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Is Lead Exposure in Early Life An Environmental Risk Factor for Schizophrenia? Neurobiological Connections and Testable Hypotheses

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Abstract

Schizophrenia is a devastating neuropsychiatric disorder of unknown etiology. There is general agreement in the scientific community that schizophrenia is a disorder of neurodevelopmental origin in which both genes and environmental factors come together to produce a schizophrenia phenotype later in life. The challenging questions have been which genes and what environmental factors? Although there is evidence that different chromosome loci and several genes impart susceptibility for schizophrenia; and epidemiological studies point to broad aspects of the environment, only recently there has been an interest in studying gene × environment interactions. Recent evidence of a potential association between prenatal lead (Pb^{2+}) exposure and schizophrenia precipitated the search for plausible neurobiological connections. The most promising connection is that in schizophrenia and in developmental Pb^{2+} exposure there is strong evidence for hypoactivity of the *N*-methyl-d-aspartate (NMDA) subtype of excitatory amino acid receptors as an underlying neurobiological mechanism in both conditions. A hypofunction of the NMDA receptor (NMDAR) complex during critical periods of development may alter neurobiological processes that are essential for brain growth and wiring, synaptic plasticity and cognitive and behavioral outcomes associated with schizophrenia. We also describe on-going proof of concept gene-environment interaction studies of early life Pb^{2+} exposure in mice expressing the human mutant form of the disrupted in schizophrenia 1 (DISC-1) gene, a gene that is strongly associated with schizophrenia and allied mental disorders.

Keywords

Schizophrenia – Lead – Pb^{2+}; Early Life; NMDA Receptor; DISC1; gene; environment; interaction

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Introduction

Schizophrenia is a severe neuropsychiatric disorder affecting approximately 1% of the world's population (Bromet and Fenning, 1999; McGrath et al., 2004). The symptoms typically begin in late adolescence or early adulthood, whereupon lifelong disability typically ensues. Its onset is defined by the emergence of psychosis in the setting of deteriorating function and other symptoms. Before psychosis onset, during a prodromal period of several weeks to years, nonspecific and variable subtle abnormalities worsen and coalesce into the classic disease features. These include alterations in the perception of reality, changes in the form and content of thoughts and speech, and social and emotional deficits including a disturbed sense of self, social dysfunction, apathy, and peculiar behavior. The symptoms of schizophrenia are often grouped into positive and negative subtypes, although there is substantial diversity in the pathophysiology of the symptoms within these groups. Positive symptoms include hallucinations and delusions, disorganized thinking or behavior, so denoted because these phenomena occur in addition to usual experiences. Negative symptoms are those that arise from the absence of normal behaviors or experiences, including affective flattening, alogia (impoverish thinking manifested by diminished speech output or content), apathy, avolition (lack of energy and drive), and social withdraw. In addition, schizophrenia patients express a pattern of cognitive dysfunction that represents a core feature of the disorder.

Genes and Environment: Etiological factors in Schizophrenia

The etiology of schizophrenia is not currently known, although there is strong evidence that genetic and environmental factors contribute to the expression of the disease (Tsuang, 2000; van Os et al., 2010; Brown, 2011). The identification of specific genes that cause schizophrenia has been less than satisfactory; although a number of genes associated with schizophrenia have been identified that together may contribute to the schizophrenia phenotype (Lewis and Lieberman 2000; Tsuang 2000; Horvath and Mirmics 2009; Nieratschker et al, 2010). Environmental risk factors have also been implicated to play a role in schizophrenia. These include birth in an urban environment, season of birth, viral infection during the prenatal or perinatal period, complications during pregnancy and delivery, nutritional and social factors (Bromet and Fenning, 1999; Tsuang, 2000; vanOs et al., 2010; Brown, 2011). It is generally thought that exposures to an environmental insult that damages or disrupts the development of the central nervous system may be associated with schizophrenia and allied mental disorders (Murray et al., 1992; Weinberger, 1996). To date, maternal exposures during the mid- to late-gestational period have been implicated. There are several reasons to suspect that chemical agents, in general, and particularly those associated with industrialization, may increase the risk of schizophrenia. Studies further suggest that some feature of urban environment may elevate the risk of schizophrenia (Pedersen et al., 2004; Pedersen and Mortensen, 2006). This may be due to chemicals or environmental agents that are more prevalent in urban settings, possibly ambient pollutants (Marcelis et al., 1998).

Are Specific Environmental Toxins Involved?

An environmental risk factor that has not been considered until recently is the possibility of early life exposure to a developmental neurotoxicant(s) pervasive in the global environment. This possibility has been brought to light by two recent studies by Opler and colleagues (2004; 2008). They showed a potential association between prenatal Pb^{2+} exposure and the increased likelihood of expressing a schizophrenic phenotype later in life. To our knowledge this is the first time that prenatal exposure to a specific environmental agent has been associated with schizophrenia. Lead (Pb^{2+}) has been known as a developmental neurotoxin

in the medical literature since the early part of the 20th century. It has been associated with psychosis following acute exposure in adults, and more recently, with deficits in intelligence, impaired attention and executive function, and juvenile delinquency following prenatal and perinatal exposure (Needleman et al., 1979; Dietrich et al., 2001; Kaneshiro-Olympio et al, 2009). While some studies have followed samples with perinatal exposure into adolescence (Ris et al., 2004), there is limited information on long-term effects of Pb^{2+} exposure, particularly on the subsequent risk of mental disorders in adulthood.

Relationships between early life exposure to Pb^{2+} and neuropsychological abnormalities have been observed from infancy to adolescence (Bellinger et al., 1991; Pocock et al., 1994; Kim et al., 1995). For example, the Yugoslavia Prospective Study reported that Pb^{2+} exposure during mid-pregnancy was associated with deficits in neuropsychiatric function at 24 months of age (Factor-Litvak et al., 1999). Further assessments of this cohort identified persistent decrements in measures of attention, cognition, and verbal comprehension at ages 4, 7, 10, and 12 (Wasserman et al., 2000).

Studies by Needleman and colleagues found associations between dentine Pb^{2+} levels measured in deciduous teeth (ages 6-8) and failure to graduate from high school (Needleman et al., 1990) and other studies have found poor end-of-grade performance in Pb^{2+}-exposed children (Miranda et al, 2007). In a prospective study conducted in Cincinnati, prenatal childhood blood Pb^{2+} concentrations were reported to be associated with increased delinquent behavior later in life (Dietrich et al., 2001). Nevin (2007) has found a very strong association between preschool blood Pb^{2+} and subsequent crime rate trends over several decades in various countries. This suggests that prenatal Pb^{2+} exposure may be a risk factor for other adolescent and adult-onset outcomes, possibly psychiatric disorders. Schizophrenia is one plausible candidate, as some of its premorbid features such as reduced attention, neurocognitive impairment, and diminished educational attainment (Jones et al., 1993) strongly resembles the behavioral deficits associated with Pb^{2+} exposure.

Prenatal Lead Exposure and Schizophrenia

Opler and colleagues (2004; 2008) have conducted studies on prenatal cohorts to assess the risk of schizophrenia following Pb^{2+} exposure. The principle technique for assessing Pb^{2+} exposure is through direct measurement of Pb^{2+} in maternal blood. They used stored sera, not whole blood containing the Pb^{2+}-sequestering erythrocytes required for direct analysis. A biological marker of Pb^{2+} exposure, δ-aminolevulinic acid (δ-ALA) can be detected in urine, plasma and serum. Feasibility studies were conducted to assess the utility of this marker in small volumes of stored maternal serum. It was determined that the second trimester serum was likely to be the best indicator of prenatal Pb^{2+} exposure, as both Pb^{2+} and corresponding δ-ALA levels are believed to be relatively stable at mid-pregnancy. A single aliquot of second trimester samples was made available for each subject and a cutoff value (15 μg/dL) was used to categorize the samples by Pb^{2+} exposure. Samples were coded and blinded with respect to case status. Using this approach, Pb^{2+} exposure as measured by elevated δ-ALA was associated with about a two-fold increase in risk of schizophrenia spectrum disorders in these studies (OR=2.3, 95% CI: 1.0-4.3; p=0.05). Because these studies used a biological marker of exposure, serum δ-ALA, rather than direct measure of Pb^{2+}, an increase in risk in schizophrenia cannot be directly ascribed to Pb^{2+} exposure. Nevertheless, these findings illustrate how prenatal cohorts with archived specimens can take a leap forward in terms of defining and ascertaining exposure status and timing. At the very least, they allow researchers to say with more certainty than before that certain classes of exposure (e.g. infectious agents and/or environmental toxins) are risk factors that merit more detailed investigations. Although the studies by Opler and colleagues (2004; 2008) have certain limitations, it brings to light the possibility that prenatal Pb^{2+} exposure may be

a putative risk factor for the expression of schizophrenia later in life. This potentially important connection between schizophrenia and exposure to a known developmental neurotoxicant should be re-examined using a larger cohort of subjects in which Pb^{2+} concentrations are directly measured in biological samples. Nevertheless, the potential link of expressing a schizophrenia phenotype as a result of prenatal exposure to a known developmental neurotoxicant that has been present in the global environment since antiquity deserves closer examination. Although impossible to do in a single document, the goal of this review is to examine the current understanding of the behavioral, anatomical, biochemical and neuropathological endpoints in schizophrenia and those resulting from developmental Pb^{2+} exposure. Despite the fact that research in these two arenas have occurred independently, there is a great deal of overlap in behavioral outcomes and neurochemical systems affected.

