré M, Ortuño J, Mas M, Brenneisen R, Roset PN, Segura J, Camí J (2000) Non-linear pharmacokinetics of MDMA ('ecstasy') in humans. Br J Clin Pharmacol 49 (2):104–109

De-Carolis C, Boyd GA, Mancinelli L, Pagano S, Eramo S (2015) Methamphetamine abuse and "meth mouth" in Europe. Med Oral Patol Oral Cir Bucal 20(2):e205–e210

Delany FM, Byrne ML, Whittle S, Simmons JG, Olsson C, Mundy LK, Patton GC, Allen NB (2015) Depression, immune function, and early adrenarche in children. Psychoneuroendocrinology 63:228–234

Desplats P, Dumaop W, Cronin P, Gianella S, Woods S, Letendre S, Smith D, Masliah E, Grant I (2014) Epigenetic alterations in the brain associated with HIV-1 infection andmethamphetamine dependence. PLoS One 9(7):e102555

Do HT, Bruelle C, Pham DD, Jauhiainen M, Eriksson O, Korhonen LT, Lindholm D (2015) Nerve growth factor (NGF) and pro-NGF increase low-density lipoprotein (LDL) receptors in neuronal cells partly by different mechanisms: role of LDL in neurite outgrowth. J Neurochem 2015 Oct 20. doi:10.1111/jnc.13397. [Epub ahead of print]

Doebel S, Zelazo PD (2013) Bottom-up and top-down dynamics in young children's executive function: Labels aid 3-year-olds' performance on the Dimensional Change Card Sort. Cogn Dev 28(3):222–232

Doucette TA, Tasker RA (2016) Perinatal domoic acid as a neuroteratogen. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Doucette TA, Strain SM, Allen GV, Ryan CL, Tasker RAR (2000) Comparative behavioural toxicity of domoic acid and kainic acid in neonatal rats. Neurotoxicol Teratol 22:863–869

Doucette TA, Bernard PB, Husum H, Perry MA, Ryan CL, Tasker RA (2004) Low doses of domoic acid during postnatal development produce permanent changes in rat behaviour and hippocampal morphology. Neurotox Res 6(7,8):555–563

Fialová M, Šírová J, Bubeníková-Valešová V, Šlamberová R (2015) The effect of prenatal methamphetamine exposure on recognition memory in adult rats. Prague Med Rep 116(1):31–39

Fornai F, Bassi L, Bonaccorsi I, Giorgi F, Corsini GU (1997) Noradrenaline loss selectivity exacerbates nigrostriatal toxicity in different species of rodents. Funct Neurol 12(3–4):193–198

Fredriksson A, Schröder N, Eriksson P, Izquierdo I, Archer T (1999) Neonatal iron exposure induces neurobehavioural dysfunctions in adult mice. Toxicol Appl Pharmacol 159(1):25–30

Fredriksson A, Schröder N, Eriksson P, Izquierdo I, Archer T (2000) Maze learning and motor activity deficits in adult mice induced by iron exposure during a critical postnatal period. Brain Res Dev Brain Res 119(1):65–74

Fredriksson A, Stigsdotter IM, Hurtig A, Ewalds-Kvist B, Archer T (2011) Running wheel activity restores MPTP-induced functional deficits. J Neural Transm 118(3):407–420

Fu R, Sutcliffe D, Zhao H, Huang X, Schretlen DJ, Benkovic S, Jinnah HA (2015) Clinical severity in Lesch-Nyhan disease: the role of residual enzyme and compensatory pathways. Mol Genet Metab 114(1):55–61

Fukushima S, Furube E, Itoh M, Nakashima T, Miyata S (2015) Robust increase in microglia proliferation in the fornix of hippocampal axonal pathway after single LPS stimulation. J Neuroimmunol 285:31–40

Furukawa S (2015) Basic research on neurotrophic factors and its application to medical uses. Yakugaku Zasshi 135(11):1213–1226

Futamura T, Kakita A, Tohmi M, Sotoyama H, Takahashi H, Nawa H (2003) Neonatal perturbation of neurotrophic signaling results in abnormal sensorimotor gating and social interaction in adults: implication for epidermal growth factor in cognitive development. Mol Psychiatry 8(1):19–29

Galbally M, Roberts M, Buist A; Perinatal Psychotropic Review Group (2010) Mood stabilizers in pregnancy: a systematic review. Aust NZJ Psychiatry 44(11):967–977

Gao Y, Liu L, Li Q, Wang Y (2015) Differential alterations in the morphology and electrophysiology of layer II pyramidal cells in the primary visual cortex of a mouse model prenatally exposed to LPS. Neurosci Lett 591:138–143

Gill DA, Ramsay R, Tasker RA (2010) Selective reductions in subpopulations of GABAergic neurons in a developmental rat model of epilepsy. Brain Res 1331:114–123

Godino A, Jayanthi S, Cadet JL (2015) Epigenetic landscape of amphetamine and methamphetamine addiction in rodents. Epigenetics 10(7):574–580

Gong L, Kostrzewa RM, Fuller RW, Perry KW (1992) Supersensitization of the oral response to SKF 38393 in neonatal 6-OHDA-lesioned rats is mediated through a serotonin system. J Pharmacol Exp Ther 261:1000–1007

Gong L, Kostrzewa RM, Brus R, Fuller RW, Perry KW (1993a) Ontogenetic SKF 38393 treatments sensitize dopamine D_1 receptors in neonatal 6-OHDA-lesioned rats. Brain Res Dev Brain Res 76(1):59–65

Gong L, Kostrzewa RM, Perry KW, Fuller RW (1993b) Dose-related effects of a neonatal 6-OHDA lesion on SKF 38393- and m-chlorophenylpiperazine-induced oral activity responses of rats. Brain Res Dev Brain Res 76(2):233–238

Gong L, Kostrzewa RM, Li C (1994) Neonatal 6-OHDA and adult SKF 38393 treatments alter dopamine D_1 receptor mRNA levels: absence of other neurochemical associations with the enhanced behavioral responses of lesioned rats. J Neurochem 63:1282–1290

Göttle M, Prudente CN, Fu R, Sutcliffe D, Pang H, Cooper D, Veledar E, Glass JD (2014) Loss of dopamine phenotype among midbrain neurons in Lesch-Nyhan disease. Ann Neurol 76(1):95–107

Grados M, Sung HM, Kim S, Srivastava S (2014) Genetic findings in obsessive-compulsive disorder connect to brain-derived neutrophic factor and mammalian target of rapamycin pathways: implications for drug development. Drug Dev Res 75(6):372–383

Graham DL, Amos-Kroohs RM, Braun AA, Grace CE, Schaefer TL, Skelton MR, Williams MT, Vorhees CV (2013) Neonatal +-methamphetamine exposure in rats alters adult locomotor responses to dopamine D_1 and D_2 agonists and to a glutamate NMDA receptor antagonist, but not to serotonin agonists. Int J Neuropsychopharmacol 16(2):377–391

Grayson DR, Guidotti A (2015) Merging data from genetic and epigenetic approaches to better understand autistic spectrum disorder. Epigenomics. 2015 Nov 9. [Epub ahead of print] PMID: 26551091

Grayson B, Barnes SA, Markou A, Piercy C, Podda G, Neill JC (2016) Postnatal phencyclidine (PCP) as a neurodevelopmental model of schizophrenia pathophysiology and symptpmatology: a review. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Groves NJ, McGrath JJ, Burne TH (2014) Vitamin D as a neurosteroid affecting the developing and adult brain. Annu Rev Nutr 34:117–141

