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D-amphetamine withdrawal-induced decreases in brain-derived neurotrophic factor in sprague-dawley rats are reversed by treatment with ketamine

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ABSTRACT

Withdrawal from chronic D-amphetamine (D-AMPH) can induce negative emotional states, which may contribute to relapse and the maintenance of addiction. Diminished levels of brain-derived neurotrophic factor (BDNF), particularly in the hippocampus has been observed after exposure to stress, and recent data indicate that treatment with the N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine may reverse these changes. However, it is unclear whether BDNF levels in the hippocampus or other regions of the limbic system are altered following the stress of D-AMPH withdrawal and it is not currently known if treatment with ketamine has any effect on these changes. The goals of this study were to examine BDNF levels throughout the limbic system following D-AMPH withdrawal and determine whether ketamine treatment would alter D-AMPH-induced changes in BDNF. Sprague–Dawley rats were treated with D-AMPH and BDNF protein examined in the prefrontal cortex, nucleus accumbens, amygdala and hippocampus at 24 h and 4 days of withdrawal. Our data show that at 24 h post-D-AMPH, BDNF levels were increased in the nucleus accumbens and decreased in the hippocampus. At 4d post-D-AMPH, BDNF protein levels were decreased in all areas examined, and these decreases were reversed by treatment with ketamine. These data suggest that diminished BDNF may contribute to the negative affect seen following D-AMPH withdrawal, and that ketamine treatment could offer relief from these symptoms.

1. Introduction

Psychostimulant addiction is a chronic, relapsing disorder that continues to elude effective treatment (Aharonovich et al., 2006). Abusers of psychostimulants report dysphoria (general unease or dissatisfaction with life) and anhedonia (loss of interest or pleasure in most or all activities) after excessive psychostimulant intake and abstinence (Coffey et al., 2000; Gawin and Kleber, 1986), and animals undergoing withdrawal from D-amphetamine (D-AMPH) show decreased motivation for natural reinforcers (Barr et al., 1999; Barr and Phillips, 1999, 2002; Cryan et al., 2003; Murray et al., 2014b). It is thought that the negative affective states that are observed following psychostimulant withdrawal may contribute to the relapse and maintenance of addiction (Aharonovich et al., 2006; Barr and Markou, 2005; Barr et al., 2002).

The production of emotional states is governed by the limbic system, which also mediates the rewarding and reinforcing properties of drugs of abuse. In particular, drugs of abuse enhance the activity of the dopaminergic mesocorticolimbic pathway, which is a circuit that consists of the mesolimbic pathway, containing projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), amygdala and hippocampus and the mesocortical pathway, containing projections from the VTA to the prefrontal cortex (Cami and Farre, 2003; Feltstein and See, 2008; Wise, 1996). These pathways are thought to operate in parallel (Cami and Farre, 2003), with the NAc mediating the reinforcing effects of drugs of abuse (Di Chiara, 2002; Volkow et al., 2003), the hippocampus mediating emotional cognition and memory that is thought to be involved in addiction, the amygdala mediating the processing of emotional information, (Cardinal et al., 2002; Fuchs et al., 2007, 2005; Rogers and See, 2007; See, 2005) and the prefrontal cortex, including the prelimbic cortex, regulating emotional responses, cognition and executive function (Cardinal et al., 2002; Kalivas and Volkow, 2005; Volkow et al., 1993). The prefrontal

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cortex and NAc send reciprocal connections to the VTA, modulating the activity of this nucleus and its subsequent output to limbic structures (Berendse et al., 1992; Bortolozzi et al., 2005; Christie et al., 1985; Vásquez-Borsetti et al., 2009), while convergent inputs from the amygdala, hippocampus and prefrontal cortex to the NAc modulates outputs to motor relay circuits that oversee motor actions and outcomes (Burns et al., 1994; Gorelova and Yang, 1997; Jentsch and Taylor, 1999; O'Donnell and Grace, 1995; Robbins et al., 1989). Together, these pathways coordinate reward-related associative learning and motivated behaviors and changes in the neurochemistry of these limbic and limbic-associated pathways by drugs of abuse are thought to contribute the alterations in learning, memory and behavior that underlie addiction (Feltstein and See, 2008; Hyman et al., 2006; Jentsch and Taylor, 1999).

Brain-derived neurotrophic factor (BDNF) is a growth factor that contributes to glutamate-dependent synaptic plasticity and has been implicated in addiction (Thoenen, 1995; Yamada et al., 2002). BDNF protein is found throughout the structures of the limbic system, and BDNF mRNA highly expressed in the VTA, prefrontal cortex, hippocampus and amygdala (Altar et al., 1997; Altar and DiStefano, 1998; Conner et al., 1997; Lessmann et al., 2003). BDNF is thought to mediate the behavioral changes observed following psychostimulant withdrawal, and may also contribute to the neurochemical adaptations that occur in response to psychostimulants, most likely due to its effects on the glutamatergic and dopaminergic neurons within the limbic system (Autry and Monteggia, 2012; Grimm et al., 2003; Li et al., 2013; Meredith et al., 2002). A number of previous studies have examined BDNF in the context of the incubation of craving following long-term withdrawal from cocaine, with a focus on the mesolimbic pathway (Grimm et al., 2003; Li et al., 2013; Lu et al., 2004a, 2004b, 2003). However, relatively few studies have examined the changes in BDNF that might occur during shorter-term withdrawal from D-AMPH, during which time where there may be marked anhedonia and dysphoria, and there is little information on changes in BDNF other regions, such as the hippocampus following D-AMPH withdrawal. Since diminished BDNF levels in the hippocampus are associated with exposure to stress (Autry and Monteggia, 2012; Yu and Chen, 2011), it is possible that decreased hippocampal BDNF levels will also be observed following the stress of D-AMPH withdrawal.

Ketamine has recently been shown to up-regulate BDNF synthesis in the hippocampus of animals exposed to a stressful stimulus, (Autry and Monteggia, 2012; Murrough, 2012; Murrough et al., 2013). Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist, and these receptors are found in high density in the hippocampus, cortex and other regions of the limbic system (Brose et al., 1993; Eiler and Yost, 2012; McDonald, 1994; Tarazi et al., 1998; Wedzony and Czyrak, 1997). Blockade of NMDA receptors by ketamine deactivates eukaryotic elongation factor-2 (eEF2) kinase, which results in reduced eEF2 phosphorylation and increased BDNF translation (Autry and Monteggia, 2012; Murrough, 2012; Murrough et al., 2013). Thus, we sought investigate whether ketamine will alter BDNF levels throughout the limbic system following D-AMPH withdrawal, with the potential for ketamine to be used as a treatment to alleviate the symptoms of psychostimulant withdrawal.

2. Methods and materials

2.1. Animals

Male Sprague–Dawley rats (Harlan Laboratories, Indianapolis, IN, USA), weighing 250–350 g were used in all experiments. Rats were housed in groups of four in plastic cages in a temperature-controlled room. Rats were on a 12:12 h light/dark cycle and had free access to food and water. All animal care and experimental manipulations were approved by the Institutional Animal Care and Use Committee of Mercer University School of Medicine and were in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*. The minimum possible number of animals (based on power analyses) was used for our experiments.

