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Differential interactions of desipramine with amphetamine and methamphetamine: evidence that amphetamine releases dopamine from noradrenergic neurons in the medial prefrontal cortex.

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Running head title: Differential interactions of desipramine with amphetamines

Abstract

Amphetamine is more effective than methamphetamine at raising dopamine levels in the prefrontal cortex. The present study tested the hypothesis that norepinephrine transporters are involved in this difference. Using microdialysis, dopamine, norepinephrine, and serotonin were measured in the rat prefrontal cortex after administration methamphetamine or amphetamine, with and without perfusion of desipramine. Amphetamine raised norepinephrine levels more than methamphetamine did. Desipramine raised dopamine and serotonin levels but did not alter metabolite levels. Desipramine attenuated the increase in dopamine by amphetamine while increasing the dopamine released by methamphetamine. These data suggest that methamphetamine and amphetamine differ in altering prefrontal cortical dopamine levels and in interacting with norepinephrine transporters. It is proposed that amphetamine releases dopamine in the prefrontal cortex primarily through norepinephrine transporters, while methamphetamine interacts minimally with norepinephrine transporters.

Keywords: methamphetamine, amphetamine, dopamine, norepinephrine, microdialysis, medial prefrontal cortex.

Introduction

Methamphetamine (METH) and amphetamine (AMPH) are both abused psychostimulants (1). Previously, we have shown that 2 mg/kg AMPH was more effective than 2 mg/kg METH at raising extracellular dopamine (DA) levels in the prefrontal cortex (PFC), even though the two drugs had similar effects in the nucleus accumbens (NAC) (2).

However, DA uptake blockers, which increase DA in the NAC, have been shown to have no effect in the PFC (3). This may be because the PFC has sparse DA innervation, with a low density of DA transporters (DAT), and few DAT per DA terminal (4). The PFC does, however, have a large norepinephrine (NE) innervation compared to its DA innervation (5) and NE transporters (NET) have a higher affinity for DA than NE (6). This has led to the speculation that NET may be largely responsible for DA clearance in the PFC (7). Indeed, NET blockers have been shown to increase PFC DA levels (7,8). The NAC, which has less NE innervation and a higher level of DAT, removes DA primarily by DAT with little or no contribution from NET (9).

One experiment found that in the hippocampus, AMPH was more effective than METH at raising NE levels, suggesting that AMPH may be more effective than METH at blocking NET (10). Therefore, it may be expected that in the PFC, where NET may contribute to the clearance of DA, AMPH's greater effectiveness than METH at raising DA levels may be due to AMPH's greater

effectiveness at blocking DA removal through NET. If this were the case, then AMPH would also be more effective than METH at raising NE levels in the PFC. This would also explain why METH and AMPH could differ in raising DA levels in the PFC but have similar effects in the NAC, where NET has little effect on DA levels.

In order to test this hypothesis, the effects of METH and AMPH on NE levels in the PFC were measured using *in vivo* microdialysis on awake and freely moving Sprague-Dawley rats. To determine if blocking NET would eliminate the difference between the effects of METH and AMPH on DA in the PFC, DA and the DA metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were measured after METH or AMPH administration during reverse dialysis of the NET blocker desipramine. Serotonin (5-HT) levels were also measured. This experiment aimed not only to elucidate the mechanisms by which AMPH and METH release DA in the PFC but also to clarify the dynamics of DA clearance in the PFC; and this is the first study to measure DA metabolite levels during desipramine administration. If desipramine increases PFC DA mainly by blocking DA uptake by NET, then an accompanying decrease in DOPAC levels should result from the decrease in intracellular DA. Furthermore, this is also the first study to measure the effects of local desipramine on 5-HT levels in the PFC. The results of this study may have important implications for the treatment of

METH and AMPH addiction and further clarify the complex interactions between DA, NE, and 5-HT in the PFC.

Experimental Procedure

Animals

Naïve adult female Sprague-Dawley rats (Taconic, Germantown, NY, USA) weighing 250 – 275 g at the start of the experiments were used. Animals were group housed in clear polyurethane cages in a colony room controlled for temperature and humidity on a twelve-hour light dark schedule (lights on at 0700 h). Standard chow and water were available *ad libitum*. All experiments were carried out in accordance with *the NIH Guide for the Care and Use of Laboratory Animals* and were approved by the Albany Medical College Institute Animal Care and Use Committee.

