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NEUROTOXIC (+)-METHAMPHETAMINE TREATMENT INCREASES BRAIN-DERIVED NEUROTROPHIC FACTOR AND TROPOMYOSIN RECEPTOR KINASE B (TrkB) EXPRESSION IN MULTIPLE BRAIN REGIONS

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Abstract

Methamphetamine (MA) is an abused stimulant which can result in cognitive deficits and monoamine depletions. Animal models of neurotoxic MA exposure show reductions in dopamine, serotonin, and their associated transporters. MA abuse can result in long-term attention, working memory, and executive function deficits in humans and deficits in route-based egocentric learning, novel object recognition, and novel odor preference in rodents. MA has also been shown to affect brain-derived neurotrophic factor (BDNF) in humans and rodents. This experiment examined the effects of a MA binge dosing regimen (10 mg/kg × 4 at 2 h intervals, s.c.) in Sprague-Dawley rats on BDNF, tropomyosin receptor kinase B (TrkB), and tyrosine hydroxylase (TH) mRNA expression, and plasma corticosterone. Tissues were collected 1, 7, and 24 h following the last MA dose. Expression of BDNF and TrkB mRNA was analyzed using *in situ* hybridization with cRNA probes. Frontal, parietal, and entorhinal cortical BDNF mRNA expression were increased by MA exposure at all time-points. Increases in BDNF mRNA message were also seen in the hippocampal CA1, prefrontal cortex (PFC), piriform cortex, and locus coeruleus but only at specific times. TrkB mRNA expression was modified in several subregions of the hippocampus as well as in PFC and striatum. TH mRNA was increased at the 1 h time-point in the substantia nigra pars compacta with no differences noted at the other times. Corticosterone levels were increased at all three time-points. The findings suggest that BDNF and its receptor may be upregulated as a compensatory mechanism after MA exposure.

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Keywords

Methamphetamine; brain-derived neurotrophic factor; BDNF; tropomyosin receptor kinase B; TrkB

Methamphetamine (MA) is an addictive psychostimulant widely abused in the United States with 52% of 50 year old and 11% of 18 year old high school graduates reporting use of at least one type of amphetamine in their lifetime (Johnson et al., 2009). With the percentage of substance abuse treatment admissions for primary MA abuse more than doubling between 1995 and 2005, and long-term abuse leading to health complications, understanding the mechanism of action and developing treatments for MA users is of increasing importance (Substance Abuse and Mental Health Services Administration, 2008).

Acutely, MA heightens attention, decreases fatigue, suppresses appetite, and increases anxiety (Meredith et al., 2005). It also causes sympathetic nervous system stimulation and increases cortisol (Fehm et al., 1984). Chronic MA abuse produces memory impairments, reductions in sustained attention, deficits in executive function, and neurochemical changes (Barr et al., 2006). Autopsy and imaging studies show that chronic MA users exhibit reductions in brain dopamine (DA) content, dopamine transporter (DAT) density (Wilson et al., 1996), brain serotonin (5-HT), tyrosine hydroxylase (TH) levels (Kish et al., 2009), serotonin reuptake transporter (SERT) density (Sekine et al., 2006), and in cases of extreme abuse, reductions in striatal VMAT2 (Kitamura et al., 2007). Binge MA exposure in rodent models do not fully mimic human abuse patterns of intake but importantly they do induce similar neurochemical changes in the brain. For example, rats show reductions in brain DA and 5-HT and their transporters (DAT and SERT) following exposure to 3–4 doses of MA (Chapman et al., 2001;Fukumura et al., 1998). Decreased activity of TH is also observed within 6 h following binge doses of MA that persist for at least 30 days post-exposure (Hotchkiss et al., 1979;Hotchkiss and Gibb, 1980). Deficits in cognitive function (egocentric navigation, novel object recognition, non-spatial recognition memory, fixed-route motor learning, and novel odor preference) have also been observed following binge doses of MA in rodents, with little or no effects on spatial learning (Belcher et al., 2005;Bisagno et al., 2002;Chapman et al., 2001;Daberkow et al., 2005;Friedman et al., 1998;He et al., 2006;Herring et al., 2008b;O'Dell et al., 2010;Schroder et al., 2003).