2.2. Drug treatments

Escalating doses of D-AMPH (Sigma, St. Louis, MO, USA) were administered to rats, based on a schedule that has been previously shown to decrease responding for natural reinforcers and depression-like behaviors (Barr et al., 1999; Barr and Phillips, 1999, 2002; Murray et al., 2014b). All drug doses were calculated as the free base and were dissolved in normal saline. D-AMPH was administered subcutaneously and given in a volume of 1 ml/kg. Animals were given a total of 12 doses of D-AMPH, three times a day for four days. Rats were injected at 9 am, 12 pm and 5 pm, starting with a dose of 1 mg/kg and escalating by 1 mg/kg on each subsequent dose, for the first nine doses. On the fourth and final day, rats were given three doses of D-AMPH at 10 mg/kg. Subjects were weighed each morning before the 9 a.m. injection in order to adjust for any decreases in body weight due to the D-AMPH treatment. Control animals were given normal saline under the same schedule as the D-AMPH-treated rats. Animals were sacrificed 24 h or 4d after the final injection. On day 4 of withdrawal a sub-set of animals were given saline or ketamine at 10 mg/kg, i.p., which is a dose previously shown to exhibit antidepressant effects in rats in the forced swim test (Garcia et al., 2008; Li et al., 2010, 2011) at 9 am and sacrificed at 5 pm.

2.3. BDNF immunohistochemistry

Animals were euthanized by exposure to CO_2 for 1 min followed by decapitation. The brains were rapidly harvested, quick-frozen in isopentane on dry ice and stored at −80 °C until they were cut into 12-μm sections through the prelimbic cortex (PRL; at approximately +3.7 mm from bregma), NAc (at approximately +2.0 mm from bregma), hippocampus and basolateral amygdala (BLA; at approximately −2.3 mm from bregma; (Paxinos and Watson, 2005) on a cryostat (Minotome Plus, Triangle Biomedical Sciences, Durham, N.C., USA). Sections were post-fixed in 4% paraformaldehyde/0.9% NaCl and then rinsed three times in 0.1 M phosphate-buffered saline (PBS). Slides were then blocked with 10% bovine serum albumin (BSA)/0.3% Triton X-100 (TX)/0.1 M PBS for 2 h followed by overnight incubation at 4 °C with polyclonal antibody for BDNF (Santa Cruz Biotechnology, Santa Cruz, CA), diluted in 1:100 in 0.3% TX/0.1M PBS/5% BSA. The slides were then washed several times in PBS and incubated for 2 h at room temperature in biotinylated goat anti-rabbit IgG antiserum (Vector Laboratories, Burlingame, CA) diluted 1:200 in 0.1 M PBS/5% BSA. Slides were then washed three times in PBS, incubated 1 h in ABC solution (Elite ABC Kit, Vector Laboratories), and washed three more times in PBS. Bound antibody was detected using a 3′,3-diaminobenzidine/Ni^{2+} solution (Vector Laboratories). Slides were washed with deionized H_2O, dehydrated in a series of alcohols, and cover-slipped out of xylene.

2.4. Image analysis

BDNF labeled brains (6–10 animals per treatment group) were captured using a VistaVision microscope (VWR, Radnor, PA, USA) with a video camera (CCD Moticam 2300, Motic, Richmond, BC, Canada), and a 10X objective. Immunoreactivity was measured in the both hemispheres of each brain in the following pixel areas based on previously described procedures (Horner et al., 2011; Murray et al., 2014a): 300 × 500 for PRL, 200 × 300 for NAc core, 200 × 300 for NAc shell, 400 × 100 for dentate gyrus of the hippocampus, and 350 × 300 for BLA (Fig. 1). The number of BDNF-labeled particles that exceeded the threshold density in each region of interest was determined using the particle analysis option in ImageJ. Prior to analysis, the pixel range for particle size was determined by outlining approximately 15–20 positively labeled cells from 10 to 15 randomly selected sections and determining the average size of the labeled cells in terms of pixel area. The lower limit for a "labeled cell" on the particle analysis setting was then set to the smallest number of pixels measured for any cell, whereas the upper limit was set at the maximal particle size on the particle analysis option on ImageJ. The threshold density was adjusted such that background staining was eliminated and the number of immunoreactive pixels per the selected area in each region of interest was measured above this threshold. The number of BDNF-immunoreactive particles in the right and left hemispheres was then averaged for each animal in each region of interest. In order to circumvent differences in the density of labeling between the different regions of brain being analyzed, the final number of particles for each region of interest was expressed as a percent of control.

2.5. Statistical analysis

The effect of repeated escalating D-AMPH treatment and withdrawal on BDNF imunoreactivity (BDNF-ir) was analyzed using a Student's t-test for each region analyzed. A two-way analysis of variance was used to determine the effects of ketamine treatment during D-AMPH withdrawal on BDNF-ir (withdrawal x post-treatment). *Post hoc* analysis of significant effects was performed using Tukey multi-comparison tests. The alpha level for all analyses was set at 0.05.

