A Candidate Molecule Approach to Defining Developmental Pathology in Schizophrenia

by Cynthia Shannon Weickert and Daniel R. Weinberger

Abstract

The evidence that schizophrenia may have its origins from early in life, possibly during prenatal brain development, is based primarily on a constellation of nonspecific anatomical findings and on the results of surveys of obstetrical complications and of childhood neurological and psychological adjustment. The developmental processes implicated by this evidence are uncertain, but speculation has centered around abnormalities of neuronal proliferation, migration, and connection formation. These developmental milestones are the results of complicated cellular processes involving molecular interactions between cells and between the extracellular and intracellular milieus. To understand how these abnormalities could relate to schizophrenia, it is necessary to characterize the molecular events that define the processes. In this article, we discuss the potential impact of a number of molecules that are important in the sequence of cellular events implicated in schizophrenia. In particular, we focus on molecular mechanisms related to cell proliferation, axonal outgrowth, cell migration, cell survival, synaptic regression, myelination, and developmental aspects of early adult life. These various candidate molecules regulate different aspects of cell growth and cell-cell interactions and are involved in the regulation of deoxyribonucleic acid (DNA) expression. Very few of these molecules have been studied in the schizophrenic brain.

Key words: Puberty, hormone receptors, growth factors, myelination.


Schizophrenia is a brain disease whose cellular and molecular substrates are unknown. Clinically, schizophrenia can be recognized by a set of symptoms that vary from subject to subject but still are remarkably stereotyped across individuals and across cultures (Cutting 1995). This similarity implies that there may be a common underlying pathology in the diseased brain. Although this pathology could have many causes, it is likely that common brain systems or neural circuitry are involved in most, if not all, cases of schizophrenia. While neither the neuroanatomical nor the biochemical basis for schizophrenia has been definitively identified, there are provocative leads. Brain imaging studies often demonstrate structural or physiological abnormalities in prefrontal cortex, cingulate cortex, temporal cortex, or hippocampal formation (Liddle 1995). These findings concur, in general, with neuropathological studies of the schizophrenic brain that find evidence of generalized limbic lobe and prefrontal cortical abnormalities (Falkai and Bogerts 1995). In addition, the fact that the symptoms of schizophrenia are exacerbated by certain pharmacological agents and ameliorated by others has fueled speculation that these brain abnormalities affect the function of specific neuronal systems, especially those using dopamine, serotonin, glutamate, and gamma-aminobutyric acid (GABA) (Owen and Simpson 1995).

Neurobiologists attempt to discern the function of the brain from a highly reductionist perspective; ultimately, they attempt to understand how the brain functions on cellular and molecular levels. Those working on schizophrenia hope to determine which cells in the brain are affected by the disease and how the molecules within affected brain cells are altered. Working at the microscopic level, neuropathologists throughout this century have searched the schizophrenic brain for evidence of neuronal dropout. While some potential clues have been discovered through this approach, such as evidence of pyramidal neuronal loss in the entorhinal cortex of schizophrenia patients

Reprint requests should be sent to Dr. D.R. Weinberger, Clinical Brain Disorders Branch, IRP/NIMH/NIH, NIMH Neuroscience Center at St. Elizabeths, 2700 Martin Luther King Jr. Ave., SE, Washington, DC 20032.
Schizophrenia and Brain Development. One of the more intriguing recent research directions has been guided by the increasingly popular notion that schizophrenia is a neurodevelopmental disorder. The neurodevelopmental hypothesis suggests that a brain "lesion" is present or acquired early in life but does not fully manifest itself until late adolescence or early adulthood (Weinberger 1987, 1995a). A number of lines of evidence suggest that the "lesion" does not appear to be progressive in neuropsychological terms: no progression of cerebral ventricular size over the course of the illness in most studies (Jaskiw et al. 1994); no cognitive deterioration over the course of the illness (Hyde et al. 1994); no evidence of increased glial membrane turnover signals in magnetic resonance spectroscopy in either chronic schizophrenia patients or at the time of disease onset (Bertolino et al. 1996); and no active brain gliosis in most of the postmortem studies (Roberts et al. 1986; Falkai et al. 1988; Bruton et al. 1990; Benes 1993). Other evidence indicates that subtle abnormalities of nervous system development occur early in the lives of patients who manifest schizophrenia later (Jones et al. 1994) and that obstetrical abnormalities are more frequent in such individuals than in their unaffected relatives (McGrath and Murray 1995). The neurobiological plausibility of the developmental hypothesis of schizophrenia has received support from animal studies showing that a limbic cortical lesion sustained early in life can remain quiescent until after puberty, when it influences behavioral and neuropharmacological phenomena that mimic schizophrenia to a considerable degree (Lipska and Weinberger 1993, 1996; Lipska et al. 1993; Flores et al. 1996).

