

## **Chapter 14**

### **Animal Models of Prenatal Protein Malnutrition Relevant for Schizophrenia**

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#### **Key concepts**

- Protein malnutrition during development results in behavioral, structural and neurochemical changes in adulthood that mimic many of the characteristics of psychiatric diseases, including schizophrenia.
- Animal models have been used extensively to study the effects of protein malnutrition during development.
- Animal models have been, and will continue to be, a valuable tool for elucidating the environmental, genetic and epigenetic consequences of protein malnutrition and its role in the development of schizophrenia and other psychiatric disorders.

Exposure to a variety of environmental challenges *in utero* has been shown to elevate risk for schizophrenia and other psychiatric disorders (for reviews see Weiss, 2001; Meyer & Feldon, 2009). In particular, retrospective studies in human populations support a link between prenatal exposure to nutritional deficiency and an increased risk for development of schizophrenia (Brown & Susser, 2008; St Clair et al., 2005; Susser et al., 1996; Susser & Lin, 1992; Xu et al., 2009). A large natural experiment on prenatal nutrition in humans occurred at the end of World War II. A Nazi-imposed blockade that affected the six largest cities in the Netherlands resulted in a famine called the “Dutch hunger winter.” During the height of the famine, daily food rations for all residents were limited to 1,000 calories and, eventually, 500 calories. Retrospective studies identified neuropsychiatric and other disorders in the offspring of women exposed to the Dutch famine during gestation. Adults conceived during the famine have an increased risk for schizophrenia (Brown & Susser, 2008; Hoek, Brown, & Susser, 1998) and major affective disorder (Brown et al., 1995; Brown et al., 2000). Similar studies of offspring that were *in utero* during the Chinese famine of 1959-1961 confirmed an increased prevalence of schizophrenia (St Clair et al., 2005; Xu et al., 2009).

It is impossible to use human subjects to identify the causative nutrient(s) or to establish a mechanism for the role of prenatal nutrition on schizophrenia or other psychiatric disorders due to the obvious practical and ethical challenges. Animal models provide an alternative means to study the role of gestational environment, and particularly malnutrition, on brain development and adult behavior.

## **Neurodevelopmental Hypothesis of Schizophrenia**

Schizophrenia is a neurodevelopmental disorder with a complex etiology resulting from both genetic and environmental factors. Evidence suggests that environmental insults acting on individuals with an existing genetic predisposition can cause developmental alterations that are present long before the onset of psychotic symptoms. Research has identified at least two windows of developmental vulnerability: the pre- or perinatal period and early adolescence. Animal models offer the advantage of manipulating the environment at multiple time points during development and measuring outcomes across the lifespan. Because schizophrenia symptoms normally appear in late adolescence or early adulthood, brain and behavioral abnormalities that are observed only in adult and not young animals may provide particularly attractive models for further study.

A number of early environment insults that are linked to increased risk for schizophrenia in humans have also been modeled in animals. Among the most replicated include maternal infection, maternal stress, obstetric complications and maternal dietary malnutrition (both Vitamin D and protein deprivation). Other chapters in this volume focus on maternal immune activation, stress and Vitamin D deficiency. The present chapter provides a detailed review of protein malnutrition in animal models and discusses the behavioral, neurochemical and neurophysiologic effects in relation to schizophrenia.

Animal models of nutritional deficiency result in a number of phenotypic outcomes, including metabolic, cardiovascular and mental disorders, among others (for a review see Armitage et al., 2004). Dietary manipulations in animals can be limited to a particular time during development, in adulthood or across the lifespan. A review of all of these models would be beyond the scope of a single chapter. Instead, we limit our discussion to protein malnutrition

that occurs prenatally and peri- or postnatally. Maternal protein deprivation is defined as a dietary manipulation in females that begins prior to breeding and can end at any time during pregnancy or extend through gestation and weaning into adulthood. Peri- or postnatal protein deprivation is defined as dietary manipulations that begin mid-gestation or immediately at birth and can last throughout weaning and/or into adulthood. Development in rodents lags behind human development and many relevant developmental processes that occur *in utero* in humans occur in the postnatal period in rodents (Clancy, Darlington, & Finlay, 2001; Morgane et al., 1993). Therefore, studies intended to include the entire early brain developmental period in humans should include protein deprivation in the early postnatal period, as well as during embryogenesis in the rodent.