Neurotrophins may play a role in some of the effects of MA. In rodents alterations in basal levels of brain-derived neurotrophic factor (BDNF) decrease MA-induced neurotoxicity (Dluzen et al., 2002;Dluzen, 2004). In MA-dependent human abusers, plasma BDNF levels remain elevated after 30 or more days of abstinence (Kim et al., 2005). Through binding to its high affinity receptor tropomyosin receptor kinase B (TrkB), BDNF enhances neuronal growth, maintenance, and survival, is involved in neuronal plasticity and firing rates, and influences long-term potentiation and memory consolidation (Barbacid, 1995;Merlio et al., 1992;Thoenen, 1995). BDNF also modulates DA and 5-HT levels, contributes to the survival and maintenance of DA neurons, and can alter neurotransmitter synthesis, metabolism, and release (Guillin et al., 2001;Hyman et al., 1991;Lyons et al., 1999;Yurek and Seroogy, 2001;Altar et al., 1997).

The time-dependent effects of binge doses of MA on BDNF and TrkB expression have not been examined. The present experiment investigated the effects of a binge MA dosing regimen on BDNF and TrkB mRNA in brain regions important in the cognitive deficits associated with MA exposure. Given the catecholamine changes previously demonstrated following MA treatment (Herring et al., 2008b), mRNA levels of TH were included in selected regions. Plasma levels of corticosterone were determined as an additional marker of

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MA effects (Herring et al., 2008b). Corticosterone is known to affect levels of neurotrophins and their receptors (Schaaf et al., 1998;Schaaf et al., 2000;Smith et al., 1995).

2. Experimental Procedures

2.1 Animals

Adult male Sprague-Dawley CD IGS rats (250–275 g) were acquired from Charles River Laboratories, Raleigh, NC. Three days after arrival, rats were implanted with subcutaneous temperature transponders (IPTT-200, Biomedic Data Systems, Seaford, DE) under isoflurane anesthesia. Animals were initially housed 2 per cage and all procedures were in compliance with the Institutional Animal Care and Use Committee.

2.2 Methamphetamine administration

(+)-Methamphetamine-HCl (expressed as the freebase, provided by the National Institute on Drug Abuse, Rockville, MD, >95% pure) was administered subcutaneously in the dorsum in four doses of 10 mg/kg with 2 h intervals between doses. Control animals received saline (SAL; 3 ml/kg). During dosing, animals were maintained in $28 \times 16 \times 12$ cm^3 cages in a separate room from the colony at an ambient temperature of 23.8 ± 1°C. Body weights were obtained prior to treatment. Body temperatures were monitored at 30 min intervals beginning with the first injection and for 8 h thereafter. Animals were cooled in a shallow water bath if transponder readings reached 40.2°C to prevent severe hyperthermia (Herring et al., 2008a).

2.3 Tissue collection

Animals were decapitated 1, 7, or 24 h after the last injections (N = 3–5/time point/group). Blood for corticosterone analysis was collected in 2% EDTA (0.05 ml/tube). Brains were removed, mounted on tissue-freezing medium (Ted Pella, Inc., Redding, CA), and frozen on dry ice.

2.4 Assessment of corticosterone

Blood was centrifuged (1399 RCF) for 25 min at 4°C, and then plasma was collected and stored at −80°C until assayed. Plasma was diluted 3:1 in assay buffer and assayed in duplicate for corticosterone with an EIA kit (Immunodiagnostic Systems Inc., Fountain Hills, AZ).

