Effects of Exogenous Agents on Brain Development: Stress, Abuse and Therapeutic Compounds

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SUMMARY

The range of exogenous agents likely to affect, generally detrimentally, the normal development of the brain and central nervous system defies estimation although the amount of accumulated evidence is enormous. The present review is limited to certain types of chemotherapeutic and “use-and-abuse” compounds and environmental agents, exemplified by anesthetic, antiepileptic, sleep-inducing and anxiolytic compounds, nicotine and alcohol, and stress as well as agents of infection; each of these agents have been investigated quite extensively and have been shown to contribute to the etiopathogenesis of serious neuropsychiatric disorders. To greater or lesser extent, all of the exogenous agents discussed in the present treatise have been investigated for their influence upon neurodevelopmental processes during the period of the brain growth spurt and during other phases up till adulthood, thereby maintaining the notion of critical phases for the outcome of treatment whether prenatal, postnatal, or adolescent. Several of these agents have contributed to the developmental disruptions underlying structural and functional brain abnormalities that are observed in the symptom and biomarker profiles of the schizophrenia spectrum disorders and the fetal alcohol spectrum disorders. In each case, the effects of the exogenous agents upon the status of the affected brain, within defined parameters and conditions, is generally permanent and irreversible.

Introduction

Normal brain development, whether at regional, circuitry, or neuronal levels, follows a programmed pathway that differentiates specific and distinctive regional structural characteristics and functions in the adolescent and adult [1,2], with the influence of epigenetic factors (e.g., mutant strains) of increasing importance [3]. A wide range of exogenous agents will alter the course of brain development thereby threatening the integrity of regional structure and function with permanent consequences [4–8] that often lead to dire neurodevelopmental [9] and neuropsychiatric [10] outcomes. Both agents released into the environment [11–13] and abuse substances, for example, cocaine [14–23], have highly detrimental effects on the development of brains of human and subhuman species. Although cocaine is not the fo-

cus of this review, the extent of personal and financial affliction caused by the drug is difficult to overestimate. Of major significance for the developing brain is the period of brain growth spurt [24]: in humans from the third trimester of gestation till about 2 years of age, even according to some accounts extending from the 6th month of gestation to several years after birth whereas other accounts maintain the sensitive nature of brain development into adolescence [25]. In rodents, it extends throughout the first three postnatal weeks, almost exclusively a postnatal event, with cell migration, neuronal elongation, dendritic arborization and synaptogenesis, and proliferation of astroglial and oligodendroglial cells [26,27]. Defects that occur in the neurodevelopmental process may exert profound consequences upon the structure and function of the “mature” brain, in these cases often distinguished by a lack of maturity that is

expressed generally in epigenetic and developmental behavioural abnormalities of the underlying psychopathology [28].

The effects of the vast majority of exogenous agents are detrimental to normal brain development, often through interference (generally a destruction-enhancing acceleration) of the process of apoptosis, a ubiquitous process involved in many biological systems. Physiological apoptosis, or programmed cell death, is a naturally occurring process inherent to the developing brain [29] that is critical for both the turnover of cells and normal development, in shaping the embryonic brain [30–33]. It has been proposed that apoptosis is an essential requirement for the evolution of all animals, and in fact the apoptotic program is highly conserved from nematodes to mammals [cf. 34–36], and is a tactic employed by multicellular organisms to eliminate damaged or unnecessary cells. Alterations in apoptosis at any stage during the brain growth spurt, sometimes referred to as developmental period of synaptogenesis [37], due to drugs, hypoxia or brain trauma will determine extent of damage to neuronal circuitry and expression of neurobiological dysfunctions [38–43]. The brain growth spurt occurs in different species at different times relative to birth; it is a period in fetal and neonatal human development, lasting for several years, during which immature central nervous system (CNS) neurons are sensitive to many exogenous environmental agents (increasingly more numerous) that set off widespread neurodegeneration by inducing specific abnormal changes in the synaptic environment.

There are numerous exogenous agents that have been used and/or abused by pregnant mothers, for example, smoking (nicotine), alcohol (ethanol), phencyclidine (PCP, angel dust), ketamine (Special K), nitrous oxide (laughing gas), barbiturates, benzodiazepines, and many medicinal compounds used in obstetric and pediatric medicine as sedatives, anticonvulsant or anesthetic agents (all general anesthetics are either NMDA antagonists or GABA mimetics), and continue to be so [cf. 44–47]. Neurotransmitters and neuromodulators exert pleiotropic effects, that is, induce multiple diverse effects by serving as regulators of distinct cellular functions during different phases of the neurodevelopmental process [48]; a variety of exogenous agents induce disruptive effects on these systems. Thus, manipulations involving each of these drugs/exogenous agents will influence the integrity of more than one neurotransmitter systems, bearing in mind that neurotransmitters may be viewed as the lowest common denominators in the constellations of synaptic signals and communications between neurons (or first messengers). Progenitor cells of the brain can express receptors for most neurotransmitter receptors, and neurotransmitters may be important signals in-

