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Commentary

A "deficient environment" in prenatal life may compromise systems important for cognitive function by affecting BDNF in the hippocampus

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Abstract

The intrauterine environment has the capacity to mold the prenatal nervous system. Particularly, recent findings show that an adverse prenatal environment produces structural defects of the hippocampus, a critical area sub-serving learning and memory functions. These structural changes are accompanied by a disruption in the normal expression pattern of brain-derived neurotrophic factor (BDNF) and its cognate tyrosine kinase B (TrkB) receptor. The important role that the BDNF system plays in neural modeling and learning and memory processes suggests that fetal exposure to unfavorable intrauterine conditions may compromise proper cognitive function in adult life. These findings have implications for disorders that involve a dysfunction in the BDNF system and are accompanied by cognitive deficits.

Keywords: Prenatal life; Cognitive function; Hippocampus

Introduction. Over the last decade, scientific research has inundated us with findings of how life style, namely enriched environment, diet, and exercise, can sculpt the neural circuits and systems in the adult animal. These studies have shown us that life style can alter the expression of one neurotrophin in particular, brain-derived neurotrophic factor (BDNF), in the hippocampus, an area implicated in promoting and maintaining learning and memory. A striking and compelling feature of these findings was that changes in hippocampal BDNF levels were associated with improved cognitive function (Falkenberg et al., 1992; Molteni et al., 2004). Therefore, it stands to reason that during the organization of the nervous system, when the brain is especially malleable, the environmental effects on brain structures and systems supporting cognitive function would be even more pronounced. In fact, a resounding finding in human cases, where prenatal life is exposed to a compromised intrauterine environment, is that reductions in regional brain volumes are many times associated with long-term cognitive impairments (Peterson, 2003), which include difficulties in learning (Isaacs et al., 2001; Lefebvre et al., 1988; Lloyd et al., 1988; Larroque and Samain, 2001) and memory (Briscoe et al., 2001; Isaacs et al., 2000). It is believed that several neurological disorders, such as Schizophrenia, which are marked by deficits in cognitive function in postnatal life, may be partially the result of an adverse intrauterine environment, which compromised normal brain development in prenatal life (Cornblatt et al., 1999; Thome et al., 1998; Waddington, 1993, 1998, 1999). Although schizophrenia is a complex disorder, believed to involve many contributing factors, such as genetic and environmental stressors and maternal viral infection during gestation, these findings imply that BDNF may be a critical system involved.

A recent finding by Dieni and Rees published in Experimental Neurology, entitled "BDNF and TrkB protein expression is altered in the fetal hippocampus but not the cerebellum after chronic prenatal compromise" has lent striking implications concerning the possible impact of the intrauterine environment to fetal cognitive development. The intrauterine environment experienced by the fetus may affect neurotrophin systems that support learning and memory and

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the development of brain structures that are critical for proper cognitive function. Echoing the findings from studies, which have shown us that the environment modulates BDNF levels in the adult brain, Dieni and Rees found that a fetus exposed to a compromised intrauterine environment exhibits hippocampal structural defects and changes in the levels of BDNF and its cognate TrkB receptor. Given the importance of the hippocampus in supporting cognitive function and the role that BDNF plays in learning and memory, these findings have valuable implications of how a chronic, adverse intrauterine environment may compromise proper cognitive function in adult life.

Neurotrophins are important for learning and memory. Neurotrophins consist of a structurally related group of homodimeric proteins, which include nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), and neurotrophin-6 (NT-6). The effects of the neurotrophin family are mainly mediated by their binding to tyrosine kinase receptors (Trks): NGF to TrkA; BDNF and Trk-4/5 to TrkB; and NT-3 to TrkC (Barbacid, 1994). Neurotrophins are powerful factors that promote neuronal survival and differentiation during development (Barde, 1994a).