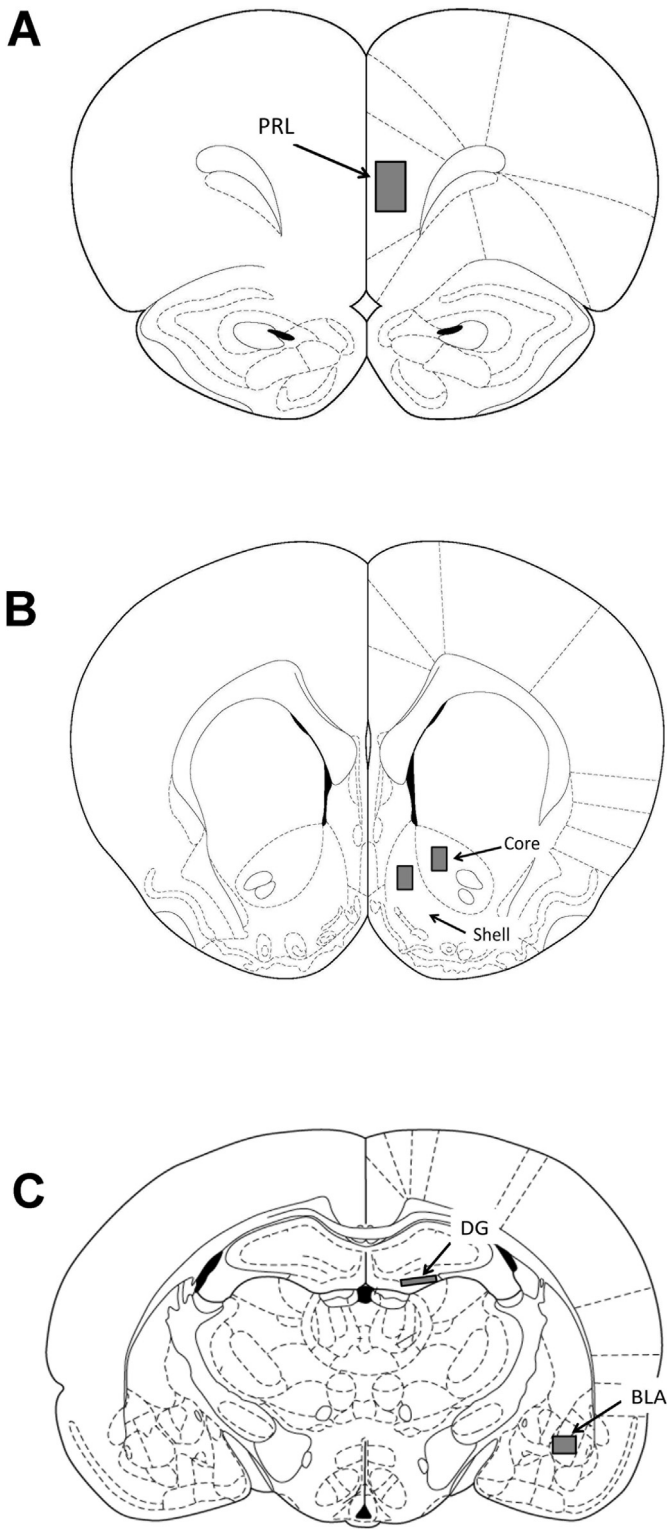

Fig. 1. Schematic diagram of the rostral to caudal sections of rat brain used for the analysis of BDNF-immunoreactivity (BDNF-ir). Measurements are given relative to bregma. The regions used for analysis are highlighted in gray and consist of the PRL (+3.7 mm, **A**); NAcC and NAcS; (+2.0 mm, **B**), DG and BLA (−2.0 mm, **C**). PRL, prelimbic cortex; NAcC, nucleus accumbens core; NAcS, nucleus accumbens shell; DG, dentate gyrus; BLA, basolateral amygdala.

3. Results

3.1. Changes in BDNF-ir 24 h following D-AMPH withdrawal

BDNF-ir appeared to be increased in the NAc shell and diminished in the dentate gyrus, 24 h following D-AMPH withdrawal, while BDNF-ir did not seem to be altered in the PRL, NAc core or BLA following 24 h of D-AMPH withdrawal (Fig. 2). Semi-quantitative analysis of BDNF-ir revealed that in the shell of the NAc there was a significant increase in the number of BDNF-labeled particles ($t = 2.407$, $p = 0.029$, df = 16), while in the dentate gyrus of the hippocampus, the number of BDNF-labeled particles was significantly decreased ($t = 2.331$, $p = 0.033$, df = 16; Fig. 3) following 24 h of D-AMPH withdrawal. There was no significant effect of 24 h of D-AMPH withdrawal on the number of BDNF-labeled particles in the PRL ($t = 1.271$, $p = 0.223$, df = 15), NAc core ($t = 1.055$, $p = 0.306$. df = 17) or BLA ($t = 0.5346$, $p = 0.600$, df = 16; Fig. 3).

3.2. Changes in BDNF-ir 4d following D-AMPH withdrawal

In contrast to the region-specific changes in BDNF-ir observed after 24 h of D-AMPH withdrawal, 4d of D-AMPH withdrawal appeared to induce a widespread diminution of BDNF-ir across all regions of interest (Fig. 4). Semi-quantitative analysis of BDNF-ir revealed that at 4d post-AMPH withdrawal, the number of BDNF-labeled particles were significantly decreased in all areas examined: PRL ($t = 3.47$, $p = 0.003$, df = 13), core ($t = 2.40$, $p = 0.032$, df = 13) and shell ($t = 2.27$, $p = 0.04$, df = 14) of NAc, dentate gyrus of hippocampus ($t = 2.95$, $p = 0.01$, df = 15) and BLA ($t = 2.945$, $p = 0.012$, df = 12; Fig. 5).

3.3. Effects of ketamine administration on BDNF-ir following 4d of D-AMPH withdrawal

Based on the widespread decreases in BDNF-ir observed at 4d following D-AMPH withdrawal, this time point was chosen to determine whether ketamine treatment would ameliorate the reduction in BDNF-ir observed in all regions of interest. When given at 4d post-D-AMPH withdrawal, ketamine treatment appeared reverse the D-AMPH-induced decreases in BDNF-ir in the PRL, core and shell of NAc, dentate gyrus of hippocampus, but not the BLA (Fig. 6).

In the PRL, two-way analysis of the effects of ketamine treatment on BDNF-ir following 4d of D-AMPH withdrawal revealed a significant main effect of D-AMPH withdrawal ($F_{1, 23} = 15.0$, $p = 0.007$), significant main effect of ketamine treatment ($F_{1, 23} = 4.8$, $p = 0.038$) and a significant ketamine treatment x D-AMPH-withdrawal interaction ($F_{1, 23} = 7.0$, $p = 0.015$). *Post-hoc* analysis of significant interaction effects revealed that D-AMPH withdrawal significantly decreased BDNF protein levels in VEH-treated animals ($p < 0.05$). Furthermore, *post-hoc* analysis revealed that there were significantly greater levels of BDNF-ir in KET/D-AMPH-treated animals as compared to VEH/D-AMPH-treated animals ($p < 0.05$), while there was no significant difference between KET/SAL and KET/D-AMPH-treated animals ($p > 0.05$; Fig. 7A).

In the NAc core, two-way analysis of the effects of ketamine treatment on BDNF-ir following 4d of D-AMPH withdrawal revealed a significant overall main effect of ketamine treatment ($F_{1, 27} = 9.5$, $p = 0.026$) and a significant ketamine treatment x D-AMPH-withdrawal interaction ($F_{1, 27} = 5.5$, $p = 0.007$), but not a significant overall main effect of D-AMPH withdrawal ($F_{1, 27} = 0.11$, $p = 0.74$). However, *post-hoc* analysis revealed that BDNF-ir was significantly decreased in VEH/D-AMPH-treated animals versus

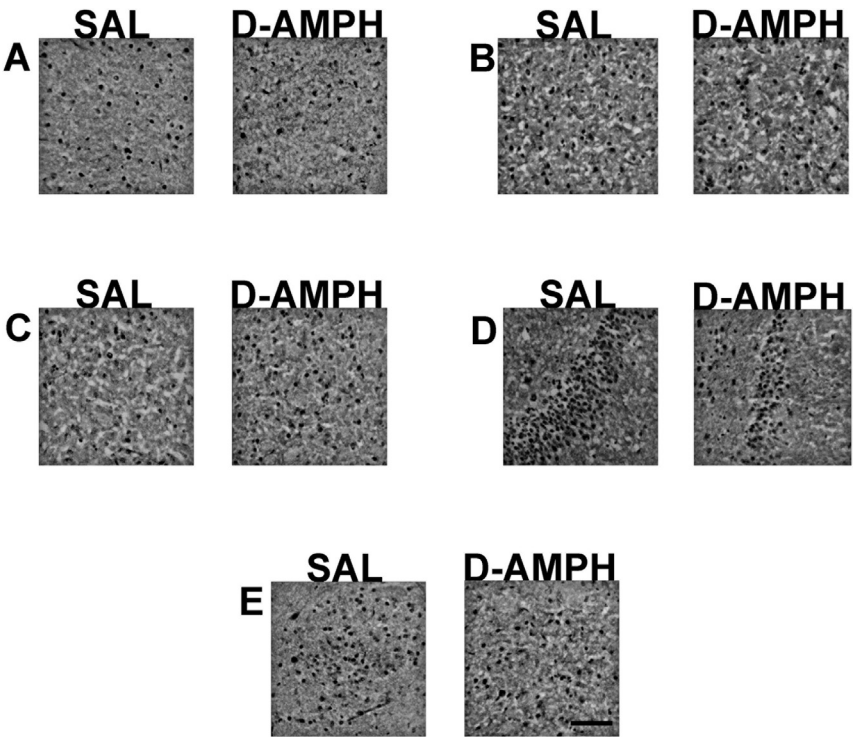

Fig. 2. Photomicrographs of BDNF-ir following 24h of D-AMPH withdrawal. D-AMPH withdrawal-induced changes BDNF-ir in the PRL (**A**), NAcC (**B**), NAcS (**C**), DG (**D**) and BLA (**E**) at 24 h following the last dose of D-AMPH. The levels of BDNF-ir appear to be increased in the NAcS, but decreased in the DG, while all other regions appear to be unaffected 24 h following D-AMPH withdrawal. Scale bar = 100 μM.