fluencing cell proliferation, differentiation, synaptogenesis and maturation and the survival of neurons [e.g., 48]. They may be involved also in the “targeting” of migrating neurons and guidance of growing axons during the formation of neural circuits [cf. 49]. In the neocortex of mammals, the balance between glutamatergic (excitatory) and GABAergic (inhibitory) neurons is relatively conserved [50] with the delicate equilibrium between excitation and inhibition a necessity for burgeoning cortical and cortico-limbic circuitry. During normal postnatal development, the functional maturation of local inhibitory (or excitatory) connections is essential for cortical plasticity [51]. Inherited or environmentally originating entities (exogenous agents) may cause disruptions of inhibitory-excitatory interactions, with respective neurotrophin participation, thereby contributing to the etiopathogenesis of neuropsychiatric disorders, for example, schizophrenia, depression, epilepsy, and/or developmental disorders [52–58]. For example, both brain-derived neurotrophic factor expression and receptor availability are dependent upon neuronal activity such that marked increase in excitatory (glutamatergic) synaptic connections will upset the homeostatic regulation of developing neural networks with concurrent suppression of GABAergic (inhibitory) synaptic input [59].

Antianxiety Sleep-inducing and Antiepileptic Compounds

The apoptotic neurodegenerative effects of this class of compounds that includes, diazepam, clonazepam, phenobarbital, valproic acid, and vigabatrin, administered between postnatal days 0 and 14, have been examined closely in rodents [e.g., 40,60]. Bittigau et al. [61] administered rat pups, aged 3–30 days, with either phenytoin, phenobarbital, diazepam, clonazepam, vigabatrin, or valproic acid. Their histological, electron microscopic examinations of the brains of these animals revealed that these drugs cause widespread and dose-dependent apoptotic neurodegeneration in the developing rat brain during the brain growth spurt period. These effects were particularly the case in wide-ranging regions of the brain, including the medial septum, nucleus accumbens, thalamic and hypothalamic nuclei, subiculum, globus pallidus, piriform and entorhinal cortices, amygdala, frontoparietal, cingulate, and retrosplenial cortices. Apoptotic neurodegeneration was induced at plasma drug levels, for example, equivalent to a threshold dose of phenytoin, 28 mg/kg that yields plasma concentrations of 10–15 $\mu\text{g/mL}$ over 4 h, relevant for seizure control in humans. They showed also that antiepileptic drugs lead to reduced expression of neurotrophins and decreased concentrations of the

active forms of ERK1/2, RAF, and AKT. β -Estradiol, which stimulates pathways that are activated by neurotrophins, a class of growth factors, secreted proteins which are capable of signaling particular cells to survive, differentiate, or grow, attenuated the neurodegenerative effects of this class of agents. Neurotrophic factors are secreted by target tissue and act by preventing the associated neuron from initiating apoptotic programmed cell death thereby allowing the affected neurons to survive. Sedative and anticonvulsant agents that reduce neuronal excitability via antagonism at N-methyl-D-aspartate receptors (NMDARs) and/or agonism at gamma-aminobutyric acid subtype A receptors (GABA(A)Rs) are applied frequently in obstetric and pediatric medicine. Kaindl et al. [62] showed that a 1-day treatment of infant mice at postnatal day 6 (P6) with the NMDAR antagonist dizocilpine or the GABA(A)R agonist phenobarbital not only has acute but also long term effects on the cerebral cortex. Changes of the cerebral cortex proteome 1 day (P7), 1 week (P14), and 4 weeks (P35) following treatment at P6 suggest that a suppression of synaptic neurotransmission during brain development dysregulates proteins associated with apoptosis, oxidative stress, inflammation, cell proliferation, and neuronal circuit formation. These effects appear to be age-dependent as most protein changes did not occur in mice subjected to such pharmacological treatment in adulthood. Bercker et al. [63], using a summation score of the density of apoptotic cells, found marked neurodegenerative effects of the anesthetic drugs, propofol, and sevoflurane, substances acting via GABAA agonism and/or NMDA antagonism, in neonatal rat pups, further supporting the involvement of NMDA blockade [64–66].

Anesthetic Compounds

Several anesthetic agents, for example, Isoflurane, induce cell death in the developing rodent brain [67–69]. Recently, Stratmann et al. [70] administered isoflurane to rat pups at postnatal day 7 at 1 minimum alveolar concentration for 0, 1, 2, or 4 h. One group of rats was treated during 4 h with carbon dioxide to control for the respiratory depressant effects of the anesthetic compound. The fluoro-Jade, an anionic fluorochrome that selectively stains degenerating neurons in brain slices [71–72] staining technique was used following termination of each intervention. Eight weeks later, the neurocognitive performance of the rats was assessed 8 weeks later by testing fear conditioning, spatial reference memory, and spatial working memory tasks. It was found that widespread brain cell death was caused by 2 and 4 h of postnatal isoflurane and by 4 h of carbon dioxide. The extent and distribution of thalamic cell death

