Chronic Exposure of Mutant DISC1 Mice to Lead Produces Sex-Dependent Abnormalities Consistent With Schizophrenia and Related Mental Disorders: A Gene-Environment Interaction Study

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The glutamatergic hypothesis of schizophrenia suggests that hypoactivity of the N-methyl-d-aspartate receptor (NMDAR) is an important factor in the pathophysiology of schizophrenia and related mental disorders. The environmental neurotoxicant, lead (Pb²⁺), is a potent and selective antagonist of the NMDAR. Recent human studies have suggested an association between prenatal Pb²⁺ exposure and the increased likelihood of schizophrenia later in life, possibly via interacting with genetic risk factors. In order to test this hypothesis, we examined the neurobehavioral consequences of interaction between Pb²⁺ exposure and mutant disrupted in schizophrenia 1 (mDISC1), a risk factor for major psychiatric disorders. Mutant DISC1 and control mice born by the same dams were raised and maintained on a regular diet or a diet containing moderate levels of Pb²⁺. Chronic, lifelong exposure of mDISC1 mice to Pb²⁺ was not associated with gross developmental abnormalities but produced sex-dependent hyperactivity, exaggerated responses to the NMDAR antagonist, MK-801, mildly impaired prepulse inhibition of the acoustic startle, and enlarged lateral ventricles. Together, these findings support the hypothesis that environmental toxins could contribute to the pathogenesis of mental disease in susceptible individuals.

Key words: schizophrenia/Pb²⁺ exposure/DISC1/ gene-environment interaction/NMDA receptor/MRI

Introduction

Gene-environment interactions (GEI) are believed to contribute to schizophrenia and other major mental illnesses. However, mechanistic studies of GEI have been impeded by paucity of animal models. We have proposed that in vivo and in vitro preparations based on functional genetic mutations and etiologically relevant environmental factors can facilitate elucidating the molecular mechanisms of GEI. We developed a transgenic model of inducible expression of dominant-negative mutant human disrupted in schizophrenia 1 (mDISC1), a strong genetic risk factor for schizophrenia, depression, and bipolar disorder. Transgenic mDISC1 mice exhibit mild neurobehavioral abnormalities, suggesting that exposure of these mice to environmental adversities could synergistically exacerbate the preexisting pathology or even produce new phenotypic changes.

Epidemiological studies have suggested that an urban environment may elevate the risk of schizophrenia and this may be due to environmental toxins. Indeed, recent reports have demonstrated a potential association between prenatal Pb²⁺ exposure and the increased likelihood of schizophrenia later in life. Notably, the association of Pb²⁺ exposure and schizophrenia is supported by the neurochemical properties of Pb²⁺ as a potent antagonist of the N-methyl-d-aspartate receptor (NMDAR) possibly by negatively modulating the glycine site. If Pb²⁺ contributes to mental disease, it is likely that it occurs in vulnerable individuals. Therefore, we sought to test this hypothesis by evaluating neurobehavioral consequences of chronic Pb²⁺ exposure in mutant DISC1 mice. Relevant to this interaction, there are data to show that DISC1 binds to proteins of the NMDAR complex and to serine racemase to regulate d-serine production by...
astrocytes.\textsuperscript{14,15} Thus, the NMDAR could be a convergent target for Pb\textsuperscript{2+} and DISC1.

Our findings demonstrate that chronic exposure of mDISC1 mice to Pb\textsuperscript{2+} was not associated with gross developmental abnormalities but produced sex-dependent hyperactivity, exaggerated responses to the NMDAR antagonist, MK-801, mildly impaired prepulse inhibition (PPI) of the acoustic startle, and enlarged lateral ventricles—

the phenotypes that are relevant to schizophrenia and related disorders. These results support the hypothesis that environmental toxins could contribute to psychiatric disease via interactions with genetic risk factors.

Material and Methods

\textit{Animals Breeding}

The detailed breeding protocol is described in online supplementary materials. Briefly, homozygous female mDISC1 mice were mated with hemizygous male CAMKII-tTA mice. This breeding produces a litter that contains \textasciitilde50\% of double transgenic mice that express mDISC1 (mutant mice) and \textasciitilde50\% of single transgenic DISC1 mice that have mDISC1 transgene but do not express mDISC1 (control mice).