VEH/SAL-treated animals ($p < 0.05$) and that ketamine significantly increased BDNF-ir in D-AMPH withdrawn animals, as there was a significant difference between VEH/AMPH vs. KET/AMPH treated animals ($p < 0.05$), but not a significant difference between KET/SAL vs. KET/D-AMPH-treated animals ($p > 0.05$; Fig. 7B).

In the NAc shell, two-way analysis of the effects of ketamine treatment on BDNF-ir following 4d of D-AMPH withdrawal revealed an overall significant main effect of ketamine treatment ($F_{1, 23} = 28.0$, $p < 0.0001$) and a significant ketamine treatment x D-AMPH-withdrawal interaction ($F_{1, 23} = 16.0$, $p = 0.0006$), but not a significant overall main effect of D-AMPH withdrawal ($F_{1, 23} = 0.56$, $p = 0.46$). *Post-hoc* analysis revealed that BDNF-ir was significantly decreased in VEH/D-AMPH-treated animals versus VEH/SAL-treated animals ($p < 0.05$) and that ketamine significantly increased BDNF-ir in D-AMPH withdrawn animals, as there was a significant difference between VEH/AMPH vs. KET/AMPH treated animals ($p < 0.05$), but not a significant difference between KET/SAL vs. KET/D-AMPH-treated animals ($p > 0.05$; Fig. 7C).

In the dentate gyrus, two-way analysis of the effects of ketamine treatment on BDNF-ir following 4d of D-AMPH withdrawal revealed a significant main effect of ketamine treatment ($F_{1, 28} = 16.0$, $p = 0.0004$) and a significant ketamine treatment x D-AMPH-withdrawal interaction ($F_{1, 28} = 6.1$, $p = 0.02$), but not a significant overall effect of D-AMPH withdrawal ($F_{1, 28} = 1.9$, $p = 0.18$). *Post-hoc* analysis revealed that BDNF-ir was significantly decreased in VEH/D-AMPH-treated animals versus VEH/SAL-treated animals ($p < 0.05$) and that ketamine significantly increased BDNF-ir in D-AMPH withdrawn animals, as there was a significant difference between VEH/AMPH vs. KET/AMPH treated animals ($p < 0.05$), but not a significant difference between KET/SAL vs. KET/D-AMPH-treated animals ($p > 0.05$; Fig. 7D).

In the BLA, two-way analysis of the effects of ketamine treatment on BDNF-ir following 4d of D-AMPH withdrawal revealed an overall significant main effect of D-AMPH withdrawal ($F_{1, 19} = 7.7$, $p = 0.012$) but not a significant effect of ketamine treatment ($F_{1, 19} = 0.21$, $p = 0.65$), or significant interaction between ketamine treatment and D-AMPH withdrawal ($F_{1, 19} = 3.6$, $p = 0.07$). *Post-hoc* analysis revealed that there was significantly less BDNF-ir in D-AMPH treated animals, regardless of the post-treatment that was given ($p = 0.011$; Fig. 7E).

4. Discussion

The goals of this study were to determine the impact of repeated, escalating doses of D-AMPH, followed by 24 h or 4 days of withdrawal on BDNF protein levels in the limbic regions of the rat brain, and to examine the effects of treatment with ketamine during the withdrawal period on D-AMPH-induced changes in BDNF levels. At 24 h following D-AMPH withdrawal, BDNF-ir was significantly increased in the shell, but not core of NAc, decreased in the dentate gyrus of the hippocampus and unchanged in the PRL and BLA. However, at 4 days following D-AMPH withdrawal, BDNF-ir was significantly decreased in all regions examined. Treatment with ketamine on the fourth day of withdrawal restored BDNF-ir to control levels in the PRL, NAc, and dentate gyrus, but not in the BLA. These data are among the first to demonstrate that widespread changes in BDNF levels occur in the limbic system following withdrawal from repeated D-AMPH treatment and that treatment with ketamine during the withdrawal period can restore diminished levels of BDNF. Furthermore, these data raise the possibility that the negative effects of psychostimulant withdrawal could be the result of impairment of the BDNF system.

A number of studies have shown that BDNF is necessary for normal synaptic transmission, spine maintenance and regulation of neuroplasticity in several of regions of the limbic system, including the prefrontal cortex, hippocampus and amygdala (Chen et al., 2006; Liu et al., 2012; von Bohlen and Halbach et al., 2006; Yu et al., 2012). Besides altering learning and memory functions, the