Hamdi A, Kostrzewa RM (1991) Ontogenic homologous supersensitization of dopamine D_1 receptors. Eur J Pharmacol 203:115–120

Harro J (2015) Neuropsychiatric adverse effects of amphetamine and methamphetamine. Int Rev Neurobiol 120:179–204

Hasan W, Smith PG (2014) Decreased adrenoceptor stimulation in heart failure rats reduces NGF expression by cardiac parasympathetic neurons. Auton Neurosci 181:13–20

He N, Li F, Li Y, Guo L, Chen L, Huang X, Lui S, Gong Q (2015) Neuroanatomical deficits correlate with executive dysfunction in boys with attention deficit hyperactivity disorder. Neurosci Lett 600:45–49

Hertz L, Chen Y, Waagepetersen HS (2015) Effects of ketone bodies in Alzheimer's disease in relation to neural hypometabolism, β-amyloid toxicity and astrocyte function. J Neurochem 134(1):7–20

Hirsch MA, Iyer SS, Sanjak M (2015) Exercise-induced neuroplasticity in human Parkinson's disease: what is the evidence telling us? Parkinsonism Relat Disord 22(Suppl 1):S78–S81

Hoftman GD, Lewis DA (2011) Postnatal developmental trajectories of neural circuits in the primate prefrontal cortex: identifying sensitive periods for vulnerability to schizophrenia. Schizophr Bull 37(3):493–503

Hohsfield LA, Ehrlich D, Humpel C (2014) Intravenous infusion of nerve growth factor-secreting monocytes supports the survival of cholinergic neurons in the nucleus basalis of Meynert in hypercholesterolemia Brown-Norway rats. J Neurosci Res 92(3):298–306

Holmes GL, Sarkisian M, Ben-Ari Y, Chevassus-Au-Louis N (1999) Mossy fiber sprouting after recurrent seizures during early development in rats. J Comp Neurol 22:537–553

Hongwanishkul D, Happaney KR, Lee WS, Zelazo PD (2006) Assessment of hot and cool executive function in young children: age-related changes and individual differences. Dev Neuropsychol 28(2):617–644

Hrebíčková I, Malinová-Ševčíková M, Macúchová E, Nohejlová K, Šlamberová R (2014) Exposure to methamphetamine during first and second half of prenatal period and its consequences on cognition after long-term application in adulthood. Physiol Res 63(Suppl 4): S535–S545

Huang N-Y, Kostrzewa RM, Li C, Perry KW, Fuller RW (1997) Increased spontaneous oral dyskinesias persist in haloperidol-withdrawn rats neonatally lesioned with 6-hydroxydopamine: absence of an association with the B_{max} for [^{3}H]raclopride binding to neostriatal homogenates. J Pharmacol Exp Ther 280:268–276

Ibi D, González-Maeso J (2015) Epigenetic signaling in schizophrenia. Cell Signal 27(10):2131–2136

Iulita MF, Cuello AC (2014) Nerve growth factor metabolic dysfunction in Alzheimer's disease and Down syndrome. Trends Pharmacol Sci 35(7):338–348

Iwakura Y, Zheng Y, Sibilia M, Abe Y, Piao YS, Yokomaku D, Wang R, Ishizuka Y, Takei N, Nawa H (2011a) Qualitative and quantitative re-evaluation of epidermal growth factor-ErbB1 action on developing midbrain dopaminergic neurons in vivo and in vitro: target-derived neurotrophic signaling (Part 1). J Neurochem 118(1):45–56

Iwakura Y, Wang R, Abe Y, Piao YS, Shishido Y, Higashiyama S, Takei N, Nawa H (2011b) Dopamine-dependent ectodomain shedding and release of epidermal growth factor in developing striatum: target-derived neurotrophic signaling (Part 2). J Neurochem 118(1):57–68

Jablonski SA, Williams MT, Vorhees CV (2016) Neurobehavioral effects from developmental methamphetamine exposure. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Jacobowitz D, Kostrzewa R (1971) Selective action of 6-hydroxydopa on noradrenergic terminals: mapping of preterminal axons of the brain. Life Sci I 10(23):1329–1342

Jacobsen PE, Henriksen TB, Haubek D, Østergaard JR (2014) Prenatal exposure to antiepileptic drugs and dental agenesis. PLoS One 9(1):e84420

Jain P, Wadhwa PK, Jadhav HR (2015) Reactive astrogliosis: role in Alzheimer's disease. CNS Neurol Disord Drug Targets 14(7):872–879

Jeste DV, Caligiuri MP (1993) Tardive dyskinesia. Schizophr Bull 19:303–315

Jinnah HA, Jones MD, Wojcik BE, Rothstein JD, Hess EJ, Friedmann T, Breese GR (1999) Influence of age and strain on striatal dopamine loss in a genetic mouse model of Lesch-Nyhan disease. J Neurochem 72(1):225–229

Jo WK, Zhang Y, Emrich HM, Dietrich DE (2015) Glia in the cytokine-mediated onset of depression: fine tuning the immune response. Front Cell Neurosci 9:268

Jonsson G, Hallman H, Ponzio F, Ross S (1981) DSP4 (N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine)—a useful denervation tool for central and peripheral noradrenaline neurons. Eur J Pharmacol 72:173–188

Jonsson G, Hallman H, Sundström E (1982) Effects of the noradrenaline neurotoxin DSP4 on the postnatal development of central noradrenaline neurons in the rat. Neuroscience 7(11):2895–2907

Kaalund SS, Riise J, Broberg BV, Fabricius K, Karlsen AS, Secher T, Plath N, Pakkenberg B (2013) Differential expression of parvalbumin in neonatal phencyclidine-treated rats and socially isolated rats. J Neurochem 124(4):548–557

Kato T, Abe Y, Sotoyama H, Kakita A, Kominami R, Hirokawa S, Ozaki M, Takahashi H, Nawa H (2011) Transient exposure of neonatal mice to neuregulin-1 results in hyperdopaminergic states in adulthood: implication in neurodevelopmental hypothesis for schizophrenia. Mol Psychiatry 16(3):307–320

Kehoe P, Callahan M, Daigle A, Mallinson K, Brudzynski S (2001) The effect of cholinergic stimulation on rat pup ultrasonic vocalizations. Dev Psychobiol 38(2):92–100

Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP (2015) Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. Front Cell Neurosci 9:392

Kim KC, Kim P, Go HS, Choi CS, Yang SI, Cheong JH, Shin CY, Ko KH (2011) The critical period of valproate exposure to induce autistic symptoms in Sprague-Dawley rats. Toxicol Lett 201(2):137–142

Kim JW, Seung H, Kwon KJ, Ko MJ, Lee EJ, Oh HA, Choi CS, Kim KC, Gonzales EL, You JS, Choi DH, Lee J, Han SH, Yang SM, Cheong JH, Shin CY, Bahn GH (2014) Subchronic treatment of donepezil rescues impaired social, hyperactive, and stereotypic behaviour in valproic acid-induced animal model of autism. PLoS One 9(8):e104927

Kirsten TB, Lippi LL, Bevilacqua E, Bernardi MM (2013) LPS exposure increases maternal corticosterone levels, causes placental injury and increases Il-1B levels in adult rat offspring: relevance to autism. PLoS One 8(12):e82244

