REVIEW

Prenatal Nutritional Deprivation as a Risk Factor in Schizophrenia: Preclinical Evidence

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We will review evidence from preclinical literature that prenatal nutritional deprivation produces neurochemical, morphological, and electrophysiological effects reminiscent of those seen in clinical studies of schizophrenia. We will focus on effects of nutritional deficiency that are likely to have implications for schizophrenia. These include disruption of neurotransmitter systems such as dopamine and serotonin and dysgenesis of the hippocampal formation. Preclinical studies show enhanced release and turnover of dopamine and serotonin following prenatal and early postnatal nutritional deficiency. Morphology of the hippocampus, as well as electrophysiology and hippocampally-mediated behaviors are also altered. Although intriguing, these studies have not been conducted with schizophrenia in mind, and thus, outcome measures that may be more specifically related to schizophrenia have not been examined. We propose that further preclinical studies that examine the consequences of prenatal nutritional deficiency, which may lead to altered neuronal migration and other developmental abnormalities, may be useful in understanding the etiology of schizophrenia. ***[Neuropsychopharmacology 11:227–235, 1994]***

KEY WORDS: *Schizophrenia; Prenatal nutritional deprivation; Neurotransmitters; Neuropathology; Neurodevelopmental disorder*

This article provides evidence from preclinical literature that prenatal nutritional deficiencies produce neurochemical, morphological, and electrophysiological effects reminiscent of those seen in clinical studies of schizophrenia. This evidence lends plausibility to prenatal nutritional deficiency as one of several risk factors involved in the pathogenesis of schizophrenia. We believe that studying the consequences of a developmental manipulation (e.g., prenatal nutritional deficiency) which may lead to altered neuronal migration and other developmental abnormalities may be of importance in understanding the etiology of schizophrenia.

Evidence from several sources now suggests that schizophrenia may be, in some cases, a neurodevelopmental disorder (Weinberger 1987; Bogerts et al, 1990; Pulver et al. 1992; Susser and Lin 1992; Akbarian et al. 1993a,b; Bloom 1993; Lipska et al. 1993; Pilowsky et al. 1993; Waddington 1993a,b). Either genetic or prenatal environmental exposures could affect the embryological development of the brain. Among the environmental exposures that have been shown to do so, the most studied is prenatal nutritional deficiency (Smithells et al. 1980; Laurence et al. 1981; Jordan et al. 1982; Bedi 1991; Diaz-Cintra et al. 1991; Susser and Lin 1992). However, in a literature search, we were unable to locate any paper that explicitly discussed the implications of this body of research for schizophrenia.

The hypothesis that early prenatal nutritional deficiency may be a risk factor for schizophrenia dates at least to the 1950s (Pasamanick et al. 1956; Richardson-Andrews 1992). Indeed, seasonal variation in first trimester prenatal nutrition has long been suggested as an explanation for the season of birth findings in

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schizophrenia (Pasamanick et al. 1956; Machon et al. 1983; Pulver et al. 1992). Prenatal nutritional deficiency has also been listed as a plausible etiology for ventricular enlargement in this illness (Andreasen et al. 1990).

In a series of recent studies, Susser and co-workers (Susser and Lin 1992; Susser et al. submitted) have found evidence of an association between prenatal nutritional deprivation and an increased risk for schizophrenia in a follow-up study of individuals in utero during the Dutch Hunger Winter between 1944 and 1945. In a first study (Susser and Lin 1992), women who were exposed to famine as first-trimester fetuses showed a more than two-fold increase in the risk for schizophrenia, and in men there was a trend toward increased risk. In a subsequent study based on more precise measures of both nutritional exposure and psychiatric outcome, an increased risk of schizophrenia after early prenatal nutritional deficiency was firmly established in both men and women (Susser et al. submitted). The parsimonious interpretation is that the effects of prenatal nutritional deficiency on neurodevelopment may be one factor that increases the risk of schizophrenia. It should be noted that other factors such as second trimester maternal virus infection have also been suggested as neurodevelopmental factors which may increase the risk of schizophrenia (Mednick et al. 1988; Torrey et al. 1988).