was similar in 4 h isoflurane-treated and 4 h carbon dioxide-treated rats. Only the 4-h interval of isoflurane caused a long-term neurocognitive deficit affecting both spatial reference memory and spatial working memory. General anesthetics are strong pharmacological modulators of neuronal activity. Thus, the question regarding whether or not, and how, these compounds may affect the development of synaptic networks was addressed by De Roo et al. [73]. To this end it must be considered that experience-driven activity plays an essential role in the development of brain circuitry during critical periods of early postnatal life, a process that depends upon a dynamic balance between excitatory and inhibitory signals, chemical signals. The authors studied the effects of anesthetic compounds on synapse growth and dynamics. Anesthetic compounds that either enhanced GABAergic inhibition or blocked NMDA receptors rapidly induced marked increases in dendritic spine density in the somatosensory cortex and hippocampus, a developmentally regulated effect that is transient but lasts for several days. These effects were produced also by selective antagonists of excitatory receptors. These alterations were mediated increased rates of protrusions formation, a better stabilization of newly formed spines, and led to the formation of functional synapses [73].

Glutamic acid is an excitatory amino acid that is active at NMDARs. It provides for trophic functions through endogenous factors in the developing brain [74–78]. These agents influence synaptic plasticity and promote cell proliferation and migration of neuronal progenitors (e.g., human neuronal progenitor cells, or NPCs), cells that have a capacity to differentiate into a specific type of cell, unlike stem cells, they are more specific, being “pushed” to differentiate into their “target” cell, and may divide only a *limited* number of times [79–80]. For example, neurotrophic factor-3 (NT-3) and brain-derived neurotrophic factor (BDNF) exert a profound effect on the types of neurotransmitter receptors expressed on postnatal spiral ganglion neurons (SGNs) [81]. Histological evaluations of the brains revealed widespread apoptosis and decreased cell proliferation following drug treatments that reduce that NMDA, or “glutamate,” in infancy in several species [82]. It has been found that the antagonism of glutamate NMDA receptors or the excessive excitation of GABA receptors during the period of the brain growth spurt or synaptogenesis induces apoptotic neurodegeneration [83–87]. A decade ago, Ikonomidou et al. [88] administered either ketamine (at postnatal day 7), MK-801 (at postnatal days 0, 3, or 7), carboxypiperazine-4-yl-propyl-1-phosphoric acid, CPP (at postnatal 7) or phencyclidine, PCP (at postnatal 7) in order to antagonize NMDA glutamate receptors over a period of several hours during the late fetal or early postnatal

development of rat pups. The widespread apoptotic neurodegeneration resulting from these treatments indicated that glutamate controls neuronal survival. Ikonomidou et al. [89] described the effects of transient blockade of NMDA receptors or the excessive activation of GABA receptors through postnatal administration of anesthetic compounds (ketamine, nitrous oxide, isoflurane, propofol, and halothane), anticonvulsant compounds (benzodiazepines, barbiturates), and abuse compounds (phencyclidine, ketamine, and ethanol). They indicated that there were three different peaks for the apoptotic neurodegeneration that was induced; these were associated with three different peaks for brain cell death: on postnatal day 0 (early stage), postnatal day 2 (mid stage) and postnatal day (late stage), with the pattern of regional neurodegeneration specific for each stage.

These inductions of apoptotic neurodegeneration have implied harmful effects upon function: Fredriksson et al. [90] examined the neurobehavioural deficits of potentiated apoptosis by administering either ketamine (50 mg/kg, s.c.) or diazepam (5 mg/kg, s.c.), or the combination of ketamine + diazepam or vehicle (saline) to postnatal NMRI male mouse pups on day 10 after birth. Following this, on postnatal day 11, mouse pups from each of the four treatment groups were sacrificed and their brain regionals were analyzed for neuronal cell degeneration using the Fluoro-Jade staining technique. Ketamine caused severe cell degeneration in the parietal cortex whereas diazepam did so in the laterodorsal parietal cortex, and the combination of the caused the most severe neurodegeneration. Motor activity testing at 60 days-of-age indicated that the ketamine and ketamine+diazepam groups displayed marked habituation deficits to the test chambers. Concurrently, in the radial maze task there were marked deficits in acquisition and retention as well as deficits in shift-learning, a test of selective attention and retention [6,7,91], in the circular water maze task [92]. Thus, the potential hazards for normal brain development, through postnatal administration of anesthetic agents with the pharmacological profile of glutamate antagonists, that suggests an accelerated rate of neuronal degeneration expressed in the marked functional deficits of the adult animal, ought to be noted [93–95]. Abekawa et al. [96] exposed rats prenatally (E15–E18) to the NMDA glutamate antagonist, MK-801, and observed a reduction in the density of parvalbumin-immunoreactive neurons in rat medial prefrontal cortex on postnatal day 63 (P63) and enhanced PCP-induced hyperlocomotion, but not the acute effects of METH (methamphetamine) on P63 or the development of behavioral sensitization. They concluded that prenatal blockade of NMDA receptors disrupts GABAergic neurodevelopment in the medial pre-

frontal cortex, and that this disruption of GABAergic development may be related to the enhancement of the locomotion-inducing effect of PCP in postpubertal but not juvenile offspring. The GABAergic deficit was unrelated to the effects of METH. This GABAergic neurodevelopmental disruption and the enhanced PCP-induced hyperlocomotion in adult offspring prenatally exposed to MK-801 may prove useful as a new model of the neurodevelopmental process of pathogenesis of schizophrenia.