2.5 In situ hybridization

Frozen brains were serially sectioned on a cryostat (at 10 µm thickness) throughout the rostrocaudal aspects of the prefrontal cortex (PFC), striatum, hippocampus, ventral midbrain, and locus coeruleus (LC), thaw-mounted onto Superfrost Plus microslides (VWR, Batavia, IL), and stored at −20°C until hybridization. Semiadjacent sections from each area and time point were subsequently hybridized with ^{35}S-labeled cRNA probes at a concentration of 1×10^6 cpm/50 µl for detection of BDNF and TrkB mRNAs, as well as for TH mRNA in the ventral midbrain and LC. Pretreatment, hybridization, and post-hybridization treatment of tissue sections were performed as described in detail previously (Numan, 1998;Numan et al., 2005;Seroogy and Herman, 1997). The BDNF cDNA plasmid (a gift from Christine Gall, University of California at Irvine) produced antisense RNA transcripts of 540 bases (Isackson et al., 1991). The TrkB plasmid resulted in antisense RNA transcripts of 200 bases (Dixon and McKinnon, 1994). The TH cDNA plasmid (provided by James Herman, University of Cincinnati) resulted in an antisense RNA transcript of 366 bases. The sections were incubated in hybridization solution at 60°C in a humidified chamber for 18–24 h. Following post-hybridization treatment, the slides were exposed to

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BioMax MR film (Kodak, Rochester, NY) for an appropriate amount of time for each region (TH = 1 day; BDNF = 10–15 days; TrkB = 8–17 days) for detection and localization of hybridization signal. The films were subsequently developed with GPX developer and fixer (Kodak).

2.6 Analysis

Semi-quantitative in situ hybridization analysis of the film autoradiographs was performed using Scion Image (NIH) software. The optical density (OD) of hybridization signal for each probe was obtained at each time point to compare densities of hybridization between MA- and SAL-treated animals. Anatomical delineations were determined according to a rat brain atlas (Paxinos and Watson, 1986). At least six measurements were taken from each region analyzed for each cRNA probe for each animal. A background control value was taken for each section (from an unlabeled region; e.g., corpus callosum) and the value was subtracted from the OD of the region examined to give the mean corrected grey level. The hybridization data were analyzed using t-tests at each time point and data for MA-treated animals are expressed as a percentage of controls. Plasma BDNF levels have been shown to be increased in humans following long-term MA exposure (Kim et al., 2005), in rodents after developmental MA exposure (Grace et al., 2008;Skelton et al., 2007), or after adult MDMA exposure (Hemmerle et al, submitted); hence increases were predicted and unidirectional t-tests were used for BDNF comparisons while two-tailed tests were used for all other comparisons. Body weight and corticosterone levels were analyzed using repeated measure analysis of variance (ANOVA, Proc Mixed, SAS 9.2, SAS Institute, Cary, NC). Body temperatures at 7 h and 24 h were analyzed similarly. Significance was set at $p \leq 0.05$ and trends at $p \leq 0.10$.

3. Results

3.1 Body Weight and Temperature

No differences in body weights were found between groups prior to treatment (SAL: 320.2 ± 2.6 g; MA: 324.1 ± 2.7 g). Two SAL animals had malfunctioning transponders and were not included in the temperature analysis. There were significant main effects of treatment ($F(1, 51.5) = 29.13$, $p < 0.001$) and time ($F(16, 414) = 9.21$, $p < 0.001$) on body temperature with MA-treated animals showing increased temperature compared with SAL controls (Fig. 1). A significant treatment × time interaction ($F(16, 414) = 2.09$, $p < 0.01$) was obtained such that animals treated with MA began showing hyperthermia 60 min following the first dose ($p < 0.001$) and this continued for the remainder of the monitoring period ($p < 0.05$ to 0.001) with the exception of the 150 and 180 min time points, where there were no significant differences in temperature (initial N = 16/MA, 14/SAL; last 2 time points N = 10/MA, 9/SAL).

3.2 Corticosterone Levels

Corticosterone levels were increased in MA-treated animals across all time points compared to SAL-treated animals ($F(1,23) = 17.57$, $p < 0.001$) (Fig. 2). Time was also significant ($F(2,23) = 19.75$, $p < 0.001$), whereas only a trend was observed for the treatment × time interaction ($F(2,23) = 2.58$, $p < 0.10$).