Much of our knowledge of the effects of prenatal nutritional deficiency on the developing brain is derived from preclinical studies. Although there is clear evidence that prenatal nutritional deficiency causes neurodevelopmental disorders in humans such as neural tube defects and cretinism (Pharaoh et al. 1980; Smithells et al. 1980; Laurence et al. 1981; World Health Organization 1990), it has not been possible to precisely specify the morphological, electrophysiological, neurotransmitter, and behavioral changes that are related to prenatal nutritional deficiency in humans. Therefore, we turn to the preclinical literature for an understanding of the likely effects on the brain and of the potential implications for schizophrenia.

The purpose of this review is to join some of the diverse preclinical literature that may have relevance for clinical studies of schizophrenia rather than to provide a comprehensive review of preclinical studies of early nutritional deficiency. For indepth critical reviews of the effects of early nutritional deficiency on brain development and behavior, we refer the reader to several excellent reviews (Dobbing and Smart 1973; Morgane et al. 1978; Huether 1990; Morgane et al. 1993).

In reviewing the preclinical literature, we will cite studies of the effects of both prenatal and early postnatal nutritional deficiency on development. We will do this for two reasons. First, while the clinical studies of Susser and co-workers (Susser and Lin 1992; Susser et al. submitted) found that early prenatal nutritional deprivation is critical in increasing the incidence of schizophrenia in male and female offspring, the timing of neuronal development in experimental organisms such as the rat and in the human take place at different stages. For instance, whereas neuronal multiplication is complete by midgestation in the human fetus, it takes place primarily in the latter part of fetal development in the rat (Morgane et al. 1978). In addition, the growth spurt, which is concerned with elaboration of neuronal connections, myelination, and neurogenesis of hippocampal dentate granule cells begins in midgestation in humans, but in rats it takes place in the first 25 days after birth (Schlessinger et al. 1975; Morgane et al. 1978). Second, there is controversy in rodent research regarding the effects of prenatal versus early postnatal nutritional deficiency. Whereas Dobbing and co-workers (Smart and Dobbing 1971; Dobbing 1981) contend that the rodent brain is spared during gestation, but affected during the postnatal growth spurt, Morgane et al. (1993) report that postnatal neurogenesis is affected by prenatal nutritional deficiency. Thus, we will review the preclinical literature regarding the effects of both prenatal and early postnatal nutritional deficiency.

This review will focus on the effects of nutritional deficiency that are likely to have implications for schizophrenia. These include the disruption of neurotransmitters such as dopamine and serotonin and dysgenesis of the hippocampal formation. Regarding dopamine function, extensive research has focused on the role of dopamine in schizophrenia beginning with the well-rehearsed hypothesis of increased dopamine function in schizophrenia. Currently, some researchers believe that there is a defect in plastic adaptive functioning of dopamine systems in schizophrenia (Friedhoff 1986, 1988; Grace 1991). The role of serotonin in schizophrenia is also of interest because a number of new, clinically effective, atypical antipsychotic drugs have serotonin-2 blocking activity (Meltzer 1989).

We now turn to preclinical studies examining the effects of early nutritional deprivation on neurotransmitter functioning. Studies show that prenatal and early postnatal nutritional deficiency have longlasting effects on dopaminergic and serotonergic neuronal systems (Table 1).

DISRUPTION OF NEUROTRANSMITTER SYSTEMS

Prenatal nutritional deficiency can alter neurotransmitter functioning. In particular, the dopamine and serotonin systems, which, as reviewed previously, have been implicated in schizophrenia, may be profoundly affected by prenatal nutritional deficiency.

There are several causal pathways by which alterations in these neurotransmitters could be involved in

Table 1. Summary of Effects of some Types of Prenatal and Early Postnatal Nutritional Deficiency on Brain Development: Preclinical Studies

Disruption of Neurotransmitters		Effects on Hippocampus		
DA	**5HT**	**Morphology**	**Electrophysiology**	**Behavior**
↑ Release	↑ Release	↓ DNA content	↓ Establishment and maintenance of long-term potentiation following granule cell stimulation	↓ Exploration of novel environment
↑ Turnover	↑ Turnover	↓ Width, thickness, cell number in granule cell layer of dentate gyrus		↑ Time to make choice in a maze
↓ Or no change in concentrations	↑ Concentration		↓ Seizure threshold in kindling studies	↓ Ability to learn complex visual task
↓ DA receptors in striatum		↓ Dendritic branching and spine number on apical dendrites of granule cells	↑ Number of kindling stimulations needed to produce motor convulsions indicative of fully kindled state	↓ Acquisition of task requiring withholding of responses for reinforcement
		↓ Cell number of hippocampal subfields CA1, CA3, CA4		No deficit in working memory task