Neurotrophic factors have become recognized as prominent mediators of activity-dependent structural and functional plasticity in the adult nervous system, especially surfacing as critical modulators of activity-driven synaptic changes that are believed to underlie many adaptive behaviors in animals (Alleva et al., 1996; Poo, 2001; Tyler et al., 2002). Particularly, BDNF has been implicated to comprise the molecular mechanisms underlying activity-dependent plasticity in the hippocampus. Impressively, BDNF has gained notoriety for its ability to regulate cognitive and neuronal function in the adult brain. In fact, the distribution of BDNF in the brain may emphasize the magnitude of its role in supporting cognitive function; although distributed throughout the adult brain, the hippocampus expresses the highest levels of BDNF (Ernfors et al., 1991). Actual learning and memory tasks (Falkenberg et al., 1992) and/or long-term potentiation (LTP), the electrophysiological correlate of learning and memory, selectively increase BDNF mRNA levels in the hippocampus (Patterson et al., 1992, 2001). Evidence from several studies suggest that BDNF may be constitutive for proper cognitive function; transgenic animals with diminished BDNF expression sustain a deficit in LTP (Patterson et al., 1996) and are impaired in learning a spatial memory task (Linnarsson et al., 1997). Moreover, reinstating BDNF into the depleted hippocampus, with exogenous BDNF application (Patterson et al., 1996) or transfection of hippocampal slices with a BDNF expressing adenovirus (Korte et al., 1995) restores LTP. The take home message from these studies, which have shown us that altering the levels or activity of BDNF can compromise neuronal and cognitive function, becomes strikingly significant for the human condition with the recent finding that individuals expressing a specific BDNF polymorphism exhibit learning impairments (Egan et al., 2003).

Dieni and Rees used a guinea pig model of chronic placental insufficiency (CPI) to mimic suboptimal prenatal complications that can arise during human pregnancy (Naeye et al., 1989), in order to investigate the resultant structural and neuronal alterations that may contribute to compromise cognitive function. Studying the guinea pig provides an opportunity to relate experimental findings to humans, as elements such as a long gestation period and the degree of brain maturation at birth are comparable to homosapien developmental events in utero. The experimental paradigm of CPI involves a sustained reduction in blood supply during the second half of gestation, thereby reducing the nutrient and blood supply to the developing fetus. These conditions result in growth-restricted fetuses that are chronically hypoxemic, malnourished, and hypoglycemic (Jones and Parer, 1983), have an altered endocrine balance (Jones et al., 1990), and reduced cerebral blood flow (Jensen et al., 1996). Diene and Rees found that in their guinea pig model of chronic placental insufficiency, fetuses, who are severely growth restricted, show pronounced structural changes in the hippocampus. The hippocampus seems to be particularly susceptible to incurring the effects of CPI. Previous findings have documented significant reductions in total hippocampal volume at term with particular focus on decreases in stratum oriens volume (Mallard et al., 1999), the number of CA1 pyramidal cells in the first postnatal week (Mallard et al., 2000), and the dendritic outgrowth of CA1 and dentate granule cells (Dieni and Rees, 2002). These disturbances in the two neuronal populations of the hippocampus may be particularly informative to how a compromised prenatal intrauterine environment can lead to cognitive and neural deficits in adult life, as they compose principle components of the trisynaptic circuitry believed to be important for learning and memory formation in both animals and humans (Squire, 1992). These conspicuous earlier findings entertained the notion that levels of growth factors, such as BDNF, that have been known to influence dendritic density, may be disturbed following CPI. Particularly, as the hippocampus shows pronounced immunoreactivity for BDNF and its TrkB receptor during the prenatal period (Dieni and Rees, 2002), BDNF and its TrkB receptor may be specifically adversely affected by CPI.

The finding that an adverse intrauterine environment can compromise BDNF levels in the hippocampus may explain the origin of many developmental disorders with marked elements of cognitive dysfunction. Recent studies suggest that BDNF transcription may be compromised in developmental disorders such as Retts syndrome and autism spectrum disorders (Auranen et al., 2000; Carney et al., 2003; Lam et al., 2000; Samaco et al., 2004; Zoghbi, 2003), which are characterized by pervasive and persistent deficits in cognitive function (Rapin and Katzman, 1998). In these studies, it was found that methyl-CPG binding protein