Other types of functional deficits have been observed also: Fredriksson and Archer [97] performed an experiment to study the effects of postnatal administration of glutamate receptor antagonists, on either Day 11 (dizocilpine = MK-801, 3×0.5 mg/kg, s.c., injected at 0800, 1600 and 2400 h) or Day 10 (Ketamine, 1×50 mg/kg, s.c., or Ethanol-Low, 1×2.5 mg/kg, or Ethanol-High, 2×2.5 mg/kg, s.c., with 2-h interval) to male mice pups, on spontaneous motor behavior, habituation to a novel situation and D-amphetamine-induced activity in the adult animals. It was found that mice administered MK-801 showed initial hypoactivity followed by hyperactivity over the later (20–40 and 40–60 min) periods of testing. Mice administered Ketamine and Ethanol-High similarly displayed an initial hypoactivity followed by hyperactivity over the later time (20–60 min) of testing. Habituation to the novel activity test chambers was reduced drastically in the MK-801 mice compared with vehicle-treated mice. Similarly, mice administered Ketamine and Ethanol-High displayed too drastically reduced habituation behavior. The low dose of D-amphetamine (0.25 mg/kg) reduced the hyperactivity of neonatal MK-801-treated mice, particularly from 30 to 60 min onwards, and elevated the activity level of the vehicle-treated mice. Similarly, the low dose of D-amphetamine (0.25 mg/kg) reduced the hyperactivity of neonatally Ketamine-treated and Ethanol-High-treated mice, particularly from 30 to 60 min onwards, and elevated the activity level of the respective vehicle-treated mice. Fluoro-jade staining per mm² regional brain tissue of MK-801 mice pups expressed as percent of vehicle mice pups showed also that the extensiveness of staining was markedly greater in the parietal cortex, hippocampus, frontal cortex, and lesser so in the laterodorsal thalamus. Ketamine-treated mice showed cell degeneration mainly in the parietal cortex, whereas the Ethanol-High mice showed marked cell degeneration in both the parietal and laterodorsal cortex. The present findings that encompass a pattern of regional neuronal degeneration, disruptions of spontaneous motor activity, habituation deficits and reversal of hyperactivity by a low dose of D-amphetamine suggest a model of Attention Deficit Hyperactivity Disorder (ADHD) that underlines the intimate role of NMDA glutamate receptors in the

developing brain. Recently, Jensen et al. [98] described results indicate that functional impairments in glutamatergic synaptic transmission may be one of the underlying mechanisms leading to the abnormal behavior in SHR, an animal model of ADHD, and possibly in human ADHD. Carrey et al. [99] examined 13 ADHD patients and 10 healthy controls and found that striatal glutamate, glutamate/glutamine (Glx) and creatine concentrations were greater in the ADHD subjects at baseline as compared to controls. Using magnetic resonance imaging, Perlov et al. [100] found a significant reduction of the combined glutamate/glutamine to creatine ratio in the right anterior cingulate cortex in patients with ADHD was found, suggesting that glutamatergic alterations, as measured with magnetic imaging, may contribute to the pathogenesis of adult patients with ADHD. Lindahl et al. [101] found that prenatal NMDA receptor blockade reduces the level of progenitors and that the surviving cells are arrested at an immature stage. This premature arrest appears to result in fewer fully differentiated, mature oligodendrocytes that are capable of producing myelin. These results have interesting implications for the role of glutamate and glutamate receptors in white matter abnormalities in neurodevelopmental disorders, including ADHD. Finally, several epigenetic studies have implicated glutaminergic involvement in neurodevelopmental alterations underlying the etiopathogenesis of both ADHD and the response to methylphenidate treatment [102–105].

Effects of Nicotine and Alcohol

Nicotine and alcohol may exert detrimental effects on brain development at different age-levels, for example, at prenatal, postnatal and adolescent age-levels. Both nicotine and alcohol are neuroteratogens affecting adversely cell differentiation in the developing brain [106–108] with several apoptotic neurodegenerative effects [109–111] advancing well into adolescent ages [112–114]. Both nicotine [115–117] and alcohol [118–121] administration during adolescence induce long-lasting developmental disruption resulting from neuronal damage and attrition. These drugs induce also marked, and as yet not fully understood, interactive effects on neurodevelopment and function [122–128]. Recently, Oliveira-da-Silva et al. [129] exposed C57BL/6 mice to either (i) combined nicotine (50 $\mu\text{g/mL}$) and ethanol (25%, 2 g/kg injected every other day, or (ii) nicotine, or (iii) ethanol, or (iv) vehicle during postnatal days 30–45. Ethanol induced an increase in cell degeneration (Tunel assay) relative to the vehicle group in all hippocampal regions. Nicotine did so too in the CA1 and molecular layers, compared to vehicle, with similar reductions in neuronal and glial cell densities.