Kjaerby C, Bundgaard C, Fejgin K, Kristiansen U, Dalby NO (2013) Repeated potentiation of the metabotropic glutamate receptor 5 and the alpha 7 nicotinic acetylcholine receptor modulates behavioural and GABAergic deficits induced by early postnatal phencyclidine (PCP) treatment. Neuropharmacology 72:157–168

Kjaerby C, Broberg BV, Kristiansen U, Dalby NO (2014) Impaired GABAergic inhibition in the prefrontal cortex of early postnatalphencyclidine (PCP)-treated rats. Cereb Cortex 24(9):2522–2532

Knapp DJ, Breese GR (2016) Perinatal 6-hydroxydopamine to produce a rodent model of Lesch-Nyhan disease. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Kokoshka JM, Metzger RR, Wilkins DG, Gibb JW, Hanson GR, Fleckenstein AE (1998) Methamphetamine treatment rapidly inhibits serotonin, but not glutamate, transporters in rat brain. Brain Res 799(1):78–83

Kostrzewa RM (1988) Reorganization of noradrenergic neuronal systems following neonatal chemical and surgical injury. Prog Brain Res 73:405–423. Review

Kostrzewa RM (1995) Dopamine receptor supersensitivity. Neurosci Biobehav Rev 19:1–17

Kostrzewa RM (2016) Perinatal effects of 6-hydroxydopa, a noradrenergic neurotoxin and AMPA receptor excitotoxin. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Kostrzewa RM, Brus R (1991) Ontogenic homologous supersensitization of quinpirole-induced yawning in rats. Pharmacol Biochem Behav 39:517–519

Kostrzewa RM, Brus R (2016) Lifelong rodent model of tardive dyskinesia-persistence after antipsychotic drug withdrawal. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Kostrzewa RM, Garey RE (1976) Effects of 6-hydroxydopa on noradrenergic neurons in developing rat brain. J Pharmacol Exp Ther 197:105–118

Kostrzewa RM, Garey RE (1977) Sprouting of noradrenergic terminals in rat cerebellum following neonatal treatment with 6-hydroxydopa. Brain Res 124:385–391

Kostrzewa RM, Gong L (1991) Supersensitized D_1 receptors mediate enhanced oral activity after neonatal 6-OHDA. Pharmacol Biochem Behav 39(3):677–682

Kostrzewa RM, Harper JW (1974) Effect of 6-hydroxydopa on catecholamine-containing neurons in brains of newborn rats. Brain Res 69(1):174–181

Kostrzewa R, Jacobowitz D (1972) The effect of 6-hydroxydopa on peripheral adrenergic neurons. J Pharmacol Exp Ther 183(2):284–297

Kostrzewa R, Jacobwitz D (1973) Acute effects of 6-hydroxydopa on central monoaminergic neurons. Eur J Pharmacol 21(1):70–80

Kostrzewa RM, Kostrzewa FP (2012) Neonatal 6-hydroxydopamine lesioning enhances quinpirole-induced vertical jumping in rats that were quinpirole primed during postnatal ontogeny. Neurotox Res 21(2):231–235

Kostrzewa RM, Brus R, Kalbfleisch J (1991) Ontogenetic homologous sensitization to the antinociceptive action of quinpirole in rats. Eur J Pharmacol 209:157–161

Kostrzewa RM, Gong L, Brus R (1992) Serotonin (5-HT) systems mediate dopamine (DA) receptor supersensitivity. Acta Neurobiol Exp 53:31–41

Kostrzewa RM, Brus R, Rykaczewska M, Plech A (1993a) Low dose quinpirole ontogenically sensitizes to quinpirole-induced yawning in rats. Pharmacol Biochem Behav 44:487–489

Kostrzewa RM, Guo J, Kostrzewa FP (1993b) Ontogenetic quinpirole treatments induce vertical jumping activity in rats. Eur J Pharmacol 239:183–187

Kostrzewa RM, Brus R, Kalbflesich JH, Perry KW, Fuller RW (1994) Proposed animal model of attention deficit hyperactivity disorder. Brain Res Bull 34:161–167

Kostrzewa RM, Reader TA, Descarries L (1998) Serotonin neural adaptations to ontogenetic loss of dopamine neurons in rat brain. J Neurochem 70:889–898

Kostrzewa RM, Kostrzewa JP, Brus R (2000) Dopaminergic denervation enhances susceptibility to hydroxyl radicals in rat neostriatum. Amino Acids 19:183–199

Kostrzewa RM, Kostrzewa JP, Brus R (2002) Neuroprotective and neurotoxic roles of levodopa (L-DOPA) in neurodegenerative disorders relating to Parkinson's disease. Amino Acids 23:57–63

Kostrzewa RM, Kostrzewa JP, Brus R (2003) Dopamine receptor supersensitivity: an outcome and index of neurotoxicity. Neurotox Res 5:111–118

Kostrzewa RM, Nowak P, Kostrzewa JP, Kostrzewa RA, Brus R (2004) Dopamine D_2 agonist priming in intact and dopamine-lesioned rats. Neurotox Res 6:457–462

Kostrzewa RM, Nowak P, Kostrzewa JP, Kostrzewa RA, Brus R (2005) Peculiarities of L-DOPA treatment of Parkinson's disease. Amino Acids 28:157–164

Kostrzewa RM, Kostrzewa JP, Brus R, Kostrzewa RA, Nowak P (2006) Proposed animal model of severe Parkinson's disease: neonatal 6-hydroxydopamine lesion of dopaminergic innervation of striatum. J Neural Transm Suppl 70:277–279

Kostrzewa RM, Huang N-Y, Kostrzewa JP, Nowak P, Brus R (2007) Modeling tardive dyskinesia: predictive 5-HT_{2C} receptor antagonist treatment. Neurotox Res 11(1):41–50

Kostrzewa RM, Kostrzewa JP, Kostrzewa RA, Nowak P, Brus R (2008) Pharmacological models of ADHD. J Neural Transm 115(2):287–298

Kostrzewa RM, Kostrzewa JP, Kostrzewa RA, Kostrzewa FP, Brus R, Nowak P (2011) Stereotypic progressions in psychotic behavior. Neurotox Res 19:243–252

Kostrzewa JP, Kostrzewa RA, Kostrzewa RM, Brus R, Nowak P (2016a) Perinatal 6-hydroxydopamine modeling of ADHD. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Kostrzewa JP, Kostrzewa RA, Kostrzewa RM, Brus R, Nowak P (2016b) Perinatal 6-hydroxydopamine to produce a lifelong model of severe Parkinson's disease. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Kostrzewa RM, Nowak P, Brus R, Brown RW (2016c) Perinatal treatments with the dopamine D_2-receptor agonist quinpirole produces permanent D_2-receptor supersensitization: a model of schizophrenia. Neurochem Res 2015 Nov 7. [Epub ahead of print] PMID: 26547196 In press

Krasnova IN, Cadet JL (2009) Methamphetamine toxicity and messengers of death. Brain Res Rev 60:379–407

Kulaga S, Sheehy O, Zargarzadeh AH, Moussally K, Bérard A (2011) Antiepileptic drug use during pregnancy: perinatal outcomes. Seizure 20(9):667–672