(MeCP2), a critical regulator of BDNF transcription, is adversely affected (Auranen et al., 2000; Carney et al., 2003; Lam et al., 2000; Samaco et al., 2004; Zoghbi, 2003). Moreover, MeCP1 knockout mice show impairment in both LTP and learning (Zhao et al., 2003). What is even more astounding is that the preclusion of normal BDNF expression is a repeated characteristic in many disorders of cognitive function that occur later in life, such as Schizophrenia (Egan et al., 2003), dementia (Ando et al., 2002), and Alzheimer's disease (Tsai et al., 2004). Alzheimer brains exhibit region specific decreases of BDNF in the hippocampus (Connor et al., 1997; Hock et al., 2000; Phillips et al., 1991), which are also accompanied by decreases in the expression of BDNF's cognate TrkB receptor (Ferrer et al., 1999). Likewise, post-mortem studies show reduced levels of BDNF mRNA in the hippocampus of schizophrenic patients (Durany et al., 2001). Although there is no direct evidence that these conditions are related to the amount of prenatal BDNF, given the critical role that BDNF plays in development, it should be considered that, in addition to other environmental and genetic factors, tempering with the amount of BDNF in prenatal life can possibly initiate the earlier onset of age-dependent pathological diseases. In other words, a compromised BDNF system in the hippocampus early in fetal life may be especially detrimental to BDNF-modulated function in adult life.

BDNF can affect neural development in an activity-dependent mode. Our incipient knowledge of BDNF and other neurotrophins initially delimited them to a role in regulating the survival, growth, and differentiation of neurons during development (Barde, 1994b). Ironically, it seems necessary that we hearken back to earlier findings for BDNF in the developing nervous system, to gain insights into how this activity-driven neurotrophin can modulate the functional complexity of neuronal circuits in the prenatal hippocampus.

The efficacy of BDNF in modeling functional neuronal circuitry is most prominently demonstrated by its effect on the formation of ocular dominance columns in the cat visual cortex (Cabelli et al., 1995, 1997). During development, it is believed that ocular dominance columns are formed by activity-dependent competition between thalamic glutaminergic afferents from both eyes. Studies have shown that BDNF seems to be necessary for stabilizing the synaptic contact of the thalamic afferent to one eye. As each eye competes for a limited supply of neurotrophic factor, afferent thalamic activity from visual stimuli drives the delivery of the limited endogenous BDNF supply to excited synapses, thereby resulting in the pattern formation of the ocular dominance columns (Katz and Shatz, 1996). Interestingly, BDNF may also be involved in the selective pruning of synaptic connections, as studies show that BDNF decreases retinal ganglion cell dendritic arbor complexity (Lom and Cohen-Cory, 1999) and infusing an excess of BDNF into the developing kitten visual cortex impairs the formation of ocular dominance columns (Cabelli et al., 1995). Taken together, these findings suggest that BDNF is highly critical for promoting the selective formation of synaptic circuitry in the brain.

Reminiscent of ocular dominance column formation, the development of the hippocampus is patterned and stereotyped and involves target layer specificity (Super, 1994; Super et al., 1998; Woodhams and Terashima, 1999). In concert with its role as a powerful promoter of neuronal survival and differentiation, BDNF can critically affect the developing neuronal circuitry of the hippocampus; BDNF, via the activation of its TrkB receptor, has been shown to promote the survival and growth of dentate granule cells (Lowenstein and Arsenault, 1996) and pyramidal neurons (Bartrup et al., 1997; Ip et al., 1993). Moreover, BDNF can regulate both the number of synapses and the complexity of axonal arborization in the hippocampus. Studies conducted using transgenic mice have shown that BDNF regulates the expression of synaptic vesicle proteins and the density of synaptic innervation: BDNF knockout mice are deficient compared to their control counterparts in the number of innervating axons and synapses in the sympathetic system (Causing et al., 1997). Furthermore, in vivo imaging experiments have visually illustrated the ability of BDNF to regulate synaptogenesis in arborizing axon terminals (Alsina et al., 2001). Indeed, studies have shown that limiting the ability of BDNF to bind to its cognate receptor by using TrkB knockout mice produced a significant reduction in axonal arborization and the number of synapses during hippocampal development (Martinez et al., 1998).

