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Brain development: anatomy, connectivity, adaptive plasticity, and toxicity

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Abstract

The developing brain is inherently more vulnerable to injury than the adult brain because brain development is extraordinarily complex, with periods of unique susceptibility. When brain developmental processes are suspended or delayed by any external influence, virtually no potential exists for subsequent regeneration and repair. This inevitably leads to long-lasting or permanent consequences. Recent genetic studies have contributed to a better understanding of the dynamic adaptive changes that occur in the developing brain as a consequence of genetic and environmental processes. Many industrial and environmental chemicals such as lead, methyl-mercury, polychlorinated biphenyls, arsenic, and toluene are recognized causes of neurodevelopmental disorders that lead to clinical or subclinical brain dysfunction. A number of these developmental disabilities arise from interactions between environmental factors and individual gene susceptibility. In addition, neurodevelopmental disorders of unknown origin, such as mental retardation, attention deficit disorder, cerebral palsy, and autism are becoming increasingly prevalent, with costly consequences for the family and society. The aim of this review is examine brain developmental anatomy, connectivity, adaptive plasticity, and toxicity in the context of current knowledge and future trends.

1. Introduction

Several studies during the last decade have contributed significantly to our understanding of the dynamic adaptive changes that occur in the developing brain as a consequence of genetic and environmental processes [1,2]. Childhood is a time when the brain undergoes considerable changes in anatomical structure and connectivity [3]. These changes are possible because of the brain's plasticity during this period—changes that are shaped by the organism's complex aggregate of responses to the environment. Responses of neuronal systems stem from simple circuits and have predetermined developmental futures [4].

"Critical periods" or "sensitive periods" during brain development are highly plastic brief, defined periods of development during which the brain is particularly vulnerable for disruption by environmental influences. Therapeutic or preventive interventions at these time points may have long-term functional consequences. As mechanisms of neuronal circuitry development become better understood, phenomena surrounding "critical periods" are being redefined in terms of plasticity of the immature brain [2,5].

2. Brain development anatomy and connectivity

Normal architecture of the cerebral cortex is established during prenatal development by neurons proliferating from early precursor cells, which migrate radially outward from the ventricular zone [5,6]. After this neuronal migration, dendrites and axons sprout and arborize extensively forming numerous synapses and neuronal networks. The human brain at birth has an overproduction of neurons (100 billion neurons) that undergo selective apoptosis later during postnatal life, resulting in a loss of up to 50% of cortical neurons [7]. In addition, during the early postnatal period, synaptic density increases markedly [8,9] and reaches far above adult levels. These synapses are "pruned" during childhood and adolescence to mature adult levels with primary sensory and motor regions maturing before regions involved in more complex functions [5,10]. Further functional organization involves complex interaction with an array of signals between cortical neurons, progenitors, and environmental stimuli [11].

Although the cerebellum comprises only 10% of the total brain volume, the mature cerebellum contains more than 50% of all the central nervous system neurons [5]. The

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cerebellum is the most sexually dimorphic part of the brain and is critical for motor learning in vertebrates. Although it is one of first brain structures to differentiate, it is the last one to achieve maturity. Cellular organization of the cerebellum continues to change for many months after birth, making it susceptible to disruptions during this protracted developmental stage [12,13].

3. Brain development: adaptive/compensatory plasticity

Neuroplasticity is a term used to describe the unique capacity of the mammalian brain that enables it to use the activity induced by a given experience to modify function in neuronal circuitry, which in turn adjusts subsequent thoughts, feelings, and behavior [1]. This change occurs in molecular and structural features in response to various environmental stimuli. As a consequence of disease processes, neuroplastic changes can be seen either in postmortem tissue or in biomarkers detectable by neuroimaging, electroencepalography, or other noninvasive indicators of brain structure and function.

Synaptic plasticity, on the other hand, is the term used to describe the activity-dependent modification of the strength of synaptic transmission. For more than a century, the incorporation of transient (temporary) experiences into permanent memory (consolidation) has been attributed to synaptic plasticity. In addition, synaptic plasticity is considered to be key in the early development of neuronal circuits, and recent evidence shows that impairment in synaptic plasticity contributes to several major neuropsychiatric disorders. Several forms and mechanisms of synaptic plasticity have been described. The following are the most established forms of synaptic plasticity and the role they play in adaptive brain functions during early brain development which, in turn, impacts on cognitive behavior and on our understanding of a wide range of brain disorders.

3.1. Short-term synaptic plasticity

In the mammalian brain, short-term synaptic plasticity influences the information processing function of synapses, enabling them to act as filters with a wide range of properties [14]. The filtering characteristics of a synapse can be adjusted through modulation of the initial release of neuromodulators that, via activation of presynaptic receptors, reduce the probability of release. This changes the filtering characteristics of the synapse, causing synaptic facilitation to become predominant over synaptic depression. In this way, presynaptic inhibition can "convert" a synapse from excitatory to inhibitory or vice versa.

3.2. Long-term synaptic plasticity (long-term potentiation and long-term depression)

Long-term synaptic plasticity has been the object of intense investigation because it provides an important key to understanding some of the cellular and molecular mechanisms by which memories are formed [15]. Most synapses that exhibit long-term potentiation (LTP) also express long-term depression (LTD)—a key concept which demonstrates the fact that synaptic activity is bidirectional and modifiable by different patterns of activity [14]. The most extensively studied forms of synaptic plasticity are LTP and LTD in the CA1 region of the hippocampus—sites that are triggered by the activation of *N*-methyl-D-aspartate receptors. The current view of the mechanisms underlying LTP is that synaptic remodeling occurs at the presynaptic active zone and involves post- and presynaptic protein interactions, with likely candidates being cell adhesion molecules such as the cadherins or neuroligin/neurexin. The size of the presynaptic active zone increases such that the potentiated synapses are "permanently" enlarged. Maintenance of these changes depends on transcription as well as local dendritic protein synthesis [14].

