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Brief Report

BRIEF REPORT

BDNF-Deficient Mice Show Reduced Psychosis-Related Behaviors Following Chronic Methamphetamine

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Abstract

Background: One of the most devastating consequences of methamphetamine abuse is increased risk of psychosis. Brain-derived neurotrophic factor has been implicated in both psychosis and neuronal responses to methamphetamine. We therefore examined persistent psychosis-like behavioral effects of methamphetamine in brain-derived neurotrophic factor heterozygous mice.
Methods: Mice were chronically treated with methamphetamine from 6 to 9 weeks of age, and locomotor hyperactivity to an acute D-amphetamine challenge was tested in photocell cages after a 2-week withdrawal period.
Results: Methamphetamine-treated wild-type mice, but not brain-derived neurotrophic factor heterozygous mice, showed locomotor sensitization to acute 3 mg/kg D-amphetamine. Qualitative analysis of exploration revealed tolerance to D-amphetamine effects on entropy in methamphetamine-treated brain-derived neurotrophic factor heterozygous mice, but not wild-type mice.
Conclusions: Chronic methamphetamine exposure induces contrasting profiles of behavioral changes in wild-type and brain-derived neurotrophic factor heterozygous mice, with attenuation of behaviors relevant to psychosis in methamphetamine-treated brain-derived neurotrophic factor heterozygous mice. This suggests that brain-derived neurotrophic factor signalling changes may contribute to development of psychosis in methamphetamine users.

Keywords: methamphetamine, brain-derived neurotrophic factor, psychosis, exploration

Introduction

Methamphetamine (METH) availability is escalating worldwide (UNODC, 2013), and many countries are dealing with the devastating impact of this highly addictive drug. One of the most severe consequences of METH abuse is increased risk of psychosis (McKetin et al., 2010, Callaghan et al., 2012). Studies have demonstrated disrupted cognition and persistent psychiatric symptoms in METH users who experience psychosis (Zweben et al., 2004), likely contributing to poorer functional outcomes.

METH-induced psychosis may follow a number of different trajectories, and while many users will experience only transient psychotic symptoms while taking the drug, others will suffer from long-term psychotic symptoms that persist even

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when the drug is not used (Zweben et al., 2004, McKetin et al., 2010). There is growing evidence that this persistent psychosis is similar to the onset of schizophrenia (Callaghan et al., 2012), which is supported by shared familial and genetic risk between schizophrenia and METH-induced psychosis (Ikeda et al., 2013).

Despite the prevalence and significant impact of METH-induced psychosis, vulnerability factors that determine whether a METH user is at risk of developing psychosis are poorly understood. Brain-derived neurotrophic factor (BDNF) has been implicated in both the pathophysiology of schizophrenia (Hashimoto et al., 2005) and the neural response to stimulant drugs, including METH (Horger et al., 1999; Saylor and McGinty, 2008). BDNF plays a critical role in neuroplasticity in the adult brain (Monteggia et al., 2004; Pu et al., 2006); therefore, BDNF may also be involved in the development of persistent behavioral changes relevant to psychosis following METH abuse. BDNF expression is reduced in both the prefrontal cortex and hippocampus of postmortem tissue from patients with schizophrenia (Hashimoto et al., 2005; Wong et al., 2009), likely contributing to disrupted functioning of those regions in the disorder. In contrast, studies examining the role of BDNF expression in psychostimulant sensitization have largely focused on the striatum (Saylor and McGinty, 2008); however, changes in other brain regions have also been reported (Pu et al., 2006).

Amphetamine-induced hyperactivity is a widely used behavioral paradigm in preclinical schizophrenia research, modelling increased subcortical dopamine signalling thought to contribute to psychosis (van den Buuse, 2010). Although hyperactivity is the primary behavioral measure used to assess sensitivity to the effects of amphetamine, qualitative measures of exploratory behavior, including entropy (a measure of the disorder of activity sequences) and spatial D (a measure of the geometric complexity of movement), can help to describe the specific profile of behavioral effects elicited by different types of psychostimulant drugs (Paulus and Geyer, 1991). Detailed characterization of exploratory activity has also recently been used to describe the behavioral profile of different psychotic illnesses (Perry et al., 2009). Compared with healthy controls, schizophrenia patients exhibited high entropy values and low spatial D, indicating the illness is associated with behavioral abnormalities. These findings support the use of qualitative measures of the effects of amphetamine in preclinical research relevant to psychosis.