Lahiri DK, Maloney B, Zawia NH (2009) The LEARn model: an epigenetic explanation for idiopathic neurobiological diseases. Mol Psychiatry 14(11):992–1003

Laviola G, Adriani W, Rea M, Aloe L, Alleva E (2004) Social withdrawal, neophobia, and stereotyped behavior in developing rats exposed to neonatal asphyxia. Psychopharmacology 175:196–205

Le Magueresse C, Monyer H (2013) GABAergic interneurons shape the functional maturation of the cortex. Neuron 77(3):388–405

Leanza G, Nilsson OG, Wiley RG, Björklund A (1995) Selective lesioning of the basal forebrain cholinergic system by intraventricular 192 IgG-saporin: behavioural, biochemical and stereological studies in the rat. Eur J Neurosci 7(2):329–343

Leanza G, Nilsson OG, Nikkhah G, Wiley RG, Björklund A (1996) Effects of neonatal lesions of the basal forebrain cholinergic system by 192 immunoglobulin G-saporin: biochemical, behavioural and morphological characterization. Neuroscience 74(1):119–141

Lemaire V, Koehl M, Le Moal M, Abrous DN (2000) Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. Proc Natl Acad Sci USA 97(20):11032–11037

Levy SE, Mandell DS, Schultz RT (2009) Autism. Lancet 374(9701):1627–1638

Lian H, Zheng H (2015) Signaling pathways regulating neuron glia interaction and their implications in Alzheimer's disease. J Neurochem. 6 Nov 2015. doi:10.1111/jnc.13424. [Epub ahead of print] Review

Lloyd KA (2013) A scientific review: mechanisms of valproate-mediated teratogenesis. Bioscience Horizons 6:hzt003

Lyons WE, Fritschy JM, Grzanna R (1989) The noradrenergic neurotoxin DSP-4 eliminates the coeruleospinal projection but spares projections of the A5 and A7 groups to the ventral horn of the rat spinal cord. J Neurosci 9:1481–1489

Maccari S, Darnaudery M, Morley-Fletcher S, Zuena AR, Cinque C, Van Reeth O (2003) Prenatal stress and long-term consequences: implications of glucocorticoid hormones. Neurosci Biobehav Rev 27:119–127

Malinová-Ševčíková M, Hrebíčková I, Macúchová E, Nová E, Pometlová M, Šlamberová R (2014) Differences in maternal behavior and development of their pups depend on the time of methamphetamine exposure during gestation period. Physiol Res 63(Suppl 4):S559–S572

Maple AM, Perna MK, Parlaman JP, Stanwood GD, Brown RW (2007) Ontogenetic quinpirole treatment produces long-lasting decreases in the expression of Rgs9, but increases Rgs17 in the striatum, nucleus accumbens and frontal cortex. Eur J Neurosci 26(9):2532–2538

Maple AM, Smith KJ, Perna MK, Brown RW (2015) Neonatal quinpirole treatment produces prepulse inhibition deficits in adult male and female rats. Pharmacol Biochem Behav 137:93–100

Marco EM, Velarde E, Llorente R, Laviola G (2016) Disrupted circadian rhythm as a common player in developmental models of neuropsychiatric disorders. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

McDonnell-Dowling K, Kelly JP (2015) The consequences of prenatal and/or postnatal methamphetamine exposure on neonatal development and behaviour in rat offspring. Int J Dev Neurosci 47(Pt B):147–156

Meier TB, Drevets WC, Wurfel BE, Ford BN, Morris HM, Victor TA, Bodurka J, Kent Teague T, Dantzer R, Savitz J (2015) Relationship between neurotoxic kynurenine metabolites and reductions in right medial prefrontal cortical thickness in major depressive disorder. Brain Behav Immun pii: S0889-1591(15) 30048-30049

Miller FD, Kaplan DR (2001) Neurotrophin signalling pathways regulating neuronal apoptosis. Cell Mol Life Sci 58:1045–1053

Mizuno M, Kawamura H, Takei N, Nawa H (2008) The anthraquinone derivative emodin ameliorates neurobehavioral deficits of a rodent model for schizophrenia. J Neural Transm 115(3):521–530

Mizuno M, Kawamura H, Ishizuka Y, Sotoyama H, Nawa H (2010) The anthraquinone derivative emodin attenuates methamphetamine-induced hyperlocomotion and startle response in rats. Pharmacol Biochem Behav 97(2):392–398

Mohl B, Ofen N, Jones LL, Robin AL, Rosenberg DR, Diwadkar VA, Casey JE, Stanley JA (2015) Neural dysfunction in ADHD with reading disability during a word rhyming continuous performance task. Brain Cogn 99:1–7

Monden Y, Dan I, Nagashima M, Dan H, Uga M, Ikeda T, Tsuzuki D, Kyutoku Y, Gunji Y, Hirano D, Taniguchi T, Shimoizumi H, Watanabe E, Yamagata T (2015) Individual classification of ADHD children by right prefrontal hemodynamic responses during a go/no-go task as assessed by fNIRS. Neuroimage Clin 9:1–12

Mossakowski AA, Pohlan J, Bremer D, Lindquist R, Millward JM, Bock M, Pollok K, Mothes R, Viohl L, Radbruch M, Gerhard J, Bellmann-Strobl J, Behrens J, Infante-Duarte C, Mähler A, Boschmann M, Rinnenthal JL, Füchtemeier M, Herz J, Pache FC, Bardua M, Priller J, Hauser AE, Paul F, Niesner R, Radbruch H (2015) Tracking CNS and systemic sources of oxidative stress during the course of chronic neuroinflammation. Acta Neuropathol 130(6):799–814

Mouton M, Harvey BH, Cockeran M, Brink CB (2015) The long-term effects of methamphetamine exposure during pre-adolescence on depressive-like behaviour in a genetic animal model of depression. Metab Brain Dis 18 Nov 2015 [Epub ahead of print]

Müller N, Weidinger E, Leitner B, Schwarz MJ (2015) The role of inflammation in schizophrenia. Front Neurosci 9:372

Myint AM (2013) Inflammation, neurotoxins and psychiatric disorders. Mod Trends Pharmacopsychiatri 28:61–74

Nagano T, Mizuno M, Morita K, Nawa H (2016) Pathological implications of oxidative stress in patients and animal models with schizophrenia: the role of epidermal growth factor receptor signaling. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Nakatani-Pawlak A, Yamaguchi K, Tatsumi Y, Mizoguchi H, Yoneda Y (2009) Neonatal phencyclidine treatment in mice induces behavioral, histological and neurochemical abnormalities in adulthood. Biol Pharm Bull 32(9):1576–1583

Narita N, Kato M, Tazoe M, Miyazaki K, Narita M, Okado N (2002) Increased monoamine concentration in the brain and blood of fetal thalidomide- and valproic acid-exposed rat: putative animal models for autism. Pediatr Res 52(4):576–579

Neill JC, Harte MK, Haddad PM, Lydall ES, Dwyer DM (2014) Acute and chronic effects of NMDA receptor antagonists in rodents, relevance to negative symptoms of schizophrenia: a translational link to humans. Eur Neuropsychopharmacol 24(5):822–835

Niewiadomska G, Baksalerska-Pazera M, Riedel G (2009) The septo-hippocampal system, learning and recovery of function. Prog Neuropsychopharmacol Biol Psychiatry 33:791–805