The potential and real threats posed by nicotine for the developing brain may be ascertained from the situation, quite recent, that 21% of adult individuals in the USA have indicated that they are regular smokers (CDC, 2006). Taken together with the situation of an almost insuperable rate of smoking relapse (97%) by addicted individuals [130,131], the scenario for all the potential offspring of these individuals may be fraught with severe risk. Maternal smoking during pregnancy has been associated consistently with disruptive behaviour in the offspring, particularly male [cf. 132]. Exposure to tobacco poses innumerable health risks for the developing fetus, not least with regard to the developing brain [133–136], with effects upon maturation of neuronal circuitry and plasticity [cf. 137]. In terms of possible consequence, Wu and Anthony [138] studied a group of young individuals in an epidemiological setting, consisting of 1731 children and adolescents (aged 8–9 to 13–14 years) attending public schools in a mid-Atlantic metropolitan area (assessed at least twice from 1989 to 1994). A survival analysis was used to examine the temporal relationship from antecedent tobacco smoking to subsequent onset of depressed mood, as well as from antecedent depressed mood to subsequent initiation of tobacco use, suggesting a possible causal link from tobacco smoking in late childhood and early adolescence to later depressed mood in the adult.

Nicotine, the main psychoactive agent in tobacco, exerts neurotoxic effects on the developing brain, for example, by reducing the total number of whole brain cells in the fetal and early postnatal period consistent with nicotine receptor involvement in apoptosis [139–141]. It has been shown that prenatal administration of nicotine affects the developing brain at doses that do not retard general growth [142]. Prenatal nicotine, from cigarette smoking, affects placental vasculature and nicotinic acetylcholine receptor binding in fetal membranes that trigger a cascade of events that dysregulate developing nicotinic, muscarinic, catecholaminergic and serotonergic neurotransmitter systems [143]. Prenatal nicotine, through a cascade of effects, evokes neurodevelopmental abnormalities by disrupting the timing of neurotrophic actions [144]. Both prenatal exposure and adolescent exposure to tobacco smoke was associated with increased fractional anisotropy, a measure often used in diffusion imaging where it is thought to reflect fibre density, axonal diameter, and myelination in white matter, in anterior cortical white matter [145]. Slotkin et al. [146] found that following prenatal nicotine, indices of cell number and size showed few abnormalities by 6 months, yet persistent deficits in cerebrocortical choline acetyltransferase activity and hemicholinium-3 binding to the presynaptic choline transporter, a pattern consistent with

cholinergic hypoactivity, with effects were more prominent in male than in female rats. The expression of serotonin (5-HT) receptors also showed permanent effects in male rats, with suppression of the 5-HT(1A) subtype and upregulation of 5-HT(2) receptors. Adolescent nicotine exposure induced similar effects. However, prenatal exposure followed by adolescent exposure caused these adverse effects of the drug to extend also to the female rats [146; see also 147,148 for effects of gender in humans]. Postnatal exposure to nicotine (6.0 mg/kg/day) from postnatal days (PD) 4–9, during the period of the brain growth spurt, induced marked levels of hyperactivity compared to two control groups [149]. Recently, Dwyer et al. [150] reviewed the existing evidence that nicotine interfered with catecholamine and brainstem autonomic nuclei development during rodent prenatal periods (equivalent to human first and second trimesters), neocortex, hippocampus, and cerebellum development during the early postnatal period (human third trimester) and limbic and monoamine maturation during adolescence. Finally, it was shown that prenatal nicotine altered parameters of cell development that lasted into adolescence, wherein these effects accumulated with those elicited directly by adolescent nicotine; thus, the neurotoxicant actions of the drug may thereby contribute to the association between maternal smoking and subsequent smoking in the offspring [151], as well as increased risk for several other psychiatric conditions [115,152–153].

Perinatal exposure to alcohol (ethanol) causes wide-ranging and debilitating effects that affect the structure and function of the developing brain both in clinical reality and in the animal laboratory [154,155]. Ethanol is a major hazard to the normal development of the fetal brain and CNS and gestational consumption poses huge risks for structure and function [156–166]. It ought to be noted too that the prenatal exposure to alcohol may result in a variety of functional deficits, in both cognitive and emotional domains, despite the absence of obvious physical/somatic/structural abnormalities with diagnostic criteria and classifications under the “umbrella” term, fetal alcohol spectrum disorders [167]. Neurostructural abnormalities, as described by magnetic resonance imaging, have been applied to distinguish diagnostic subclassifications pertaining to regional volume, level of exposure, magnitude of FAS facial phenotype, neuropsychological deficits and extent of brain dysfunction [168–170]. Alcohol exposure during the period of brain synaptogenesis, both prenatal and postnatal in humans but mainly postnatal in rodents, induces marked apoptotic neurodegeneration [89,171–173]. The neurobehavioural disruptions, linked to morphological damage generally, are alarmingly widespread: from hyperactive syndromes (including inability to habituate to familiar environments) to

serious perceptual cognitive-emotional deficits that are manifested at child, adolescent and adult age-levels, essentially the disorder termed fetal alcohol syndrome or effect [174–179]. In this respect, the lipid peroxidation expressed in brain is an indicator of oxidative stress following acute administrations of alcohol [180,181]. The hematopoietic cytokine, erythropoietin (EPO), recently shown to be expressed in the brain and CNS [182,183], possesses antiapoptotic effects [184], antioxidative effects [185] and antiinflammatory effects [186]; also recombinant human EPO reduces lipid peroxidation in erythrocytes of preterm infants [187].