In animal models, protein deprivation is normally achieved by modifying the amount of casein in the diet while maintaining the caloric value by the addition of extra carbohydrates. The fraction of protein in a deficient diet ranges from 5% to 9%, while protein in normal diets ranges from 16% to 25%.

### **Protein Malnutrition and Effects on the Developing Nervous System**

Most neurotransmitter systems have been implicated in schizophrenia based on functional characteristics and/or the efficacy of receptor modulators (i.e. pharmacological manipulation with agonists and antagonists) to ameliorate, exacerbate or mimic symptoms of the disease. Evidence for a functional role of the dopaminergic, glutamatergic, serotonergic and GABAergic systems have been reviewed in detail elsewhere (Geyer & Vollenweider, 2008; Jones et al., 2008; Paz et al., 2008; Stone, Morrison, & Pilowsky, 2007; Toda & Abi-Dargham, 2007) and

efforts toward understanding the effects of protein deprivation during development on each system have been assessed in animal models.

**Structural changes.** Structural changes in the brain have been observed in schizophrenia, including increased ventricular volume and decreased whole brain volume (for reviews see Hulshoff Pol & Kahn, 2008; Fatemi & Folsom, 2009). Although reduced brain and body weight have been reported in animals that were exposed to low protein *in utero* (Barnes et al., 1968; Marichich, Molina, & Orsingher, 1979; Smart et al., 1973), gross structural abnormalities have not been observed. Rather, the deficits resulting from prenatal protein malnutrition tend to be subtle and relate to deficits within specific neurotransmitter systems, although some generalized abnormalities have been reported. For example, exposure to prenatal protein deficiency for the first 2 weeks of gestation in rats results in significant abnormalities in brain development in newborn pups, including delayed astrocytogenesis, abnormal neuronal differentiation (as shown by reduced microtubule associated protein-5 (MAP-5) and increased MAP-1 expression), abnormal synaptogenesis and decreased apoptosis (Gressens et al., 1997). Importantly, however, all of these deficits are normalized by adulthood (P63). A subtle, region-specific change that has been consistently noted in response to prenatal protein malnutrition is a reduction in cell number in the hippocampus. Because the anatomy and circuitry of the hippocampus is well-defined, the effect of prenatal protein malnutrition on this structure has been the focus of numerous groups. A reduced number of cells in CA1 (but no other hippocampal regions) and a reduced subiculum volume have been reported (Lister et al., 2005), while other groups have found changes in cell number more broadly across the dentate gyrus, CA1 and CA3 (extensively detailed by Diaz-Cintra and colleagues (Díaz-Cintra et al., 1991; Díaz-Cintra et al., 1994; Cintra et al., 1997a, 1997b)). Beyond these few notable deficits, numerous subtle changes in neurotransmitter

expression and function have been identified. Yet these findings are complex and can vary in sign across different brain regions or assessment time points.

**Dopamine (DA).** All currently prescribed antipsychotic drugs have an affinity for dopamine D2 receptors. The longstanding DA dysfunction hypothesis of schizophrenia has been supported by the observation of increases in striatal DA D2 receptor binding and differences in DA dynamics in the brains of schizophrenic patients (Howes et al., 2009; Joyce, Lexow, Bird, & Winokur, 1988; Seeman et al., 1987). An increase in D2 receptor binding in the striatum and a decrease in DA transporter binding has also been reported in rats exposed to prenatal protein deprivation (Palmer et al., 2008). Studies examining DA release and tissue concentration in the hippocampus of protein-deprived animals have been less consistent. Chen et al. (1995) reported an increased release of DA and its metabolites in hippocampal slices from prenatally protein malnourished animals, and a decrease in DA was detected in the hippocampus in prenatally malnourished animals by Kehoe et al. (2001). A decrease in basal DA was also detected (by microdialysis) in the prefrontal cortex of prenatally malnourished animals, tested as adults, as well as an absence of restraint stress-induced release of DA (Mokler et al., 2007). However, in a separate study, the expected increase in hypothalamic DA in response to isolation stress was intact in the prenatally-malnourished animals tested as adults (Kehoe et al., 2001).