The possibility that schizophrenia is a neurodevelopmental disorder challenges developmental neurobiologists in two broad areas. First, the molecular nature of the early lesion in the schizophrenia patient must be identified, and second, the peripubertal molecular trigger of the phenotypic dysfunction must be defined. As a first step, molecules that are important in normal brain development must be delineated; with the advent of modern molecular techniques, hundreds of developmentally important molecules have already been discovered. The purpose of this review is to discuss, in the broad context of brain development, some of the types of molecules that may play a role in developmental processes putatively associated with schizophrenia (see table 1). We believe that in addition to defining structural and functional brain anomalies and outlining alterations in fast-acting neurotransmitter systems, it will be important to search for aberrant expression or function of developmentally important molecules that are capable of interacting with brain elements over the course of weeks to months to years.

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Note.—HOX = homeotic genes; FGF = fibroblast growth factor; EGF = epidermal growth factor; NCAM = neural cell adhesion molecule; LAMP = limbic associated membrane protein; GAP = growth associated protein; NGF = nerve growth factor; BDNF = brain-derived neurotrophic factor.
Molecular Brain Development Broadly Defined. Development of a multicellular organism requires that each genetically identical cell of the body, which is derived initially from one individual cell, take on a dissimilar or differentiated phenotype. Initially, brain development is driven by a genetic program that activates a molecular cascade of events leading to the turning on and turning off of particular genes in cells (Purves and Lichtman 1985; Gilbert 1991; Jacobson 1991; Ptashne et al. 1983; Cooke 1988; Patel 1994; Rubenstein et al. 1994). As an organism grows, specification of cell fate relies increasingly on molecular signals extrinsic to the developing cell. Such signals can be derived from cell surface molecules on neighboring cells or diffusible chemicals emanating from both nearby and distant cells. Coordinated brain development results from activation and inactivation of genes in certain cells and not others, and this process produces a spatially and temporally unique pattern of proteins that, in turn, determines which cells are capable of sending or receiving messages from other cells.

Genes, Neurodevelopment, and Schizophrenia. A large number of genetic studies have indicated that inheriting certain genes imparts risk for developing schizophrenia (Asherson et al. 1995). If a faulty gene has been inherited by an individual not yet exhibiting symptoms of schizophrenia, it may affect brain development and susceptibility to schizophrenia in two general ways. First, one may speculate that this gene normally transcribes proteins that are important for normal brain development or, alternatively, that the “wild-type” allele of this gene becomes activated only at the time of early adulthood when the protein product becomes necessary. Second, defective genes may impart susceptibility to the illness by sensitizing the organism to environmental adversity. It has been postulated that the “lesion” results from an abnormal prenatal, natal, or early postnatal environment that adversely affects the developing brain and alters the normal course of developmental events (Weinberger 1995b). A genetic deficit could conceivably predispose an individual to this adversity or modify its effects. By either mechanism, it is apparent that the brain “lesion” in schizophrenia could be caused by genetic factors, environmental factors, or more likely some combination of both.