3.3 Gene Expression

3.3.1 BDNF mRNA—Results are shown in Table 1. MA-treated animals had significantly increased BDNF mRNA expression in the entorhinal cortex (1 h: $t(8) = 3.73$, $p < 0.01$; N = 5/group; 7 h: $t(7) = 2.44$, $p < 0.05$; N = 4/MA, 5/SAL; 24 h: $t(8) = 2.68$, $p < 0.01$; N = 5/group) and the parietal cortex (1 h: $t(4) = 14.42$, $p < 0.001$; N = 3/group; 7 h: $t(6) = 7.80$, p <

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0.001; N = 3/MA, 5/SAL; 24 h: $t(8) = 3.10$, $p < 0.01$; N = 5/group) relative to SAL-treated controls. In the anterior cingulate cortex (Acc) elevated BDNF mRNA expression in MA-treated rats was observed at 1 h, but not 7 or 24 h compared with controls ($t(4) = 2.29$, $p < 0.05$; N = 3/group).

In the PFC, BDNF mRNA was increased 1 h and 24 h post MA treatment (1 h: $t(4) = 6.72$, $p < 0.001$; 24 h: $t(4) = 2.46$, $p < 0.05$; N = 3/group) compared to controls, but no change was seen at 7 h. In the frontal cortex (FC), MA treatment increased BDNF mRNA expression at all three time points (1 h: $t(4) = 15.35$, $p < 0.001$; N = 3/group; 7 h: $t(6) = 2.39$, $p < 0.05$; N = 3/MA, 5/SAL; 24 h: $t(8) = 7.01$, $p < 0.001$; N = 5/group).

Increased BDNF mRNA expression was also seen in the CA1 region of the hippocampus (1 h ($t(5) = 2.16$, $p < 0.05$; N = 4/MA, 3/SAL) and 24 h ($t(6) = 2.02$, $p < 0.05$; N = 3/MA, 5/SAL) following MA treatment but no change at 7 h. In the hippocampal CA3 region, a trend was seen at 24 h for increased BDNF mRNA in MA-treated animals compared to SAL-treated animals ($t(6) = 1.57$, $p = 0.08$, N = 3/MA, 5/SAL) with no differences at the 1 (N = 4/MA, 3/SAL) or 7 h (N = 4/MA, 5/SAL) time points. No differences were observed in BDNF mRNA in the stratum granulosum of the dentate gyrus (DG).

For BDNF mRNA in the locus coeruleus (LC), expression significantly increased 1 h post MA treatment ($t(7) = 2.73$, $p < 0.01$; N = 4/MA, 5/SAL), with a trend towards increased expression at 7 h ($t(6) = 1.72$, $p = 0.07$; N = 4/group), but no difference from SAL was observed at 24 h. Freezer malfunction caused loss of tissue for the 1 h time point for the piriform cortex. No alteration in BDNF mRNA expression in the piriform cortex was seen 7 h post MA treatment, however hybridization was significantly increased 24 h later ($t(8) = 3.79$, $p < 0.01$; N = 5/group) compared to controls.

No significant difference in BDNF mRNA was seen in the ventral tegmental area (VTA) or substantia nigra pars compacta (SNpc) following MA exposure.

3.3.2 TrkB mRNA—Results are shown in Table 2. In the parietal cortex, TrkB mRNA levels were elevated 7 h ($t(6) = 2.42$, $p < 0.05$; N = 5/group) post-treatment but were not different from controls at 24 h. A trend toward increased TrkB expression in the FC was present at 7 h ($t(6) = 2.05$, $p = 0.09$; N = 3/MA, 5/SAL) in MA-treated animals, with no difference from SAL-treated animals observed at 24 h. The 1 h data were not available from the same freezer malfunction.