**Serotonin (5-HT).** Serotonin dysfunction, in particular the 5-HT<sub>2A</sub> receptor, is implicated in some symptoms of schizophrenia based on the ability of 5-HT<sub>2A</sub> agonists, such as lysergic acid diethylamide (LSD) or psilocybin, to induce psychotic symptoms, working memory deficits and sensorimotor gating abnormalities (Vollenweider et al., 1998; Umbricht et al., 2003). Atypical antipsychotics also have a higher affinity for 5-HT<sub>2A</sub> receptors than D2 receptors (Garzya et al., 2007).

Serotonergic changes in protein-deprived animals are generally consistent across studies. Increased 5-HT and/or its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), is detected in the hippocampus (via microdialysis or in tissue) (Kehoe et al., 2001; Mokler, Galle, & Morgane, 2003; Mokler et al., 2007), throughout the brain (Resnick & Morgane, 1984), in hippocampal slices (Chen et al., 1995) and in hypothalamus (Kehoe et al., 2001). Further, in response to stress, an increased release is detected in hippocampus, as opposed to a decrease in control animals (Mokler et al., 2007). Animals from prenatally-malnourished dams also show an altered response to dl-fenfluramine, which blocks the 5-HT transporter and stimulates 5-HT release. These offspring show a decreased behavioral response (inhibition of food intake) and reduced Fos immunoreactivity in the paraventricular nucleus of the hypothalamus in response to dl-fenfluramine (Souza et al., 2008). Another study also detected 5-HT abnormalities within the hippocampus, including a decrease in 5-HT fiber density in dentate gyrus (DG) and CA3, decreased 5-HT uptake in CA3 and CA1 and decreased expression of 5-HT<sub>1A</sub> receptor in CA3 (Blatt et al., 1994). Contrary to the other reports, however, these authors did not find an increase in 5-HT within the hippocampus.

**Glutamate.** N-methyl-d-aspartate (NMDA) receptor blockers like phencyclidine (PCP), ketamine and dizocipine (MK-801) produce psychotomimetic effects in healthy individuals and precipitate psychotic episodes in schizophrenics (Large, 2007). In addition, NMDA receptor and mGluR2/3 agonists are effective in treating schizophrenia (Javitt, 2006; Patil et al., 2007). Therefore, glutamatergic dysfunction, and particularly NMDA receptor hypofunction, is hypothesized to play a role in schizophrenia.

Abnormalities in the glutamate system have been detected in protein-deprived animals. For example, increased MK-801 binding is observed in the adult cortex, striatum and hippocampus

of prenatally protein deprived rats, indicating decreased glutamatergic activity (Palmer et al., 2004, 2008). Increased kainate receptor binding is also detected in CA3 of prenatally protein-deprived animals. The authors speculate that this may be a compensation for reduced glutamatergic input from mossy fibers (Fiacco et al., 2003). Further, a decreased sensitivity to quinolinic acid (an NMDA agonist) was detected in prenatally-malnourished, adult animals (Schweigert et al., 2005).

**Gamma-aminobutyric acid (GABA).** GABAergic interneurons are a core component of the circuitry that controls network oscillations, information processing and sensorimotor gating – all processes that are disturbed in schizophrenia (Benes & Berretta, 2001). Therefore, alterations of the GABAergic system have been examined in protein-deprived animals as a functional model for symptoms of schizophrenia.

Defects in the GABA system have been detected in adult rodents that were protein-deprived *in utero*. An increase in the expression of GAD-67, a rate-limiting enzyme in GABA synthesis, is detected in the dentate gyrus of prenatally-malnourished animals (Díaz-Cintra et al., 2007). Alterations in the expression of GABA-A receptors are also detected in prenatally protein-restricted rats, including decreased GABA-A  $\gamma$ 2L mRNA in septum (Steiger et al., 2002), decreased GABA-A (alpha 1, beta 2) in hippocampus and an increase in alpha 3 expression in hippocampus (Steiger et al., 2003). Higher GABA uptake by cortical and hippocampal slices is also observed in malnourished rats (Schweigert et al., 2005).