Candidate Molecules

Early Pattern Formation. Some of the first tasks accomplished by the developing organism are neural tube induction and specification of cell position within the neural tube (Purves and Lichtmen 1985). Signals originating from the notochord are believed to convey dorsal-ventral positioning information to the cells in the developing neural tube. Initial rostro-caudal cell positioning is related to activation of distinct genes that regulate the orientation of parallel segments of the anterior-posterior body axis. These genes encode transcription factors that share a deoxyribonucleic acid (DNA) binding motif (the “homeobox”), allowing them to act as master switches to direct the morphogenetic development of each segment of the embryo (McGinnis et al. 1984; Scott and Weiner 1984; Gehring 1987; Ingham 1988). Protein products of homeobox genes, including, for example, homeotic genes (HOX) family members, return to the cell nucleus and bind to certain DNA sequences, enabling the activation or inactivation of other genes in spatially restricted domains of the embryo (Holland and Hogan 1988; Goulding and Gruss 1989; Wilkinson et al. 1989; Lufkin et al. 1991). If one of these early acting gene products were altered in schizophrenia, one might expect to find much greater alterations in gross brain morphology than the subtle ones found in the schizophrenic brain. Indeed, a recent report has confirmed that a mutation in a homeobox gene is associated with marked schizencephaly, a gross defect in telencephalic fusion (Brunelli et al. 1996). However, other families of homeobox-like transcription factors can operate later in development or appear only in defined brain regions. An example of these more specific transcription factors can be found among the so-called POU family of genes (Ingraham et al. 1988; Treacy and Rosenfeld 1992). For example, SCIP, a homeodomain protein member of the POU III family, is expressed specifically in layer V neurons of the adult cortex and only begins expression in this population of neural cells after they have started to differentiate (Frantz et al. 1994). Other POU III family members have been shown to be activated at various times before and after birth in discrete regions of the brain (Le Moine and Young 1992; Mathis et al. 1992). Therefore, transcription family molecules that fit this developmental temporal pattern are more likely to be candidate molecules in schizophrenia.

Cell Proliferation. Another very early event in brain development is the exponential increase of cell number inside the neural tube (Jacobson 1991). Some reports have shown a reduced number of neurons in the adult schizophrenic brain (Hopf 1952; Vogt and Vogt 1952; Colon 1972; Benes et al. 1986). One possible explanation is that fewer neurons were produced at the outset, either because of reduced proliferation or because fewer neurons in the diseased brain differentiated. Protein molecules have been shown to regulate these events by stimulating receptors on the cell surface of dividing cells. These extracellular sig-
nals include classes of molecules, termed growth factors or cytokines, that stimulate the proliferation and differentiation of brain cell precursors (Gospodarowicz 1983). Among these are members of the fibroblast growth factor (FGF) family (Bouvier and Mytilineou 1995) and the epidermal growth factor (EGF) family (Reynolds and Weiss 1992; Reynolds et al. 1992). Many growth factors can exist in both membrane/substrate bound and secreted forms, and accordingly they are thought to exert contact-dependent and diffusible effects (Carpenter and Cohen 1990). Most growth factors bind to cell surface receptors and activate tyrosine kinase second messenger systems to transduce mitogenic signals (Pawson and Bernstein 1990). It is conceivable that a decreased level or an altered form of growth factor or growth factor receptor limits the production of neuronal cells early in the brain development of a schizophrenia patient.

A surprising result highlighted by recent basic research demonstrates that the proliferation of neurons continues in the adult avian and rodent brain in a specialized area called the subependymal zone (Altman 1969; Alvarez-Buylla et al. 1990). This putative neurogenic zone lies just under the ependymal cell layer surrounding the lateral ventricle in the adult. Members of the EGF family of growth factors have been shown to stimulate the proliferation of these adult stem cells in the brains of rodents (Weickert and Blum 1995; Craig et al. 1996). Thus, some of the factors that may be involved in stimulating fetal brain cells to divide may still be inducing proliferation of stem cells in the adult brain. Recent evidence gathered from cultures of human temporal lobe biopsies suggests that neuronal production may also continue in the adult human brain (Kirschchenbaum et al. 1994).

By examining the putative mitogenic subependymal layer in adult human neuropathological specimens, researchers may be able to define the factors shared by adult and fetal neurogenesis. This zone may provide researchers with a window for exploring molecules that have operated during development of the fetal brain. Currently, nothing is known about which growth factor molecules or receptors continue to be expressed in the adult human putative neurogenic zones. If neurogenesis occurs in adult human brains, then either a reduction in neuron number without gliosis or a neuronal overabundance could reflect abnormalities in postnatal neuronal proliferation. As our knowledge about brain development expands, our ideas of the potential mechanism for the developmental “lesion” in schizophrenia will likely evolve along with it.

