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Research Report

Prenatal protein deprivation alters dopamine-mediated behaviors and dopaminergic and glutamatergic receptor binding

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ABSTRACT

Epidemiological evidence indicates that prenatal nutritional deprivation may increase the risk of schizophrenia. The goal of these studies was to use an animal model to examine the effects of prenatal protein deprivation on behaviors and receptor binding with relevance to schizophrenia. We report that prenatally protein deprived (PD) female rats showed an increased stereotypic response to apomorphine and an increased locomotor response to amphetamine in adulthood. These differences were not observed during puberty. No changes in haloperidol-induced catalepsy or MK-801-induced locomotion were seen following PD. In addition, PD female rats showed increased ^{3}H-MK-801 binding in the striatum and hippocampus, but not in the cortex. PD female rats also showed increased ^{3}H-haloperidol binding and decreased dopamine transporter binding in striatum. No statistically significant changes in behavior or receptor binding were found in PD males with the exception of increased ^{3}H-MK-801 binding in cortex. This animal model may be useful to explore the mechanisms by which prenatal nutritional deficiency enhances risk for schizophrenia in humans and may also have implications for developmental processes leading to differential sensitivity to drugs of abuse.

1. Introduction

Considerable evidence suggests that schizophrenia may be a neurodevelopmental disorder in which early abnormities in brain development result in brain malfunction and symptomatology that emerges in early adulthood (Ursula et al., 2006; St Clair et al., 2005; Arnold 1999; Pilowsky et al., 1993; Weinberger 1996). Prenatal nutritional deficiency has been

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hypothesized to be a risk factor for schizophrenia since the 1950s (Pasamanick et al., 1956). A series of studies of the Dutch Hunger Winter showed that birth cohorts exposed to famine during early gestation had a two-fold increase in risk of schizophrenia in male and female offspring (Susser et al., 1998 Hoek et al., 1998; Susser et al., 1996; Susser and Lin, 1992). These findings have been replicated in a much larger cohort in China (St. Clair et al., 2005). Further, there was an increase in schizoid personality disorder when male offspring from the Dutch Hunger Winter were studied (Hoek et al., 1996). A recent seroepidemiologic study from a large birth cohort in northern California revealed an association between elevated maternal homocysteine, a marker of folic acid deficiency, and schizophrenia (Brown et al., 2007). Other epidemiologic and laboratory studies of schizophrenia have found evidence of other potential pre- and perinatal etiologies, including prenatal exposure to infections including influenza toxoplasmosis and genital/reproductive infection (Romero et al., 2008; Smith et al., 2007; Brown, 2006) and obstetric complications (Hultman et al., 1999; McNeil et al., 2000a). In addition to epidemiological studies, neuroimaging studies have found that ventriculomegaly and decreased hippocampal volume in schizophrenia are related to obstetric complications (McNeil et al., 2000b) and neuropathology studies have found cytoarchitectonic abnormalities in temporal lobe and prefrontal cortex in post-mortem brains of patients with schizophrenia indicative of prenatal damage and possibly altered neuronal migration (Akbarian et al., 1996, 1993).

Previous studies show parallels between long-term effects of prenatal protein deprivation in animals and clinical studies of schizophrenia. For instance, clinical studies as well as animal studies show altered dopamine neurochemisty (Almeida et al., 1996a; Butler et al., 1999; Chen et al., 1995, 1997; Toda and Abi-Dargham, 2007), changes in morphology of the hippocampal formation, including dendritic abnormalities (Cintra et al., 1997; Diaz-Cintra et al., 1991, 1994; Rosoklija et al., 2000), deficits in learning and memory (Tonkiss and Galler 1990; Tonkiss et al., 1990, 1991; Goldman-Rakic 1994; Barch and Smith 2008; Ranganath et al., 2008) and changes in anxiety-like behavior and physiological parameters (Watkins et al., 2008). The few studies to have examined the effects of prenatal protein deprivation on dopamine and glutamate mediated behaviors have shown increased sensitivity to dopamine agonists (Brioni et al., 1986; Shultz et al., 1999) and NMDA antagonists (Tonkiss et al., 1998). However, these studies examined behaviors only in adulthood. In our previous study, we identified deficits in pre-pulse inhibition and accompanying changes in NMDA receptor binding following prenatal protein deprivation in female, but not male rats (Palmer et al., 2004); these changes were present at postnatal day 56 (PDN 56; young adult) but not PND 35 (puberty).

Another example of a developmental model examining long-term effects of a perinatal lesion is the work of Lipska and colleagues (Al-Amin et al., 2000; Lipska et al., 1993, 1995; Lipska and Weinberger 1993; Tseng et al., 2007). These investigators and others found that ventral hippocampal lesions in seven day old rat pups increased dopamine- and glutamate-mediated behaviors (Al-Amin et al., 2000; Lipska et al., 1993; Lipska and Weinberger 1993), produced deficits in learning and memory (Le Pen et al., 2000) and produced alterations in prepulse inhibition of startle (Le Pen et al., 2000; Lipska et al., 1995) that emerged in post- rather than pre-pubertal rats. However, some cognitive impairment and deficits in social behavior occurred pre- as well as post-pubertally (Chambers et al., 1996; Sams-Dodd et al.,

Table 1 – Offspring born, number surviving, and distribution for testing

Group	# Dams mated	# Gave birth	Mean # offspring	# Litters cross-fostered	Culled to	# Survived	# Tested for behavior
Protein deprived							
Group 1	10	7 (70%)	13.4	6	26M 22F	19M 68% 13F 59%	11M 7F 1–3 of each sex from 4 litters
Group 2	10	9 (90%)	13.7	6	24M 24F	19M 79% 20F 83%	10M 10F 1–2 of each sex from 6 litters
Pd total	20	16 (80%)	13.6	12	50M 46F	38M 76% 33F 72%	21M 17F 1–3 of each sex from 10 litters
Non-deprived							
Group 1	20	13 (65%)	14.2	6	24M 24F	24M 100% 24F 100%	15M 17F M: 3/litter from 5 litters F: 2–3/litter from 6 litters
Group 2	20	12 (60%)	15.3	6	24M 24F	24M 100% 24F 100%	10M 10F 1–2 of each sex from 6 litters
Nd total	40	25 (63%)	14.7	12	48M 48F	48M 100% 48F 100%	25M 27F M:1–3/litter from 11 litters F:1–3/litter from 12 litters

All litters were culled to 4 males and 4 females with the exception of one litter in PD Group 1 which was culled to 6 males and 2 females as it only included 2 females.