To examine whether BDNF is involved in the development of persistent behavioral changes relevant to psychosis following METH exposure, BDNF heterozygous mice (HETs) and wild-type (WT) littermate controls were tested in a D-amphetamine–induced hyperactivity paradigm following 2 weeks withdrawal from chronic METH exposure during late adolescence and early adulthood. The effects of D-amphetamine on activity levels and qualitative measures of exploration were compared to characterize in detail the effect of BDNF genotype on locomotor sensitization.

Methods

All experiments were approved by the institutional animal experimentation ethics committee. BDNF HETs and WT littermates were derived from a breeding colony at the Florey Institute for Neuroscience and Mental Health, University of Melbourne, Australia. The animals were group-housed by sex in individually ventilated cages with ad libitum access to standard chow and water. Methamphetamine HCl was obtained from the National Measurement Institute (Sydney, Australia) and D-amphetamine sulphate was obtained from Sigma-Aldrich (Australia). Starting at 6 weeks of age, mice were treated with escalating doses of METH (Paulson et al., 1991; Manning and van den Buuse, 2013), or saline vehicle, for 3 weeks (saline treated: male WT n = 12, male BDNF HET n = 13, female WT n = 10, female BDNF HET n = 11; METH treated: male WT n = 12; male BDNF HET n = 12, female WT n = 10, female BDNF HET n = 10). Briefly, mice received i.p. injection of 1 mg/kg METH or vehicle once daily in the morning for 5 consecutive days during the first week, 2 mg/kg METH or vehicle twice daily in the morning and late afternoon for 5 consecutive days during week 2, and 4 mg/kg METH or vehicle twice daily during the third week. Mice were not treated on weekends. Following the final METH treatment, mice were left undisturbed for 2 weeks before commencement of behavioral testing.

Mice were tested in 3 sessions of 3 hours each in automated photocell arenas (Med Associates, St. Albans, VT). During each session they were allowed to acclimatize to the arena for 1 hour prior to injection of the challenge drug. All mice received saline in the first session, 1 mg/kg D-amphetamine in the second session, and 3 mg/kg D-amphetamine in the third session, with 3 to 4 days washout between sessions. After injection, the mice were allowed to explore the arena for a further 2 hours, with distance travelled data automatically calculated in 5-minute bins. Raw 50-msec-resolution data files were used for analysis of patterns of exploration (Paulus and Geyer, 1991; Perry et al., 2009; Adams et al., 2013). Sequential patterns of exploration were defined by the measure entropy, which describes whether movements are repetitive (low entropy) or random (high entropy). Geometrical patterns of exploration were defined by the measure spatial D, which describes whether movements are straight (low D) or convoluted (high D). Entropy and spatial D can only be calculated during periods when the mouse is moving. Because some mice were inactive during the second hour of saline treatment sessions, qualitative analysis was restricted to the first hour.

SYSTAT 13.1 software was used to perform repeated-measures ANOVA to test the effects of sex, genotype, and METH treatment (between-subjects factors) and challenge drug and time following challenge drug administration (within-subjects factors). Analysis of drug effects was performed by comparing drug and saline vehicle data in a repeated-measures ANOVA. Because there were no significant sex differences in any of these effects, data for male and female mice were pooled.

Results

Dose-Dependent Disruption of Sensitization to D-Amphetamine in BDNF HETs

When locomotor hyperactivity following challenge with 1 mg/kg and 3 mg/kg D-amphetamine was compared with that following saline administration, there was a dose-dependent interaction between BDNF genotype and prior METH exposure (Figure 1: dose x time x genotype x METH treatment interaction, $F_{(46,2852)} = 1.6$, $P = .004$). Therefore, separate ANOVAs were used to compare each dose of D-amphetamine with saline to further explore this relationship.

Following acute injection with 3 mg/kg D-amphetamine, all groups showed robust hyperactivity relative to acute saline injections. Prior METH treatment produced sensitization to D-amphetamine, whereby mice showed a greater hyperactivity response (D-amphetamine x METH treatment interaction, $F_{(1,82)} = 10.3$, $P = .002$). There was a strong trend for this to be altered in BDNF HETs (METH treatment x genotype x D-amphetamine x time interaction, $F_{(21,1722)} = 1.9$, $P = .084$). Separate ANOVAs on each genotype revealed that, while there

was robust sensitization in WT mice (D-amphetamine x METH treatment interaction, $F_{(1,40)} = 13.7$, $P = .001$), sensitization was not observed in BDNF HETs. In fact, saline-treated BDNF HETs showed a similar hyperactivity response to the sensitized METH-treated groups (saline-treated WT and HETs: D-amphetamine x genotype x time, $F_{(21,882)} = 3.0$, $P = .041$).