Cell Migration. In both the adult brain and the developing brain, after a cell exits the cell cycle and has become committed to the neuronal phenotype, it must migrate away from the zone of origin to an appropriate brain layer in the maturing brain (Jacobson 1991). Recent evidence has suggested that there are an abnormally high number of neurons in white matter areas of schizophrenic brain (Akbarian et al. 1993, 1996). One possibility is that these displaced neurons may not have successfully migrated to their appropriate cortical layer during development. Such aborted migration could be the result of inappropriate migratory cues along the migratory route or an inability of the neurons to respond to those cues. At a molecular level, cell migration is thought to result from the combinatorial adhesive or repulsive action of many cell surface proteins and glycoproteins present on the neuron and along the migratory route (commonly, radial glia). Three main families of adhesion molecules can be located on the cell surface: the immunoglobulin superfamily, the cadherins, and the integrins (Jessell 1991). Cell adhesion proteins exist in more than one form, and these forms may be related to specific developmental or functional abilities. For example, the neural cell adhesion molecule (NCAM), a member of the immunoglobulin superfamily, has a heavily polysialated (PSA) form that has been shown to be involved in promoting the migration of immature neurons out of the adult neurogenic subependymal layer (Ono et al. 1994). The PSA residue makes the NCAM molecule less sticky so it facilitates neuronal movement (Acheson et al. 1991; Ono et al. 1994). One study suggests that there may be a lower number of neurons expressing the polysialic form of the NCAM molecule in the schizophrenic hippocampus (Barbeau et al. 1995). The abnormal levels of PSA–NCAM in the schizophrenic brain might lead to migration abnormalities, resulting in inwardly displaced neurons.

Extracellular matrix molecules and glial cell adhesion molecules should also be considered components of molecular migration machinery (Gao et al. 1992). When an extracellular matrix protein molecule is altered during brain development, a dramatic phenotype can result. In the mutant mouse reeler, for example, later-born cortical neurons are unable to migrate past the earlier-born cortical neurons, resulting in an atypical “inside-out” pattern of cortical lamination (Caviness and Rakic 1978). This reorganization of cortical lamination was recently found to be the result of a mutation in a single gene, the reelin gene, which codes for a secreted protein localized to the extracellular matrix (D’Arcangelo et al. 1995). Little is known about extracellular matrix molecules in schizophrenia. Clearly, more postmortem studies on brains from schizophrenia patients are needed to examine this interesting and diverse group of molecules that promote neuronal cell adhesion.

Axonal Outgrowth. Once a cell body of a neuron has migrated to the appropriate cortical location, axonal con-
nections with other neurons are established. The swollen tip of a growing axon, the growth cone, is thought to integrate extracellular signals in order to ensure proper phosphorylation and dephosphorylation of cytoskeletal elements, which in turn propel the growing tip of the axon in an anatomically correct direction (Kater and Guthrie 1990). Neuroscientists have hypothesized that either fewer cortico-cortical connections or dysfunctional ones may underlie the deficits in higher level cognitive tasks that are manifested by most patients with schizophrenia (Weinberger and Lipska 1995). The diminution of cortical neuropil and the reduction in synapse marker proteins in the cortex support the idea that there are fewer cortical connections in the diseased brain (Browning et al. 1993; Eastwood and Harrison 1995; Eastwood et al. 1995a; Selemon et al. 1995).

One may speculate that fewer cortico-cortical connections are initially established in the developing schizophrenic brain. Many different proteins are involved in the complex process of axon elongation; these molecules range from cell adhesion molecules and neurotransmitter receptors to microtubules and neurofilaments (Kater and Guthrie 1990; Reichardt et al. 1990). One example of a cell adhesion molecule critical to axon elongation is limbic associated membrane protein (LAMP). LAMP is highly expressed by cortical and subcortical neurons comprising the limbic system and has been shown to promote selective neurite outgrowth from limbic cortical neurons (Levitt 1984; Pimenta et al. 1995; Zhukareva and Levitt 1995). Abnormal expression of LAMP could underlie the functional and pathological alterations in limbic system connectivity implicated in the schizophrenic brain; therefore, LAMP would be well worth investigating in post-mortem specimens.