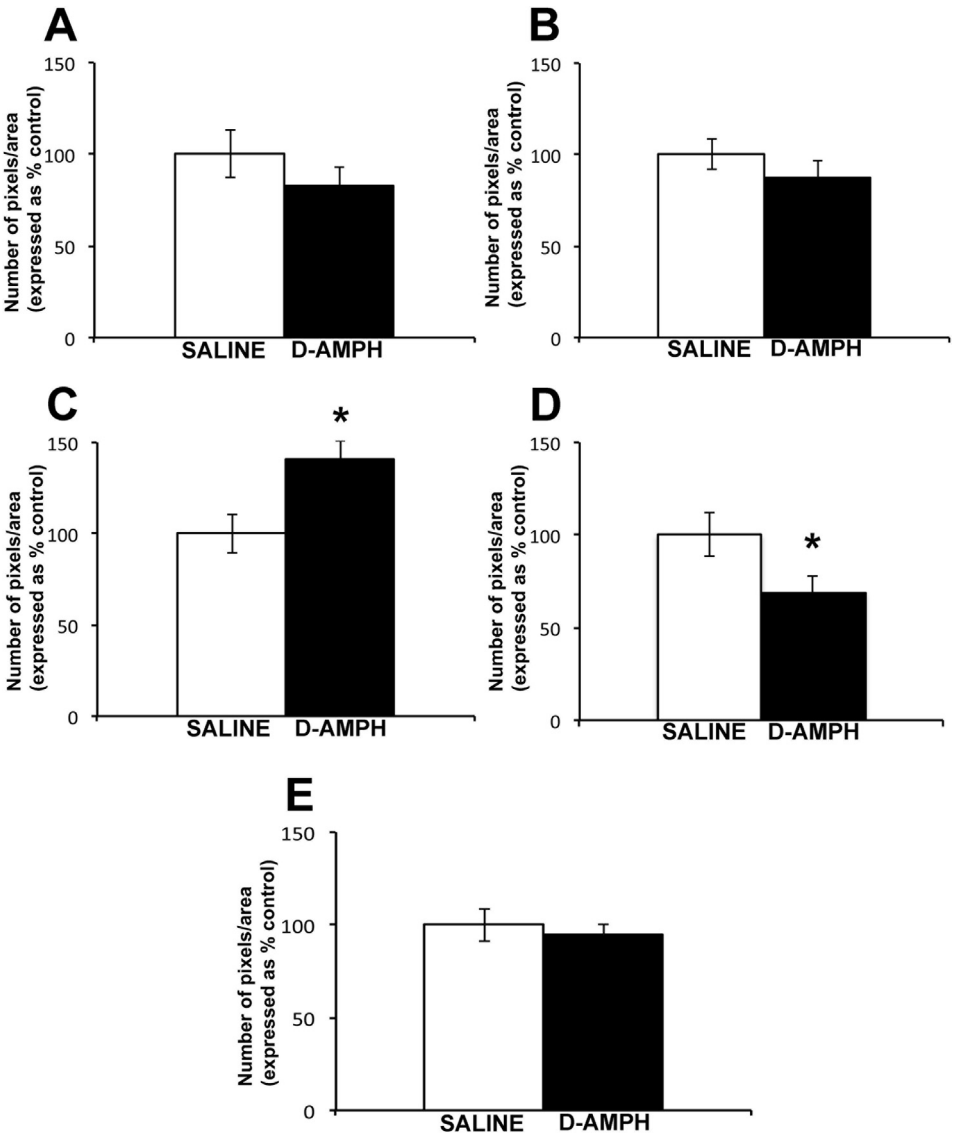

Fig. 3. Semi-quantitative analysis of BDNF-ir following 24h of D-AMPH withdrawal. Data are presented as the percentage of BDNF-ir particles in saline-treated control animals in the PRL (**A**), NAcC (**B**), NAcS (**C**), DG (**D**) and BLA (**E**). The levels of BDNF-ir were significantly increased in the NAcS, and significantly decreased in the DG, 24 h following the last dose of D-AMPH. $^{*}p < 0.05$ vs. saline-treated animals.

disruption of neuroplasticity has also been linked to the pathophysiology of mood disorders (Bath et al., 2012; Ninan et al., 2010). The binding of BDNF to tropomyosin related kinase B (trkB) receptors results in the activation of the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K)/Akt signaling pathways, which are two pathways that are thought to modulate mood through the regulation of spinogenesis and synaptogenesis (Jiang and Salton, 2013; Qi et al., 2009; Reichardt, 2006). A loss of BDNF, such as the diminution of BDNF in the PRL, hippocampus and BLA observed in the current study, may lead to deficits in local protein translation, and could result in disruptions in neuroplasticity and may ultimately lead to alterations in mood, as well as disruption of learning and memory functions, (Duman and Aghajanian, 2012).

Previous work indicates that decreased neuronal activation in the prefrontal cortex, including the PRL, is associated with psychostimulant withdrawal and may underlie the cognitive, emotional and motivational impairments associated with this disorder (Clow and Hammer, 1991; Goldstein and Volkow, 2002; Horner et al., 2009; Persico et al., 1995; Persico and Uhl, 1996; Volkow et al., 2003). Diminished BDNF in the PRL has also been observed with exposure to stress, and infusion of BDNF into this region can alter stress-induced behaviors (Duman, 2009; Gourley et al., 2009; Peters et al., 2010). Furthermore, BDNF protein levels are diminished in the prefrontal cortex following withdrawal from chronic cocaine treatment (Fumagalli et al., 2007) and infusion of BDNF into the prefrontal cortex prevents reinstatement of drug-taking behaviors (Berglind et al., 2007). Our data show that at 4 days following D-AMPH withdrawal, BDNF levels are significantly decreased in the PRL. As BDNF is necessary for normal neuronal functioning, a decrease in BDNF levels in this region could result in cortical hypoactivity, as recent data indicate that BDNF suppresses GABAergic inhibition of the prefrontal cortex (Lu et al., 2010). Thus, the release of GABAergic neurotransmission from inhibition as a result of diminished BDNF levels within the prefrontal cortex may contribute to the impairments in cognition and motivation that may be seen following D-AMPH withdrawal. It is also important to note that BDNF is transported to the NAc from glutamatergic

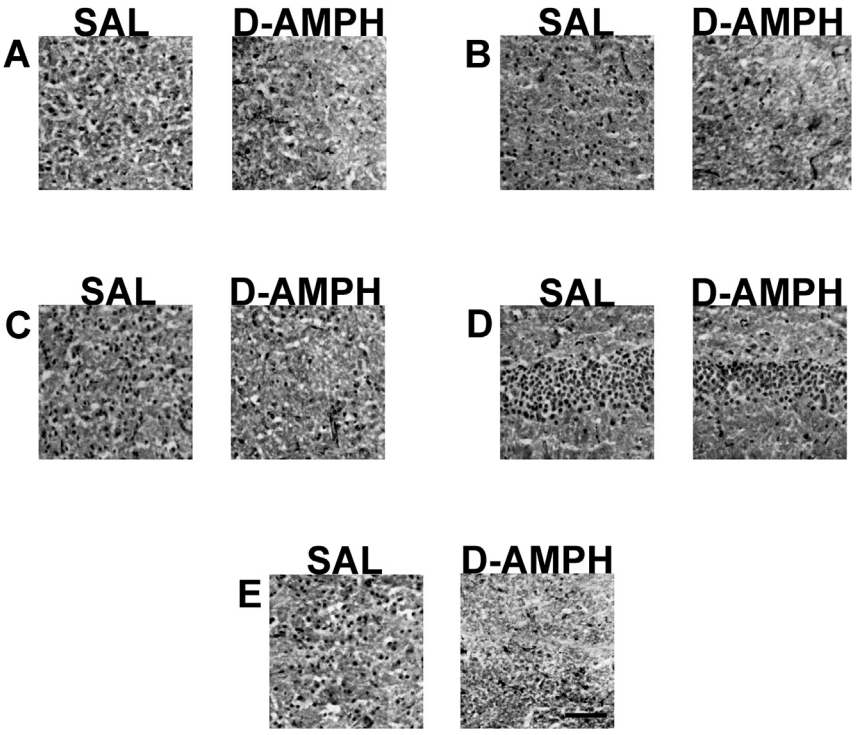

Fig. 4. Photomicrographs of BDNF-ir following 4d of D-AMPH withdrawal. D-AMPH withdrawal-induced changes BDNF-ir in the PRL (**A**), NAcC (**B**), NAcS (**C**), DG (**D**) and BLA (**E**) at 4d following the last dose of D-AMPH. The levels of BDNF-ir appear to be diminished in all regions of interest. Scale bar = 100 μM.

neurons in the prefrontal cortex (Altar and DiStefano, 1998). Because the corticoaccumbal pathway is thought to mediate relapse into drug-seeking behaviors, and given the network of reciprocally interconnected structures within the limbic system, BDNF activity within the prefrontal cortex may play a crucial role in drug-induced plasticity in mesolimbic neurons, and could impact the functioning of the limbic system as a whole (McGinty et al., 2010).