Behavioral manifestations in Schizophrenia and early life Pb^{2+} exposure

As previously noted, the clinical diagnosis of schizophrenia is based on behavioral observations and self-reported abnormal mental experiences (Pearlson, 2000). Symptoms of schizophrenia are divided into “positive” and “negative” types (Kay and Opler, 1987). Positive symptoms are usually defined as the presence of intrusive or abnormal neurobehavioral phenomenon, such as delusions (presence of false beliefs), hallucinations (including visual, auditory, olfactory, tactile, and gustatory modalities), formal thought disorder and unusual motoric and social behaviors. Negative symptoms are conceptualized as the absence of normal functions, including blunted affect, social withdrawal, apathy, poor initiative and motivation, difficulty in planning, impaired problem solving and abstract reasoning. Impairments in cognitive functions include those related to attention, executive functions and working memory. Keeping these symptoms in mind, there is evidence that some of these same behavioral and cognitive alterations have been described as a result of early life Pb^{2+} intoxication.

The effects of childhood Pb^{2+} intoxication on the central nervous system have been documented since the early part of the 20^{th} century. In the classic paper by Byers and Lord (1943) it was recognized that Pb^{2+} intoxication in children produces mental retardation with cognitive impairments and maladaptive behaviors. In this classic paper, a series of 20 children exposed to Pb^{2+} from infancy (although it is highly likely that *in utero* exposure also occurred) were described as expressing “*intellectual difficulties and sensorimotor deficits*”. Behavioral difficulties were common in all children including “*unreliable impulsive behavior*”, “*cruel impulsive behavior*” and “*short attention span*”. It is interesting to quote some of the descriptions given for the Pb^{2+}-intoxicated children: “*It made several of the children friendless and difficult at home and in school. Three were excluded from school based on behavior, one for setting fires in the school, another for repeatedly getting up and dancing on the desks and other furniture and the third for sticking a fork into another's child face*”. Another example provided was about a girl at 11 years of age that upon medical examination was described as “*sullen, withdrawn and insecure*”. A previous examination of the same girl at age of 5 did not find any signs of psychological difficulties. These observations suggest a developmental trajectory for the expression of the psychological symptoms. Based on this limited information it is difficult to classify any of these children as schizophrenics but clearly some of these behaviors can be categorized within the range of “positive” or “negative” symptoms of schizophrenia. Other cardinal features of schizophrenia were also described such as a child having “*enlarged ventricles upon pneumoencephalographic examination at 12 years of age*”.

The more recent human literature at Pb^{2+} exposures levels lower that those during the times of Byers and Lord (1943) confirms and extends the effects of childhood Pb^{2+} intoxication on

behavioral and cognitive outcomes. Epidemilogical studies clearly show that besides the well-documented effects of Pb^{2+} on IQ (Bellinger et al 1991; Needleman et al 1979; Wasserman et al., 2000; Canfield et al 2003), children exposed to Pb^{2+} also perform poorly on tests of working memory, attentional flexibility, and planning and problem solving (Canfield et al., 2004). As these authors point out, the effects of early life Pb^{2+} exposure is not restricted to global indexes of general intellectual functioning, but executive processes may be at particular risk in Pb^{2+} intoxicated children (Canfield et al 2004). School children with elevated blood Pb^{2+} levels are also more likely to display antisocial behavior (Bellinger et al., 1994; Needleman et al., 1996; Roy et al., 2009) and perform poorly in end of grade examination (Miranda et al, 2007). These behavioral and cognitive problems are persistent even after cessation of Pb^{2+} exposure in early life (White et al., 2007). Prenatal and/or childhood Pb^{2+} exposure has also been associated with delinquent behavior at adolescense (Dietrich et al., 2001). They resemble endophenotypes described in schizophrenia in which poor performance on attentional, working memory, and executive functioning and increased incidence of violent behavior are observed (Pearlson, 2000; Ross et al., 2006).

Neuroimaging Studies of Brain Volume and Chemistry

Major advances in neuroimaging technologies such as Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS) and Diffusion Tensor Imaging (DTI) during the last two decades have provided important clinical tools to probe the anatomical and biochemical bases of neurological and mental disease. Studies performed with these techniques in schizophrenia patients have provided valuable information that previously was only possible from post-mortem studies. The emerging evidence is that a common finding in schizophrenia patients is enlargement of the ventricles and decreased cerebral cortex volume especially in frontal and temporal lobes (Woods et al., 1996; Harrison, 1999; Pearlson, 2000; Andreasen et al., 2011; Horga et al., 2011). Reductions in the volume of the hippocampus, basal ganglia, thalamus and amygdala have also been documented (Harrison 1999; Horga et al., 2011). The loss of neurons or neuronal elements such as axons and dendrites has been demonstrated *in vivo* in the brain of schizophrenia patients by the use of MRS in which reductions in the levels of N-acetylaspartate (NAA)/creatine (Cr) ratios have been measured. The loss of the NAA signal has been associated with frank neuronal loss or reductions in brain neuropil in a number of neurodegenerative disorders (Ross et al., 1997; Block et al., 2002; Stork and Renshaw, 2005). At a different level of analysis, post-mortem studies have revealed abnormalities in neuronal architecture in many of these brain regions with alterations in neuronal density and reductions in the size of neurons (Arnold and Trajanowski, 1996; Cannon, 1996). Importantly, it appears that these changes in neuronal mass and size are present in the absence of gliosis suggesting that schizophrenia may not be due to an active neurodegenerative process but rather the result of an earlier developmental insult (Harrison, 1997; 1999; Schnieder and Dwork, 2011).

Relative to schizophrenia, there is a paucity of data on the neuroanatomical and brain chemistry changes in humans resulting from prenatal or perinatal Pb^{2+} exposure despite the fact that a high percentage of children and adults have been and continue to be exposed to this neurotoxicant in the United States and throughout the world. This is largely due to the fact that most human studies on the effects of Pb^{2+} exposure have been epidemiological in nature with little or no use of state-of-the-art neuroimaging techniques to examine brain structure and function. However, in the last decade, there are a growing number of research groups that are begining to utilize neuroimaging techniques in their studies and are providing valuable information on the effects of early life Pb^{2+} exposure and alterations in brain volume and chemistry.

The first literature reports were in small groups of Pb^{2+}-exposed children (Trope et al., 1998; 2001) and one report on adult monozygotic twins with Pb^{2+} poisoning (Weisskopf et al., 2004). A more extensive series of studies in a larger cohort of Pb^{2+}-exposed children has been reported by the Cincinnati group (Cecil et al., 2008; Brubaker et al., 2009; 2010). The two reports by Trope and colleagues in children used MRS to examine regional brain metabolite levels such as N-acetylaspartate (NAA), choline (Cho), myoInositol (mI) and creatine (Cr). In the first report, a 10 years old child with documented blood Pb^{2+} levels of 51 μg/dL at 38 months and 44 μg/dL at 41 months was compared to a 9 year-old cousin. Both children lived in the same household and shared the same socioeconomic background and home environment but one was exposed to Pb^{2+} during stays at his grandmother's house. The Pb^{2+}-exposed child exhibited significant performance deficits in a number of neuropsychological and cognitive tests while his cousin's performance was in the normal range. The MRS results indicated a significantly lower NAA/Cr ratio in grey matter in the frontal cortex of the Pb^{2+}-exposed child relative to his normal cousin. There were no apparent differences in the Cho/Cr ratio, but interestingly there was a significant decrease in the mI/Cr ratio in the Pb^{2+}-exposed child. This latter observation is important because the mI peak consists of 70% mI, but 15% of the peak signal is also contributed by glycine an amino acid that is decreased in schizophrenia patients (Sumiyoshi et al., 2004). The MRI studies did not find any apparent structural abnormalities. In summary, this study indicates the possibility of neuronal loss or dysfunction in the absence of gliosis in the frontal cortex of a 10 year-old Pb^{2+}-exposed child with decline in intellectual functioning.