As noted in text, some of these effects are specific to certain types of deficiency.

the etiology of schizophrenia. One possibility is that an overactive or underactive neuronal pathway might directly contribute to manifestations of schizophrenia in adult life. For instance, when offspring are studied when they reach adulthood, numerous studies demonstrate that early nutritional deprivation leads to long lasting alterations in neurotransmitter functioning. The great majority of studies suggest that the dopamine and serotonin systems are affected by nutritional deficiency. Another possibility is that prenatal nutritional deficiency disrupts these neurotransmitters in utero, and thereby interferes with processes of neuronal migration and development.

In both the dopamine and serotonin systems, there is enhanced release and turnover following certain types of prenatal and early postnatal nutritional deficiency (Shoemaker and Wurtman 1971; Smart et al. 1976; Miller et al. 1977b; Marichich et al. 1979; Resnick and Morgane 1984). One mechanism for this activation is proposed by Huether (1990). The effects on monoamine levels appear to occur by an altered availability of individual precursor amino acids, including tryptophan (Trp) and tyrosine (Tyr). Alterations in these precursor amino acids may affect the rate and synthesis of their respective transmitter amines, serotonin, and the catecholamines, dopamine and norepinephrine. Protein deprivation causes a greater depletion of the plasma pool of the branched chain, large, neutral amino acids which compete with Trp and Tyr for a common active transport system for brain uptake. The resulting elevation in brain concentrations of the precursor amino acids, Trp and Tyr, is thought to explain the elevation of monoamines and their metabolites found by several investigators in the brains of animals with nutritional deficiencies (Miller et al. 1977a,b; Resnick and Morgane 1984).

In the dopamine system, increased turnover is not associated with increased concentrations of this neurotransmitter. Studies show a decrease (Shoemaker and Wurtman 1971, 1973; Ramanamurthy 1977) or no change (Sobotka et al. 1974; Ahmad and Rahman 1975) in brain dopamine content in rats following prenatal and early postnatal nutritional deficiency. The decrease in brain dopamine content has been suggested to be primarily due to decreased catecholamines in the corpus striatum, the area with the highest dopamine content in the brain (Shoemaker and Wurtman 1973; Wiggins et al. 1984).

Receptor binding studies show decreased numbers of dopamine binding sites in striatum (Wiggins et al. 1984) in rats exposed to nutritional deficiency during early development. In one study, early postnatal dietary iron deficiency led to a loss of 50% of dopamine type 2 receptors in the rat caudate (Youdim et al. 1986), though this work was not replicated by Dwork et al. (1990). Wiggins et al. (1984) suggest that a decreased number of dopaminergic binding sites may be indicative of activation of dopaminergic neurons including increased presynaptic activity (e.g., increased release) of this neurotransmitter. Studies of dopamine binding in striatum of patients with schizophrenia are inconsistent. Some positron emission tomography (PET) studies show that patients have increased dopamine receptor density in striatum (Wong et al. 1986; Tune et al. 1993) and others show no change (Farde et al. 1990; Martinot et al. 1990, 1991). Though it is clear that early nutritional deficiency affects dopamine receptor density, presently it is undetermined if the direction of these

changes is similar to that seen in the pathogenesis of schizophrenia.