Nowak P (2016) Selective lifelong destruction of brain monoaminergic nerves through perinatal DSP-4 treatment. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Nowak P, Brus R, Kostrzewa RM (2001) Amphetamine-induced enhancement of neostriatal in vivo microdialysate dopamine content in rats, quinpirole-primed as neonates. Pol J Pharmacol 53:319–329

Nowak P, Kostrzewa RM, Kwięcinski A, Bortel A, Łabus L, Brus R (2005) Neurotoxic action of 6-hydroxydopamine on the nigrostriatal dopaminergic pathway in rats sensitized with D-amphetamine. J Physiol Pharmacol 56(2):325–333

Nowak P, Bortel A, Dąbrowska J, Oświęcimska J, Drosik M, Kwieciński A, Opara J, Kostrzewa RM, Brus R (2007) Amphetamine and mCPP effects on dopamine and serotonin striatal in vivo microdialysates in an animal model of hyperactivity. Neurotox Res 11(2):131–144

Nowak P, Kostrzewa RA, Skaba D, Kostrzewa RM (2010) Acute L-DOPA effect on hydroxyl radical- and DOPAC-levels in striatal microdialysates of Parkinsonian rats. Neurotox Res 17 (3):299–304

Ong HH, Creveling CR, Daly JW (1969) The synthesis of 2,4,5-trihydroxyphenylalanine (6-hydroxydopa). A centrally active norepinephrine-depleting agent. J Med Chem 12(3):458–462

Ornoy A, Weinstein-Fudim L, Ergaz Z (2015) Prenatal factors associated with autism spectrum disorder (ASD). Reprod Toxicol 56:155–169

Oswiecimska J, Brus R, Szkilnik R, Nowak P, Kostrzewa RM (2000) 7-OH-DPAT, unlike quinpirole, does not prime a yawning response in rats. Pharmacol Biochem Behav 67(1):11–15

Papadeas ST, Breese GR (2014) 6-Hydroxydopamine lesioning of dopamine neurons in neonatal and adult rats induces age-dependent consequences. In: Kostrzewa RM (ed) Handbook of neurotoxicity. Springer, New York, pp 133–198. ISBN 978-1-4614-5835-7 (print); ISBN 978-1-4614-5836-4 (eBook); ISBN 978-1-4614-7458-6 (print and electronic bundle). doi:10.1007/978-1-4614-5836-4_59

Pappas BA, Davidson CM, Fortin T, Nallathamby S, Park GA, Mohr E, Wiley RG (1996) 192 IgG-saporin lesion of basal forebrain cholinergic neurons in neonatal rats. Brain Res Dev Brain Res 96(1–2):52–61

Pappas BA, Payne KB, Fortin T, Sherren N (2005) Neonatal lesion of forebrain cholinergic neurons: further characterization of behavioral effects and permanency. Neuroscience 133(2):485–492

Pariante CM (2015) Neuroscience, mental health and the immune system: overcoming the brain-mind-body trichotomy. Epidemiol Psychiatr Sci 27:1–5

Paterak J, Stefański R (2014) 5,6- and 5,7-dihydroxytryptamines as serotoninergic neurotoxins. In: Kostrzewa RM (ed) Handbook of neurotoxicity. Springer, New York, pp 299–325. ISBN 978-1-4614-5835-7 (print); ISBN 978-1-4614-5836-4 (eBook); ISBN 978-1-4614-7458-6 (print and electronic bundle). doi:10.1007/978-1-4614-5836-4_76

Pekny M, Wilhelmsson U, Pekna M (2014) The dual role of astrocyte activation and reactive gliosis. Neurosci Lett 565:30–38

Pelly L, Vardy C, Fernandez B, Newhook LA, Chafe R (2015) Incidence and cohort prevalence for autism spectrum disorders in the Avalon Peninsula, Newfoundland and Labrador. CMAJ Open 3(3):E276–E280. doi:10.9778/cmajo.20140056

Perez SE, He B, Nadeem M, Wuu J, Scheff SW, Abrahamson EE, Ikonomovic MD, Mufson EJ (2015) Resilience of precuneus neurotrophic signaling pathways despite amyloid pathology in prodromal Alzheimer's disease. Biol Psychiatry 77(8):693–703

Pérez-Gómez A, Tasker A (2014) Domoic acid as a neurotoxin. In: Kostrzewa RM (ed) Handbook of neurotoxicity. Springer, New York, pp 399–419. ISBN 978-1-4614-5835-7 (print); ISBN 978-1-4614-5836-4 (eBook); ISBN 978-1-4614-7458-6 (print and electronic bundle). doi:10.1007/978-1-4614-5836-4_87

Perna MK, Brown RW (2013) Adolescent nicotine sensitization and effects of nicotine on accumbal dopamine release in a rodent model of increased dopamine D_2 receptor sensitivity. Behav Brain Res 242:102–109

Petrosini L, De Bartolo P, Tutuli D (2014) Neurotoxic effects, mechanisms and outcome of 192-IgG saporin. In: Kostrzewa RM (ed) Handbook of neurotoxicity. Springer, New York, pp 591–609. ISBN 978-1-4614-5835-7 (print); ISBN 978-1-4614-5836-4 (eBook); ISBN 978-1-4614-7458-6 (print and electronic bundle). doi:10.1007/978-1-4614-5836-4_79

Petrosini L, De Bartolo P, Cutuli D, Gelfo F (2016) Perinatal IgG saporin as neuroteratogen. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Phiel CJ, Zhang F, Huang EY, Guenther MG, Mitchell AL, Klein PS (2001) Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen. J Biol Chem 276:36734–36741

Pyndt Jørgensen B, Krych L, Pedersen TB, Plath N, Redrobe JP, Hansen AK, Nielsen DS, Pedersen CS, Larsen C, Sørensen DB (2015) Investigating the long-term effect of subchronic phencyclidine-treatment on novel object recognition and the association between the gut microbiota and behavior in the animal model of schizophrenia. Physiol Behav 141:32–39

Racine RJ (1972) Modification of seizure activity by electrical stimulation. II. Motor seizure. Electroencephalogr Clin Neurophysiol 32:281–294

Radonjić NV, Knezević ID, Vilimanovich U, Kravić-Stevović T, Marina LV, Nikolić T, Todorović V, Bumbasirević V, Petronijević ND (2010) Decreased glutathione levels and altered antioxidant defense in an animal model of schizophrenia: long-term effects of perinatal phencyclidine administration. Neuropharmacology 58(4–5):739–745

Radonjić NV, Jakovcevski I, Bumbaširević V, Petronijević ND (2013) Perinatal phencyclidine administration decreases the density of cortical interneurons and increases the expression of neuregulin-1. Psychopharmacology 227(4):673–683

Ranger P, Ellenbroek BA (2016) Perinatal influences of valproate on brain and behavior: an animal model for autism. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Reynolds GP, Abdul-Monim Z, Neill JC, Zhang ZJ (2004) Calcium binding protein markers of GABA deficits in schizophrenia—postmortem studies and animal models. Neurotox Res 6 (1):57–61

Ricaurte GA, Guillery RW, Seiden LS, Schuster CR, Moore RY (1982) Dopamine nerve terminal degeneration produced by high doses of methylamphetamine in the rat brain. Brain Res 235(1):93–103

Ricceri L, Calamandrei G, Berger-Sweeney J (1997) Different effects of postnatal day 1 versus 7 192 immunoglobulin G-saporin lesions on learning, exploratory behaviors, and neurochemistry in juvenile rats. Behav Neurosci 111(6):1292–1302