In a second larger study of Pb^{2+}-exposed children with blood Pb^{2+} levels in the 23-65 μg/dL range, the same group of investigators were able to confirm the Pb^{2+}-induced decrease in NAA/Cr ratio in the grey matter relative to non-exposed controls (Trope et al., 2001). Thus, from these studies it appears that one consequence of early life Pb^{2+} exposure is the possible loss of neurons or neuronal elements such as axons and dendrites in the brain. The decrease in the NAA signal in the brain of Pb^{2+}-exposed children is consistent with what is observed in the brain of schizophrenia subjects (Deicken et al., 1997; Bertolino et al., 1998). Although no apparent structural abnormalities were present in the brain of these Pb^{2+}-exposed children, it may have been too early in the developmental process for measurable changes to occur in brain size and it is possible that at a latter age structural abnormalities may be apparent [See studies below].

Weisskopf and colleagues (2004) have presented a case report in which seventy-one year old monozygotic twins with Pb^{2+} poisoning were examined with MRI and MRS. Both brothers had elevated blood and bone Pb^{2+} concentrations relative to the general population of the same age and one brother had much higher levels than his sibling. Neurocognitive tests indicated that working memory/executive function were below expectations and the brother with the higher Pb^{2+} burden performed dramatically worse in tests of short-term memory indicative of frontal lobe dysfunction. Hippocampal dysfunction was also worse in the brother with higher Pb^{2+} levels. Importantly, the brother with the lower scores in the neurocognitive test battery and with a higher Pb^{2+} burden had a lower NAA/Cr ratio in the hippocampus, frontal cortex and midbrain. This finding is consistent with the previous two studies in children indicating that neuronal loss or dysfunction (based on decreased NAA/Cr ratio) is a consequence of Pb^{2+} exposure. Thus, one known aspect that is similar to schizophrenia is the decrease in NAA/Cr ratio in the hippocampus and cerebral cortex.

The most comprehensive series of studies on the effects of childhood Pb^{2+} exposure in brain chemistry changes in young adults comes from the Cincinnati group headed by Cecil and colleagues. In their first study (Cecil et al., 2008) using a total of 157 participants from the Cincinnati Lead Study ranging in age from 19 to 24 years of age with average blood Pb^{2+} levels of 13.3 μg/dL, they found significant decreases in grey matter volume in brain

structures associated with executive function, mood regulation and decision-making. These included the anterior cingulate cortex, postcentral gyrus, inferior parietal lobe, medial frontal gyrus, and paracentral gyrus. Interestingly, they find that the loss in brain volume was greater in males than females independent of sex-related differences in blood Pb^{2+} concentrations and other demographic factors. This study provides neuroanatomical evidence that childhood Pb^{2+} exposure results in the loss of brain volume in regions affected in schizophrenia patients. It shows decreased brain volume in young adults with previous childhood Pb^{2+} exposure.

In a subsequent study from the same group using the same cohort of Pb^{2+}-exposed subjects, they performed diffusion tensor imaging (DTI) to examine white matter effects (Brubaker et al., 2009). They found significant and persistent effects on white matter microstructure with evidence of axonal injury and myelin damage. Finally, in the most recent study, they find inverse associations between gray matter volume loss and yearly mean blood Pb^{2+} measurements that are most pronounced in the frontal lobes of males than females (Brubacker et al., 2011). These series of studies provide compelling evidence of the widespread impact of childhood Pb^{2+} exposure on brain volume loss in young adults and in particular the frontal cortex and hippocampus.

A series of reports from Schwartz and colleagues have found highly significant effects of previous Pb^{2+} exposure and longitudinal declines in cognitive function and loss of brain volume in aging. These studies made used of two population groups: 1) former organo-lead manufacturing workers, and 2) 50-70 year old Baltimore residents with environmental Pb^{2+} exposure. They find that previous exposure to Pb^{2+} results in longitudinal declines in cognitive function (Schwartz et al., 2000; Shih et al., 2006; Stewart and Schwartz, 2007; Bandeen-Roche et al., 2009) independent of socio-economic status and despite the fact that exposure to Pb^{2+} had stopped. They also show that previous cumulative Pb^{2+} dose was associated with persistent brain lesions, in particular, higher tibia Pb^{2+} levels was negatively associated with smaller total brain volume, frontal and total gray matter volume and parietal white matter volume (Stewart et al., 2006). Together, the MRI/MRS/DTI neuroimaging studies strongly suggest an association of cumulative Pb^{2+} exposure earlier in life and the loss of brain volume in young adults and in aging and these structural changes have been associated with cognitive decline.

Post-mortem studies

There is a lack of information on the effects of Pb^{2+} exposure on the human brain from post-mortem studies. The limited number of human brain samples from children that expressed Pb^{2+} encephalopathy were perform more than 25 years ago and they lacked the use of current advances in neuroanatomical methods such as unbiased stereological counting of cell number and size. Nevertheless, examination of the literature indicates that upon neuropathological examination, a common feature of the Pb^{2+}-exposed brain in children is the presence of small brain infarcts (Winder et al., 1983). A common pathological abnormality present in the brain of patients with schizophrenia, are small infarcts that may be suggestive of vascular impairments (Harrison, 1999). Analysis of the same human brain samples from the Pb^{2+}-exposed children did indicate gliosis, a condition that it does not appear to be an active event in the brain of schizophrenia patients (Harrison, 1999; Schnieder and Dwork, 2011).

Most of the knowledge base on the effects of Pb^{2+} exposure on brain pathology is provided by studies on experimental animals. Based on the Pb^{2+} dose given and time of exposure, studies have found some of the same features expressed in the brain of schizophrenia patients. These include: 1) reduction in brain weight, 2) reduced forebrain weight, 3)

reduced cortical thickness, 4) reduced neuronal size, 5) increased neuronal packing density, 6) decreased synapse per neuron and decreased dendritic spine density (Krigman et al., 1974; Petit and LeBoutillier, 1979; Winder et al., 1983). The hippocampus is a brain structure with documented abnormalities as a result of early life Pb^{2+} exposure. For example, a number of studies have documented the loss of dendritic arborization and reductions in dendritic spines in the hippocampus of Pb^{2+}-exposed rats (Alfano and Petit, 1982; Campbell et al., 1982; Kiraly and Jones, 1982; Petit et al., 1983). Similar changes have also been documented in the brain of schizophrenia patients (Harrison, 1999; Pearlson, 2000).

A more recent observation related to the hippocampus is that Pb^{2+}-exposed rats exhibit reductions in mossy fiber innervation to the CA3 region of the hippocampus (Verina et al., 2007), a finding that has been documented in the brain of schizophrenia subjects (Kolomeets et al., 2005). The mossy fiber pathway is essential for sensory gating and memory and learning.

Behavioral findings in Animal Models of Schizophrenia and Developmental Pb^{2+} Exposure

One of the difficulties in developing animal models of schizophrenia is the complexity of the symptoms. Therefore, animal models of schizophrenia have for the most part attempted to model specific aspects of the disorder and there are many reviews on the topic (Marcotte et al., 2001; Boksa 2004; Lipska 2004; Ayhan et al., 2009; Inta et al., 2010). Schizophrenia patients have deficits in attention and sensory information processing such as prepulse inhibition (PPI). Prepulse inhibition is a model of sensorimotor gating mechanism in the brain that has been used in animals to study basic neuronal mechanisms in schizophrenia research (Weiss and Feldon, 2001; Van den Buuse et al., 2003). Prepulse inhibition of the acoustic response is the normal suppression of a startle response to a strong acoustic stimulus when it is preceded by a weak sound stimulus or prepulse. Alterations in PPI are commonly found in neurodevelopmental models of schizophrenia (Weiss and Feldon, 2001; Van den Buuse et al., 2003) and in rodents that have been exposed to Pb^{2+} during development (Commissaris et al., 2000).