Another molecule integral to normal axonal outgrowth and targeting of a more general nature is growth associated protein 43 (GAP-43). GAP-43, an internal phosphoprotein essential to growth cone migration, is localized subcellularly to the inner leaflet of the presynaptic membrane (Skene 1989; Shea et al. 1991). GAP-43, messenger ribonucleic acid (mRNA), and protein have been found to be abundantly expressed in neurons that reside in areas of the adult human brain that are thought to be highly plastic, such as the limbic and prefrontal cortices (Neve et al. 1987, 1988; Benowitz et al. 1989). This finding implies that GAP-43 not only functions during developmental axon outgrowth, but also may have an important role in the modulation of neuronal connections later in life. In ongoing studies, we have found that the levels of GAP-43 mRNA are reduced in the adult schizophrenic prefrontal cortex (Geethabali et al. 1996). This may suggest that there are fewer connections emanating from the schizophrenic prefrontal cortex, or that the connections made by these neurons are less plastic. A recent study that employed 31P nuclear magnetic resonance found a decrease in the growth of membranes and an increase in the breakdown of membranes in the prefrontal cortex of first-episode schizophrenia patients compared with healthy controls (Pettegrew et al. 1991). These findings, along with our own, suggest that there may be a reduction in growth-associated activities in the schizophrenic prefrontal cortex and that molecules implicated in axonal growth and synaptic plasticity should be investigated further in the schizophrenic brain.

**Survival of Neuronal Connections.** The ability to maintain connections with other neurons or postsynaptic sites is necessary for long-term neuron survival (Purves and Lichtman 1985). During brain development, neurons initially send out an exuberance of connections, and waves of these connections, especially the excitatory ones, are eventually pruned (Cowan et al. 1984). Pruning of connections can result from a reduction of axon collaterals or from the actual death of neurons. Thought of in another way, pruning may reflect the failure of competitive survival of connections. Neurons compete for limited amounts of target-derived growth factors, which are taken up by axon terminals and transported back to the nerve cell body to promote neuron survival (Levi-Montalcini and Booker 1960; Levi-Montalcini and Angeletti 1968; Levi-Montalcini 1987). Reports show decreased cortical volume, smaller neuron size, and reduced neuropil in the schizophrenic brain (Falkai and Bogerts 1995; Selemon et al. 1995). Thus, neurons found in a schizophrenic brain may be less viable than those harbored in a healthy brain, and this decreased viability could result from alterations in the availability of growth factors.

Neuronal growth factors consist of many different families of growth factor peptides, some of which may overlap with the mitogenic growth factors previously described (Casper 1996). The neurotrophin growth factor (NGF) family is the best example of peptides that induce process outgrowth, increase soma size, and support the survival of central nervous system neurons (Glass and Yancopoulos 1993). Some examples of the NGF family that have been shown to support the survival and process outgrowth of dopaminergic, serotonergic, glutamatergic, and GABAergic neurons are brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT4/5) (Glass and Yancopoulos 1993). In preliminary studies, investigators in our laboratory have found a reduction in BDNF mRNA in the hippocampus of schizophrenic patients compared with controls, suggesting that there may be less trophic support available to hippocampal afferents in the schizophrenic brain (Brouha et al. 1996). The finding of less capability of neurotrophic factor synthesis in
Programmed Cell Death. A reduction in trophic support to a neuron is thought to result not only in synaptic pruning, but also in the initiation of so-called programmed cell death of the neuron, a complex involutorial cellular process involving a sequence of cellular and genetic steps and ultimately leading to DNA fragmentation (Steller 1995). In the developing nervous system, about 50 percent of the neurons originally generated undergo programmed cell death (Oppenheim 1991). Programmed cell death, or apoptosis, is often contrasted with necrosis, which refers to death of a cell by some injury or insult, as in mechanical damage, infarction, and infection (Fawthrop et al. 1991). Necrosis is accompanied by an inflammatory response, whereas programmed cell death is not believed to trigger inflammation. The exact distinction between these two types of cell death is still being debated, however, and probably will involve some overlap (Server and Mobley 1991). Most of the studies that show a reduction of numbers of neurons in the schizophrenic brain do not report an increase in numbers or reactivity of glial cells (Falkai and Bogerts 1995). The absence of gliosis may be a signal that the "damage," or putative loss of neurons, in the schizophrenic brain has occurred much earlier and therefore the astrocytic response either did not occur or was resolved long before the tissue was examined. Alternatively, fewer neurons in the schizophrenic brain could be the result of an increase in programmed cell death.