\textit{Pb\textsuperscript{2+} Exposure Paradigm}

Beginning from the conception and until sacrifice (life-long exposure), prospective parents, pregnant mice, nursing mothers, and weaned offspring were maintained on either a regular diet or a diet containing moderate levels of Pb\textsuperscript{2+} as previously described.\textsuperscript{16} The same number of litters \((n = 8)\) was exposed to the regular or Pb\textsuperscript{2+} diet. We did not cross-foster pups because each litter had both control and mDISC1 mice.

\textit{Experimental Groups}

No more than 2 animals were used from each litter to produce an experimental group. We generated the following groups: single transgenic DISC1 male and female mice that did not express mutant DISC1 and were exposed to either (1) regular diet (control-regular) or (2) Pb\textsuperscript{2+}-containing diet (control-lead) and double transgenic male and female mice that expressed mDISC1 and were exposed to either (3) regular diet (mutant-regular) or (4) Pb\textsuperscript{2+}-containing diet (mutant-lead). Pups were weaned on P21, genotyped, and housed in sex-matched groups of 5 in standard mouse cages in accordance with Johns Hopkins University Animal Care and Use Committee guidelines.

\textit{Behavioral Tests}

Behavioral tests were performed on mice of 3–6 months of age. The interval between different behavioral tests was at least 1 week. The tests were performed in the following order: open field test, elevated plus maze, Y maze, PPI of the acoustic startle response, drug challenge test, and fear conditioning. The behavioral protocols used were described in our previous publications\textsuperscript{3,5,17} Drug-induced activity in the open field was assessed over a 90-minute period as previously described\textsuperscript{15} (for details, see online supplementary material).

Upon completion of behavioral testing, mice were sacrificed and their blood was collected for Pb\textsuperscript{2+} analysis. One half of mice were prepared for MRI analyses. The other half were used for preparing brain samples to evaluate expression of mutant human and endogenous mouse DISC1 as described in detail in the online supplementary material.

\textit{Statistical Analysis}

The data for body weights, lead blood levels, elevated plus maze, spontaneous alternation, spatial recognition in Y maze, the amplitudes of the acoustic startle, volumetric MRI measures for each region, and expression of mutant human DISC1 and endogenous mouse DISC1 were analyzed with 2-way ANOVA with genotype and diet as independent variables. The data for locomotor activity in open field and fear conditioning for each day were analyzed with repeated measures ANOVA with genotype, diet, and time points as independent variables. The data for PPI of the acoustic startle were analyzed with 3-way ANOVA with genotype, diet, and type of prepulse as independent variables. The data for MK-801-induced locomotor activity were with 3-way ANOVA with genotype, diet, and time points as independent variables. Significant effects were explored further with lower level ANOVAs and/or post hoc multiple comparisons. \(P < .05\) was used for the significance level.

\textit{Results}

\textit{Pb\textsuperscript{2+} Levels}

The data for body weights and Pb\textsuperscript{2+} levels are presented in the online supplementary material. In brief, Pb\textsuperscript{2+} exposure did not alter body weight gain in control or mutant mice (online supplementary figure 1A) and blood Pb\textsuperscript{2+} levels were significantly elevated in exposure groups relative to controls (online supplementary figure 1B).

\textit{Behavioral Tests}

\textit{Novelty-Induced Activity}. Novelty-induced activity in open field measures 2 simultaneously occurring but conflicting behaviors in rodents, ie, general exploratory activity (eg, rearing) and anxiety (central vs peripheral activity).\textsuperscript{18} In male mice, central activity was decreased in mutant mice compared with control animals, a significant effect of genotype, \(F(1,298) = 22.16, P < .001\). Exposure to Pb\textsuperscript{2+} significantly increased central activity in control and moderately in mutant mice, \(F(1,298) = 17.1, P < .001\), a significant overall effect of diet (figure 1A). In contrast, Pb\textsuperscript{2+}
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decreased peripheral activity in control mice and increased that in mutant mice, a significant genotype × diet interaction, \( F(1,297) = 4.74, P < .03 \) (figure 1B). Consistent with increased peripheral activity as a measure of anxiety, \( \text{Pb}^{2+} \) also decreased rearing activity in mutant mice only, while the number of rears displayed by control mice on \( \text{Pb}^{2+} \) diet was much higher compared with control mice on regular diet, a significant effect of genotype × diet interaction, \( F(1,298) = 7.76, P = .006 \) (figure 1C).