In contrast to the 3-mg/kg dose, in response to a subthreshold dose of D-amphetamine (1 mg/kg), which did not induce a robust hyperactivity response in saline-pretreated controls, sensitization was observed in both genotypes (METH treatment x D-amphetamine interaction $F_{(1,82)} = 27.0$, $P < .001$).

Genotype-Dependent Effects of METH Treatment on Entropy following Amphetamine

As reported previously, administration of a D-amphetamine challenge increased entropy (Figure 2: main effect dose, $F_{(2,160)} = 208.3$, $P < .001$), reflecting more random patterns of activity, and reduced spatial D (main effect dose, $F_{(2,160)} = 99.0$, $P < .001$), reflecting straighter patterns of exploration. These effects of D-amphetamine were affected by prior METH exposure (dose x METH treatment interaction: entropy, $F_{(2,160)} = 6.3$, $P = .001$; spatial D, $F_{(2,160)} = 2.9$, $P = .05$).

Acute administration of 1 mg/kg D-amphetamine increased entropy, but only in METH-pretreated mice, similar to the locomotor sensitization observed at the same dose (D-amphetamine x METH treatment interaction, $F_{(1,81)} = 14.2$, $P < .001$). There was no genotype difference in this sensitization to METH. In contrast, while prior METH treatment attenuated the increase in entropy produced by 3 mg/kg D-amphetamine, it did so in a genotype-dependent manner (amphetamine x METH treatment x genotype interaction, $F_{(1,82)} = 8.6$, $P = .004$). Whereas METH pretreatment had no effect in WT mice, BDNF HETs treated with METH were less sensitive to the effects of a D-amphetamine challenge on entropy (BDNF HETs only: drug x METH treatment interaction, $F_{(1,42)} = 9.7$, $P = .003$).

Prior METH treatment also produced sensitization to the effects of the low-dose D-amphetamine challenge (1 mg/kg) on spatial D (amphetamine x METH treatment interaction, $F_{(1,81)} = 9.6$, $P = .003$), similar to what was observed for locomotor distance moved and entropy. Again, there was no genotype difference in this sensitization. In contrast, sensitization was not observed in the effects of 3 mg/kg amphetamine on spatial D. However, there was a trend for larger effects of D-amphetamine on spatial D in BDNF HETs treated with METH relative to saline-treated BDNF HETs (amphetamine x genotype x METH treatment interaction, $P = .072$).

Discussion

These studies demonstrate that deficient BDNF signalling attenuates behavioral changes relevant to psychosis induced by METH. Unlike the METH-induced changes in behavior observed in WT mice, relative to their saline-pretreated BDNF HET controls, METH-pretreated BDNF HETs did not show increased hyperactivity and instead showed reduced entropy following a D-amphetamine challenge. This disruption of D-amphetamine-induced behaviors relevant to psychosis in METH-pretreated BDNF HETs suggests that BDNF signalling changes may be involved in mediating the persistent effects of METH leading to psychosis. The effects of BDNF depletion were specific to the acute behavioral change induced by a high-dose D-amphetamine challenge, whereas the effects of a subthreshold challenge dose (1 mg/kg) were sensitized similarly in BDNF HETs and WT mice. No sex differences were observed even though previous studies have described male-female differences in BDNF heterozygous mice with respect to dopaminergic activity (Birbeck et al., 2014) and in other gene-environment paradigms (Klug et al., 2012).

Disruption of Locomotor Sensitization in BDNF HETs

BDNF has been strongly implicated in plasticity thought to contribute to sensitization to cocaine (Horger et al., 1999; Pu et al., 2006); however, the role of BDNF in METH sensitization is less clear. BDNF HETs are more sensitive to the behavioral effects of acute D-amphetamine (current study; Dluzen et al., 2001; Saylor and McGinty, 2008). In agreement with this, the TrkB receptor agonist, 7,8-dihydroxyflavone, attenuated the acute locomotor stimulant effects of METH. However, the same study also found that coadministration of the TrkB agonist with METH blocked sensitization (Ren et al., 2014), contrasting with our finding of disrupted sensitization in BDNF-deficient mice. One interpretation of the current findings is that dynamic changes in