In addition to extracellular trophic molecules that are thought to be able to prevent this programmed cell death, many intrinsic factors, such as molecules that act primarily inside the cell, are involved in executing the cell death response itself. One factor is the peptide BCL-2, first discovered in B-cell lymphomas (Tsujimoto et al. 1984). Overexpression of the BCL-2 protein, normally located in the inner membrane of mitochondria, allows neural cells to survive the withdrawal of growth factors, an event that otherwise leads to cell death (Zhong et al. 1993). BCL-2 is the prototypical member of a family of related cytoplasmic proteins whose members can induce or prevent programmed cell death, including BCL-X, BAX, and BAD (Davies 1995). A variety of protein factors that reside in the nucleus have also been shown to be key regulators of programmed cell death. One of these nuclear factors, p53, can mediate DNA repair, and another, cyclin D, is involved in cell cycle regulation (Freeman et al. 1994; Wood and Youle 1995). Some of the factors thought to be involved in cancer can also be key regulators of programmed cell death (Fischer et al. 1986). Interestingly, there have been several reports of a resistance to cancer in schizophrenia patients despite frequent nicotine abuse (Gopalswamy and Morgan 1986; Harris 1988; Mortensen 1994). Little is known about the expression or regulation of cell death factors in the normal or schizophrenic central nervous system. Programmed cell death regulators and effectors may be important molecules to add to the list of candidate molecules for further study in the schizophrenic brain.

Cortical Subplate. A transient layer of cortical neurons, termed the subplate, lies underneath the developing cortical mantle, below the future cortical layer (Shatz et al. 1990). The early maturing subplate neurons form the first connections between cortical-subcortical and cortical-cortical areas and are believed to provide a scaffold required for the proper formation of adult cortical afferents and efferents (Shatz et al. 1990). Approximately 80 to 90 percent of subplate neurons undergo cell death during development, and thus very few subplate neurons are normally found in the adult brain (Kostovic and Rakic 1990; Shatz et al. 1990). The cellular and molecular mechanisms responsible for the developmental reduction in numbers of subplate neurons are not known, but neurotrophic factors and apoptotic factors are likely to be involved. The finding of increased neurons in the cortical white matter of some schizophrenia patients, described previously, has been interpreted as an overrepresentation, or increased survival, of these early subplate neurons (Akbarian et al. 1993a, 1993b, 1995a). It may be that subplate neurons in the schizophrenic brain make anomalous and sustainable connections that prevent their programmed cell death and their normal disappearance during development. Alternatively, the subplate neurons in the schizophrenic patient may have abnormal apoptotic molecular machinery normally required for executing the programmed cell death response and therefore the subplate neurons survive. In the schizophrenic brain, subplate neurons may survive longer because they encounter less competition for target-derived trophic support. If this were the case, then the displaced subplate neurons would not be the site of primary pathology, but would merely reflect an absence of neurons elsewhere and thus a loss of competing afferents. Studies of molecules that regulate survival and death of human cortical subplate neurons in the schizophrenic brain seem advisable.

Myelination. Central nervous system neurons that make long-distance connections may have their axons ensheathed in the insulating substance myelin, produced by oligodendroglia during many stages of brain develop-
Developmental Pathology in Schizophrenia

Molecular Aspects of Emergent Psychosis. Most of the major developmental brain events considered previously are thought to have taken place before the onset of adolescence, although we consider certain “developmental” events as ongoing processes. One of the most characteristic clinical aspects of schizophrenia is its onset in early adulthood. The reason for this is unknown. One could speculate that the maturational events that normally occur in late adolescence or early adulthood do not proceed successfully in the schizophrenic brain. Numerous neurobiological substrates of peripubertal brain changes include changes in dopaminergic, serotonergic, adrenergic, glutamatergic, GABAergic, and cholinergic neurotransmitter systems (Brooksbank et al. 1981, 1982; Goldman-Rakic and Brown 1982; Rakic et al. 1986; Lidow et al. 1991; Lidow and Rakic 1992; Court et al. 1993). It has been suggested that adolescence may be a time of marked synaptic pruning in normal development and that synaptic pruning is altered in schizophrenia (Feinberg 1982). However, in the widely cited study examining the density of synaptic profiles in the postnatal human prefrontal cortex, few teenage human brains were actually examined (Huttenlocher 1979). In fact, adolescence (i.e., between the ages of 12 and 20) is a time of considerable brain growth in certain areas of the human cortex. Indeed, peripubertal changes occurring in the human brain represent a combination of regressive and progressive events (Thatcher et al. 1987; Jernigan et al. 1991; Buchsbaum et al. 1992).