Ricceri L, Hohmann C, Berger-Sweeney J (2002) Early neonatal 192 IgG saporin induces learning impairments and disrupts cortical morphogenesis in rats. Brain Res 954(2):160–172

Ricceri L, Cutuli D, Venerosi A, Scattoni ML, Calamandrei G (2007) Neonatal basal forebrain cholinergic hypofunction affects ultrasonic vocalizations and fear conditioning responses in preweaning rats. Behav Brain Res 183(1):111–117

Robertson RT, Gallardo KA, Claytor KJ, Ha DH, Ku KH, Yu BP, Lauterborn JC, Wiley RG, Yu J, Gall CM, Leslie FM (1998) Neonatal treatment with 192 IgG-saporin produces long-term forebrain cholinergic deficits and reduces dendritic branching and spine density of neocortical pyramidal neurons. Cereb Cortex 8(2):142–155

Rodier PM, Ingram JL, Tisdale B, Croog VJ (1997) Linking etiologies in humans and animal models: studies of autism. Reprod Toxicol 11(2–3):417-422. Review

Rodriguez M, Rodriguez-Sabate C, Morales I, Sanchez A, Sabate M (2015) Parkinson's disease as a result of aging. Aging Cell 14(3):293–308

Roman-Urrestarazu A, Lindholm P, Moilanen I, Kiviniemi V, Miettunen J, Jääskeläinen E, Mäki P, Hurtig T, Ebeling H, Barnett JH, Nikkinen J, Suckling J, Jones PB, Veijola J, Murray GK (2015) Brain structural deficits and working memory fMRI dysfunction in young adults who were diagnosed with ADHD in adolescence. Eur Child Adolesc Psychiatry 26 Aug 2015. [Epub ahead of print]

Roos A, Kwiatkowski MA, Fouche JP, Narr KL, Thomas KG, Stein DJ, Donald KA (2015) White matter integrity and cognitive performance in children with prenatalmethamphetamine exposure. Behav Brain Res 279:62–67

Rosenberg PA, Loring R, Xie Y, Zaleskas V, Aizenman E (1991) 2,4,5-trihydroxyphenylalanine in solution forms a non-N-methyl-D-aspartate glutamatergic agonist and neurotoxin. Proc Natl Acad Sci USA 88(11):4865–4869

Ross SB, Renyi AL (1976) On the long-lasting inhibitory effect of N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP 4) on the active uptake of noradrenaline. J Pharm Pharmacol 28:458–459

Ross SB, Stenfors C (1915) DSP4, a selective neurotoxin for the locus coeruleus noradrenergic system. A review of its mode of action. Neurotox Res 27(1):15–30. Review

Ross SB, Johansson JG, Lindborg B, Dahlbom R (1973) Cyclizing compounds. I. Tertiary N-(2-bromobenzyl)-N-haloalkylamines with adrenergic blocking action. Acta Pharm Sueccica 10:29–42

Roullet FI, Lai JK, Foster JA (2013) In utero exposure to valproic acid and autism–a current review of clinical and animal studies. Neurotoxicol Teratol 36:47–56. Review

Ruan L, Kang Z, Pei G, Le Y (2009) Amyloid deposition and inflammation in APPswe/PSIde9 mouse model of Alzheimer's disease. Curr Alz Res 6:531–540

Sabers A, Bertelsen FC, Scheel-Krüger J, Nyengaard JR, Møller A (2015) Corrigendum to "Long-term valproic acid exposure increases the number of neocortical neurons in the developing rat brain" [Neurosci.Lett. 580 (2014) 12–16] A possible new animal model of autism. Neurosci Lett 588:203–207

Sachs C, Jonsson G (1972a) Degeneration of central and peripheral noradrenaline neurons produced by 6-hydroxy-DOPA. J Neurochem 19(6):1561–1575

Sachs C, Jonsson G (1972b) Selective 6-hydroxy-DOPA induced degeneration of central and peripheral noradrenaline neurons. Brain Res 40(2):563–568

Sachs C, Jonsson G, Fuxe K (1973) Mapping of central noradrenaline pathways with 6-hydroxy-DOPA. Brain Res 63:249–261

Sakai M, Kashiwahara M, Kakita A, Nawa H (2014) An attempt of non-human primate modeling of schizophrenia with neonatal challenges of epidermal growth factor. J Addict Res Ther 5:1

Salavert J, Ramos-Quiroga JA, Moreno-Alcázar A, Caseras X, Palomar G, Radua J, Bosch R, Salvador R, McKenna PJ, Casas M, Pomarol-Clotet E (2015) Functional imaging changes in the medial prefrontal cortex in adult ADHD. J Atten Disord 2015 Oct 29. pii: 1087054715611492. [Epub ahead of print]

Sanders JD, Happe HK, Bylund DB, Murrin LC (2011) Changes in postnatal norepinephrine alter alpha-2 adrenergic receptor development. Neuroscience 192:761–772

Scattoni ML, Calamandrei G, Ricceri L (2003) Neonatal cholinergic lesions and development of exploration upon administration of the GABAa receptor agonist muscimol in preweaning rats. Pharmacol Biochem Behav 76(2):213–221

Schroeder SR, Oster-Granite ML, Berkson G, Bodfish JW, Breese GR, Cataldo MF, Cook EH, Crnic LS, DeLeon I, Fisher W, Harris JC, Horner RH, Iwata B, Jinnah HA, King BH, Lauder JM, Lewis MH, Newell K, Nyhan WL, Rojahn J, Sackett GP, Sandman C, Symons F, Tessel RE, Thompson T, Wong DF (2001) Self-injurious behavior: gene-brain-behavior relationships. Ment Retard Dev Disabil Res Rev 7(1):3–12

Sealey LA, Hughes BW, Steinemann A, Pestaner JP, Gene Pace D, Bagasra O (2015) Environmental factors may contribute to autism development and male bias: Effects of fragrances on developing neurons. Environ Res 142:731–738

Seiden LS, Fischman MW, Schuster CR (1976) Long-term methamphetamine induced changes in brain catecholamines in tolerant rhesus monkeys. Drug Alcohol Depend 1:215–219

Shaywitz BA, Klopper JH, Yager RD, Gordon JW (1976a) Paradoxical response to amphetamine in developing rats treated with 6-hydroxydopamine. Nature 261(5556):153–155

Shaywitz BA, Yager RD, Klopper JH (1976b) Selective brain dopamine depletion in developing rats: an experimental model of minimal brain dysfunction. Science 191(4224):305–308

Siniscalco D (2015) Commentary: the impact of neuroimmune alterations in autism spectrum disorder. Front Psychiatry 6:145

Sircar R (2003) Postnatal phencyclidine-induced deficit in adult water maze performance is associated with N-methyl-D-aspartate receptor upregulation. Int J Dev Neurosci 21(3):159–167

Sitte HH, Freissmuth M (2010) The reverse operation of Na^+/Cl^--coupled neurotransmitter transporters—why amphetamines take two to tango. J Neurochem 112:340–355

Šlamberová R, Vrajová M, Schutová B, Mertlová M, Macúchová E, Nohejlová K, Hrubá L, Puskarčíková J, Bubeníková-Valešová V, Yamamotová A (2014) Prenatal methamphetamine exposure induces long-lasting alterations in memory and development of NMDA receptors in the hippocampus. Physiol Res 63(Suppl 4):S547–S558