Another common behavioral outcome in animal models of schizophrenia is increased locomotion or “hyperactivity” in response to a low dose of amphetamine (Snyder, 1972, Boksa, 2004) or to a novel environment (Kvajo et al., 2011). The response of increased locomotion to a low dose of amphetamine is used in rodents as a behavioral read out of activity of the dopaminergic system. Importantly, one of the well-documented effects of developmental Pb^{2+} exposure is hyperactivity (Winneke et al., 1977; Petit and Alfano, 1979; Burdette and Goldstein, 1986; Moreira et al., 2001), an effect that is believe to be mediated via a hyperactive mesolimbic dopaminergic system (Zuch et al., 1998).

Alterations in other behaviors that have been measured in animal models believed to be relevant to schizophrenia are deficits in social interaction, working memory, and spatial learning (Boksa 2004; Kvajo et al., 2011). Many of these same behaviors are also affected in developing animals exposed to Pb^{2+} (Brockel and Cory-Slechta, 1998, 1999; Nihei et al., 2000; Moreira et al., 2001). For example, several laboratories including our own have extensively documented the effects of developmental Pb^{2+} exposure on spatial learning (Nihei et al., 2000; Guilarte et al., 2003), a behavioral task that is mediated by the hippocampus.

The “dopaminergic” hypothesis of schizophrenia

The original hypothesis underlying the neurochemical abnormalities in schizophrenia was based on the use of antipsychotics as the first effective treatment (Carlsson and Lindqvist, 1963). Subsequent studies showed that the therapeutic value of antipsychotic drugs was mediated by blocking D2-dopamine receptors (Seeman and Lee, 1975; Creese et al., 1976; Snyder, 1981). Experimental evidence suggests that dysregulation of dopamine function plays an important role in the expression of positive symptoms in schizophrenia (Snyder, 1972, 1981; Lieberman et al 1987). PET studies in schizophrenia subjects and animal models of schizophrenia have provided evidence of hyperactivity of the dopaminergic system, with an apparent selectivity to the mesolimbic and mesocortical pathways (Laurelle et al., 1996; Abi-Dargham et al., 1998; Harrison, 1999; Lindstram et al., 1999; Pearlson, 2000; Thaker and Carpenter, 2001). In a similar fashion, the dopaminergic system is also affected by Pb^{2+} neurotoxicity. Seminal studies by Cory-Slechta and colleagues have shown that exposure to Pb^{2+} in early life results in hyperactivity of the dopaminergic system (Zuch et al., 1998; Pokora et al., 1996; Cory-Slechta et al., 2002; Bauter et al., 2003).

An important study by Cory-Slechta and colleagues (1997) is related to the modulation of dopaminergic drugs on the effects of Pb^{2+} exposure on NMDAR levels. They showed that Pb^{2+} exposure started at weaning resulted in significant increases (short term exposure) and decreases (long-term exposures) on NMDAR levels in the frontal cortex, nucleus accumbens and dorsal striatum. These Pb^{2+}-induced changes in NMDAR levels as measured by [^{3}H]-MK-801 binding could be abrogated by the administration of the D2-dopamine receptor agonist apomorphine, but not by the D1-receptor agonist SKF-82958. These findings clearly implicate interplay between the glutamatergic and dopaminergic systems in the Pb^{2+}-exposed brain similar to what has been found in schizophrenia (Simpsom et al., 2010). However, despite the years of research on the involvement of the dopaminergic system in the pathophysiology of schizophrenia, it has become clear that dysregulation of the dopaminergic system alone does not explain the negative symptoms and cognitive dysfunction in schizophrenia and alterations of the glutamatergic system has emerged as a viable hypothesis.

The “glutamatergic” hypothesis of schizophrenia

The glutamatergic hypothesis of schizophrenia originated from the observations that administration of *N*-methyl-D-aspartate receptor (NMDAR) non-competitive antagonists such as phencyclidine (PCP) or ketamine exacerbates psychotic symptoms in schizophrenia patients and produces schizophrenia symptoms in normal subjects (Javitt and Zukin, 1991; Lahti et al., 1995; Thaker and Carpenter, 2001; Coyle et al., 2003). Compared to dopaminergic agents, NMDAR antagonists induce negative and cognitive symptoms of schizophrenia as well as positive symptoms. Thus, convergent evidence has accumulated to support a primary role of glutamatergic NMDAR hypofunction in schizophrenia (Marek et al., 2010; Javitt, 2010). Consistent with this notion, clinical trials with the NMDAR co-agonists glycine, d-serine and glycine transporter inhibitors that enhance endogenous glycine levels have provided encouraging reports in the treatment of schizophrenia (Javitt et al., 1994; Huresco-Levy et al., 1999; Lin et al., 2011).

The NMDAR is an excitatory amino acid receptor subtype that is known to play an essential role in neuronal development, synaptic plasticity and in learning and memory (Guilarte, 1998). The administration of PCP or other NMDA receptor antagonists to experimental animals, models certain aspects of the disease (Kilts, 2001). Further, genetic manipulation of the NMDAR to down regulate NR1 and NR2A subunit expression (Mohn et al., 1999; Miyamoto et al., 2001) or its selective deletion in the frontal cortex of mice (Belforte et al.,

2010) results in behavioral manifestations consistent with those in schizophrenia providing further support to the important role of NMDAR hypoactivity in the pathophysiology of schizophrenia. In humans, a microsatellite repeat in the promoter of the NR2A subunit gene that represses transcriptional activity correlates with chronic outcomes in schizophrenia (Itokawa et al., 2003) indicating the importance of the NR2A subunit of the NMDAR in schizophrenia.

From an etiological perspective, NMDAR antagonists such as PCP, ketamine and MK-801 are drugs of abuse or anesthetic agents that are used to model schizophrenia symptoms, and humans are unlikely to be exposed at a global scale, although ketamine is still used as a pediatric anesthetic agent. This raises the question, is it possible that a chemical or classes of chemicals that are NMDAR antagonist and are ubiquitous in the global environment can result in widespread human exposures and be a risk factor for schizophrenia? The heavy metal lead (Pb^{2+}) fits all of these characteristics. That is, Pb^{2+} is not only a well-recognized ubiquitous, global environmental and developmental neurotoxicant, but it is also a potent NMDAR antagonist. Since the early 1990s, there is experimental evidence that Pb^{2+} is a potent and selective non-competitive antagonist of the NMDAR (Alkondon et al., 1990; Guilarte and Miceli, 1992) and disrupts neuronal processes that are mediated via NMDAR activation.

A substantial body of evidence has shown that exposure to Pb^{2+} during development, in the same concentration range as implied in the work by Opler et al., (2004; 2008), alters gene and protein expression of NMDAR subunits in the developing and young adult rat hippocampus (Table 1). The hippocampus is part of the limbic system involved in learning and memory and it is a principal brain region affected in schizophrenia (Tsai and Coyle, 2002; Konradi and Heckers, 2003) and in Pb^{2+} neurotoxicity (Krigman et al 1974; Petit and LeBoutillier, 1979; Winder et al 1983; Guilarte and McGlothan, 1998; Nihei et al 2000).

A consistent change in NMDAR subunits expression observed in Pb^{2+}-exposed animals is alterations in the expression of the NR1 and NR2A subunits (See Tables 1 and 2). Guilarte and McGlothan (1998) have shown that developmental Pb^{2+} exposure increases the gene expression of the NR1 subunit but decreases NR2A subunit expression with no change in NR2B subunit in the hippocampus during early postnatal life. A subsequent study showed that Pb^{2+} exposure decreased both NR1 and NR2A subunit gene expression in several hippocampal regions in post adolescent rats (Nihei et al., 2000). Further, NR2B subunit expression was either not changed or slightly increased, but only in the CA3 region of the hippocampus (Nihei et al., 2000). Thus, there are age-dependent changes in the expression of the NR1, NR2A and NR2B subunit genes as a result of developmental Pb^{2+} exposure (Toscano and Guilarte, 2005). These findings resemble some of the changes in NMDAR subunit expression described in the brain of schizophrenia patients (Tsai and Coyle, 2002; Konradi and Heckers, 2003; Meador-Woodruff et al., 2003; Nudmamud-Thanoi and Reynolds, 2004; See Tables 1 and 2) and in the frontal cortex of rodents exposed to a sub-chronic administration of the NMDAR antagonist MK-801 (Xi et al., 2009). In the latter study they show that NMDAR subunit expression is dynamically regulated based on MK-801 dose. Together these studies suggest that based on the dose, timing of dose and chronicity of NMDAR antagonist dosing, NMDAR subunit expression are likely to be up or down regulated differentially.