### **Effects of prenatal protein malnutrition on rodent behavior.**

Assessing the effects of prenatal protein deprivation in animals requires the use of appropriate behavioral, neurochemical and physiological assays that can accurately reflect

human schizophrenia symptomatology. An animal model encompassing the entire spectrum of schizophrenia symptoms is impossible. Instead, the focus of animal research has been to model specific symptoms of the disease and/or to examine endophenotypes. Human behavioral symptoms of schizophrenia can be grouped into two general categories: positive (e.g. hallucinations, delusions), and negative (e.g. social withdrawal, working memory deficits). Currently available medications for schizophrenia are more effective at treating positive rather than negative symptoms (Javitt et al., 2008). Animal models for both positive and negative symptoms exist and have been widely used in rodents (see **Table 14.1**). In addition, endophenotypes, which are traits that are enriched in affected individuals but are not symptoms of the disease, are also useful for developing animal models (Gottesman & Gould, 2003). Specific endophenotypes have been developed for schizophrenia. Models of disease symptoms and endophenotypes should provide face, predictive and construct validity (Geyer & Markou, 1995). Many behavioral models of schizophrenia respond to human pharmacotherapies and are modulated by the same brain regions and neurotransmitter pathways (Li et al., 2009).

Numerous studies have reported on the behavioral effects of pre-, peri- or postnatal protein deprivation on adult offspring. **Table 14.2** lists most of the studies that have examined the behavioral phenotype resulting from protein deprivation *in utero*, with a focus on animal models of behaviors that model symptoms and/or endophenotypes of schizophrenia.

**Prepulse inhibition (PPI).** Behavioral and physiological models of schizophrenia have mainly focused on negative symptoms and endophenotypes. Sensorimotor gating is one of the most widely-studied endophenotypes. PPI is a well-validated neurophysiological test of sensorimotor gating that has almost identical human behavioral correlates and responds to atypical antipsychotics in both human (reviewed in Braff, Geyer, & Swerdlow, 2001; Swerdlow

et al., 2008) and animal studies (reviewed in Geyer et al., 2001 and Swerdlow et al., 2008). Schizophrenics and asymptomatic first-degree relatives show deficits in PPI. In animal models, these deficits can be replicated by both developmental and pharmacological manipulations that affect neurotransmitter pathways and brain regions involved in the disease – most notably by DA agonists (Swerdlow et al., 1994; Geyer et al., 2001), 5-HT agonists (Dulawa et al., 2000), NMDA receptor antagonists (Geyer et al., 2001), GABA antagonists (Swerdlow et al., 1990), maternal infection and immune activation (Patterson, 2009; Patterson this book), maternal stress (Patterson this book) and neonatal ventral hippocampal lesions (Lipska et al., 1995). PPI is also disrupted in other disorders, including Alzheimer disease (Ueki et al., 2006), bipolar disorder (Perry et al., 2001) and obsessive compulsive disorder (Shanahan et al., 2009), indicating that this behavioral deficit is not specific to schizophrenia.

Despite the widespread use of PPI as an endophenotype for schizophrenia (Swerdlow et al., 2008), only one study has been published that examines PPI following prenatal protein malnutrition. Palmer et al. (2004) reported that protein deprivation *in utero* is associated with lower PPI in young adult female rat offspring (postnatal day (PND) 56). However, no such deficit is observed in young adult males in this experiment. Moreover, PPI deficits are not observed in adolescent (PND 35) male or female rats exposed to maternal protein deprivation. The significant decrease in PPI in young adult female rats exposed to protein deprivation *in utero* is consistent with adult onset of schizophrenia and supports the role of prenatal protein malnutrition in the development of this particular endophenotype.

Differences in startle reactivity have been reported in patients with schizophrenia (Geyer & Braff, 1982; Braff, Grillon, & Geyer, 1992) and related disorders (Cadenhead, Geyer, & Braff, 1993), and are hypothesized to reflect a defect in central inhibitory mechanisms. Palmer et al.

(2004) also observed a decrease in initial startle response in protein-deprived rats. However, a more recent study reported no difference in startle response among protein-deprived versus control rats (Francolin-Silva, Brandao, & Almeida, 2007). There are several technical differences between this and the Palmer et al. study. Whereas Francolin-Silva limited protein malnutrition to the perinatal period, from birth up to PND 28, Palmer used a prenatal protein deprivation model that started 5 weeks before mating, lasting until PND 0. Also, the startle response amplitude measure used by Francolin-Silva et al. was averaged over 30 trials, whereas Palmer et al. observed a difference in startle response only in the initial presentations of the startle stimulus.