Šlamberová R, Pometlová M, Macúchová E, Nohejlová K, Stuchlík A, Valeš K (2015) Do the effects of prenatal exposure and acute treatment of methamphetamineon anxiety vary depending on the animal model used? Behav Brain Res 292:361–369

Smith LM, Diaz S, LaGasse LL, Wouldes T, Derauf C, Newman E, Arria A, Huestis MA, Haning W, Strauss A, Della Grotta S, Dansereau LM, Neal C, Lester BM (2015) Developmental and behavioral consequences of prenatal methamphetamineexposure: a review of the Infant Development, Environment, and Lifestyle (IDEAL) study. Neurotoxicol Teratol 51:35–44

Snyder AM, Zigmond MJ, Lund RD (1986) Sprouting of serotoninergic afferents into striatum after dopamine-depleting lesions in infant rats: a retrograde transport and immunocytochemical study. J Comp Neurol 245(2):274–281

Soligo M, Protto V, Florenzano F, Bracci-Laudiero L, De Benedetti F, Chiaretti A, Manni L (2015) The mature/pro nerve growth factor ratio is decreased in the brain of diabetic rats: analysis by ELISA methods. Brain Res 1624:455–468

Sotoyama H, Zheng Y, Iwakura Y, Mizuno M, Aizawa M, Shcherbakova K, Wang R, Namba H, Nawa H (2011) Pallidal hyperdopaminergic innervation underlying D_2 receptor-dependent behavioral deficits in the schizophrenia animal model established by EGF. PLoS One 6(10): e25831

Sotoyama H, Namba H, Chiken S, Nambu A, Nawa H (2013) Exposure to the cytokine EGF leads to abnormal hyperactivity of pallidal GABA neurons: implications for schizophrenia and its modeling. J Neurochem 126(4):518–528

Steardo L Jr, Bronzuoli MR, Iacomino A, Esposito G, Steardo L, Scuderi C (2015) Does neuroinflammation turn on the flame in Alzheimer's disease? Focus on astrocytes. Front Neurosci 9:259

Stojković T, Radonjić NV, Velimirović M, Jevtić G, Popović V, Doknić M, Petronijević ND (2012) Risperidone reverses phencyclidine induced decrease in glutathione levels and alterations of antioxidant defense in rat brain. Prog Neuropsychopharmacol Biol Psychiatry 39(1):192–199

Sygnecka K, Heine C, Scherf N, Fasold M, Binder H, Scheller C, Franke H (2015) Nimodipine enhances neurite outgrowth in dopaminergic brain slice co-cultures. Int J Dev Neurosci 40:1–11

Takuma K, Hara Y, Kataoka S, Kawanai T, Maeda Y, Watanabe R, Takano E, Hayata-Takano A, Hashimoto H, Ago Y, Matsuda T (2014) Chronic treatment with valproic acid or sodium butyrate attenuates novel object recognition deficits and hippocampal dendritic spine loss in a mouse model of autism. Pharmacol Biochem Behav 126:43–49

Tan L, Yu JT, Tan L (2012) The kynurenine pathway in neurodegenerative diseases: mechanistic and therapeutic considerations. J Neurol Sci 323(1–2):1–8

Tartaglione AM, Venerosi A, Calamandrei G (2016) Anna Maria Tartaglione1,2, Aldina Venerosi 1, Gemma Calamandrei1Early life toxic insults and onset of sporadic neurodegenerative diseases. an overview of experimental studies. In: Kostrzewa RM, Archer T (eds) Neurotoxin modeling of brain disorders-lifelong outcomes in behavioral teratology. Springer, New York

Tasker RA, Strain SM, Drejer J (1996) Selective reduction in domoic acid toxicity in vivo by a novel non-N-methyl-D-aspartate receptor antagonist. Can J Physiol Pharmacol 74:1047–1054

Teitelbaum J (1990) Acute manifestations of domoic acid poisoning: case presentations. Can Dis Wkly Rep 16:5–6

Terranova JP, Chabot C, Barnouin MC, Perrault G, Depoortere R, Griebel G, Scatton B (2005) SSR181507, a dopamine D(2) receptor antagonist and 5-HT(1A) receptor agonist, alleviates disturbances of novelty discrimination in a social context in rats, a putative model of selective attention deficit. Psychopharmacology 181(1):134–144

Thacker SK, Perna MK, Ward JJ, Schaefer TL, Williams MT, Kostrzewa RM, Brown RW (2006) The effects of adulthood olanzapine treatment on cognitive performance and neurotrophic factor content in male and female rats neonatally treated with quinpirole. Eur J Neurosci 24(7):2075–2083

Thoenen H, Tranzer JP (1968a) Chemical sympathectomy by selective destruction of adrenergic nerve endings with 6-hydroxydopamine. Naunyn Schmiedebergs Arch Exp Pathol Pharmakol 261(3):271–288

Thoenen H, Tranzer JP (1968b) [On the possibility of chemical sympathectomy by selective destruction of adrenergic nerve endings with 6-hydroxydopamine (6-OH-DA)]. Naunyn Schmiedebergs Arch Exp Pathol Pharmakol 260(2):212–213. German

Tizabi Y, Copeland RL Jr, Brus R, Kostrzewa RM (1999) Nicotine blocks quinpirole-induced behavior in rats: psychiatric implications. Psychopharmacol 145:433–441

Tohmi M, Tsuda N, Mizuno M, Takei N, Frankland PW, Nawa H (2005) Distinct influences of neonatal epidermal growth factor challenge on adult neurobehavioral traits in four mouse strains. Behav Genet 35(5):615–629

Tohyama M, Maeda T, Kashiba A, Shimizu N (1974a) Fluorescence and electron microscopic analysis of axonal change of coerulo-cortical noradrenaline neuron system following destruction of locus coeruleus and administration of 6-hydroxydopa in the rat brain. Med J Osaka Univ 24(4):205–221

Tohyama M, Maeda T, Shimizu N (1974b) Detailed noradrenaline pathways of locus coeruleus neuron to the cerebral cortex with use of 6-hydroxydopa. Brain Res 79(1):139–144

Tuszynski MH, Blesch A (2004) Nerve growth factor: from animal models of cholinergic neuronal degeneration to gene therapy in Alzheimer's disease. Prog Brain Res 146:441–449

Uchida H, Sakata H, Fujimura M, Niizuma K, Kushida Y, Dezawa M, Tominaga T (2015) Experimental model of small subcortical infarcts in mice with long-lasting functional disabilities. Brain Res 1629:318–328

Uhrbrand A, Stenager E, Pedersen MS, Dalgas U (2015) Parkinson's disease and intensive exercise therapy—a systematic review and meta-analysis of randomized controlled trials. J Neurol Sci 353(1–2):9–19

Ungerstedt U (1968) 6-Hydroxy-dopamine induced degeneration of central monoamine neurons. Eur J Pharmacol 5(1):107–110

Ungerstedt U (1971) Postsynaptic supersensitivity after 6-hydroxy-dopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiol Scand Suppl 367:69–93

Verdoorn TA, Johansen TH, Drejer J, Nielsen EO (1994) Selective block of recombinant GluR6 receptors by NS-102, a novel non-NMDA receptor antagonist. Eur J Pharmacol 269:43–49