In the serotonergic system, both concentration and turnover are increased. Most (Sobotka et al. 1974; Stern et al. 1974, 1975; Smart et al. 1976; Miller et al. 1977b; Kohaska et al. 1980; Miller and Resnick 1980; Resnick and Morgane 1984), though not all (Ahmad and Rahman 1975; Dickerson and Pao 1975; Ramanamurthy 1977) studies show increased brain serotonin concentrations following prenatal or early postnatal nutritional deficiency. Most regions examined show an increase in serotonin concentration, with the greatest increases in the midbrain, cerebellum, and brainstem (Sobotka et al. 1974; Stern et al. 1975; Miller et al. 1977b; Resnick and Morgane 1984), the latter containing the majority of serotonin perikarya in the central nervous system (CNS). Importantly, serotonin synthesis remains high in animals receiving nutritional deficiency briefly during infancy (Smart et al. 1976). There also appears to be increased serotonin turnover as seen by increased concentrations of the serotonin metabolite 5-HIAA (Sobotka et al. 1974; Stern et al. 1974, 1975; Miller et al. 1977b; Kohsaka et al. 1980; Miller and Resnick 1980; Resnick and Morgane 1984). In addition, in terms of hippocampal functioning, recent studies show that prenatally protein- or 50% total calorie-deprived rats, when studied in adulthood, had increased serotonin release from hippocampal slices (Chen et al. 1992), and increased serotonin turnover in the hippocampus (Smart et al. 1976). Fuenmayor and Garcia (1984) found that fasting increased serotonin turnover in the whole brain, hippocampus, striatum, cortex, and pons-medulla.

The effects of prenatal nutritional deficiency on neurodevelopment depend on the stage of brain development. As reviewed by Huether (1990), at relatively early stages of development, monoamines appear to act as morphogenetic or developmental signals. Serotonin and norepinephrine are involved in regulating neuronal proliferation, migration, outgrowth of processes, synaptogenesis, and cell death (Olson and Seiger 1972; Lauder and Bloom 1974; Huether 1990, for review). These changes in monoamine levels lead to further alterations in expression of functional monoamine receptors, which persist into later life. Thus, nutritional deficiency, by affecting neuronal development and monoaminergic systems at an early, critical period of brain maturation, may lead to permanent changes of brain morphology and function.

EFFECTS ON THE HIPPOCAMPAL FORMATION

Dysgenesis of the hippocampal formation is also of interest in schizophrenia. A number of anatomical studies suggest altered morphology of the medial temporal lobe in patients with schizophrenia. Cytoarchitectonic studies have suggested altered orientation of hippocampal neurons (Scheibel and Kovelman 1981; Kovelman and Scheibel 1984; but see Christison et al. 1989), and brain imaging studies have shown a decreased volume of the hippocampus and entorhinal cortex in the absence of gliosis (Falkai et al. 1988; Suddath et al. 1990; Shenton et al. 1992; Bogerts et al. 1993). These studies support the hypothesis of developmental alterations in schizophrenia and have been interpreted as a failure of the orderly migration of cells from the proliferative zone adjacent to the fetal cerebral ventricles to their appropriate cortical layer. Recent studies by Akbarian and colleagues (Akbarian et al. 1993a,b) provide further support for a neurodevelopmental hypothesis. These authors found a decrease in neurons staining for the enzyme nicotinamide-adenine dinucleotide phosphate-diaphorase (NADPH-d) in the hippocampal formation and neocortex of the temporal lobe as well as in the superficial white matter and overlying cortex of the dorsolateral prefrontal cortex in postmortem tissue of patients with schizophrenia. In addition, these patients had increased numbers of NADPH-d staining neurons in the parahippocampal white matter and deep white matter of the prefrontal cortex. These findings suggest a disturbance of orderly migration of neurons and programmed cell death.

Findings of neuropathology in the hippocampus are extremely important because this area is thought to be involved in the generation of positive symptoms of schizophrenia (Zec and Weinberger 1986). Further, patients with schizophrenia frequently show cognitive deficits including memory impairment and inability to "tune out" (gate) irrelevant incoming stimuli (see Venables 1992, for review). The hippocampus is involved in memory processing and in the ability to gate incoming sensory information (Venables 1992).

We now turn to preclinical studies examining the effects of early nutritional deficiency on morphology and function of the hippocampus. These preclinical effects (Table 1) are similar to those reported in clinical studies of schizophrenia.

Morphology

Prenatal and early postnatal nutritional deficiency can markedly affect the morphology of the hippocampus, particularly the granule cells of the dentate gyrus on which the major input pathway to the hippocampus (i.e., the perforant path) synapses. We review the effects of postnatal, combined prenatal and postnatal, and prenatal nutritional deficiency on hippocampal morphology.