An ever-accumulating volume of evidence shows that even moderate levels of alcohol during the period of major brain development induces alterations in neurobehavioural parameters, with or without obviously accompanying morphological, that are expressed through educational challenges [188–190]. For example, social behavior, which is an essential ingredient of normal function, is consistently disrupted in the offspring of mothers administered alcohol [191,192]. In the animal laboratory, the damaging effects of alcohol upon the developing brain and CNS are reflected in both the functional and neurobiological mechanisms implicated in the pathophysiology of the observed range of deficits [193]. Thus, several reports confirm the persistence of defective social behaviours in rodents, species with particularly developed social behaviour [194–196]. Recently, Hamilton et al. [197] examined the effects of prenatal exposure to moderate levels (4-h bouts of 5% ethanol during gestation with maternal serum levels monitored) upon the social behaviour of the adult offspring and effects upon dendritic morphology, structural plasticity, and activity-related immediate early gene (IEG) expression in the agranular insular and prelimbic regions of the frontal cortex. They report that male ethanol rats displayed more wrestling rather than social interaction following 24-isolation and decreases in dendritic length and spine density in the agranular insular region. Interestingly, they obtained robust increases in activity-related IEG expression (as a marker for neural activity during social interaction) in the agranular insular region (*c-fos* and *arc*) and prelimbic region (*c-fos*) following social interaction in saccharin-exposed (control) rats but not in the ethanol-exposed rats. These two regions were targeted for their involvement in social behaviour and damage to the area is associated with response perseveration [198], which has been observed too in rats that had been exposed prenatally to high doses of alcohol [199–201]. Finally, Thomas et al. [202] have demonstrated that following prenatal alcohol a choline supplementation attenuated significantly the adverse effects of the drug on birth and brain, incisor emergence and other markers of behavioral

development, including eye-opening, righting reflex, geotactic reflex, cliff avoidance, reflex suspension and hindlimb coordination, in rats.

Exogenous Agents of Endogenous Origin

Mazur-Kolecka et al. [203] showed that sera from children with autism alter the maturation of human neuronal progenitor cells (NPCs) in culture. Their results suggest that preprogrammed neurogenesis, that is, neuronal proliferation, migration, differentiation, growth, and circuit organization, can be affected differently by factors present in autistic sera. Mazur-Kolecka et al. [204] tested the effect of autistic sera on the vulnerability of NPCs to oxidative stress—a recognized risk factor of autism. They showed that mild oxidative stress reduced proliferation of differentiating NPCs but not immature NPCs. This decrease of proliferation was less prominent in cultures treated with sera from children with autism than from age-matched controls. These results suggest that altered response of NPCs to oxidative stress may play a role in the etiology of autism (see next section, for neuroinflammatory factors). The specific genetic background that alters vulnerability to some environmental insults has been suggested in the etiology of autism; however, the specific etiopathomechanisms have not yet been identified sufficiently although it remains clear that the factors contributing to the etiopathogenesis of brain disorders that have origins during development are numerous [see 204].

Hepatocyte growth factor (HGF) and its receptor *c*-Met are widely expressed in the developing and adult brain. However, little is known about the role of HGF during the development of the human dopaminergic neuronal system. Lan et al. [205] established telomerase-immortalized dopaminergic progenitor cells isolated from the fetal striatum that express markers for NPCs and tyrosine hydroxylase. They have shown that the cells were able to differentiate into dopaminergic neurons and release dopamine. Exogenous HGF-induced proliferation was inhibited by U0126, whereas migration was completely blocked by LY294002. Their study demonstrates that HGF regulates the proliferation and migration of dopaminergic progenitor cells. Modulating dopaminergic progenitor cells in the striatum may prove to be a new approach for treating Parkinson's disease.

Influence of Stress

Stress-inducing agents may disrupt the course of brain development in a variety of ways. Some common types include:

Oxidative Stress

Agents enhancing oxidative stress may affect the process of preprogrammed neurogenesis, involving neuronal proliferation, migration and cell differentiation, growth and circuit organization during embryogenesis and the early postnatal period as observed in autistic individuals [206,207]. Enhanced oxidative stress and decreased antioxidant enzyme activity [208–210], together with epigenetic factors will increase sensitivity to exogenous oxidative agents during neurogenesis [7,211–213]. Altered brain development during embryogenesis and early postnatal life has been hypothesized to be responsible for the abnormal behaviors of people with autism [214]. For example, in a cell culture model of neurogenesis, NPCs exposed to amyloid-beta, that induces oxidative stress displayed disruptions in cell maturation and differentiation [215]. Mazur-Kolecka et al. [203] applied human NPCs stimulated with sera from autistic children as a cell culture model of neurogenesis in autism. Other exogenous oxidative stress agents produce similar development-disrupting effects. Bisphenol A (BPA) is an environmental endocrine disruptor that widely used in the manufacture of plastics and epoxy resins. Kim et al. [216] studied the effects of BPA a murine-derived multipotent neural progenitor cells (NPCs), observing that pretreatment of BPA significantly decreased proliferation of NPCs in a concentration-dependent manner and at a high concentration ($>400 \mu\text{M}$) was cytotoxic to NPCs. It was shown too that reactive oxygen species were elevated in NPCs exposed to high concentrations of BPA, indicating oxidative stress-related cytotoxicity, underlying adverse effects of BPA on neonatal brain development.

Psychosocial Stress

Environmental stress initiates a cascade of events resulting in elevated circulating glucocorticoids and brain catecholamines [217] that, if present during the prenatal phase of brain development, induce marked disruptions of structure and function [218,219]. Perinatal stress is associated with long-term neurodevelopmental, functional deficits and greater risk for brain disorders [220–226]. The hypothalamic–pituitary–adrenal (HPA) axis is highly responsive to stress during the final weeks of gestation with heightened foetal responses to increased glucocorticoid levels [e.g., 227–229]. For example, prenatal malnutrition (i.e., maternal food deprivation) induces disruptions in neurobehavioural parameters and stress hormone levels [230–232]. Mabandla et al. [233] have developed a mild prenatal stress rat model to analyze the long-term effects on brain functioning in the adult offspring, describing effects on open-field behaviour and

adrenocorticotrophic hormone. Administration of dexamethasone, the synthetic glucocorticoid, to pregnant rodents during the third trimester of pregnancy alters permanently the functioning of the HPA axis with impaired negative feedback sensitivity in the offspring, as adults, that is expressed in several different types of neurobehavioural tests [234–237]. Hossain et al. [238,239] demonstrated that, following prenatal dexamethasone treatment, the startle response amplitude in response to glucocorticoid agonist or antagonist, demonstrated in the control rats, was abolished in dexamethasone rats and the activation of the BDNF exon IV promoter in the paraventricular nucleus of these rats was impaired. Thus, prenatal stress is linked to alterations in proteins and cellular mechanisms involved in neuronal plasticity, underlying development, that influence the expression of trophic factors [240,241], changes in neurogenesis [242,243] and NMDA receptor-dependent synaptogenesis [244]. Fumagalli et al. [245] have shown that chronic prenatal stress interfered with the responsiveness of specific determinants of glutamatergic synapses during adulthood in a regional specific manner. These effects were expressed through a loss of ability to mount an homeostatic glutamatergic response to subsequent stress during the adult ages of the offspring that placed the normally functioning stress response at risk for disruption [245].

An ever-accumulating abundance of evidence underlines the notion that stressful events that are experienced early in life are linked intimately with neuropsychiatric disorders later in life. Stress induction during the immediate postnatal period is also highly detrimental for brain development [246–249]. Even stressful events during adolescence will prove detrimental to normal brain development [250]. The types of postnatal stress exposure, for example, maternal separation or “handling,” and the degree of stress will induce different levels of stress [251–254] and therefore differential effects on brain development [255–257]. As the mother–infant relation is essential in most mammalian species, the early deprivation from maternal care and nurture may induce serious alteration in brain development and impart life long vulnerability to the infant [258], with enhanced susceptibility for neuropsychiatric disorder [259,260]. Maternal deprivation increases DA turnover in mesolimbic brain regions of guinea pig pups in the laboratory [261]. Oitzl et al. [262] have proposed four linked hypotheses: (i) the classical *Glucocorticoid Cascade Hypothesis*, whereby inability to cope with chronic stress causes a vicious cycle of excess glucocorticoid and downregulation of glucocorticoid receptors in the hippocampus triggering a feed-forward cascade of degeneration and disease, (ii) the *Balance Hypothesis*, whereby limbic mineralocorticoid re-

ceptors are involved in an integral limbic *mineralocorticoid receptor: glucocorticoid receptor* imbalance causal to altered processing of information in circuits underlying fear, reward, social behaviour and resilience, dysregulation of the HPA axis and impairment of behavioural adaptation. The *mineralocorticoid receptor: glucocorticoid receptor* balance is altered by gene variants of these receptor complexes and experience-related factors, which can induce lasting epigenetic changes in the expression of these receptors, (iii) the Maternal Mediation Hypothesis, whereby the maternal environment is a fundamental and particularly potent epigenetic stimulus. The outcome of perinatal gene–environment interaction, and thus of *mineralocorticoid receptor: glucocorticoid receptor*-mediated functions depends on the degree of “matching” with environmental demands during later life. Finally, (iv) the Predictive Adaptation Hypothesis provides a conceptual framework outlining the role of glucocorticoids in understanding individual phenotypic differences in stress-related behaviours over the lifespan [263,264].