Verkhratsky A, Parpura V, Pekna M, Pekny M, Sofroniew M (2015) Glia in the pathogenesis of neurodegerative disease. Biochem Soc Trans 42(5):1291–1301

Vieira AC, Aleman N, Cifuentes JM, Bermudez R, Lopez Pena M, Botana LM (2015) Brain pathology in adult rats treated with domoic acid. Veterinary Pathol 52:1077–1086

Visser JE, Smith DW, Moy SS, Breese GR, Friedmann T, Rothstein JD, Jinnah HA (2001) Oxidative stress and dopamine deficiency in a genetic mouse model of Lesch-Nyhan disease. Brain Res Dev Brain Res 133(2):127–139

Vorhees CV, Ahrens KG, Acuff-Smith KD, Schilling MA, Fisher JE (1994a) Methamphetamine exposure during early postnatal development in rats: I. Acoustic startle augmentation and spatial learning deficits. Psychopharmacology 114(3):392–401

Vorhees CV, Ahrens KG, Acuff-Smith KD, Schilling MA, Fisher JE (1994b) Methamphetamine exposure during early postnatal development in rats: II. Hypoactivity and altered responses to pharmacological challenge. Psychopharmacology 114(3):402–408

Vorhees CV, Skelton MR, Grace CE, Schaefer TL, Graham DL, Braun AA, Williams MT (2009) Effects of (+)-methamphetamine on path integration and spatial learning, but not locomotor activity or acoustic startle, align with the stress hyporesponsive period in rats. Int J Dev Neurosci 27(3):289–298

Vrajová M, Schutová B, Klaschka J, Stěpánková H, Rípová D, Šlamberová R (2014) Age-related differences in NMDA receptor subunits of prenatallymethamphetamine-exposed male rats. Neurochem Res 39(11):2040–2046

Waddington JL (1990) Spontaneous orofacial movements induced in rodents by very long-term neuroleptic drug administration: phenomenology, pathophysiology and putative relationship to tardive dyskinesia. Psychopharmacology 101:431–447

Waddington JL, Cross AJ, Gamble SJ, Bourne RC (1983) Spontaneous orofacial dyskinesia and dopaminergic function in rats after 6 months of neuroleptic treatment. Science 220:530–532

Waite JJ, Chen AD, Wardlow ML, Wiley RG, Lappi DA, Thal LJ (1995) 192 immunoglobulin G-saporin produces graded behavioral and biochemical changes accompanying the loss of cholinergic neurons of the basal forebrain and cerebellar Purkinje cells. Neuroscience 65(2):463–476

Wang C, McInnis J, Ross-Sanchez M, Shinnick-Gallagher P, Wiley JL, Johnson KM (2001) Long-term behavioral and neurodegenerative effects of perinatal phencyclidine administration: implications for schizophrenia. Neuroscience 107(4):535–550

Wang Y, Musich PR, Serrano MA, Zou Y, Zhang J, Zhu MY (2014) Effects of DSP4 on the noradrenergic phenotypes and its potential molecular mechanisms in SH-SY5Y cells. Neurotox Res 25(2):193–207

Weinstock M (2008) The long-term behavioural consequences of prenatal stress. Neurosci Biobehav Rev 32:1073–1086

Wenk GL, Stoehr JD, Quintana G, Mobley S, Wiley RG (1994) Behavioral, biochemical, histological, and electrophysiological effects of 192 IgG-saporin injections into the basal forebrain of rats. J Neurosci 14(10):5986–5995

White IM, Minamoto T, Odell JR, Mayhorn J, White W (2009) Brief exposure to methamphetamine (METH) and phencyclidine (PCP) during late development leads to long-term learning deficits in rats. Brain Res 1266:72–86

Wingate M, Kirby RS, Pettygrove S, Cunniff C, Schulz E, Ghosh T, Robinson C, Lee LC, Landa R, Constantino J, Fitzgerald R, Zahorodny W, Daniels J, Nicholas J, Charles J, McMahon W, Bilder D, Durkin M, Baio J, Christensen D, Braun KV, Clayton H, Goodman A, Doernberg N, Yeargin-Allsopp M, Lott E, Mancilla KC, Hudson A, Kast K, Jolly K, Chang A, Harrington R, Fitzgerald R, Shenouda J, Bell P, Kingsbury C, Bakian A, Henderson A, Arneson C, Washington A, Frenkel G, Wright V (2014) Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2010. MMWR Surveill Summ. 63(2):1–21

Winn LM, Wells PG (1999) Maternal administration of superoxide dismutase and catalase in phenytoin teratogenicity. Free Radic Biol Med 26(3–4):266–274

Wischhof L, Irrsack E, Osorio C, Koch M (2015) Prenatal LPS-exposure—a neurodevelopmental rat model of schizophrenia—differentially affects cognitive functions, myelination, and parvalbumin expression in male and female offspring. Prog Neuropsychopharmacol Biol Psychiatry 57:17–30

Wong DF, Harris JC, Naidu S, Yokoi F, Marenco S, Dannals RF, Ravert HT, Yaster M, Evans A, Rousset O, Bryan RN, Gjedde A, Kuhar MJ, Breese GR (1996) Dopamine transporters are markedly reduced in Lesch-Nyhan disease in vivo. Proc Natl Acad Sci USA 93(11):5539–5543

Xi D, Peng YG, Ramsdell JS (1997) Domoic acid is a potent neurotoxin to neonatal rats. Nat Toxins 5:74–79

Xia Y, Qi F, Zou J, Yang J, Yao Z (2014) Influenza vaccination during early pregnancy contributes to neurogenesis and behavioral function in offspring. Brain Behav Immun 42:212–221

Zelazo PD, Carlson SM (2012) Hot and cool executive function in childhood and adolescence: development and plasticity. Child Devel Perspec. doi:10.1111/j.1750-8606.2012.00246.x

Zelazo PD, Müller U, Frye D, Marcovitch S, Argitis G, Boseovski J, Chiang JK, Hongwanishkul D, Schuster BV, Sutherland A (2003) The development of executive function in early childhood. Monogr Soc Res Child Dev 68(3):vii–137

Zelazo PD, Craik FI, Booth L (2004) Executive function across the life span. Acta Psychol 115 (2–3):167–183

Zhu F, Zheng Y, Ding YQ, Liu Y, Zhang X, Wu R, Guo X, Zhao J (2014a) Minocycline and risperidone prevent microglia activation and rescue behavioral deficits induced by neonatal intrahippocampal injection of liposaccharide in rats. PLoS One 9(4):e93966

Zhu F, Zhang L, Ding YQ, Zhao J, Zheng Y (2014b) Neonatal intrahippocampal injection of liposaccharide induces deficits in social behavior and prepulse inhibition and microgial activation in rats: implication for a new schizophrenia animal model. Brain Behav Immun 38:166–174

Zieher LM, Jaim-Etcheverry G (1973) Regional differences in the long-term effect of neonatal 6-hydroxydopa treatment on rat brain noradrenaline. Brain Res 60(1):199–207

Zieher LM, Jaim-Etcheverry G (1975a) 6-hydroxydopa during development of central adrenergic neurons produces different long-term changes in rat brain noradrenaline. Brain Res 86(2):271–281

Zieher LM, Jaim-Etcheverry G (1975b) Different alterations in the development of the noradrenergic innervation of the cerebellum and the brain stem produced by neonatal 6-hydroxydopa. Life Sci 17(6):987–991