TrkB mRNA hybridization in the PFC was increased at the 1 h time point ($t(4) = 6.13$, $p < 0.01$; N = 3/group), but not at 7 or 24 h in MA-treated animals relative to controls (Fig. 10A). In the striatum, MA increased TrkB expression 1 h ($t(4) = 4.02$, $p < 0.05$; N = 3/group) and 7 h ($t(4) = 2.95$, $p < 0.05$; N = 3/group) post-treatment, but no difference was observed at 24 h.

In the CA1 and DG, TrkB expression was significantly increased in MA-treated rats at 24 h (CA1: $t(6) = 3.62$, $p < 0.01$; DG: $t(6) = 5.56$, $p < 0.001$; N = 3/MA, 5/SAL) but was not different at 1 h or 7 h. A trend at 24 h for decreased TrkB expression in the CA3 region was observed in MA-treated animals compared with SAL controls ($t(6) = 2.04$, $p = 0.09$; N = 3/MA, 5/SAL).

No alterations in TrkB mRNA expression were found in the Acc, LC, SNpc, VTA, piriform or entorhinal cortices from MA treatment.

3.3.3 TH mRNA—Results are shown in Table 3. TH mRNA expression in the SNpc was increased at 1 h in MA-treated animals compared with SAL-treated animals ($t(8) = 2.36$, $p <$

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0.05; N = 5/group) with no other alterations seen. No TH expression changes were observed in MA-treated animals in the VTA or LC.

4. Discussion

Both the temperature and corticosterone increases seen in this experiment are congruent with previous studies and are indicative of the neurotoxic effects of MA using a binge exposure model in adult animals (Herring et al., 2008b;Szumlinski et al., 2001). The results demonstrate that binge MA treatment causes increases in brain BDNF mRNA expression. The data support MA regulation of BDNF expression and that such effects are likely independent of corticosterone, as previously protracted corticosterone increases have been linked with decreased BDNF protein and mRNA expression levels (Schaaf et al., 1998;Schaaf et al., 2000;Smith et al., 1995) whereas increases were seen here. While TrkB also exhibited increases in transcript levels following MA exposure, affected regions were less widespread and no expression alterations were seen across all time points in any brain region. TrkB expression was uniquely decreased in the hippocampal DG. BDNF, but not TrkB, mRNA levels were affected by MA treatment in the entorhinal and piriform cortices, Acc, and LC. These results are indicative of differential MA-induced regulation of TrkB and BDNF.

It is currently unknown what the functional effects of BDNF and TrkB mRNA increases are following MA exposure. Neurotrophins, including BDNF, are synthesized as precursor proteins prior to being cleaved into their mature form (Edwards et al., 1988). When secreted, proBDNF binds with high affinity to the proapoptotic receptor $p75^{NTR}$ (Lee et al., 2001), unlike BDNF that binds with weak affinity. It is not possible to determine if the BDNF expression increases seen herein were cleaved into the mature BDNF or not based on the current data. However, levels of proBDNF are usually small compared to BDNF (Yang et al., 2009), and prior studies have shown a neuroprotective effect of increased BDNF following a neurotoxic insult (Canals et al., 2001;Martinez-Serrano and Bjorklund, 1996;Perez-Navarro et al., 2000), not unlike the pattern of effects seen here.

The data are consistent with previous studies showing BDNF and TrkB increases following other types of CNS injury such as seizures, ischemia, excitotoxicity, traumatic injury, and hypoglycemia in multiple brain regions, including the hippocampus (Gall, 1993;Hicks et al., 1999a;Madinier et al., 2009;Merlio et al., 1993;Metsis et al., 1993;Nibuya et al., 1995;Canals et al., 1998;Canals et al., 2001;Kokaia et al., 1998;McAllister et al., 1999;Rocamora et al., 1996). The hippocampus is known to be vulnerable to injury and to exhibit BDNF and TrkB expression increases following damage (Hicks et al., 1997;Hicks et al., 1998;Hicks et al., 1999b;Merlio et al., 1993;Metsis et al., 1993;Nibuya et al., 1995). Therefore, mechanisms behind the increases seen here after MA treatment may be similar. The TrkB decreases seen in the hippocampal DG stand out as an exception to the general pattern of injury-induced increases (Merlio et al., 1993;Nibuya et al., 1995). This decrease was seen only at the 24 h time period but may reflect a longer-term biphasic response to the drug. Future experiments should assess TrkB at longer intervals to determine if this downward shift persists.