It should be noted that a number of studies have shown that Pb^{2+} exposure decreases NR2A subunit gene and protein expression (Tables 1 and 2) and this effect results in a greater proportion of NR2B-NMDAR complexes. This is a relevant observation in the Pb^{2+} exposure/schizophrenia hypoglutamatergic hypothesis because NR2A-containing NMDAR complexes are responsible for the maintenance of paravalbumin (PV) and glutamic acid

decarboxylase 67 (GAD67) positive interneurons (Kinney et al., 2006) and there is a selective decrease in these cortical GABAergic interneurons co-expressing the NR2A subunit (Woo et al., 2004) in the brain from schizophrenia patients. Further, Kocsis (2011) has demonstrated that the increase in aberrant gamma oscillations in the cerebral cortex that are associated with schizophrenia related behavioral and prepulse inhibition abnormalities was due to antagonist of NR2A-containing NMDAR complexes but not those containing the NR2B, NR2C, or NR2D subunits.

NR1 subunit splice variants mRNA expression in the brain of schizophrenia subjects showed a decrease in NR1 variants containing the C2 cassette (Clinton et al., 2003; Meador-Woodruff et al., 2003), a finding that is also observed in the brain of Pb^{2+}-exposed rats (Guilarte et al., 2000; Guilarte and McGlothan, 2003). These Pb^{2+}-induced changes in NMDAR subunit expression result in NMDAR complexes with different subunit composition (Toscano et al., 2002), synaptic expression (Guilarte and McGlothan, 2003) and alterations in calcium signaling downstream from the NMDA receptor (Toscano et al., 2002).

Examination of studies using tritiated-ligand binding to the NMDAR indicates similarities between the brain from schizophrenia subjects and brain tissue from Pb^{2+}-exposed rats. For example, using the NR1/NR2B specific ligand [^{3}H]-ifenprodil, there is increase levels of [^{3}H]-ifenprodil binding in the cerebral cortex of both schizophrenia subjects and adult rats exposed to Pb^{2+} during development (See Table 2). Similarly, there is increased [^{3}H]-MK-801 binding in the cerebral cortex of both schizophrenia subjects and adult rats exposed to Pb^{2+} during development (Table 2). These findings suggest that at least in the cerebral cortex binding studies provide evidence of an increase in the expression of NR1/NR2B-NMDAR receptors suggesting that out of the total pool of NMDAR, there is a greater proportion of receptors that express the NR2B subunit and a lower proportion of those containing the NR2A subunit.

Recent studies have also implicated NMDAR-dependent dysregulation of BDNF signaling and protein levels in the detrimental effects of Pb^{2+} on synaptic function (Neal et al., 2010; Neal and Guilarte, 2010). BDNF is a neurotrophin that is altered in the brain of schizophrenia patients (Weickert et al., 2003; Rizos et al., 2011; Buckley, 2011). A recent study has shown that BDNF exon IV mutant mice exhibit significant deficits in PV-positive GABAergic interneurons in the prefrontal cortex, an interneuron subtype that has been implicated in working memory/executive function impairment in schizophrenia (Sakata et al., 2009). These mice express impaired inhibitory transmission and abnormal appearance of spike-timing-dependent synaptic potentiation (Sakata et al., 2009). BDNF exon IV transcripts are decreased in the cerebral cortex of patients with schizophrenia with no history of anti-depressant treatment (Wong et al., 2010). This is particularly relevant to our work with Pb^{2+} exposure because we have recently shown a specific decrease of BDNF exon IV transcripts in neuronal cultures during synapse formation (Stansfield et al., 2011).

Consistent with the alterations in NMDAR function, several laboratories including our own have shown that developmental Pb^{2+} exposure produces deficits in NMDAR-dependent long-term potentiation in the hippocampus and impairments in spatial learning in young adult rats (Nihei et al., 2000; Nihei and Guilarte, 2001). Long-term potentiation is thought to represent a cellular correlate of learning and memory in the mammalian brain that is NMDAR dependent. Thus, young adult rats exposed to environmentally relevant levels of Pb^{2+} during development express some of the same neurobiological and behavioral deficits seen in animal models of schizophrenia (Tsai and Coyle, 2002; Konradi and Heckers, 2003). The common mechanism that links both conditions is dysregulation of the glutamatergic system and specifically hypoactivity of the NMDAR complex.

The glycine site of the NMDAR complex: a common molecular target?

Research in the molecular mechanisms associated with developmental Pb^{2+} exposure and schizophrenia have been performed independently, however, there is compelling evidence for a common molecular target, the glycine modulatory site of the NMDAR. The NMDAR is activated by the co-agonists glutamate and glycine in coincidence with depolarization of the neuronal membrane. This results in the removal of the magnesium block at the NMDAR channel and allows calcium entry into the cell. A proposed mechanism by which Pb^{2+} inhibits NMDAR function is by binding to a divalent cation site associated with the glycine site (Hashemzadeh-Gargari and Guilarte, 1999). The "antagonistic" effect of Pb^{2+} at the glycine site of the NMDA receptor is most effective at sub-saturating concentrations of glycine (Hashemzadeh-Gargari and Guilarte, 1999). This molecular interaction of Pb^{2+} at the glycine site is physiologically relevant since the glycine site of the NMDAR is not saturated under physiological conditions (Berger et al., 1998). Similar to the inhibitory effect of Pb^{2+} at the glycine site of the NMDA receptor, "negative" modulation of the glycine regulatory site of the NMDAR by putative endogenous antagonists has been proposed as a principal feature in the pathophysiology of schizophrenia (Coyle et al., 2003; Coyle and Tsai, 2003; 2004).

The significance of the antagonistic action of Pb^{2+} at the glycine site of the NMDAR to schizophrenia is that a potentially effective therapy that helps to ameliorate the negative symptoms and cognitive disability in schizophrenics is the activation of this site (Coyle and Tsai, 2003). The use of NMDAR glycine site agonists such as glycine, D-serine or D-cycloserine in clinical trials has demonstrated some degree of efficacy in ameliorating the negative symptoms and cognitive disabilities in schizophrenia subjects (Tsai and Coyle, 2002; Coyle and Tsai, 2004). Consistent with an important role of the glycine site of the NMDAR with the pathophysiology of schizophrenia, a recent animal model expressing an NMDAR complex with reduced glycine affinity produces some of the negative and cognitive symptoms of schizophrenia (Labrie et al., 2008). This and other evidence support the hypothesis that NMDAR hypofunction in schizophrenia is part of a complex pathophysiological network of neuronal systems that are affected in schizophrenia. For example, several schizophrenia risk genes such as DISC1, neuregulin and dysbindin interact with NMDAR to affect synaptic transmission, neuronal maturation and plasticity (Hayashi-Takagi et al., 2010; Geddes et al., 2011; Ramsey et al., 2011).

Another potential effect of Pb^{2+} exposure on the glycine regulatory site of the NMDAR is by modulating D-serine levels released from glial cells. Recent studies have shown that D-serine is synthesized in astrocytes and it is released to control NMDAR activity by being a co-agonist at the glycine site (Panatier et al., 2006; Oliet and Mothet, 2009). Since Pb^{2+} is actively taken up by astrocytes (Tiffany-Castiglion and Qian, 2001), it could potentially alter D-serine synthesis and release. Consistent with this hypothesis, Sun et al (2007) have shown that the addition of D-serine to hippocampal slices was able to reverse the Pb^{2+}-induced impairment in CA1 long-term potentiation produced by *in vivo* Pb^{2+} exposure.

Testable hypothesis

Does exposure to Pb^{2+} alter D-serine synthetic and metabolic enzymes in astrocytes and/or D-serine release to modulate NMDAR activity. If dysregulation of D-serine metabolism or release are operational in Pb^{2+} exposed animals, then D-serine regulation of NMDAR complexes can be altered implicating another pathway for dysregulation of NMDAR activity by Pb^{2+}.