Many parameters of synaptic communication change across distinct cortical regions concurrently in adolescence; a change in hormonal status may orchestrate these changes (Lidow and Rakic 1992). Puberty in humans is recognized somatically by a spurt in the growth of the bones and the head, extension of new hair follicles, and attainment of sex organ maturity (Epstein 1986). Psychological theorists have outlined specific cognitive changes that occur at the time of puberty (Kaplan and Sadock 1988). Little is known about the cellular or molecular substrates underlying these brain changes, but it would not be unreasonable to suspect that changes in the steroid hormone milieu during puberty underlie or drive the changes in neuronal populations that subserve mood, cognition, and sociality (Ojeda 1991). A recent positron emission tomography study from our group (Berman et al. 1997) has shown that sex steroids can modulate prefrontal cortical physiology during the Wisconsin Card Sorting Test (WCST; Heaton 1981), but the molecular substrate of this effect is unknown. A question for researchers working on schizophrenia is: How do the hormonal changes surrounding puberty influence the maturation or function of “higher level” cortical association areas?

The effects of steroids can be mediated directly on neurons by lipophilic diffusion of the steroid into the cell and by high affinity binding to cytoplasmic receptors. Upon binding of hormones, the steroid hormone receptor complex translocates to the nucleus and binds to hormone response elements in DNA to activate or repress gene transcription (Evans 1988; Glass 1994; Williams 1994). Steroid hormones can coordinate brain maturation through their action as transcription factors. Surprisingly, evidence of changes in estrogen and androgen receptors in the human brain during postnatal development is scarce (Tohgi et al. 1995), although work in the primate does show that androgen and estrogen receptors are distributed throughout many cortical regions during postnatal development (MacLusky et al. 1987; Clark et al. 1988). Anatomical localization of steroid hormone receptors in the human brain would be a first step toward understanding how peripubertal changes in circulating sex steroids could influence the maturation and function of brain systems possibly involved in schizophrenia.
Non-sex hormones also play a role in the maturational changes in the brain at or around the time of puberty. For example, thyroid hormone is critical for proper cortical maturation before puberty, and thyroid hormone can regulate cortical synaptogenesis (Dussault and Ruel 1987; Stein et al. 1989). Although thyroid hormone levels are reported to be in the normal range in schizophrenia patients, little is known about thyroid hormone receptors and downstream effectors of thyroid hormone action in the diseased brain. Another point worth noting is that steroids do not exert their effects in isolation; their transcriptional ability is often regulated by complex protein–protein interactions with other transcription factors (Lazar 1993; Glass 1994; Forman et al. 1995), including interactions between hormone receptor molecules such as thyroid hormone receptors, glucocorticoid receptors, and retinoic acid receptors. While an understanding of these interactions in the developing brain is still in its very early stages, schizophrenia researchers should not dismiss the steroid/thyroid hormone superfamily members as potential molecules involved in schizophrenia (Goodman 1995).

Conclusion

While maturational changes occurring in the schizophrenic brain in early adulthood may be simply unmasking the prior “lesion,” identifying which neurons undergo molecular changes around the time of puberty may help us to decipher which neurons have suffered a developmental “hit.” Delineating these molecular changes may give us insight into the molecular events involved in the activation of molecular systems that fail in schizophrenia because they depend on and interact with potentially abnormal genes or proteins. Many developmentally important molecules continue to be expressed in the adult brain, and their in vivo function is rarely firmly established; they may play a role in synaptic rearrangements thought to underlie brain plasticity and learning. Most autopsy specimens are from adult brains, and while adult expression of developmentally important molecules facilitates the study of these molecules, investigators may be left questioning the developmental significance of their findings. Ideally, it is desirable to undertake studies of normal human brain development to help determine the potential relevance of a candidate molecule to the developmental event in question.

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