Other brain regions exhibiting MA-induced changes in BDNF or TrkB expression are also involved in behavioral abnormalities caused by MA. Chronic MA use in humans is associated with impairments in working memory, attention, and executive function; behaviors mediated to a large extent by the FC, PFC, and Acc (Barr et al., 2006;Dalley et al., 2004). In rats, MA exposure causes deficits in novel object recognition (Belcher et al., 2005), a behavior mediated through the piriform cortex (Broad et al., 2002) and hippocampus (Broadbent et al., 2010), as well as causing deficits in egocentric navigation

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(Herring et al., 2008a). Egocentric learning is a navigational task that is distinct from spatial learning and relies on the integration of local and self-movement cues (Byrne, 1982;Cook and Kesner, 1988). Both the entorhinal (Moser et al., 2008) and parietal cortices (Butters et al., 1972;Sato et al., 2006) contain cell bodies critical for this type of navigation and both show BDNF mRNA increases for at least 24 h following the MA treatment.

The striatum, where TrkB increases following MA treatment were seen, is also implicated in egocentric navigation and fixed-route motor learning (Chapman et al., 2001;Cook and Kesner, 1988;Packard and Knowlton, 2002). Striatal TrkB mRNA increases have previously been shown to occur after excitotoxic injury from glutamate receptor agonists (Canals et al., 1999). With virtually no BDNF mRNA found within the striatum, the substantial levels of BDNF protein found in striatal neurons are thought to be trafficked via cortical and other afferents to this region in an activity-dependent manner (Altar et al., 1997). Cortical BDNF upregulation seen following striatal excitotoxic injury can be blocked by exogenous administration of BDNF in striatal neurons, suggesting that cortical BDNF may be an endogenous protective response to striatal insult (Canals et al., 2001).

BDNF expression in the LC was increased 1 h post-treatment. Noradrenergic neurons in the LC act as a neuroprotective agent against nigrostriatal DA neuronal toxicity following exposure to MA (5 mg/kg × 3, 2 h apart) and other DA neurotoxins (Fornai et al., 1995;Fornai et al., 1998;Weinshenker et al., 2008), and this may have occurred here, although it was beyond the scope of this experiment to test this idea.

Previously it has been found that BDNF mRNA in the ventral midbrain (VTA/SNpc) increases 24 h following binge MA exposure in conjunction with 3 weeks of MA preconditioning (Cadet et al., (2009)), but not following binge-only MA treatment. This is consistent with the present data showing no change in BDNF or TrkB mRNA levels in either the VTA or SNpc, which are present within the DA cells in this region (Numan and Seroogy, 1999;Seroogy et al., 1994). The SNpc was the only region that showed increased TH expression levels 1 h following MA treatment, indicative of increased DA content. An acute (15 mg/kg) dose of MA has also been shown to increase TH activity in the striatum 1 h after exposure and this area receives abundant projections from the SNpc (Haughey et al., 1999). These data are in contrast to the large TH reductions seen at longer intervals after binge dosing regimens of MA (Cappon et al., 2000;Krasnova and Cadet, 2009). TH mRNA expression has previously been shown to be decreased in the SNpc 13 days following binge MA exposure (Chapman et al., 2001). TH protein reductions typically occur 12–48 h after treatment, but these are different than for TH mRNA (Cappon et al., 2000).