Early postnatal total caloric or protein deficiency

produces a number of alterations in hippocampal development in rats. These include a 20% decrease in hippocampal DNA content indicative of decreased hippocampal cell number (Fish and Winnick 1969), decreased width of the granular layer of the dentate gyrus, decreased granule cell packing density (Noback and Eisenman 1981; Paula-Barbosa et al. 1989), and decreased area of the hippocampal formation at the level of the habenula (Katz and Davies 1982). These studies consistently show that nutritional deficiency particularly affects the granule cell layer of the dentate gyrus.

Similar results were seen in studies of prenatal plus postnatal nutritional deficiency in rats. Jordan et al. (1982), Lewis et al. (1979), and Bedi (1991) reported reduced cell number and thickness of the granule cell layer of the dentate gyrus and hippocampal subfields CA1, CA3, and CA4 following combined prenatal and early postnatal nutritional deprivation. In addition, Cintra et al. (1990) found that rats protein deprived during gestation and up to the time of sacrifice at 30 days, 90 days, or 220 days of age had reductions in terminal dendritic branching of dentate granule cell apical dendrites in the molecular layer and a significant decrease in dendritic spine number in the outer two thirds of these apical dendrites.

As hypothesized by Morgane and co-workers (Morgane et al. 1993) and reviewed in the introduction to this section, the prenatal period may indeed be a critical time in producing long-term alterations of hippocampal morphology. Diaz-Cintra et al. (1991) found alterations in hippocampal granule cell apical dendrites in mature rat brains when protein deprivation was restricted to the prenatal period followed by dietary rehabilitation at birth (Diaz-Cintra et al. 1991). In addition, Katz et al. (1982) demonstrated that hippocampal width was decreased only when nutritional deficiency included the period of gestation plus lactation, not when it included only the lactation or lactation plus postweaning period.

One possible explanation of altered hippocampal morphology is that it is secondary to effects of prenatal nutritional deficiency on neurotransmitter systems. Formation of the hippocampus is the result of migration of cells from the primitive conglomeration of cells beneath the lateral ventricles, which generally occurs in midgestation. As reviewed previously, neurotransmitters are believed to be important in directing this neuronal migration. Thus, effects of prenatal nutritional deficiency on early development of neurotransmitters may impede the normal process of migration by which the hippocampus is formed.

This section has provided evidence from preclinical studies that early nutritional deficiency affects the development of the hippocampus. The relevance to schizophrenia is that hippocampal structural abnormality has also been implicated in this illness, though little is known about the exact nature of the abnormalities.

Electrophysiology

Electrophysiological measures of intrinsic hippocampal functioning have been found to be altered by early nutritional deficiency. Long-term potentiation and kindling have been studied as indices of plasticity of dentate granule cells. Long-term potentiation is a long-lasting enhancement of synaptic responses induced by high-frequency stimulation as well as kindling of dentate granule cells. Alterations in synaptic plasticity of dentate granule cells, which receive the major input to the hippocampus via the perforant path, would have profound effects on the ability of the hippocampus to receive and appropriately gate incoming sensory information.

Jordan and Clark (1983) found that a 50% dietary restriction during pregnancy and lactation decreased the ability to establish and maintain the population spike component of long-term potentiation following high-frequency stimulation of hippocampal dentate granule cells. Austin et al. (1986) found that high-frequency stimulation of the perforant path had a differential effect on long-term potentiation of dentate granule cells in adult rats who had received prenatal protein deprivation. There was a significant decrease in the maintenance of potentiation of population excitatory postsynaptic potentials of dentate granule cells following perforant path stimulation, whereas the population spike component was relatively unaffected.

Kindling studies show that following prenatal protein deprivation, animals tested as adults had lower seizure thresholds than controls (Bronzino et al. 1990); however, animals receiving prenatal protein deprivation needed almost twice as many daily kindling stimulations to produce the motor convulsions indicative of the fully kindled state (Bronzino et al. 1990). There was also a significant increase in inhibition of dentate granule cell activity accompanying kindling in these prenatally nutritionally deprived animals, which suggests that the delayed behavioral manifestation of these seizures may be due to increased dentate inhibitory activity (Bronzino et al. 1991).