While diminished levels of BDNF have been observed in the hippocampus following exposure to stress and in MDD, the effects of D-AMPH withdrawal on BDNF levels in the hippocampus have not been previously examined. The hippocampus plays a role in learning and memory, as well as responses to stressful stimuli, and dysfunction of the hippocampus is observed following psychostimulant withdrawal (McEwen, 1999; Sapolsky, 2000; Thompson et al., 2004). Furthermore, as mentioned above, BDNF contributes to neuronal plasticity in the hippocampus, and is necessary for the normal functioning and survival of neurons (Kang and Schuman, 1995; Levine et al., 1995; Manji et al., 2000). Our data indicate that the dentate gyrus is especially sensitive to D-AMPH-induced changes in BDNF, as decreases in BDNF protein levels are observed at both 24 h and 4d post-AMPH treatment. It is possible that decreased BDNF contributes to the hippocampal dysfunction and memory deficits that are observed following withdrawal from chronic psychostimulant treatment (Thompson et al., 2004). On the other hand, decreases in BDNF protein levels were not apparent in the BLA until 4d following D-AMPH withdrawal. The amygdala is important for the processing of emotional information, and previous studies have shown that cocaine withdrawal or exposure to stress are associated with increased BDNF levels in the amygdala, including the BLA. In contrast, our data show that at 4d, but not 24 h post-AMPH withdrawal, BDNF levels are diminished in the BLA. However, since BDNF is necessary for neuronal function, diminished levels of BDNF observed in the current study could represent impairment of the processing of emotional stimuli by the amygdala, which may be associated with abstinence from psychostimulant use (London et al., 2004; Phelps and LeDoux, 2005).

Interestingly, while increased BDNF levels in the prefrontal cortex, hippocampus and amygdala are thought to be antidepressive, increased BDNF in the NAc has a pro-depressive effect and previous work has shown that increased BDNF levels in the NAc are associated with MDD (Berton et al., 2006; Yu and Chen, 2011). It is possible that up-regulation of BDNF in the shell of the NAc following early psychostimulant withdrawal may contribute to the reinstatement of drug seeking and drug-taking behaviors due the pro-depressive effect of BDNF in the NAc. The shell of the NAc is thought to be involved in processing of the motivational significance and emotional states, while the core may be involved in the motor execution of internally-driven behaviors (Ghitza et al., 2004; Kourrich and Thomas, 2009; Zahm, 1999). Our data indicate that at 24 h after the final dose of D-AMPH, BDNF protein levels are significantly increased in the shell, but not core of the NAc. If increased BDNF in the shell of the NAc is pro-depressive, and the shell is involved in the production of emotional states, then it is possible that up-regulation of BDNF in the shell contributes to the initial dysphoric and anhedonic effects of D-AMPH withdrawal. This is in line with previous work from our laboratory (Murray et al., 2014b) where animals that had undergone 24 h of D-AMPH withdrawal showed greater immobility in the forced swim stress test, i.e., doing the bare minimum not to drown, which is thought to be an indicator of a depressed state in the animal, (Kokkinidis et al., 1986) as compared to saline controls. However, our current data also show that by 4 days post-AMPH withdrawal, the increase in BDNF in the shell of the NAc is reversed, such that BDNF levels are significantly lower in the NAc of AMPH-treated animals versus controls. This reversal of BDNF levels in the NAc would seem to suggest that at this time point there could be a certain degree of recovery from D-AMPH induced dysphoria and anhedonia, which is in line with previous data from our laboratory which shows that at 4 days of D-AMPH withdrawal, D-AMPH-treated and control

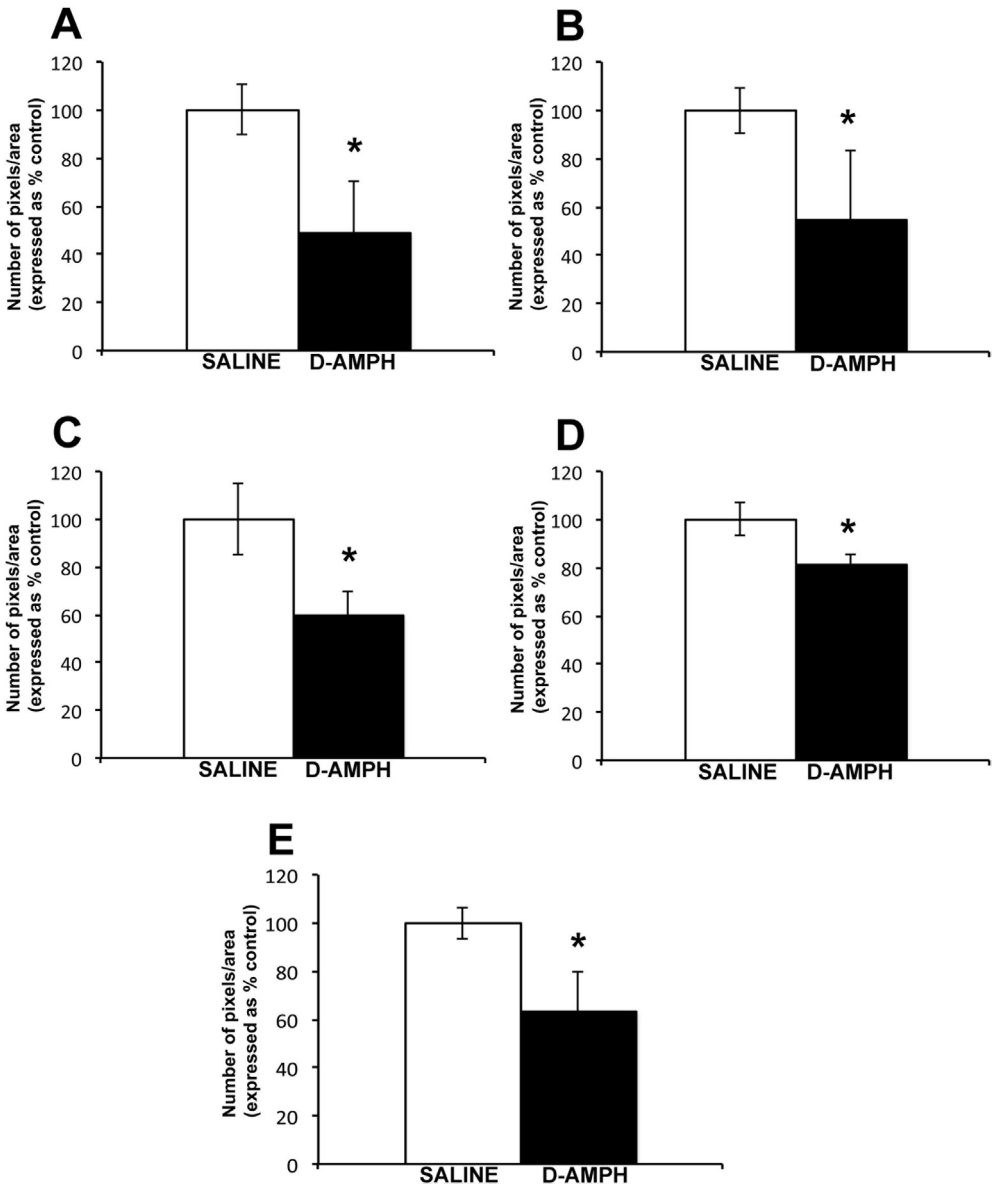

Fig. 5. Semi-quantitative analysis of BDNF-ir following 4d of D-AMPH withdrawal. Data are presented as the percentage of BDNF-ir particles in saline-treated control animals in the PRL (**A**), NAcC (**B**), NAcS (**C**), DG (**D**) and BLA (**E**). The levels of BDNF-ir were significantly decreased in all regions of interest, 4d following the last dose of D-AMPH. $^{*}p < 0.05$ vs. saline-treated animals.