**Cognitive function.** Cognitive deficits in schizophrenia largely drive functional outcomes for the disease (Arguello & Gogos, 2009) and are not well-managed by current antipsychotics (Fenton, Stover, & Insel, 2003). Appreciation of cognitive deficits as a core feature of the disease has generated an increased effort towards identification of appropriate animal models for screening novel pharmaceuticals for this disease domain. A National Institutes of Mental Health (NIMH) initiative, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), has identified seven primary cognitive domains that are affected in human schizophrenia (Green et al., 2004). A number of these cognitive features are readily measured in rodents using basic learning and memory tasks that assess working memory, attention, visual learning and social cognition (**Table 14.1**). Deficits in many of these cognitive assays are observed in lesion studies of the prefrontal cortex that replicate brain structure abnormalities observed in human patients and in animals genetically modified to express disease susceptibility genes, thus providing encouraging evidence for their usefulness in modeling the human disease (reviewed in Kellendonk, Simpson, & Kandel, 2009; Arguello et al., 2009). A desire to

understand potential developmental causes for the cognitive deficits observed in schizophrenics drives research on learning and memory deficits in protein-deprived animals.

Protein deprivation during development causes lasting changes in brain regions implicated in learning and memory (Morgane et al., 1993). Perhaps one of the simplest assays of sensory and cognitive development is the homing test in which suckling animals are tested for their ability to locate the nest after displacement. Data has consistently shown that protein-malnourished animals are deficient in the ability to return to the nest (Galler, Tonkiss, & Maldonado-Irizarry, 1994; Gallo, Werboff, & Knox, 1984; Tonkiss, Harrison, & Galler, 1996).

Protein deprivation *in utero* or during the suckling period causes significant hippocampal alterations, including long-term potentiation deficits (Austin, Bronzino, & Morgane, 1986). The hippocampus plays a critical role in the ability to learn and remember spatial information. Tests of learning and memory indicate that prenatally-malnourished rats are behaviorally inflexible (Tonkiss et al., 1993) and often show no deficits in acquisition, while being unable or unwilling to give up learned responses once acquired. For instance, prenatal protein deprivation does not affect acquisition of the alternation response in a spatial T-maze task (Goodlett et al., 1986; Tonkiss & Galler, 1990) or an operant model of the T-maze task (Tonkiss & Galler, 1990), spatial navigation in the Morris water maze (Goodlett et al., 1986; Tonkiss, Shultz, & Galler, 1994) or performance in the radial arm maze (Hall, 1983). However, rats deprived of protein *in utero* require more sessions to abolish learned alternation responses (Tonkiss & Galler, 1990). In conditioned taste aversion (CTA) studies, prenatally-malnourished rats show impaired extinction of the CTA response with repeated exposure (Tonkiss et al., 1993). Following continuous reinforcement (CRF) in an operant task, prenatally-malnourished rats exhibit impairments in acquiring a differential reinforcement of low rates of responding (DRL) task (Tonkiss et al.,

1990). These data imply that prenatal protein deprivation does not alter the ability to learn but rather makes it harder to “unlearn” once an association has been made.

There has been one report of radial arm maze performance in prenatally protein-deprived mice. Ranade et al. (2008) found that outbred Swiss mice make more reference memory and working memory errors – an interesting result that encourages further study of mice as animal models for the cognitive effects of prenatal protein deprivation.

**Social interaction.** Impaired social interactions are a hallmark of schizophrenia and improvement of social skills is an important element in treatment and outcomes for individuals with the disease. Two studies of social interaction behaviors in protein-malnourished rats reported a deficit in several social behaviors (Almeida, Tonkiss, & Galler, 1996c; Frankova, 1973). Both of these studies were performed in juvenile rats but differed in the protein deprivation protocol. Almeida et al. deprived prenatally until birth, while Frankova deprived from birth until PND 49. Contradictory results have emerged when adult offspring from dams that experienced total caloric undernutrition, as opposed to only protein malnutrition, were tested. In these studies, adult rats display increased social interaction and more aggression, rather than a decrease in social interaction (Tonkiss & Smart, 1983; Whatson, Smart, & Dobbing, 1975, 1976). The extent to which age of testing, developmental period of malnutrition or type of nutritional deficiency (overall caloric malnutrition or protein deprivation) explains these contradictory results has yet to be resolved. However, the limited results from protein-deprived juvenile rats suggest that such an experimental paradigm produces social behaviors that mimic those seen in human schizophrenia.