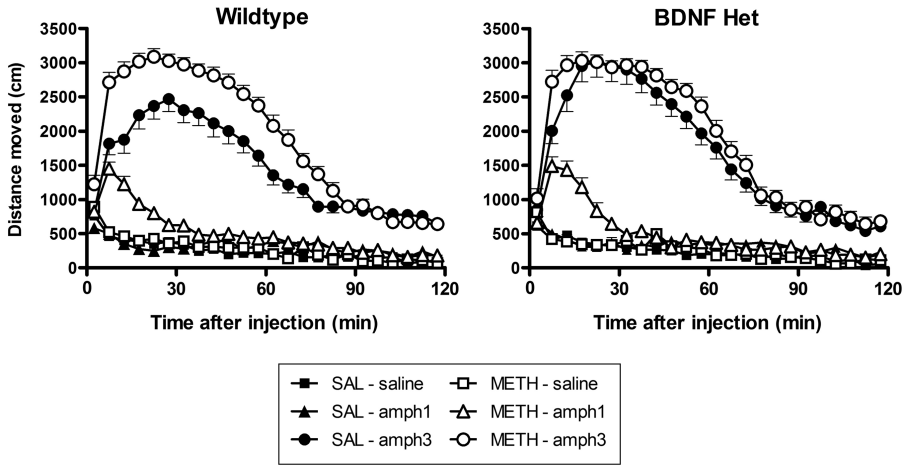

Figure 1. D-Amphetamine induced hyperactivity following chronic methamphetamine (METH) exposure. A low dose of D-amphetamine (1 mg/kg, amph1) induced hyperactivity only in mice previously pretreated with METH, and there was no genotype difference in this effect. A high dose of D-amphetamine (3 mg/kg, amph3) induced hyperactivity, and this effect was greater in METH-pretreated wild-type (WT) mice compared with saline-pretreated WT mice, but not affected by METH pretreatment in brain-derived neurotrophic factor (BDNF) heterozygous mice (HET). Saline-pretreated: male WT n = 12, male BDNF HET n = 13, female WT n = 10, female BDNF HET n = 11; METH-pretreated: male WT n = 12; male BDNF HET n = 12, female WT n = 10, female BDNF HET n = 10. For statistical comparisons, see text.

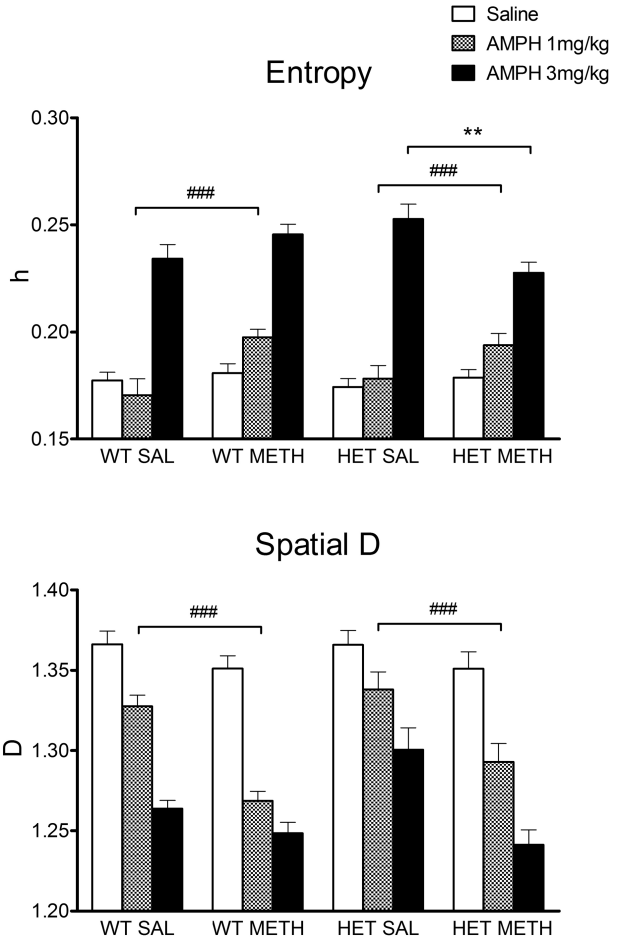

Figure 2. Amphetamine-induced changes in exploration following chronic methamphetamine (METH) exposure. Geometrical patterns of exploration were defined by the measures entropy (h, top panel), which describes whether movements are repetitive (low entropy) or random (high entropy), and spatial D (D, bottom panel), which describes whether movements are straight (low D) or convoluted (high D). A low-dose D-amphetamine challenge increased entropy and reduced spatial D, an effect which was sensitized by prior METH treatment (###$P < .005$, ANOVA METH x D-amphetamine interaction). A high-dose D-amphetamine challenge increased entropy, but this effect was reduced in brain-derived neurotrophic factor (BDNF) heterozygous mice (HET). BDNF HET mice following prior METH treatment (**$P < .005$ ANOVA METH x D-amphetamine interaction). D-amphetamine challenge also reduced spatial D but this effect was not affected by METH pretreatment or genotype. Saline-pretreated: male wild type (WT) n = 12, male BDNF HET n = 13, female WT n = 10, female BDNF HET n = 11; METH-pretreated: male WT n = 12; male BDNF HET n = 12, female WT n = 10, female BDNF HET n = 10.