The dense DA projections to the striatum and other related areas, such as the PFC, are highly sensitive to MA and have been hypothesized to mediate the DA-dependent cognitive deficits seen in MA users (i.e., they lack deficits in non-dopaminergic spatial learning processes) (Barr et al., 2006). Increases in DA release are a common characteristic of drugs of abuse, and cocaine, amphetamine, and morphine have all shown to increase BDNF expression (Le Foll et al., 2005;Meredith et al., 2002) suggesting that a DA-mediated mechanism may be involved in regulation of BDNF expression following exposure to such drugs (Guillin et al., 2001;Le Foll et al., 2005). This is in line with evidence that the BDNF/TrkB pathway can modulate MA-dependent DA release and is involved in the induction of DA-related behavior (Blochl and Sirrenberg, 1996;Guillin et al., 2001;Narita et al., 2003).

MA-induced excitotoxic damage is another potential mechanism for BDNF and TrkB expression increases. Other models of excitotoxic neuronal damage also show BDNF and TrkB mRNA increases (Canals et al., 1998;Canals et al., 1999;Dong et al., 2006;Martinez-Serrano and Bjorklund, 1996;Perez-Navarro et al., 2000), and *c-fos* and BDNF expression

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increases have been shown to be co-localized in hippocampal neurons following excitotoxic damage (Dong et al., 2006). These expression alterations have differential regulation as compared to other neurotrophins and their receptors (Canals et al., 1999;Canals et al., 2001), implying a specific role for the BDNF/TrkB pathway following exposure to excitotoxins. The BDNF increases seen following excitotoxic neuronal injury appears to be neuroprotective (Canals et al., 2001;Martinez-Serrano and Bjorklund, 1996;Perez-Navarro et al., 2000), potentially having similar involvement following neurotoxic MA exposure. *In vitro* experiments in primary cortical neurons have shown that 12 h pretreatment with recombinant BDNF provides protection from MA-induced cell death (Matsuzaki et al., 2004). In addition, mice that over- or under-express BDNF mRNA exhibit decreased striatal DA loss compared to wild-type mice following acute MA treatment (Dluzen et al., 2002;Dluzen, 2004;Joyce et al., 2004), although another study found that intrastriatal administration of BDNF 24 h prior to acute MA treatment was ineffective against striatal DA loss (Cass et al., 2006). Continued work is needed to elaborate on the potential neuroprotective effects of BDNF pret on neurotoxic MA exposure as well as to understand the role that increases in endogenous BDNF have on the brain following MA-induced insult. Furthermore, studies are needed to determine how long following the injury this response remains if, in fact, BDNF and/or TrkB exert neuroprotective effects in response to MA exposure.

In conclusion, the present data demonstrate that a binge/neurotoxic treatment regimen of MA has selective effects on BDNF, TrkB, and TH mRNA expression in different brain regions up to 24 h following exposure. Most of the brain regions affected showed BDNF and TrkB increases. These are the same regions associated with several of the CNS dysfunctions observed in chronic MA users and in rats given neurotoxic MA doses. The relationship between neurotrophic changes and the behavioral consequences of MA-induced neurotoxicity may provide insight into future ways to ameliorate such deficits.

Abbreviations

Acc anterior cingulate cortex

BDNF brain-derived neurotrophic factor

DA dopamine

FC frontal cortex

LC locus coeruleus

MA (+)-methamphetamine

PFC prefrontal cortex

5-HT serotonin

SNpc substantia nigra pars compacta

TrkB tropomyosin receptor kinase B

TH tyrosine hydroxylase

VTA ventral tegmental area

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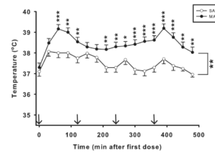

Figure 1. Body temperature of animals (mean ± SEM)

No differences in initial temperatures were observed (Time = 0); MA produced significant increases in body temperature. Arrows denote injection times. Starting N was SAL = 14; MA = 16. Final N was SAL = 9; MA = 10. *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001.

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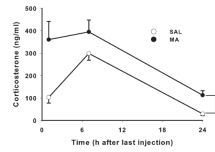

Figure 2. Plasma corticosterone levels (mean ± SEM)

CORT levels were increased following MA exposure up to 24 h after the first dose compared with control animals. N at 1 h was SAL = 16, MA = 16; N at 7 and 24 h was SAL = 10; MA = 10. ***$p \leq 0.001$.