In a previous study, Dieni and Rees have found that the pattern of TrkB expression was coincident with BDNF immunoreactivity in dentate granule cells (Dieni and Rees, 2002). It has been suggested that this dual detection of BDNF and TrkB immunoreactivity in the dentate granule cells advocates a model in which BDNF acts as a trophic molecule during early development by autocrine or paracrine means (Acheson et al., 1995; Righi et al., 2000; Wetmore et al., 1994). This is supported by the findings that with advancing gestational age, the increasing intensity of granule cell staining coincides with both an intensification in mossy fiber staining and the growth of the mossy fiber layer (Dieni and Rees, 2002). As BDNF has been found to induce axonal branching of dentate granule neurons in vitro (Lowenstein and Arsenault, 1996; Patel and McNamara, 1995), BDNF may act anterogradely on fetal granule cell axons to promote axonal growth and branching. CPI diminishes BDNF immunoreactivity in the mossy fibers (Dieni and Rees, 2004), indicating that there may be a reduced synthesis of BDNF in dentate granule cells which may limit the anterograde transport of BDNF along the mossy fiber pathways to affect the survival of postsynaptic CA3 and subsequently CA1 neurons. Strikingly, CA1 pyramidale cells numbers were previously found to be reduced following CPI (Mallard et al., 2000). These findings are consistent with what we know about the

importance of the dentate gyrus for hippocampal trisynaptic circuitry, as any distortion in its number and density could affect other hippocampal regions, CA1-CA4 (Anderson et al., 1971). Possibly, damage to the dentate gyrus, a sort of Achilles' heel of the hippocampus, may lead to secondary damage of other areas via a disruption in activity-dependent factors such as BDNF. The dentate hilus and CA3 regions are sensitive to traumatic brain injury in the adult (Lowenstein et al., 1992; Nawashiro et al., 1995). Yet, the finding that chronic placental insufficiency targets the dentate gyrus-CA3 circuitry during development suggests more long-term ramifications in hippocampal function for the adult animal.

Importantly, the studies mentioned above, illustrated how BDNF is necessary for proper nervous system development. This brings us to the question of how CPI can alter BDNF levels. During brain development, optimal levels of spontaneous neural activity are believed to be critical for shaping neural networks (Katz and Shatz, 1996; Moody, 1998). As BDNF is highly dependent on activity, it seems likely that CPI may disturb elements critical for establishing proper neuronal activity of the developing hippocampus, possibly by disturbing calcium levels. CPI induces both hypoxia and hypoglycemia, which compromise calcium homeostasis (Mishra and Delivoria-Papadopolous, 1999; Vannucci, 1990; Mattson et al., 1993). Calcium influx has been shown to be essential for regulating activity-dependent transcriptional events (Shaywitz and Greenberg, 1999; West et al., 2001), which are monumental for orchestrating specific neuronal connections and promoting synapse maturation (Katz and Shatz, 1996; Lonze and Ginty, 2002). Indeed, hypoxia causes a global decrease in gene expression, thereby precluding the activation of critical genes necessary for proper brain maturation (Loike et al., 1992). Thus, it may be that a compromised intrauterine environment alters the proper distribution of calcium signals, which in turn affects both the expression and release of BDNF (Du et al., 2000; Tao et al., 1998, for review, see Lessmann et al., 2003).

Nutritional factors can affects synaptic plasticity and cognition by modulating BDNF production and function. The nature of chronic placental insufficiency, whereby the reduced placental transport of nutrients, glucose, and oxygen, results in infants that have low birth weights, are malnourished, hypoglycemic, and hypoxic, has obvious implications and applications for maintaining a proper diet during human pregnancy. Nutritional factors may influence the BDNF system to affect hippocampal development and compromise postnatal cognitive function. Indeed, the management of dietary factors is emerging as an efficient means to modulate the capacity of the brain for plasticity (Mattson et al., 2003; Wu et al., 2004a,b). In particular, a diet high in saturated fat decreases levels of BDNF to the extent that it compromises cognitive performance (Molteni et al., 2002). This diet can also aggravate the outcome of brain insults on cognitive function (Wu et al., 2003) by disturbing mechanisms associated to the action of BDNF (Wu et al., 2003). Alternatively, maintaining a diet rich in omega-3 fatty acids is encouraged as these dietary components have been shown to be essential for normal neurological development, learning and memory, and neuronal plasticity (Green and Yavin, 1998; Hashimoto et al., 2002; Salem et al., 2001). It appears that dietary factors, such as omega-3 fatty acids, can protect the brain by using BDNF (Wu et al., 2004a,b).