NMDAR Antagonist-Induced Apoptosis in Early Life: A plausible mechanism for the loss of Brain Volume in Schizophrenia

It has been noted that schizophrenia is a neurodevelopmental disorder in which an early life event results in the loss of neurons without apparent glial cell activation suggestive of apoptotic cell death (Benes, 2004; Jarskog et al., 2004; 2005). It is possible that an early life event that causes apoptotic cell death could potentially explain the reductions in brain volume in schizophrenia in the absence of gliosis. Neuropathological examination of the brain from schizophrenia subjects has shown a relative lack of widespread neuron loss (Jarskog et al., 2004; 2005). However, other studies have shown selective reductions of neurons in discrete cortical layers and in other brain regions (Jarskog et al., 2004; 2005). Studies in rodents have shown that in the neonatal brain during a very specific window of vulnerability, the administration of NMDAR antagonists such as phencyclidine (PCP), ketamine, and MK-801 triggers apoptosis in multiple brain regions (Ikonomidou et al., 1999; Anastasio et al., 2009; Soriano et al., 2010) causing long-term behavioral deficits (Fredriksson and Archer, 2004; Yuede et al, 2010). Some of these same drugs have also been shown to produce similar apoptotic cell death in the developing primate brain (Slikker et al., 2007; Zou et al., 2009) and long-lasting cognitive deficits (Paule et al., 2011). Thus, they are likely to be relevant to the human condition. These drugs are the same types of NMDAR antagonists (PCP, ketamine, MK-801) that have been used to mimic schizophrenia symptoms in normal subjects and exacerbate symptoms in schizophrenia subjects that led to the glutamatergic hypothesis of schizophrenia. Now, a report by Dribben and colleagues (2011) shows that exposure of the neonatal mouse brain to Pb^{2+} during this same period of vulnerability reproduces the same pattern of apoptotic cell death as the other NMDAR antagonists noted above. This is an important finding because: 1) it provides additional support that *in vivo*, Pb^{2+} behaves as a potent NMDAR antagonist, and 2) it shows that Pb^{2+} exposure in early life enhances apoptotic cell death and this effect may help explain the loss in brain volume documented in Pb^{2+}-exposed children later in life (Cecil et al., 2008). The brain regions affected by NMDAR antagonist (including Pb^{2+})-induced apoptosis in early life are some of the same brain regions in which neuronal cell loss has been documented in selected cortical layers in the schizophrenia brain (Jarskog et al., 2004). This includes layer II of the frontal cortex and layers II and IV of the cingulate cortex as well as striatum and hippocampal pyramidal cell layer (Ikonomidou et al., 1999; Jarskog et al., 2004; Dribben et al 2011). Consistent with the possibility of apoptotic cell death being an important part of the pathology of schizophrenia and as a result of early life Pb^{2+} exposure, the ratio of the pro-apoptotic Bax to the anti-apoptotic Bcl-2 protein has been shown to be increased in the brain of schizophrenia subjects (Jarskog et al., 2004; 2005), a phenomenon that has also been described in the Pb^{2+}-exposed brain (Sharifi et al, 2002; 2010) and in PC12 cells exposed to Pb^{2+} (Xu et al., 2006). Other studies have shown that the ratio of Bax to Bcl-X_L (a member of the anti-apoptotic Bcl-2 gene family) is increased in the neonatal rat cortex following NMDAR antagonist administration (Wang et al., 2001). These observations have important implications for the glutamatergic hypothesis of schizophrenia and suggest that enhancement of NMDAR antagonist-induced apoptotic cell death greater than it occurs naturally during brain development may be operational in schizophrenia. It could potentially explain the brain volume loss documented in schizophrenia and as a result of early life Pb^{2+} exposure. Alternatively, apoptosis has also been noted to occur in synaptic terminals in the absence of effects at the level of the soma (Mattson et al., 1998; Gliman and Mattson, 2002; Glantz et al., 2006). Such an event occurring in early life could result in the loss of brain neuropil and contribute to the loss of brain volume observed in schizophrenia and as a result of early life Pb^{2+} exposure.

Testable Hypothesis

An intriguing question is the possibility that mutations in schizophrenia susceptibility genes may impart an increased sensitivity of the neonatal brain to NMDAR-antagonist induced cellular or synaptic apoptosis. This is a testable hypothesis that could provide novel information about gene-environment interactions in the pathophysiology of schizophrenia.

The GABAergic hypothesis of Schizophrenia

Experimental and pathological evidence indicates that besides dysregulation of the dopaminergic and glutamatergic neuronal systems, other neurotransmitter systems are also affected in schizophrenia. Most prominently amongst these is the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Postmortem brain samples from schizophrenia patients suggest that dysfunction of cortical GABAergic interneurons, in particular those containing the calcium-binding protein parvalbumin (PV), may be a core feature of the working memory deficits in schizophrenia (Lewis et al., 2005; Uhlhaas and Singer, 2010). This is supported by evidence from rodent and non-human primate studies that administration of NMDAR antagonists decreases GAD67 and PV expression in cortical GABAergic interneurons (Cochran et al., 2003; Behrens et al., 2007; Morrow et al., 2007). More specifically the activity of NR2A subunit-containing NMDAR have been shown to have an important role in the maintenance of PV and GAD67 protein levels in cultured interneurons (Kinney et al., 2006). This is consistent with the selective loss of cortical GABAergic PV+ interneurons coexpressing the NR2A subunit in the schizophrenia brain (Woo et al., 2004). The GABAergic-PV+ interneurons in the cerebral cortex are also important for oscillation synchronization of pyramidal cells (Sohal et al., 2009).

Studies by Belforte and colleagues (2010) demonstrate that early postnatal ablation of the NR1 subunit of the NMDAR in corticolimbic interneurons produces the emergence of an schizophrenia phenotype and reductions in GAD67 and PV levels that was specific for cortical interneurons with deletion of the NR1 subunit. On the other hand, deletion of the NR1 subunit in corticolimbic neurons in postadolescence did not produce such abnormalities providing strong evidence for a neurodevelopmental basis of schizophrenia. These studies link GABAergic effects of NMDAR antagonists to pathological changes observed in schizophrenia.

Relevant to the potential schizophrenia-early life Pb^{2+} exposure hypothesis, our laboratory has previously shown that Pb^{2+} decreases NR2A-containing NMDAR (Tables 1 and 2). This suggests that PV and GAD67 levels should be affected in the brain of Pb^{2+}-exposed animals since NR2A-containing NMDAR complex seems to regulate PV and GAD67 expression levels.

While an understanding of the effect of Pb^{2+} on GABAergic interneurons is much more limited, there is evidence that Pb^{2+} exposure decreases GAD protein levels and GABA release from rat brain (Lasley et al., 1999; Struzynska and Sulkowski, 2004). Electrophysiological studies by Albuquerque and colleagues have documented an inhibitory effect of Pb^{2+} on GABAergic neurotransmission in the hippocampus (Braga et al., 1999). This group of investigators also showed that Pb^{2+} increases spontaneous release of GABA from hippocampal neurons (Braga et al., 1999a). Decreased levels of brain GABA have been documented in Pb^{2+} intoxicated animals (Winder and Kitchen, 1984).

Testable hypothesis

If developmental Pb^{2+} exposure is an environmental risk factor for schizophrenia, then it should be able to reproduce the dysfunction of cortical GABergic interneurons expressing GAD67 and parvalbumin. This is a testable hypothesis that can be assessed by examining

the developmental trajectory of parvalbumin and GAD67 expression in cortical GABAergic neurons in Pb^{2+} exposed animals.

Other neurotransmitter systems: Nicotinic Cholinergic Receptors

Emerging evidence suggests involvement of nicotinic cholinergic receptors in schizophrenia. Homomeric nicotinic cholinergic receptors composed of the α7 subunit and those with a α4β2 composition are the most abundantly expressed in the brain and play an important role in memory processes (Ripoll et al., 2004; Timofeeva and Levin, 2011). Recent studies have implicated a linkage between sensory gating defect and a locus of chromosome 15q14. This locus contains the gene encoding a α7 nicotinic cholinergic receptor subunit that is involved in sensory gating (Thaker and Carpenter, 2001). Studies have documented decreased levels of α7 nicotinic cholinergic receptors in thalamus, hippocampus and cerebral cortex in schizophrenic patients (Ripoll et al., 2004). Further, alterations in α4β2 nicotinic receptors have also been measured. In this instance, decreased levels have been documented in the hippocampus and striatum with increased levels in frontal and cingulate cortex (Ripoll et al., 2004). Therefore, it appears that alterations in nicotinic cholinergic receptors may play an important role in the pathophysiology of schizophrenia.