endogenous BDNF signalling are necessary for the full expression of METH sensitization. If, for example, reduction of BDNF signalling was necessary for the expression of sensitization, then saline-treated BDNF HETs may already show these types of changes, which may explain their 'sensitized' increased sensitivity to an acute D-amphetamine challenge in the present study. METH-pretreated BDNF HETs showed similar hyperactivity to the high-dose challenge with D-amphetamine compared with METH-pretreated WT mice as well as saline-pretreated BDNF HETs. Therefore, the previously described effect of TrkB receptor agonist administration may be to compensate for METH-induced reductions in BDNF signalling during sensitization, thereby blocking the effects of chronic METH.

Sensitization of subcortical dopaminergic signalling is proposed to play a critical role in the development of psychosis in both METH users and patients with schizophrenia (Featherstone et al., 2007). It has previously been shown that BDNF HETs show a marked reduction in D3 dopamine receptor expression (Guillin et al., 2001; Saylor and McGinty, 2008), which may contribute to increased extracellular dopamine concentrations (Dluzen et al., 2001) due to suppressed negative feedback signalling. This may explain an 'endogenously sensitized' state in BDNF HETs and contribute to heightened sensitivity to psychostimulant drugs. The D3 receptor is thought to regulate sensitization, whereby reduction in expression during sensitization supresses negative feedback mechanisms allowing increased dopaminergic signalling (Richtand, 2006). BDNF regulation of D3 expression has been shown to play a critical role in this process (Guillin et al., 2001). Reduced D3 expression in BDNF HETs is therefore a likely candidate for mediating disrupted sensitization in this model. Altered D3 expression may also help to explain the dose-dependent genotype effects observed. Given the role of D3 receptors in negative feedback of dopamine signalling, this receptor likely plays a lesser role in the behavioral effects of low-dose D-amphetamine challenge, when negative feedback processes are not strongly activated, than it does for higher doses.

Tolerance to Amphetamine Effects on Entropy in BDNF HETs

The current study also highlights the value of using qualitative measures to describe changes in exploratory behavior during locomotor sensitization. This analysis revealed that BDNF HETs show changes in entropy following METH pretreatment that were not observed in WT mice. Given recent studies highlighting the utility of these measures to describe behavioral changes in patients with different psychotic disorders, ongoing investigation of the neural mechanisms regulating entropy and spatial D is warranted (Perry et al., 2009). Patients with schizophrenia and bipolar disorder both show increased entropy relative to healthy controls (Perry et al., 2009). These findings indicate patients with schizophrenia exhibit disorganized behavioral patterns. Likewise, the present results indicate that BDNF deficiency may exacerbate the behavioral disorganization induced by D-amphetamine. Attenuated effects of D-amphetamine on entropy are in agreement with loss of sensitization in BDNF HETs treated with METH, given that in both cases this reflects a reduction in the expression of psychosis-related behaviors.

Implications for Understanding of Mechanisms Underlying METH-Induced Psychosis

Understanding the signalling pathways that are differentially activated in METH users who develop psychosis and those who do not is critical for identifying those who are vulnerable to the development of persistent psychosis and for targeting early interventions. This knowledge may also aid the development of novel therapeutics, which protect against the development of METH-induced psychosis and may also show efficacy in patients with schizophrenia. Building on previous work implicating BDNF signalling in the pathophysiology of schizophrenia (Hashimoto et al., 2005) and risk for METH-induced psychosis (Sim et al., 2010), our studies demonstrate that BDNF HETs show attenuated changes in behaviors related to psychosis following METH preexposure. This suggests that dynamic changes in BDNF signalling may be critical in producing the effects of METH leading to psychosis, including sensitization of subcortical dopamine signalling. Detailed characterization of BDNF signalling changes

during the induction and expression of sensitization to METH, and examination of potential mechanisms mediating this relationship such as altered D3 receptor expression, will help to address whether this pathway can be targeted for identifying METH users at risk for developing psychosis or the development of novel therapeutics.

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Statement of Interest

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