The importance of maintaining proper nutrition during the gestational period may be especially important for postnatal hippocampal development. Experiments conducted in rats fed one half of their usual diet during different developmental periods (gestation plus lactation, lactation, or lactation plus weaning) found that hippocampal width is significantly decreased only in the offspring of rats whose dietary malnutrition included the gestational period (Katz and Davies, 1982, 1983; Katz et al., 1982). Prenatal malnutrition has been shown to affect the development of dentate granule cells, reducing granule cell size, dendritic morphology, spine density (Diaz-Cintra et al., 1991), and excitability (Bronzino et al., 1991a,b). Malnutrition also impacts the morphology of other hippocampal subfields, to decrease the somal size, dendritic branching, and spine density of CA3 pyramidal cells (Diaz-Cintra et al., 1994). Alteration of hippocampal circuitry during development could account for the finding that prenatal and lactational malnutrition have been found to adversely affect spatial memory as tested by the Morris water maze task in rats (Jordan et al., 1981). In humans, maternal nutrition during pregnancy was found to correlate with infant cognitive performance at both 6 months and 36 months of age (Klein et al., 1976). Other problems associated with maternal malnutrition such as iron deficiency during pregnancy, which also accompanies intrauterine growth restriction (Rao and Georgieff, 2002), has been shown to result in truncated dendrites of CA1 pyramidal cells in the hippocampus (Jorgenson et al., 2003). These effects of prenatal nutrition on hippocampal and cognitive function may be mediated by the BDNF system, as studies have shown that diet is a critical factor in modulating the expression of hippocampal BDNF and maintaining proper cognitive function (Molteni et al., 2002, 2004; Wu et al., 2003, 2004).

Additional factors to consider for maintaining a proper nutritional guideline for normal fetal development include cigarette smoking, alcohol and drug use. Cigarette smoking, a habit that when taken up by pregnant mothers, causes hypoxia and hypoglycemia, the same conditions produced by CPI in the guinea pig (Haustein, 1999). Consumption of alcohol during pregnancy produces toxic effects on the developing brain, particularly targeting specific brain regions such as the hippocampus (Guerri, 1998; West et al., 1994) to impair hippocampal LTP and spatial memory performance on the water maze task (Richardson et al., 2002). Similarly, prenatal drug exposure may mimic the effects of CPI. Fetal exposure to cocaine,

which results in growth restriction and premature births (Azuma and Chasnoff, 1993) produces modest decrements in performance on several cognitive tasks in humans (Singer et al., 1997) and impairs learning and memory in animals (Spear and Kirstein, 1989). As cocaine is a potent vasoconstrictive agent (Kapur et al., 1991; Thadani, 1995), it has been proposed that it compromises fetal development by uterine artery vasoconstriction to cause fetal hypoxia. As this effect is similar to Dieni and Ree's model of CPI in the guinea pig, it is not surprising that uterine cocaine exposure adversely affects hippocampal structure and function. Prenatal cocaine exposure has been shown to alter the excitability of hippocampal cells (Baraban and Schwartzkroin, 1997), protract hippocampal development (Akbari et al., 1992), and decrease hippocampal BDNF levels (Yan et al., 2004).