3.3. Molecular mechanisms in plasticity during brain development

The molecular mechanisms in developmental and adaptive/compensatory plasticity are still unknown. It is assumed that brain development requires modification of gene expression and protein production [16]. However, the role of experience-dependent activity in shaping the ultimate synaptic patterns is gaining widespread acceptance [17]. In addition, there is new evidence for plasticity in functional connectivity across modalities [18]. The refinement of cortical synaptic connections [11] requires localized increase in intracellular calcium in dendritic spines, which is typically achieved via the activation of the N-methly-D-aspartate (NMDA) subtype of glutamate receptors [14]. The activity of excitatory glutaminergic neurons is also modulated by inhibitory interneurons, which use the neurotransmitter γ-aminobutyric acid (GABA), and also provides an important inhibitory signal for the development of neural networks [19]. In addition, either the up- or down-regulation of calcium channels on both glutamatergic (NMDA) as well as GABA-ergic neurons (with resultant changes in Ca^{2+} traffic in and out of the neurons) appears to be central to the mechanisms of neuroplasticity.

3.4. Normal brain development and brain magnetic resonance imaging

Magnetic resonance imaging has made possible serial observations of human brain development and enabled us to learn how individual brains change over time [20]. Human gray matter develops nonlinearly [21]: gray matter increases during childhood and adolescence and then decreases at peak ages, differing between lobes (lobar heterogeneity). White matter myelination, on the other hand, appears to continue well into adulthood. Gray matter in developmentally essential areas such as the primary motor and sensory cortices, or the primary visual cortex matures at earlier ages, whereas brain area subserving more complex functions, such as the association cortices, matures at much later ages

[22,23]. These observations show that structural brain development parallels functional milestones in the brain representing a complex interplay between programmed development and environmental inputs.

3.5. Genetics of brain development

Imaging studies of adult twins have found a strong genetic influence on total cerebral volume and lobar gray and white matter volumes [24]. This heritability has been confirmed in same-sex twins for all brain regions except for the cerebellum [25] and is of interest because abnormal cerebellar development has been found in cases of attention deficit/hyperactivity disorder.

3.6. Diseases associated with structural brain developmental abnormalities

It is now accepted that schizophrenia is associated with structural brain abnormalities [26]. Studies of childhood-onset schizophrenia have provided the opportunity to examine the interaction of the illness with early brain development. In addition, there are many examples of delayed or impaired development across a wide sphere of behaviors seen in the childhood of many adult patients with schizophrenia [27]. Fifty percent of patients with childhood-onset schizophrenia had an anxiety disorder at initial screening, indicating a phenotype with prominent GABA-ergic abnormalities [28].

4. Brain development: toxicity of environmental agents

One of every 6 children in the United States has a developmental disability, which in most cases, affects the nervous system [29]. The most common neurodevelopmental disabilities are learning disabilities, sensory deficit, developmental delays, and cerebral palsy [29]. Recently, a considerable amount of attention has been focused on autism, attention deficit disorder, mental retardation, and cerebral palsy—conditions that are increasing in prevalence [30]. These disorders are difficult to treat, can cause lifelong disability, and are costly to the family and to society [30]. The cause of these disorders remains largely unknown.

A US National Research Council expert committee concluded a few years ago that 3% of developmental disabilities is the direct result of exposure to environmental pollutants and another 25% arise through the interactions between environmental factors and individual gene susceptibility [31].

The developing brain is far more susceptible to insults by toxic agents than adults because during the 9 months of intrauterine (prenatal) life, a small strip of ectodermal cells in the fetus must develop into a complex organ consisting of a precisely organized pattern that involves billions of cells [32] in a tightly controlled time frame and sequence. Furthermore, the blood-brain barrier in the developing brain is not completely formed until the sixth month of prenatal life, which leaves the developing brain exposed to toxins such as heavy metals in the maternal blood [32]. The vulnerability of the developing brain to environmental toxins continues into postnatal life because infants and children are unable to detoxify exogenous compounds and lipophilic substances such as pesticides and halogenated industrial compounds that are readily passed on to the infant via breast milk [32].

4.1. Bisphenol A

The chemical bisphenol A is used to produce polycarbonate plastic and epoxy resins and is found in such products as baby bottles. Tests by the US Centers for Disease Control and Prevention found the chemical in urine of 95% of 394 individuals in a reference sample of US adults [33]. A panel, convened in August 2007 by the National Toxicology Program Center for the Evaluation of Risks to Human Reproduction, “expressed some concern that exposure to BPA could have neurological or behavioral effects in pregnant women, fetuses, infants and children” [34].

5. Conclusions

Alterations in neurotransmitters such as glutamate and GABA can lead to deleterious changes in the functional architecture of the developing brain. The neuroplastic capacity of cortical circuitry in response to perturbations of normal brain developmental processes plays an important role in adaptive plasticity. A complete understanding of the vulnerability of these developmental processes, their neuroplastic capacity, and the maturation of neural circuits, during critical periods of development, is necessary to evaluate the consequences of developmental neurotoxicity. The studies reviewed above provide an update of our understanding of brain developmental processes. The increasing use of noninvasive methods to detect brain dysfunction after exposure to neurotoxic environmental chemicals during development can be expected to yield valuable information about their putative role in the pathogenesis of an array of developmental disorders.

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