In female mice, central activity was lower in mutant mice compared with control animals, a significant effect of genotype, \( F(1,329) = 27.03, P < .001 \), while the peripheral activity was greater in mutant mice vs control mice, a genotype effect, \( F(1,329) = 5.95, P = .015 \). \( \text{Pb}^{2+} \) exposure resulted in a greater central and peripheral ambulation in control and mutant mice, a significant effect of diet for central activity \( [F(1,329) = 8.74, P = .003] \) and peripheral activity \( [F(1,329) = 22.15, P < .001] \) (figures 1D and 1E). In contrast to male mice, \( \text{Pb}^{2+} \) did not significantly alter rearing in control female mice but increased rearing in mutant female mice, \( P < .05 \) (figure 1F).

**Elevated Plus Maze Test.** This test evaluates anxiety in mice.\(^{18}\) We found no effects of genotype on anxiety in mice. However, \( \text{Pb}^{2+} \) exposure significantly increased anxiety in control and mutant male [a significant effect of diet, \( F(1,39) = 10.61, P = .002 \) (figure 2A)] and female mice [a significant effect of diet, \( F(1,37) = 5.75, P = .022 \)] (figure 2B).

**Spontaneous Alternation, Spatial Recognition Memory, and Fear Conditioning Tests.** The data for the cognitive
of diet on MK-801-evoked hyperactivity in female mice compared with male mice. Notably, male mutant mice exposed to Pb\(^2+\) showed greater hyperactivity during the first 15–20 minutes after MK-801 injection (figure 3A). In contrast, mutant female mice raised on Pb\(^2+\) diet sustained their drug-induced hyperactivity for a longer time after all other groups of female mice demonstrated the baseline, preinjection activity (figure 3B, the last five 5-minute intervals).

**PPI of the Acoustic Startle Response.** PPI is a test for sensorimotor gating that can be impaired in patients with schizophrenia and other neuropsychiatric disorders. In this test, mice were initially treated with saline, and 1 week later the same animals were treated with d-serine as below.

Consistent with our prior reports, we found no significant effects of mDISC1 on PPI in male or female saline-treated mice raised on regular diet (figures 4A and 4C).

In male mice, there was a significant effect of prepulse type, \(F(4,184) = 27.5, P < .001\), and an overall effect of Pb\(^2+\) diet, \(F(1,184) = 29.8, P < .001\), suggesting an overall diet-dependent impairment in PPI in male mice (figure 4A).

In female mice, there was a significant effect of prepulse type, \(F(4,194) = 4.054, P = .004\). The effect of Pb\(^2+\) diet was also significant but less pronounced than in male mice, \(F(1,194) = 5.21, P = .024\) (figure 4C). Significance was influenced by the changes in PPI found in mDISC1 female mice. Indeed, compared with mutant mice on regular diet, female mutant mice raised on Pb\(^2+\) diet had significantly reduced PPI at 4- and 8-dB intensities, with p8 reaching significance and p4 being borderline, \(P < .05\) and \(P = .07\), respectively. No significant effects of genotype or diet were noted on the startle amplitude in male or female mice (online supplementary figures 5A and 5B).

D-Serine is a coagonist of the NMDAR and modulates N-methyl-d-aspartate (NMDA) synaptic neurotransmission that can be affected by Pb\(^2+\). We evaluated the effects of d-serine treatment (2.7 g/kg, intraperitoneally) on PPI in mice. For mutant male mice, there was a significant effect of treatment, \(F(1,199) = 6.55, P = .011\), with the d-serine-treated mice expressing more PPI vs saline-treated mice, \(P < .05\). For control males, there was no significant effect of d-serine treatment, \(P = .31\). Post hoc comparisons detected a significant difference between saline-treated and d-serine-treated mutant mice at p8, suggesting that d-serine had a moderate ameliorative effect on PPI in mutant female mice exposed to Pb\(^2+\), \(P < .05\) (figure 4D).

**Structural MRI.** Lateral ventricle enlargement and subtle volumetric changes in the cortex and hippocampus have been reported in patients with schizophrenia and DISC1 mouse models. We found no effect of genotype or Pb\(^2+\) diet on the total brain volumes.
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No overall significant effect of Pb²⁺ diet on any MRI measure was found. Expression of mutant DISC1 was associated with significantly decreased volumes of the neocortex in female mice, the hippocampus in male mice, and caudate-putamen in male and female mice, all \( P < .05 \) vs control mice (table 1). Both developmental Pb²⁺ exposure and mDISC1 produced a significant enlargement of the lateral ventricles in female mice, a significant effect of genotype \( [F(1,17) = 6.42, P = .025] \) and a significant effect of diet \( [F(1,17) = 6.51, P = .024] \) (figure 5). The largest increase in the lateral ventricles volume was observed in mutant female mice raised on Pb²⁺ diet, with the genotype \( \times \) diet interaction being at the level of significance, \( F(3,17) = 4.57, P = .05 \) (figure 5).