Studies have also shown that Pb^{2+} is a potent inhibitor of nicotinic cholinergic receptors in dissociated neurons from rat hippocampus (Ishihara et al., 1995). The inhibitory action of Pb^{2+} was dependent upon the subunit composition with α7 nicotinic receptors being the most sensitive (Ishihara et al 1995; Mike et al., 2000). Further, a study by Jett et al (2002) has shown that exposure to Pb^{2+} during brain development increases the levels of nicotinic cholinergic receptors that are labeled by [^{3}H]-epibatidine. [^{3}H]-epibatidine labels α4β2 nicotinic cholinergic receptors with some degree of overlap with other non-α7 receptors. In this study, α7 receptors were not measured, however, the increased levels of receptors labeled by [^{3}H]-epibatidine in the cerebral cortex and thalamus of Pb^{2+}-exposed rats suggests increased levels of α4β2 nicotinic cholinergic receptors in these brain structures. This is similar to the increased levels of α4β2 nicotinic cholinergic receptors in the cerebral cortex measured in schizophrenic patients (Ripoll et al., 2004).

Thus, consistent with the involvement of multiple neuronal systems in the pathophysiology of schizophrenia, Pb^{2+} exposure in early life also alters some of the same neuronal systems.

Disrupted in Schizophrenia 1 (DISC1) and early life Pb^{2+} exposure: A proof of concept gene-environment interaction study

There is evidence that understanding schizophrenia is likely to come from gene-environment interaction studies (Moffitt et al., 2005; Van Os et al., 2008; Brandon and Sawa, 2011). Schizophrenia is likely to be the result of complex interactions between many genes and multiple environmental factors that on their own they may make a small contribution but together contribute to an increased risk of schizophrenia. The main obstacle for mechanistic studies of gene-environment interplay has been the paucity of appropriate models to pinpoint the molecular mechanisms that mediate gene-environment interactions relevant to schizophrenia. Recent advances in psychiatric genetics and a plethora of experimental data from animal studies led us (TRG and MP) to suggest a new approach to gene-environment interactions in schizophrenia. We propose that *in vivo* and *in vitro* models based on genetic mutations with functional effects and measurable relevant environment factors will significantly advance studies of the molecular underpinnings of gene-environment interplay (Ayhan et al., 2009; Abazyan et al., 2010). Thus, we have initiated studies examining a

potential interaction of early life Pb^{2+} exposure and mutant Disrupted in Schizophrenia 1 (DISC1).

Mutant DISC1 is the hypothetical protein product of a balanced chromosomal translocation [t(1;11)] in a Scottish pedigree with high load of major mental disorders (LOD=7.1 for all mental disorders and 3.6 for schizophrenia) [Millar et al., 2000a; Millar et al., 2001; Brandon and Sawa, 2011]. The breakpoint is in the middle of the open reading frame for the *DISC1* gene, leading to truncation of the gene. Although expression of truncated proteins is theoretically possible, expression of truncated protein has not been demonstrated [Millar et al., 2000b]. The existence of a clear, identifiable mutation with the high LOD scores has put DISC1 in a unique position in schizophrenia research. In addition to the familial mutation of DISC1, multiple studies of associations of different DISC1 haplotypes or SNPs with mental disorders have stimulated studying the biology of DISC1 (Porteous et al., 2006; Ross et al., 2006; Mackie et al., 2007). Numerous investigations have implicated DISC1 and interacting proteins in neuronal differentiation, migration, synaptogenesis and adult neurogenesis in the hippocampus [Kamiya et al., 2005; Duan et al., 2007; Brandon, 2007; Faulkner et al., 2008; Brandon et al., 2009]. Recently generated DISC1 mouse models have advanced our understanding of the putative mechanisms whereby this protein and its interacting partners may be involved in abnormal neurodevelopment relevant to schizophrenia (Derosse et al., 2006; Koike et al., 2006; Li et al., 2007; Clapcote et al., 2007; Kvajo et al., 2008; Pletnikov et al., 2008; Shen et al., 2008; Brandon and Sawa, 2011).

We have generated a mouse model of inducible expression of mutant human DISC1 in forebrain neurons using the Tet-off system [Pletnikov et al., 2008]. In this model, expression of mutant DISC1 is regulated by the CAMK-II promoter and can be turned off by adding tetracycline or a related compound, doxycycline, to food or water. Similar to other DISC1 mouse models, expression of mutant DISC1 produced no gross developmental defects but significantly increased spontaneous locomotor activity in male but not female mice, decreased social interaction in male mice, enhanced their aggressive behavior and was associated with poorer spatial memory in Morris water maze task in female mice. The behavioral alterations have been accompanied by the enlargement of lateral ventricles in adult mice, reduced dendritic arborization in primary cortical neurons and decreased expression of a synaptic protein, SNAP-25, consistent with human post mortem studies that show decreased dendritic length and dendritic arborization in frontal cortical areas. The findings also suggest that binding of mutant human DISC1 to endogenous mouse DISC1 decreases expression of endogenous DISC1 and may disrupt its interactions with several partners (Pletnikov et al., 2008; Ayhan et al., 2011). These molecular disturbances might contribute to the observed neurobehavioral abnormalities.

An interesting feature of the model is that expression of mutant DISC1 is associated with relatively mild neurobehavioral abnormalities, consistent with the hypothesis that a genetic risk factor or a mutation is likely to interact with other genes and/or environmental factor(s) for a full-blown disease to develop (Moffitt et al., 2005; Van Os et al., 2008; Brandon and Sawa, 2011). In the context of the current review, another important aspect of the DISC1 model is that recent studies have shown that DISC1 interacts with several proteins of the NMDAR complex (e.g., PDS-95; Kalirin-7), indicating an intriguing converging target for molecular interactions between developmental Pb^{2+} exposure and mutant DISC1 (Hayashi-Takagi et al., 2010; Namba et al., 2011; Ramsey et al., 2011).

Thus, we have been using a DISC1 model to evaluate the effects of early life Pb^{2+} exposure on the neurobehavioral phenotype in mutant DISC1 mice. As our system is a double-transgenic (Tg) mouse model, we breed single mutant DISC1 mice and single transgenic tTA mice to produce double Tg animals that either express mutant DISC1 (mutants) or

single Tg control mice that have the transgene in their genome but do not express mutant protein (controls). In order to mimic developmental exposure of humans to environmental Pb^{2+}, we mated single tTA Tg female and single Tg mutant DISC1 male mice while they were given either control food or food containing low levels of Pb^{2+} (750 ppm lead acetate in the diet). Subsequently, pregnant dam and their male and female offspring were maintained on the same types of food throughout their life and while being tested in a series of behavioral tests relevant to aspects of a schizophrenia phenotype. We hypothesized that mutant DISC1 and developmental Pb^{2+} exposure will synergistically interact to produce an exaggerated or new phenotypic outcome in Tg mice.

Behavioral phenotyping included open field test to assess locomotor activity, elevated plus maze test to assess anxiety (Graeff et al., 1990; File, 1990), Y maze test to examine spatial working and recognition memory (Melnikova et al., 2006), pre-pulse inhibition (PPI) of the acoustic startle to evaluate sensorimotor gating (Swerdlow and Geyer, 1998), context- and cue-dependent fear conditioning to evaluate long-term hippocampus-dependent and independent learning and memory (Gerlai, 2001; Maren, 2008) as well as the NMDAR antagonist, MK-801 (0.3; mg/kg, ip),-induced locomotion to assess exacerbated responses to psychostimulants (Carlsson and Carlsson, 1990; Deutsch et al., 1997; Amann et al., 2010).

Although Pb^{2+} exposure produced increased anxiety in the elevated plus maze in control and mutant mice, significantly increased locomotor activity was found in Pb^{2+}-exposed mutant mice only, with female mutant mice being affected more than male mice. A similar gender-related synergistic effect of Pb^{2+} and mutant DISC1 was observed in the forced swim test, mimicking aspects of affective and negative symptoms in schizophrenia. We also observed synergistic effects on impairment in pre-pulse inhibition of the acoustic startle and elevated locomotor response to MK-801, consistent with impaired sensorimotor gating and exacerbated responses to psychostimulants in schizophrenia patients. No synergistic effects were found on spontaneous alternation or spatial recognition tests. Our preliminary data suggest that developmental Pb^{2+} exposure and mutant DISC1 may synergistically interact in producing schizophrenia-like behavioral alterations in mice. Our on-going experiments are assessing the effect of interactions on cognitive and social behaviors, brain and lateral ventricle volume as well as regional brain expression of presynaptic markers and NMDAR expression.