Differences in HPA axis stress reactions occur in rat pups during the postnatal period with hyporesponsiveness over a major portion of early postnatal development, the Stress Hyporesponsive Period (SHRP) [265–267], with the intimate involvement of 5-HT neurotransmission [268] at hypothalamic [269] and limbic [270–272] sites. Matsui et al. [273] compared Wistar rats exposed to inescapable stress on either postnatal days 11–15 or postnatal days 16–20 with increased corticosterone levels in both groups. They observed too that in the hypothalamus, amygdala and hippocampus, 5-HT and 5-HIAA were increased in the former and decreased in the latter, supporting the contention that stress exposure during different periods of postnatal developmental stages induces differential effects upon neurodevelopment. Nevertheless, during the early life phase the integrity of the developing brain is determined by several intrinsic characteristics that may or may not endow some degree of protection: for example, from postnatal day 4, infant rats enter the SHRP which lasts until postnatal day 14 and involves a reduction in adrenal sensitivity. Uysal et al. [274] have obtained results indicating that maternal deprivation increased lipid peroxidation (i.e., enhanced oxidative stress, see above) in the prefrontal cortex, striatum, and hippocampus, in infants post-SHRP, but decreased lipid peroxidation during SHRP.

Viral/Bacterial-induced Stress Affecting Brain Development

Human cytomegalovirus infection of the developing CNS is a major cause of neurological damage in newborn infants and children. Koontz et al. [275] developed a mouse

model of infection in the developing CNS. Intraperitoneal inoculation of newborn animals with murine cytomegalovirus resulted in virus replication in the liver followed by virus spread to the brain. Virus infection of the CNS was associated with the induction of inflammatory responses, including the induction of a large number of interferon-stimulated genes and histological evidence of focal encephalitis with recruitment of mononuclear cells to foci containing virus-infected cells. The morphogenesis of the cerebellum was delayed in infected animals. The defects in cerebellar development in infected animals were generalized and, although correlated temporally with virus replication and CNS inflammation, spatially unrelated to foci of virus-infected cells. Specific defects included decreased granular neuron proliferation and migration, expression of differentiation markers, and activation of neurotrophin receptors. These findings suggested that in the developing CNS, focal virus infection and induction of inflammatory responses in resident and infiltrating mononuclear cells resulted in delayed cerebellar morphogenesis. In addition, it ought to be considered also that neuroinflammatory reactions resulting in abnormalities in brain development following a range of exogenous chemical agents may underlie developmental disorders such as autism [276].

Much evidence exists to indicate that viral/bacterial infection in the mother during critical periods of pregnancy may be associated with neurodevelopmental disruptions in the offspring that may increase risk for neuropsychiatric disease states [277–280]. Thus, an accumulating amount of documentation points to links between *in utero* immune challenge, via a variety of different interventions, and the emergence of structural and neurobehavioural abnormalities in the offspring at various points in the life cycle [281–290]. Thus, maternal infection during pregnancy endows a greater risk for brain disease states in the offspring: Winter et al. [291] exposed pregnant mouse, C57BL6/J, dams to viral mimetic polyriboinosinic-polyribocytidilic acid (5 mg/kg, i.v.) or vehicle treatment on gestation Day 9, as the prenatal immune activation. They found that this intervention increased markedly dopamine (DA) and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillic acid (HVA), in several brain regions including the prefrontal cortex, nucleus accumbens, and globus pallidus, concurrent with decreases in serotonin and its metabolite, 5-HIAA, in the nucleus accumbens, globus pallidus and hippocampus, compared to the vehicle treated animals, when they were sacrificed and their brains taken for analysis during the 12th week. Also, a specific reduction in the inhibitory amino acid, taurine, was observed in the hippocampus of the prenatally treated mice. The authors concluded that maternal im-

munological activation/stimulation during early/middle pregnancy induced long-term, even permanent, alterations in brain neurotransmitter systems, likely predispositional factors for structural and functional imbalance in the adult individual. Further provocation, for example, environmental stress, would serve to precipitate the onset and expression of the respective neuropsychiatric symptom profiles. Thus, there is an ever-growing abundance of evidence supporting not only the contention regarding the microbial stress origins of agents affecting brain development but also their contributions to life-long neuropsychiatric disorder [292–298].

The present review describes a few of the exogenous agents that have a detrimental influence and continue to affect adversely brain development. These agents included anesthetic and anxiolytic compounds, nicotine and alcohol, stress whether oxidative or psychosocial, and stress inflammation stemming from activations of the immune system. As an illustrative point, the disruptive effects of prenatal adversity on immune system development may combine with adverse effects on both prenatal and postnatal neurodevelopment in contributing to the etiopathogenesis of neuropsychiatric disorders [299]. The notion that immune dysfunction, for example, pro- and antiinflammatory cytokine imbalance, is implicated in onset of prodromal and/or psychotic symptoms as well as the progressive loss of brain tissue underlying structural abnormality [300] is but one scenario involving the exogenous characters contributing to the tragedy.

Conflict of Interests

The authors have no conflict of interest.

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