**Sleep abnormalities.** Difficulties initiating or maintaining sleep occur in 30-80% of individuals with schizophrenia (Cohrs, 2008). Several studies have examined the result of

prenatal protein deprivation on circadian and sleep behaviors. Measurement of 24-hour locomotor activity indicates that, while rats deprived of protein *in utero* are not impaired in spontaneous locomotor activity and show circadian rhythmicity, they do display an advanced phase shift in locomotor activity (Castanon-Cervantes & Cintra, 2002; Duran et al., 2005). Protein-deprived rats show peak activity levels before the onset of the light phase, while control animals show peak activity after the onset of the light phase. Duran et al. (2005) observed the phase shift in locomotor activity using standard light/dark (LD) conditions in 88 day old rats, while Castanon-Cervantes and Cintra (2002) observed the phase shift in dark/dark (DD) conditions but not under a LD light cycle and in younger (55 days of age) but not older rats (550 days of age). In addition, Duran et al. used only females and the sex of the rats used in the Castanon-Cervantes study is not apparent from the publication.

The superchiasmatic nucleus (SCN) of the hypothalamus is the master pacemaker for the generation and maintenance of circadian rhythms and abnormalities in SCN development have been noted in rat pups from protein-deprived dams. Immunohistochemical examination of vasoactive intestinal peptide (VIP) and arginine vasopressin neurons within the SCN revealed altered density and morphology of these two systems within this nucleus (Rojas-Castañeda et al., 2008).

Undernutrition-driven changes in sleep behavior are a bit more complex, but several studies indicate that the amplitude of the rhythm for both wakefulness and rapid eye movement sleep (REMS) is advanced in the dark phase of the light cycle in rats that were deprived of protein *in utero* (Cintra et al., 2002; Duran et al., 2006) and that these changes are exacerbated by acute stress (Duran et al., 2006). A thorough review of stress and stress-related disorders and the relationship to psychiatric disorders was recently presented (Chrousos, 2009). In summary,

prenatal protein malnutrition in animal models appears to alter both circadian rhythms and the sleep/wake cycle. This alteration occurs primarily at the time of light change and may provide insight into the mechanisms of sleep disturbances in schizophrenia.

### **Behavioral Responses to Pharmacological Challenges**

**Dopamine.** Examination of DA-mediated behaviors in animals that were protein-deprived during development reveals lasting changes in the DA system. Most studies examining DA agonists have reported increased locomotor activity in response to amphetamine (Brioni et al., 1986; Palmer et al., 2008) and cocaine (Shultz, Galler, & Tonkiss, 1999; Valdomero et al., 2005), as well as increased stereotypy in response to apomorphine (Leahy et al., 1978; Palmer et al., 2008). Some of these differences are found in young adult female but not young adult male or adolescent rats of either sex (Palmer et al., 2008). An increase in DA release in the nucleus accumbens core following cocaine administration in cocaine-sensitized, protein-deprived rats has also been observed (Valdomero et al., 2005). These observations are consistent with the increased sensitivity to psychostimulants observed in schizophrenia (Geyer & Markou, 1995; van den Buuse et al., 2005) and indicate that prenatal protein deprivation might be a good model for DA dysfunction in human schizophrenia.

**Serotonin.** In behavioral studies, the 5-HT<sub>2</sub> receptor antagonist ritanserin decreases anxiety in the open field in postnatally protein-deprived rats but had no effect on control animals (Almeida, de Oliveira, & Graeff, 1990). Postnatally deprived rats also show decreased sensitivity to the 5-HT<sub>2A</sub> receptor antagonists, 5-methoxy-dimethyltryptamine (5-MeO-DMT) and dimethyltryptamine (DMT) in rotarod and treadmill assays, and for DMT-induced behaviors (Hall, Leahy, & Robertson, 1983; Keller et al., 1994).