Combined, long-term potentiation and kindling studies show that prenatal plus early postnatal 50% dietary restriction or prenatal protein deprivation result in permanent changes in synaptic plasticity of the hippocampus in adulthood, despite subsequent dietary rehabilitation. These changes, with the exception of lowered seizure thresholds seen in kindling studies of protein deprived rats, are generally indicative of increased inhibitory activity of neuronal systems modulating dentate granule cell activity in prenatally nutrition-

ally deprived animals. Altered plasticity, including increased inhibitory activity, could have profound effects on learning, memory, and gating of incoming information.

Behavior

Neurotransmitter studies showing dopamine alterations, morphological studies showing hippocampal damage, and electrophysiological studies showing increased inhibitory activity of dentate granule cells and lack of ability to maintain long-term potentiation suggest that prenatal nutritional deficiency would affect behavior, particularly those behaviors related to dopamine and hippocampal functioning.

Interestingly, to our knowledge, there are no published studies examining the effects of specifically prenatal nutritional deficiency on *dopamine-mediated* behaviors such as locomotion or amphetamine-induced stereotypy.

However, a number of studies have investigated hippocampally-mediated behaviors in prenatally and postnatally nutritionally deprived rats. In rats, the hippocampus is involved in the ability to monitor spatial location (Olton and Samuelson 1976), and in learning and memory (Randt and Derby 1973) including working memory (Olton et al. 1979; Kitajima et al. 1992). Indeed, hippocampal damage may underlie deficits in learning and memory seen following early damage to the nervous system (Randt and Derby 1973).

Studies have shown behavioral deficits following early nutritional deficiency that are indicative of hippocampal damage. For example, a 50% caloric reduction in pregnancy and lactation alters spatial learning ability of rats as seen in decreased exploration of a novel situation and increased time to make choices in a maze (Jordan et al. 1981). This type of early nutritional deficiency also abolished spontaneous alternation (Jordan et al. 1982). Of particular interest is the finding that the abolition of spontaneous alternation was correlated with cell count in the hippocampus (Jordan et al. 1982).

More recently, Tonkiss and co-workers, studying rats who underwent prenatal protein deficiency followed by dietary rehabilitation at birth, found a number of hippocampally-mediated behavioral deficits when these animals were studied in adulthood. The animals showed increased resistance to extinction of a food-rewarded alternation task on an elevated T-maze (Tonkiss and Galler 1990), retarded acquisition of a task involving differential reinforcement of low rates of responding in which rats are reinforced for withholding responses (Tonkiss et al. 1990), and disruption of complex visual learning (Tonkiss et al. 1991). However, on a working memory task using delayed alternation, which involves the hippocampus, animals receiving prenatal protein deprivation did not show a deficit (Tonkiss and Galler 1990). Maternal zinc deficiency also produces behavioral alterations as well as alterations in hippocampal morphology (Hunt et al. 1984) and indeed has been suggested as a possible risk factor in schizophrenia (Richardson-Andrews 1992).

Finally, Lipska et al. (1993) found that ventral hippocampal lesions in 7-day-old rat pups produced increased dopamine-mediated locomotion. This leads to the question of whether early nutritional deficiency, which may alter hippocampal morphology, may also produce changes in dopamine-mediated behaviors. Further studies are needed to examine this.

CONCLUSION

We have reviewed preclinical studies to elucidate the possible effects of prenatal nutritional deficiency on neurodevelopment in humans. These studies suggest that certain types of prenatal nutritional deficiency may not only alter dopaminergic and serotonergic neuronal functioning, but also may alter hippocampal morphology and electrophysiology and hippocampally-mediated behaviors. These effects could have implications for schizophrenia.

However, because preclinical studies of prenatal nutritional deficiency have not to date been conducted with schizophrenia in mind, studies have not focused on behavioral dependent variables or neurotransmitter alterations in areas thought to be important in schizophrenia, such as the nucleus accumbens. Thus, preclinical studies of prenatal nutritional deficiency using behavioral and biochemical endpoints that may be relevant to schizophrenia may prove important in understanding the etiology of this devastating disorder. Behavioral endpoints might include such dopamine-mediated behaviors as latent inhibition, and prepulse inhibition of startle which have been utilized in both preclinical and clinical studies of schizophrenia (Braff and Geyer 1990; Feldon and Weiner 1992). Biochemical endpoints might include dopamine turnover or receptor density in the nucleus accumbens.

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