animals performed similarly in the forced swim test, i.e., both groups showed little immobility (Murray et al., 2014b). However, as described above, our data also showed that BDNF levels were significantly decreased in the hippocampus and prefrontal cortex at 4 d post-D-AMPH withdrawal. Diminished BDNF levels in these regions are associated with depressive-like behaviors in animal models of MDD, which would suggest that at 4d post-D-AMPH, animals could still be experiencing depression-like symptoms despite performing similar to controls in the forced swim test (Borsoi et al., 2015; Gersner et al., 2014; Murray et al., 2014b; Roceri et al., 2004). Indeed, several studies have shown that depression-like symptoms, as determined by reduced levels of intracranial self-stimulation, decreased responding for a sucrose reward, or an exaggerated negative contrast to sucrose consumption following an incentive downshift can persist for several days following withdrawal from escalating doses of D-AMPH (Barr et al., 2002; Barr and Phillips, 1999, 2002; Cryan et al., 2003). Thus, it is possible that under circumstances, such as longer periods of D-AMPH withdrawal, the forced swim stress test may be a less sensitive indicator of depression-like symptoms. Future studies will examine whether decreased BDNF levels after longer periods of D-AMPH withdrawal are associated with depressive-like symptoms as measured by other behavioral indices, such as sucrose consumption.

Recent data indicates that when levels of BDNF are diminished in the hippocampus and prefrontal cortex after exposure to a stressor, treatment with ketamine can restore levels of BDNF (Autry et al., 2011; Garcia et al., 2008; Zhou et al., 2014). It has been suggested that ketamine exerts its effects on BDNF via inhibition of NMDAR-mediated EPSCs, leading to decreased phosphorylation and activity of eEF2 kinase, resulting in a rapid increase in the translation of BDNF (Autry et al., 2011). It is paradoxical that synaptic plasticity is dependent upon protein translation driven by the activation of NMDA receptors, while the effects of ketamine on BDNF expression require protein translation that is dependent upon the blockade of NMDA receptors. This apparent discrepancy

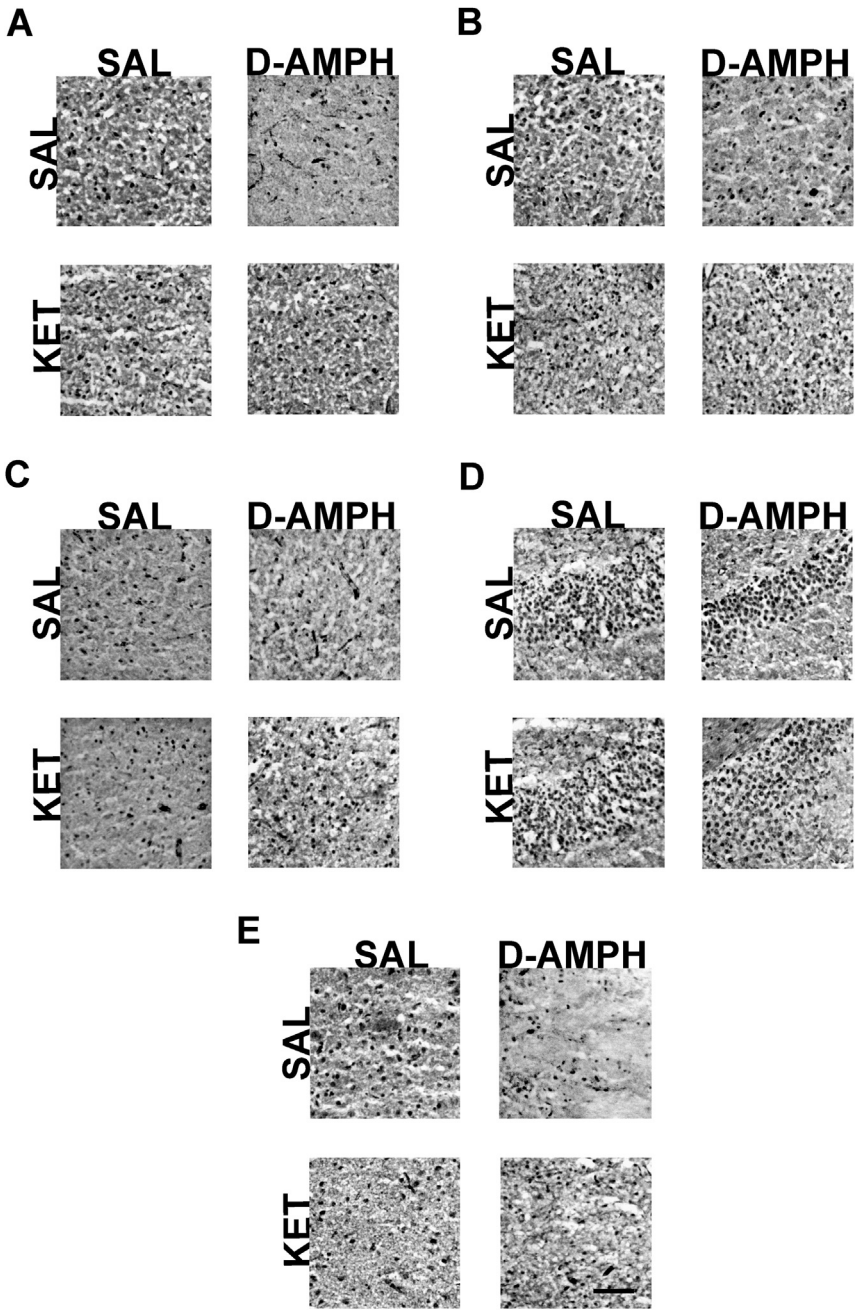

Fig. 6. Photomicrographs of BDNF-ir following 4d of D-AMPH withdrawal combined with ketamine treatment. D-AMPH withdrawal and ketamine-induced changes BDNF-ir in the PRL (**A**), NAcC (**B**), NAcS (**C**), DG (**D**) and BLA (**E**) at 4d following the last dose of D-AMPH. The levels of BDNF-ir appear to be restored by treatment on day 4 of withdrawal with ketamine in all regions of interest, except for the BLA. Scale bar = 100 μM.

may be related to the level of neuronal activity, as recent data indicates that in the absence of action potentials, resting NMDA receptor activity results in sustained phosphorylation of eEF2 thereby halting translation, while blockade of NMDA receptors at rest attenuates eEF2 phosphorylation, allowing translation to occur (Autry et al., 2011). It is possible that during psychostimulant withdrawal, there is an overall decrease in neuronal activity, allowing for NMDA receptor blockade to drive translation of BDNF. However, it has previously been shown that following repeated psychostimulant exposure, basal glutamate levels are elevated at 24 h up to 21 days after withdrawal (Lominac et al., 2012), which would suggest that there could be increased neuronal activity during this time period. Clearly additional studies are needed to further elucidate the contribution of neuronal activity and the ability NMDA receptor blockade to drive BDNF translation following psychostimulant withdrawal. Nevertheless, our findings are among the first to demonstrate that ketamine can alter the neurochemical changes that occur during psychostimulant withdrawal, as ketamine treatment reversed the D-AMPH-induced decrease in BDNF levels in the hippocampus, similar to what has been observed in studies where animals were exposed to stressor. Our data are also the first to indicate that ketamine treatment can also reverse the D-AMPH-induced decrease in BDNF levels in the PRL and NAc. However, ketamine treatment did not significantly reverse the D-AMPH-induced decrease in BDNF levels in the amygdala. It is not clear why ketamine did not alter BDNF levels in