Summary

Despite the fact that research efforts in schizophrenia and on the effects of developmental Pb^{2+} exposure on the brain have occurred independently, there is a remarkable number of similarities in outcomes between this neuropsychiatric disorder and exposure to Pb^{2+} in early life. The similarities at the behavioral, anatomical, biochemical and neuropathological level provides initial evidence that a neurobiological interaction may be plausible between a ubiquitous and pervasive global environmental pollutant and developmental neurotoxicant such as Pb^{2+} and the expression of schizophrenia later in life. Clearly, most of these putative neurobiological connections need further exploration and confirmation in animal models and in human studies. However, it is possible that individuals expressing mutations in certain genes (genetic component) may be more susceptible to the dysregulation of developmental processes produced by Pb^{2+} exposure (environmental trigger) alone or in combination with other environmental factors during a critical period of fetal or neonatal life. It is interesting to note that two environmental risk factors associated with schizophrenia may also be associated with an increased likelihood of being exposed to Pb^{2+} in the environment. These two factors are season of birth and living in an urban environment. It is widely recognized that there is a greater likelihood of a pregnant mother or a child being exposed to Pb^{2+} in urban environments. This is due to the high number of old housing units containing Pb^{2+}-

based paint as a continuing source of Pb^{2+} exposure in the United States and in many parts of the world (Jacobs et al., 2002). Second, environmental levels of Pb^{2+} in homes and in children's blood are highest during the summer months (July-August) (Yin, 2000). The latter observation makes another potentially important temporal connection between Pb^{2+} exposure and schizophrenia. The incidence of individuals with schizophrenia increases if born during the winter months (Torrey et al., 1997). For a child that is born during the winter months, the summer months in which increased exposure of the mother to Pb^{2+} is highly likely to occur in urban environments, places the exposure to the fetus during the early part of the second trimester of fetal life. This is the same gestational time point as the Pb^{2+} analysis in serum samples measured in the study by Opler et al., (2004; 2008) in which an association was noted with schizophrenia later in life, and the trimester in which the "insult" based on the neurodevelopmental hypothesis of schizophrenia is likely to occur (Roberts, 1991; Bloom, 1993).

Finally, while this review has concentrated on Pb^{2+} as a prototypical environmental toxicant and NMDAR antagonist that may be associated with schizophrenia, humans may be exposed to other heavy metals or environmental toxins that target the same neurobiological systems. For example, while Pb^{2+} is a potent NMDAR antagonist, another heavy metal manganese, with relevant exposures in children is also an NMDAR antagonist, albeit a weaker one (Guilarte and Chen, 2007). Nevertheless, several studies have recently shown that children exposed to manganese in drinking water express neuropsychological and cognitive abnormalities (Wasserman et al., 2006) and paranoid psychosis has been reported in humans occupationally exposed to high levels of manganese (Donaldson, 1987; Verhoeven et al., 2011).

Another class of environmental pollutant that has been shown to modulate NMDAR function and subunit expression is the polycyclic aromatic hydrocarbons (PAHs). Seminal studies by Hood and colleagues have shown that *in utero* exposure to Benzo(a)pyrene, a member of the PAH family results in downregulation of the NR1 subunit of the NMDAR and a subsequent impairment in hippocampal LTP (Wormley et al., 2004; Brown et al., 2007; McCallister et al., 2008). Therefore, there is significant evidence that a number of environmental anthropogenic pollutants are able to alter NMDAR function, a neuronal system whose hypofunction has been strongly implicated in the pathophysiology of schizophrenia.

While it is clear that genetics predispose humans to psychiatric disorders like schizophrenia, it is also highly likely that specific environmental chemicals or classes of chemicals may work in conjunction with genetic changes to facilitate full disease expression.

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Table 1

NMDAR subunit gene and protein expression in the brain of schizophrenia patients or in the brain of rats exposed to lead during development. DG= dentate gyrus; CA= cornus ammonis; Hipp= Hippocampus; s.v= splice variants; PN= postnatal day.

Schizophrenia			**Developmental Pb^{2+} Exposure**			
NMDAR Subunit Effect	**Brain Region**	**Reference**	**NMDAR Subunit Effect**	**Age**	**Brain Region**	**Reference**
↓ NR1	DG, Hipp	Gao et al., 2000	↓ NR1	PN50	CA, DG	Nihei et al., 2000
↑ NR2B	CA2-CA3, Hipp		↓ NR2A	PN50	DG	
			↑ NR2B	PN50	CA3	
↑ NR2B	Thalamus	Clinton et al., 2006	↓ NR1-4 s.v.	PN50	DG	
↓ NR1			↓ NR1	PN50	CA, DG	Guilarte & McGlothan, 2003
	superior temporal cortex – cognitive impairment with no cognitive impairment	Humphries et al., 1996	↓ NR1-2 s.v.	PN50	CA, DG	
– NR1			↓ NR1-4 s.v.	PN50	CA, DG	
			↓ NR1-b s.v.	PN50	CA, DG	
↓ NR1	dentate gyrus	Law & Deakin, 2001	↓ NR1	PN50	CA, DG	Guilarte et al., 2003
↓ NR1	Superior frontal cortex	Sokolov, 1998	↑ NR1	PN14	CA1	Guilarte & McGlothan, 1998
			↓ NR2A	PN14 & 21	CA1, DG	
			– NR2B	PN14 & 21	--	
↓ NR2A	anterior cingulate cortex	Woo et al., 2004				
↑ NR1	superior temporal gyrus	Le Corre et al., 2000	↓ NR2A (protein)	PN14, 21, 28	Hipp	Nihei & Guilarte, 1999
↑ NR1	dorsolateral prefrontal cortex/occipital cortex	Drachera et al., 2001	↑ NR1	PN15, 20	CA, DG	Zhang et al., 2002
			↓ NR2A	PN15, 20	CA, DG	
			↑ NR2D	PN20	CA, DG	
↓ NR1-4 s.v.	Hipp	Vrajova et al., 2010 (PCR)	– NR2B	PN20	CA, DG	
↓ NR1-2 s.v.						
↑ NR2D	prefrontal cortex	Akbarian et al., 1996	↑ NR1-a s.v.	PN14	CA	Guilarte et al., 2000
			↑ NR1-a s.v.	PN14, 21	DG	
			↑ NR1-b s.v.	PN21	CA	
			↑ NR1-2 s.v.	PN21	CA4, DG	
			↓ NR1-4 s.v.	PN14	CA3	
			↓ NR1-4 s.v.	PN21	CA3	

Table 2

Quantitative receptor autoradiography or radioligand receptor binding studies of NMDAR levels in the brain of schizophrenia patients or in the brain of rats exposed to lead during development. DG= dentate gyrus; CA= cornus ammonis; Hipp= Hippocampus; PN= postnatal day; EC= entorhinal cortex. (*) lead exposure started post-weaning.

Schizophrenia			**Developmental Pb^{2+} Exposure**			
Radioligand	**Brain Region**	**Reference**	**Radioligand**	**Age**	**Brain Region**	**Reference**
↑ ^{3}H-ifenprodil (NR1/NR2B)	Superior temporal cortex	Grinwood et al., 1999	↓ ^{3}H-MK801 No change if Pb started as adult	PN14	forebrain	Guilarte & Miceli, 1992
↑ ^{3}H-MK801/^{3}H-TCP	cerebral cortex	Komhuber et al., 1989	↑ ^{3}H-MK801	PN70-120	cerebral cortex	Guilarte et al., 1993
↑ ^{3}H-MK801/^{3}H-TCP	orbital frontal cortex	Simpson et al., 1992	↑ ^{3}H-MK801	PN56-112	occipital cortex entorhinal cortex temporal cortex	Ma et al., 1997
↓ ^{3}H-TCP	CA3-Hipp	Dean et al., 1999				
↓ ^{3}H-MK801	Hipp	Beneyto et al., 2007	↑ ^{3}H-Ifenprodil (NR1/NR2B)	PN50	cerebral cortex	Toscano et al., 2002
			↑ ^{3}H-CGP39653	adults	frontal cortex	Cory-Slechta et al., 1997[a]
			↑ ^{3}H-TCP	PN25	CA3-Hipp	Brooks et al., 1993
			↑ ^{3}H-MK801	PN56-112	DG CA1, CA2-Hipp	Ma et al., 1997
			↑ ^{3}H-MK801	PN14	Hipp, EC	Jett & Guilarte, 1995
			↑ ^{3}H-ifenprodil	PN50	Hipp	Toscano et al., 2002
			↓ ^{3}H-MK801	adults	DG, CA1-Hipp	Cory-Slechta et al., 1997[a]

[a] Pb exposure started post-weaning (PN21)