Expression of Mutant DISC1 and Endogenous DISC1 in the Brain. The data for expression of mutant and endogenous DISC1 are presented in the online supplementary materials. Consistent with our previous results, mutant mice expressed mDISC1 and had decreased levels of endogenous mouse DISC1. No effects of Pb²⁺ diet on expression of these proteins were detected.

Discussion

Our findings demonstrate that chronic exposure of mDISC1 mice to Pb²⁺ produced sex-specific elevated locomotor activity and anxiety, a prolonged behavioral activation in response to an NMDAR antagonist, enlarged lateral ventricles, and mildly impaired PPI of the acoustic startle that could be ameliorated by \( d \)-serine treatment. Notably, these alterations were not present in either control mice exposed to Pb²⁺ or mDISC1 mice raised on regular chow, suggesting that synergistic interactions between an environmental toxin and a psychiatric genetic risk factor produced the brain and behavior abnormalities consistent with schizophrenia and related mental disorders.

Our study is the first to use a relevant genetic mutation in combination with an environmental toxin implicated in schizophrenia in humans.⁸⁻¹⁰ While there is a growing acceptance of contributions of microbial, stress-related factors, and substance abuse to mental illnesses, the notion that environmental toxins can also play a role in the pathogenesis of psychiatric disease is relatively new.⁸ In addition to the epidemiological data, the present
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Mouse model of GEI has strong biological plausibility. That is, Pb²⁺ is a potent and selective noncompetitive antagonist of the NMDAR and disrupts neuronal processes that are mediated via NMDAR activation. Importantly, 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 Pb²⁺ and mutant DISC1. Thus, our findings provide a mouse model and experimental support to the hypothesis that Pb²⁺ exposure can interplay with a genetic risk factor to produce pathological changes that resemble aspects of mental conditions in humans.

The synergistic GEI-related effects in the current model were predominantly seen in female mice, in line with prior studies. In addition, while both males and females are vulnerable to the adverse effects of Pb²⁺, the severity of Pb²⁺ neurotoxicity is influenced by sex, consistent with previous reports. Animal studies also report sex-specific differences in the effects of Pb²⁺ exposure emphasizing the importance of taking sex into account when evaluating GEI models. Although the exact reasons for the observed sex-related abnormalities remain unclear, significantly higher blood Pb²⁺ levels in female control and mutant mice may provide some explanation. In addition, estrogen has been shown to influence expression of Kalirin-7 (a DISC1 partner) that plays an important role in spine formation. Thus, it is conceivable that mDISC1-induced perturbations in DISC1-Kalirin-7-NMDAR complex might be responsible for greater alterations in female mDISC1 mice exposed to Pb²⁺. This issue awaits further experimental clarifications and replications.

Our GEI model is characterized by a set of behavioral phenotypes similar to aspects of serious mental diseases. For example, Pb²⁺ produced elevated locomotor activity in all mice, and mutant female DISC1 mice demonstrated both increased ambulation and rearing. Hyperactivity is a behavioral analog of aspects of positive symptoms and has been found in a number of genetic mouse models, including rodent models of neurodevelopmental Pb²⁺ toxicity. Pb²⁺ also increased anxiety-related responses in control and mutant mice in elevated plus maze, similar to prior findings in lead-exposed animals. Notably, increased peripheral activity and reduced rearing as other indications of increased anxiety were present only in mutant DISC1 male mice, suggesting a stronger anxiety phenotype due to GEI.