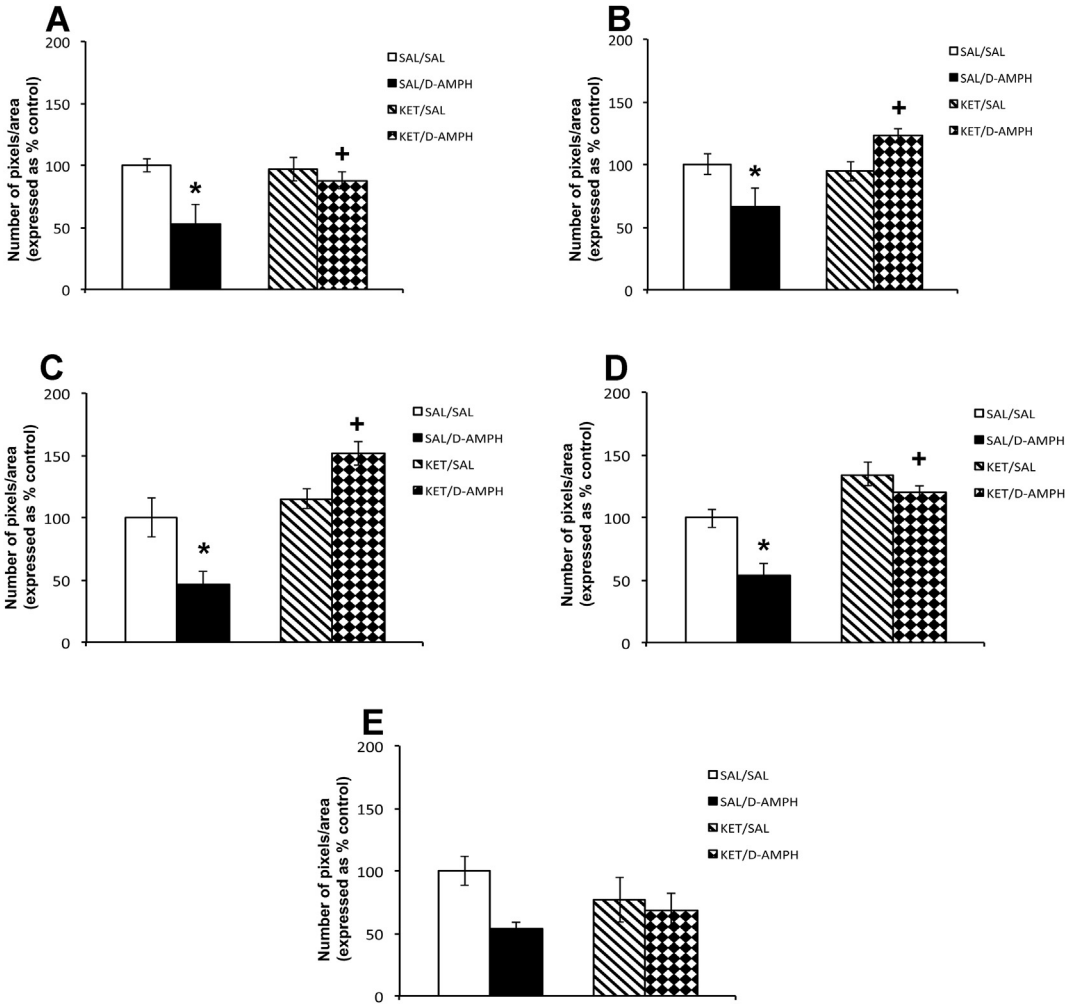

Fig. 7. Semi-quantitative analysis of BDNF-ir following 4d of D-AMPH withdrawal combined with ketamine treatment. Data are presented as the percentage of BDNF-ir particles in saline-treated control animals in the PRL (**A**), NAcC (**B**), NAcS (**C**), DG (**D**) and BLA (**E**). The levels of BDNF-ir were significantly decreased in all regions of interest, 4d following the last dose of D-AMPH. However, treatment with ketamine on day 4 of withdrawal resulted in a significant increase in BDNF-ir in all regions of interest, except for the BLA, where there was only significant overall main effect of D-AMPH treatment. $^{*}p < 0.05$ vs. saline-treated, vehicle-post-treated animals; $+p < 0.05$ vs. D-AMPH-treated, vehicle-post-treated animals.

this region, although it is possible that the timing and/or dose of ketamine were insufficient to induce a significant reversal of D-AMPH-induced decreased BDNF levels in the amygdala. Nevertheless, these data raise the possibility that ketamine could ameliorate the deleterious effects of D-AMPH withdrawal through its ability restore levels of BDNF through out the limbic system. However, additional studies are needed in order to confirm that treatment with ketamine after chronic psychostimulant exposure also reverses the depression-like behaviors that are often observed following psychostimulant withdrawal.

Interestingly, our current data show that while ketamine treatment restores diminished BDNF levels in regions such as the hippocampus in animals exposed to D-AMPH, ketamine alone does not alter BDNF levels in saline-treated control animals. This lack of effect of ketamine alone on BDNF levels in control animals may be explained by a recent study from Vasquez and co-workers (Vasquez et al., 2014). In this study, the authors posit that chronic exposure to stress results in a NMDA receptor-mediated dysregulation of calcium signaling, which leads to a decrease in BDNF levels in the hippocampus and treatment with a NMDA receptor antagonist may help to restore the balance of calcium signaling and BDNF levels. A similar dysregulation of calcium signaling could also contribute to the diminished levels of BDNF in the hippocampus following the stress of D-AMPH withdrawal. It is possible that the effects of ketamine are more pronounced following exposure to a stressor, where calcium signaling is disrupted, with NMDA receptor blockade bringing BDNF levels back into the normal range. On the other hand, non-stressed animals would presumably have normal calcium signaling and BDNF levels, and therefore may be less sensitive to the restorative effects of NMDA receptor blockade on BDNF levels.

5. Conclusion

These findings indicate that repeated, escalating doses of D-AMPH followed by 24 h or 4d of withdrawal results in widespread alterations in BDNF levels in the limbic regions of rat brain. At 24 h post-D-AMPH withdrawal, alterations in BDNF levels were restricted to the NAc shell and hippocampus, whereas by 4 d post-D-AMPH withdrawal, widespread decreases in BDNF were observed in the PRL, hippocampus, amygdala, and NAc core and shell. It is possible that decreased BDNF levels in the PRL following D-AMPH withdrawal may underlie the cognitive impairments observed with this disorder, and could also alter limbic system

pathways that mediate relapse into drug-seeking behaviors. In addition, decreases in BDNF activity in the hippocampus, amygdala and NAc could contribute to the emotional, motivational and memory impairments that are observed following withdrawal from chronic psychostimulant exposure. Our data also show that the majority of the decreases in BDNF levels observed at 4d post-D-AMPH withdrawal are responsive to treatment with ketamine resulting in a restoration of BDNF levels in the hippocampus, PRL and NAc, indicating that the neurochemical alterations and negative effects of D-AMPH withdrawal could be reversed by treatment with ketamine.

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