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Table 1

BDNF mRNA expression percent change in MA-treated animals compared to controls (mean ± SEM)

Brain Region	1 h	7 h	24 h
FC	228.9 ± 2.3 ***	137.25 ± 14.9 *	127.9 ± 2.1 ***
Acc	126.7 ± 10.2	112.3 ± 7.9	121.2 ± 17.5
PFC	151.7 ± 7.1 ***	112.3 ± 7.9	148.3 ± 10.8 *
Parietal Ctx	177.1 ± 4.6 ***	190.8 ± 12.1 ***	116.5 ± 1.2 **
Piriform Ctx	N.A.D.	109.9 ± 7.2	135.8 ± 4.9 **
Entorhinal Ctx	140.5 ± 9.1 **	123.3 ± 6.9 *	144.9 ± 14.6 **
CA1	173.0 ± 14.4 *	145.5 ± 39.0	125.3 ± 8.7 *
CA3	138.2 ± 14.9	101.5 ± 8.9	108.1 ± 4.7 t
DG	128.4 ± 16.6	117.9 ± 12.6	97.3 ± 4.0
LC	132.2 ± 9.9 **	120.5 ± 7.3 t	112.1 ± 13.9
VTA	99.5 ± 0.9	101.9 ± 1.4	106.4 ± 6.9
SNpc	89.7 ± 6.8	83.5 ± 5.4	103.1 ± 16.9

Significance denoted as difference between MA-treated groups and SAL-treated groups within each time point.

t $p \leq 0.1$;

* $p \leq 0.05$;

** $p \leq 0.01$;

*** $p \leq 0.001$.

N.A.D. = No Available Data

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Table 2

TrkB mRNA expression percent change in MA-treated animals compared to controls (mean ± SEM)

Brain Region	1 h	7 h	24 h
FC	N.A.D.	109.6 ± 3.8^{t}	100.8 ± 1.3
Acc	103.1 ± 2.5	95.7 ± 3.7	103.6 ± 11.0
PFC	120.9 ± 2.1**	107.2 ± 3.9	106.9 ± 4.1
Parietal Ctx	N.A.D.	111.2 ± 2.6*	94.6 ± 3.7
Piriform Ctx	N.A.D.	104.0 ± 1.6	106.1 ± 3.7
Entorhinal Ctx	97.63 ± 2.5	89.7 ± 4.2	110.5 ± 4.3
CA1	101.7 ± 2.8	101.7 ± 6.4	102.3 ± 0.7**
CA3	97.6 ± 6.3	103.6 ± 7.1	96.6 ± 1.9^{t}
DG	96.1 ± 4.8	85.5 ± 12.2	105.3 ± 0.6***
VTA	98.9 ± 2.3	97.8 ± 3.0	104.8 ± 2.7
SNpc	104.7 ± 2.5	97.7 ± 3.0	N.A.D.
Striatum	130.2 ± 2.7*	144.6 ± 11.9*	104.8 ± 5.2

Significance denoted as difference between MA-treated groups and SAL-treated groups within each time point.

^{t} $p \leq 0.1$;

* $p \leq 0.05$;

** $p \leq 0.01$;

*** $p \leq 0.001$.

N.A.D. = No Available Data

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Table 3

TH mRNA expression percent change in MA-treated animals compared to controls (mean ± SEM)

Brain Region	1 h	7 h	24 h
LC	97.2 ± 8.1	85.7 ± 6.6	91.6 ± 5.6
VTA	98.2 ± 2.6	101.3 ± 1.8	103.4 ± 3.4
SNpc	129.0 ± 12.1 *	96.5 ± 18.6	104.9 ± 12.9

Significance denoted as difference between MA-treated groups and SAL-treated groups within each time point.

* $p \leq 0.05$.

N.A.D. = No Available Data