Drug treatment

d-Methamphetamine HCl (METH; Sigma Chemical Co., St. Louis, Mo; $C_{10}H_{15}N^+HCl^-$, equivalent weight, 185.6) and d-amphetamine sulfate (AMPH; Sigma Chemical Co., St. Louis, Mo; $2(C_9H_{13}N) \cdot H_2SO_4$, equivalent weight, 184.5) were administered at 2 mg/kg, i.p., in 1 ml/kg saline. Doses refer to the weight of the salt, which result in METH and AMPH being administered at nearly identical equimolar doses of the free bases (10.8 $\mu\text{mol/mg}$). Saline was administered i.p. in equal volume as a control.

Desipramine (Sigma Chemical Co., St. Louis, Mo) was dissolved in the artificial cerebrospinal fluid (aCSF) perfusate at a concentration of 1 μ M and administered by reverse dialysis. Normal aCSF solution without desipramine was used as the control.

Surgery for microdialysis

Animals were anesthetized with 50 mg/kg i.p. pentobarbital. A guide cannula (CMA, Acton, MA, USA) was stereotaxically implanted, such that, when inserted, the tip of the microdialysis probe would be located in the PFC at +3.2 mm AP, 0.1 mm ML, and -6.1 mm DV(11). Animals were given at least four days of recovery from surgery and housed individually during this time to prevent disturbances to the guide cannula.

Microdialysis procedure

Animals were anesthetized with Brevital (38 mg/kg, i.p.) and a 2 mm microdialysis probe (CMA, Acton, MA, USA) was inserted through the guide cannula. Animals were perfused with normal aCSF (146 mM NaCl, 1.2 mM CaCl₂, 2.7 mM KCl, 1.0 mM MgCl₂, filtered and degassed) at a flow rate of 1 μ l/min.

The next day twenty minute samples were collected from awake and freely moving animals during the light cycle into plastic microcentrifuge vials. To prevent the oxidation of catecholamines, 2 μ l of a 0.95 N perchloric acid solution containing 1.4 mM EDTA and 2.8 mM sodium metabisulfite were added

to the vials. Baseline samples were collected for two hours. For animals receiving desipramine treatment, a liquid switch (CMA, Acton, MA, USA) was used to switch the perfusates from normal aCSF to aCSF containing 1 μ M desipramine after the baseline samples; samples were collected for an additional 80 minutes.

Animals were then injected i.p. with either 2 mg/kg METH, 2 mg/kg AMPH, or 1 ml/kg saline. Samples were collected for an additional three hours. At the end of the experiment, animals were anesthetized with Brevital (50 mg/kg, i.p.), probes were removed, and animals were sacrificed by decapitation. Brains were quickly removed and frozen for histological analysis.

HPLC analysis of DA, 5-HT, DOPAC, and HVA

The HPLC system consisted of an ESA 580 pump (ESA Inc., Chelmsford, MA) delivering mobile phase purchased from ESA (0.075 μ M sodium dihydrogenphosphate, monohydrate, 0.0017 μ M 1-octanesulfonic acid, 25 μ M EDTA in 10% HPLC grade acetonitrile, adjusted to a pH of 3 with phosphoric acid) at a flow rate of 0.53 ml/min. An ESA 540 autosampler injected 10 μ l of sample onto an ESA small bore reverse phase C-18 column (150x3, particle size 3 microns). Samples were detected by an ESA Coulochem II electrochemical detector and the ESA microdialysis cell was set to a potential of +250 mV. Chromatograms were recorded and analyzed using Hewlett-Packard Chemstation software.

HPLC analysis of NA

Samples were analyzed for NE in a similar manner, with some exceptions. The mobile phase contained 75 mM lithium acetate, 4 mM 1-heptane sulfonic acid, 100 μ M EDTA, 8% HPLC grade methanol, brought to a pH of 4.7 with acetic acid, delivered at a flow rate of 60 μ l/min. A CMA 200 refrigerated microsampler injected 5 μ L onto an ESA microbore reverse phase C-18 column (150x1, particle size 3 microns) and an ESA amperometric analytical cell set to +300 mV was used. Chromatograms were recorded and analyzed using ESA 501 Chromatograph Data System software.