Fig. 4. Reduced prepulse inhibition (PPI) is rescued by d-serine in mDISC1 female mice exposed to Pb²⁺. (A) PPI in saline-treated control (control) and mDISC1 (mutant) male mice fed regular (regular) or Pb²⁺ (lead) diet; prepulses are as follows—open bar: 4 dB; dotted bar: 8 dB; horizontal lines bar: 12 dB; right slash lines bar: 16 dB; filled bar: 20 dB. (B) PPI in d-serine-treated (2.7 g/kg, intraperitoneally) control (control) and mDISC1 (mutant) male mice raised on regular (regular) or Pb²⁺ (lead) diet. (C) PPI in saline-treated control (control) and mDISC1 (mutant) female mice raised on regular (regular) or Pb²⁺ (lead) diet; prepulses are as follows—open bar: 4 dB; dotted bar: 8 dB; horizontal lines bar: 12 dB; right slash lines bar: 16 dB; filled bar: 20 dB; *P < .05 vs the same prepulse intensity in all other groups of mice. (D) PPI in d-serine-treated (2.7 g/kg, intraperitoneally) control (control) and mDISC1 (mutant) female mice raised on regular (regular) or Pb²⁺ (lead) diet. n = 8–10 mice per group.
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Mutant mice displayed more exacerbated locomotor responses to the NMDAR antagonist and psychostimulant, MK-801, in line with our earlier findings. The enhanced pharmacological effects in mDISC1 mice may indicate supersensitivity of NMDARs, reminiscent of NMDA transmission alterations in patients. Notably, the effect of MK-801 on the locomotor activity of male mDISC1 mice was different than that in female mDISC1 mice exposed to Pb\textsuperscript{2+}. Male mDISC1 mice exposed to Pb\textsuperscript{2+} exhibited significantly enhanced locomotor activity in the first 15–20 minutes after MK-801 injection (figure 3A), while female mDISC1 mice showed significantly greater activation in the last 25 minutes (figure 3B). Notably, a different study has reported a very similar sex-specific effect of another NMDAR antagonist, PCP, in Sprague-Dawley rats. Specifically, prenatal exposure to MK-801 significantly enhanced PCP-induced locomotor activity during the first 20 minutes after PCP injection in males and during the last 20 minutes of the observation in females.

This interspecies similarity adds additional evidence that Pb\textsuperscript{2+} likely acted as a potent NMDAR antagonist in our model.

Schizophrenia patients have deficits in attention and sensory information processing that can be evaluated by PPI of the acoustic startle, also commonly used to study basic neuronal mechanisms in schizophrenia. Impaired PPI has been found in many neurodevelopmental models of schizophrenia and in rodents that have been exposed to Pb\textsuperscript{2+} during development. In contrast to other groups, mDISC1 female exposed to Pb\textsuperscript{2+} showed mild impairment in PPI at low prepulse intensities (ie, 74 and 78 dB). Reduced PPI in Pb\textsuperscript{2+}-exposed mDISC1 female mice was ameliorated with \textit{d}-serine treatment, consistent with the antagonistic effects of Pb\textsuperscript{2+} on NMDAR at the glycine site. In addition, our data are in line with a report that \textit{d}-serine reversed the lead-induced impairment of long-term potentiation in the CA1 region of the hippocampus. However, given the design’s limitations of the present pharmacological experiments (ie, repeatedly testing the

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Note: The data are means ± SEM; values are in cubic millimeter. *P < .05 vs the values for neocortex of females of the control-regular female group. **P < .05 vs the values for hippocampus of the control-regular male group. ***P < .05 vs the values for caudate-putamen of the control-regular group of the same sex.
same mice), the effects of d-serine should be interpreted with great caution, pending more studies with this model.

No effects of Pb\(^{2+}\) or mDISC1 were found on spontaneous alternations or spatial recognition memory in Y maze. Although these data appear to be dissimilar to our report with mDISC1 male mice\(^{43}\) and Pb\(^{2+}\) models,\(^{44}\) we would like to emphasize that this mouse line has a weaker expression of mDISC1.

The behavioral phenotypes were associated with volumetric brain changes. Because the mDISC1 line (1302B) used in the present study is characterized by weak expression of mDISC1,\(^{5}\) we found no significant enlargement of lateral ventricles in mDISC1 female mice raised on regular chow. Intriguingly, mDISC1 female mice exposed to Pb\(^{2+}\) had greater volumes of the lateral ventricles than any other group of mice, suggesting a GEI. Our MRI results are similar to the structural MRI findings in patients with schizophrenia.\(^{21,23}\) In addition, expression of mDISC1 was associated with decreased volumes of the neocortex, hippocampus, and caudate-putamen, consistent with our prior studies and reduced sizes of these brain regions in schizophrenia patients.\(^{23}\) It is possible that volumetric MRI measures can serve as promising endophenotypes and biological markers in GEI models to help search for novel treatments.

In conclusion, the present study demonstrates that chronic exposure of mutant DISC1 mice to Pb\(^{2+}\) results in sex-dependent brain volume changes and behavioral abnormalities resembling aspects of schizophrenia and related mental diseases. Our findings support the hypothesis that environmental toxins could contribute to the pathogenesis of psychiatric disease via interactions with genetic risk factors.

Supplementary Material
Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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