**GABA.** Benzodiazepines are positive allosteric modulators of the GABA<sub>A</sub> receptor that are commonly used as anxiolytics but also have amnesic and sedative properties. Animals that have been exposed to low protein at any time during development show a reduced sensitivity to the effects of benzodiazepines. This result has been observed repeatedly in numerous animal models of anxiety, including elevated plus maze (Almeida, de Oliveira, & Graeff, 1991; Borghese et al., 1998; Cordoba et al., 1992; Francolin-Silva et al., 2007; Laino, Cordoba, & Orsingher, 1993; Santucci et al., 1994), light/dark (Brioni & Orsingher, 1988; Santucci et al., 1994) and fear-potentiated startle tests (Francolin-Silva & Almeida, 2004). Prenatally protein-deprived rats also show a decreased sensitivity to the amnesic effects of chlordiazepoxide in the Morris water maze (Tonkiss et al., 2000) but show an increased behavioral sensitivity to the stimulus properties of chlordiazepoxide (Shultz, Galler, & Tonkiss, 2002), indicating that protein deprivation differentially affects other aspects of benzodiazepine action.

**Drug abuse.** Drug abuse has been linked to the development of schizophrenia and, as described above, protein-deprived animals show an elevated locomotor response to psychostimulants such as cocaine, amphetamine and apomorphine. However, there are also reports that these animals are more sensitive to the rewarding effects of cocaine (Valdomero et al., 2006) and show increased responding for other rewarding substances, such as morphine (Valdomero et al., 2007), food (Tonkiss et al., 1990), sweetened milk (Brioni & Orsingher, 1988) and saccharin (Tonkiss, Shukitt-Hale et al., 1990), indicating that protein deprivation during development alters drug reward circuitry and may be a useful environmental manipulation for studying the role of drug reward and abuse in the development of schizophrenia.

**Anxiety-related behaviors.** Many studies have examined the role of prenatal protein malnutrition on anxiety-related behaviors. While these behaviors are not considered to be models

of schizophrenia, there is significant comorbidity between anxiety and schizophrenia that may indicate a shared liability (Buckley et al., 2009). In any case, the data on anxiety phenotypes in protein-malnourished animals provide further insight into the behavioral effects of this environmental manipulation. In general, animals exposed to protein malnutrition during early development exhibit reduced anxiety in the elevated plus maze (Almeida et al., 1991; Almeida, Tonkiss, & Galler, 1996b; Francolin-Silva & Almeida, 2004), the light-dark assay (Brioni & Orsingher, 1988; Santucci et al., 1994), the elevated T-maze (Almeida, Tonkiss, & Galler, 1996a; Hernandez & Almeida, 2003) and the fear-potentiated startle test (Francolin-Silva et al., 2007). An exception is the report of Borghese et al. (1998), which found a decrease in the percent time spent in the open arms of the elevated plus maze. However, in this experiment the animals received a daily injection of vehicle for 15 days prior to testing. It is possible that either the vehicle or the chronic stress of receiving daily injections had an effect on behavior in the elevated plus maze. Stress is known to interact with prenatal malnutrition to modify behavior. For instance, acute immobilization stress reverses the anxiolytic behavior observed in the elevated plus maze (Francolin-Silva & Almeida, 2004), and exposure to chronic stress reverses some of the anxiolytic and antidepressant-like effects of prenatal protein deprivation (Trzctnska, Tonkiss, & Galler, 1999).

In contrast to the assays described above, assessment of protein-deprived animals in a different test of anxiety, the open field, have shown increased (Trzctnska et al., 1999; Watkins, Wilkins et al., 2008), decreased (Watkins, Ursell et al., 2008) or no change in anxiety behaviors (Brioni et al., 1986). Differences between the methods used in these studies do exist and could explain the contradictory results. It is also important to note that the studies by Watkins used mice, whereas all other studies of the effects of protein malnutrition on anxiety-related behaviors

have used rats. Obviously, differences between mice and rats are possible and additional studies are needed to understand the behavioral effects of low protein during development in mice.

Overall, most studies of anxiety-related behavior indicate decreased anxiety in animals that have been subjected to protein deprivation *in utero*, but further research is required to gain a better understanding of the mechanisms that control these behavioral responses.

### **The Role of Epigenetics**

Epigenetic mechanisms have also been proposed as possible mediators of the effects of prenatal protein deprivation on downstream phenotypes. Epigenetics is defined as inherited phenotypic variations that are not the result of variations in the DNA sequence. This includes DNA methylation, histone modifications and genomic imprinting, which can occur both pre- and postnatally and can establish either transient or long-lasting changes in gene expression.