Room for an enriched environment after birth: postnatal experience can shape neural connectivity and function. Although the findings from Dieni and Rees suggest that a deficient prenatal environment compromises proper development of the hippocampus, the nature of hippocampal circuitry may leave some hope for compensation. An important element to consider is the prenatal period used in their model of CPI. Given that Dieni and Rees used a midgestational period during which to induce CPI, there is the possibility that other critical elements of hippocampal circuitry may still be incorporated in the postnatal period, in which granule cell neurogenesis (Altman and Das, 1967) and the additional growth of granule cell dendrites (Bartesaghi and Serrai, 2001) continue to occur. Connections between the entorhinal cortex and portions of the hippocampus (the subiculum, the CA1, and CA3) via the alvear path are well developed by midgestation, but the connections from the neocortex directly to the hippocampus are still very immature (Hevner and Kinney, 1996). Because the neocortical connections are slow to develop, the hippocampus may not receive mature levels of external activation at this time. Therefore, as the maturation of dendritic spines in the hippocampus is highly dependent on activity (Drakew et al., 1999), the development of dendritic spines may be protracted. Evidence for this comes from research with rhesus monkeys in which the dendritic spines of CA3 pyramidal neurons continue to maturate during the first year after birth (Seress and Ribak, 1995a). Moreover, Hevner and Kinney (1996) found that the perforant path projections from the entorhinal cortex to the dentate gyrus are immature by midgestation. This may help explain why somata and dentrites of mossy fibers continue to develop up to 9 months after birth (Seress and Ribak, 1995b). The entorhinal cortex provides major sensory input to the hippocampus from multiple brain regions (Shepherd, 1979). Thus, this lack of stimulation from the neocortical regions and the entorhinal cortex to the hippocampus at midgestation may lengthen the developmental period of the hippocampus. As BDNF and TrkB expression progressively increases during embryonic development to attain a maximum after birth, which are retained in significant amounts in the adult (Friedman et al., 1991; Katoh-Semba et al., 1997; Maisonpierre et al., 1990; Masana et al., 1993), BDNF may still act during multiple developmental periods to model hippocampal circuitry.

To conclude on a more positive note, the hippocampus continues to alter its synaptic circuitry in postnatal and adult life, involving many instances of remodeling that are believed to involve the activity-dependent use of BDNF. Many studies have found that an enriched environment promotes neuronal plasticity such as neurogenesis in the adult hippocampal dentate gyrus (Brown et al., 2003; Kempermann et al., 2002; Nilsson et al., 1999) and an upregulated expression of neurotrophic factors, prominently BDNF (Falkenberg et al., 1992). Animals exposed to an enriched environment also perform better on spatial tests of learning and memory than their counterparts housed in standard or impoverished conditions (Janus et al., 1995; Nilsson et al., 1999). In fact, exposure to an enriched environment improves hippocampal-dependent spatial memory on the Morris water maze task in rats, which correlates with increased BDNF expression in their hippocampi (Falkenberg et al., 1992). Apart from environmental enrichment, exercise has also been shown to be a potent regulator of BDNF in the adult brain (Neeper et al., 1995; Vaynman et al., 2003), contributing to hippocampal synaptic plasticity (Vaynman et al., 2003) and learning and memory (Vaynman et al., 2004). Moreover, exposure of rats to enriched environment conditions during their adult lives has the ability to counteract the decreased learning performance associated with non-handling during early development in rats (Pham et al., 1999), a period which is believed to correspond to prenatal life in humans (Sheldon et al., 1996). Given the evidence presented that the hippocampus continues to develop and mature after birth, implementing lifestyle changes later on, especially early in postnatal life, may still have the ability to alter BDNF and associated cognitive processes.

Conclusions. The developing nervous system adapts to a wide array of stimuli, in part, by evoking activity-dependent mechanisms that signal to the nucleus and induce long-term modifications in neuronal function. Exposing the developing fetus to a compromised intrauterine environment may disturb the normal processes by which the nervous system is able to function, especially targeting the developing hippocampus to alter both its structure and the BDNF system. Given the importance of the hippocampus and the BDNF system in learning and memory processes, compromising BDNF function early on may help explain the origin of both developmental disorders such as Rett's syndrome and Autism, and neurological disorders that occur later in life, such as Schizophrenia and Alzheimer's disease. These recent findings from Dieni and Rees leave us asking whether changing the way that the brain is wired as a result of the prenatal environment can alter the way that our cognitive selves react to the environment in adulthood.

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