The role of diet in DNA methylation is fairly obvious. DNA methylation is catalyzed by DNA methyltransferases that transfer methyl groups from S-adenosylmethionine (SAM) to cytosine in CpG islands. The SAM required for methylation comes, in part, from dietary methyl group intake, and the major source of methyl groups in food is methionine. If methionine is limited in the diet, the amount of SAM available is also limited and hypomethylation is found (Vachtenheim, Horakova, & Novotna, 1994; Wainfan et al., 1989). However, there also are *de novo* pathways (one-carbon metabolism) and other dietary sources of methyl groups, including choline, folic acid and vitamin B12 (Niculescu & Zeisel, 2002). Limiting methionine in the diet during development is likely to result in some compensatory changes in these other pathways so that some level of methylation can occur (see also the chapter by Cheung et al.).

Perhaps the most dramatic example of the effects of dietary methyl groups is represented by the observation that dietary supplementation of methyl groups in pregnant black pseudoagouti ( $A^{vy}/a$ ) dams alters epigenetic regulation of agouti expression by increasing methylation at the long terminal repeat (LTR), resulting in increased agouti/black mottling in offspring (Cooney, Dave, & Wolff, 2002; Wolff et al., 1998). Gene-specific hypomethylation of peroxisomal proliferator-activated receptor alpha (PPAR $\alpha$ ) (Lillycrop et al., 2008) and the glucocorticoid receptor (GR) (Lillycrop et al., 2005) has also been observed in the offspring of rodents fed a low protein diet, and this can be prevented with folic acid supplementation. Interestingly, methyl-deficiency that causes global DNA hypomethylation can occur simultaneously with gene-specific hypo- or hypermethylation (Singh, Murphy, & O'Reilly, 2003). A methyl-deficient diet also modifies histone methylation and increases expression of both immunoglobulin factor 2 (*Igf2*) and *H19* genes, indicating that at some loci, methyl deficiency may result in chromatin modification. Importantly, hypomethylation of the IGF2 gene is also found in DNA samples from humans who were exposed to the Dutch Famine during development (Heijmans et al., 2008).

Recent technical advances are opening up the possibility of measuring changes in methylation status on a genomewide scale (Schumacher et al., 2006). Allele-specific methylation using array-based technology allows tracking of both gene- and allele-specific changes in methylation. Paired with an experimental genetic population of animals, this technique presents a powerful tool for examining the role of prenatal nutritional environment on allele-specific methylation status and its effects on behavior.

## **Conclusions and Future Directions**

The spectrum of data presented here reflects years of research on a variety of animal models, including work from many diverse disciplines, that suggests that protein deprivation during gestation and/or immediately after birth produces behavioral, neurochemical and developmental changes that accurately mirror many of the symptoms of human schizophrenia.

The challenge moving forward is to integrate these environmentally-induced behavioral, neurochemical and developmental changes with the relevant genetic factors that increase susceptibility to developing schizophrenia. Numerous genes and gene expression changes have been studied in schizophrenia (for reviews see Desbonnet, Waddington, & O'Tuathaigh, 2009; Desbonnet, Waddington, & Tuathaigh, 2009; Jones et al., 2008), and animal models of these can be subjected to protein deprivation to look for gene-environment interaction.

The identification of specific genetic and environmental causes of schizophrenia and other psychiatric diseases remains a challenge for the research community. Findings reviewed in this chapter highlight the importance of maternal nutrition, specifically adequate protein nutrition, within the prenatal, perinatal and early postnatal developmental critical periods. The availability of tools for directly assessing the impact of environmental manipulations on gene structure and expression, along with a greater appreciation for the role of gene by environment interactions in complex disease, has the potential to move the field forward in the next decade.

### **Key areas for future research**

- The use of protein deprivation as an environmental risk factor should be developed more systematically in mouse models where the current genetic and genomic tools are most advanced.
- The use of mouse models would allow for a more thorough assessment of the genetic effects of prenatal protein malnutrition (i.e. strain differences, gene by environment interactions).

- As tools develop, a more systematic genomewide assessment of epigenetic changes resulting from prenatal protein deprivation should be explored.

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