Histology

Brains were sliced at 30 micron coronal sections using a cryostat. The location of the microdialysis probe was carefully referenced to the atlas of Paxinos and Watson (11) and animals with probes outside the ventromedial portion of the PFC were removed from analysis.

Data analysis

Data were transformed to percent baseline, uncorrected for probe recovery. The effect of a single treatment was analyzed with an ANOVA with repeated measures on time. Post-hoc tests were used to compare individual time points to baseline when appropriate. Significance was achieved when a time point was significantly different ($p < 0.05$) from all 6 baseline samples. Two or more groups were compared with a two-way ANOVA (time x group). Post-hoc

tests were used to compare the same time point between groups when appropriate, significance being achieved when $p < 0.05$. Statistica software was used for all statistical calculations.

Results

Basal Levels

The basal levels (mean \pm SEM) were: 0.95 ± 0.08 picograms/6 μ l NA, 0.69 ± 0.06 picograms/10 μ l DA, 0.23 ± 0.03 picograms/10 μ l 5-HT, 82.16 ± 8.26 picograms/10 μ l DOPAC, and 153.73 ± 8.67 picograms/10 μ l HVA.

Norepinephrine release

Figure 1 shows the effect of METH and AMPH on NE release in the PFC. There was a significant time \times group interaction [$F(28,210)=10.14$, $p < 0.05$, two-way ANOVA] and both METH and AMPH significantly raised NE levels [$p < 0.05$ compared to control at same time point, LSD test]. However, AMPH raised NE levels significantly more than METH did [$p < 0.05$ at 20-40, 40-60, and 60-80 min, LSD test].

Dopamine and metabolite release

DA levels from the control groups are shown in Figure 2. Normally, control injections of saline have no effect on DA levels [Figure 2 (left)]. However, during desipramine administration DA levels became significantly elevated [Figure 2 (right); $F(18,90)=3.21$, $p < 0.05$, ANOVA; $p < 0.05$ at 0-20, 20-

40, 40-60, 100-120, 140-160 min compared to baseline, LSD test] suggesting that desipramine by itself increased DA levels. Although desipramine altered DA levels, desipramine had no effect on DOPAC [Figure 3 (left)] or HVA levels [Figure 3 (right)].

The effects of desipramine treatment on METH and AMPH induced DA release are shown in Figure 4. Desipramine treatment significantly augmented the increase in DA levels induced by METH [Figure 4 (left); $F(14,140)=10.75$, $p<0.05$, two-way ANOVA; $p<0.05$ comparing all time points after injection, LSD test]. However, desipramine treatment significantly diminished the effect of AMPH on DA levels [Figure 4 (right); $F(14,154)=4.96$, $p<0.05$, two-way ANOVA; $p<0.05$ at 20-40 and 40-60 min, LSD test]. Thus, in the presence of desipramine, METH released significantly more DA than AMPH did [Figure 5; $F(36,270)=8.42$, $p<0.05$, two-way ANOVA; $p<0.05$ comparing all time points after injection, LSD test].

Serotonin release

The 5-HT data is graphed in Figure 6. Desipramine immediately increased 5-HT levels and 5-HT levels remained elevated throughout the reverse dialysis of desipramine [Figure 6 (left); $F(18,270)=6.22$, $p<0.05$, ANOVA, main effect of time; $p<0.05$ at all time points after desipramine perfusion compared to baseline, LSD test]. There were no significant effects of drug treatment, indicating that the increase in 5-HT levels were due to desipramine alone. As

shown in the right panel, during perfusion of control aCSF, neither METH nor AMPH increased 5-HT levels.

Discussion

The role of NET in amphetamine DA release in the PFC

As we have previously reported, AMPH has a greater effect on DA levels in the PFC than METH does, even though METH and AMPH have similar effects on DA levels in the NAC (2). In the PFC, where the NE to DA ratio is high, NETs are believed to play an important role in the removal of extracellular DA. In the NAC, where NE innervation is scarce, NETs are believed to have little or no effect on DA levels (9). Since we found AMPH to release more NE than METH does, the difference in DA release in the PFC between METH and AMPH could be due to differences in their effects on NETs.

Administration of the NET blocker desipramine antagonized the DA released by AMPH, a result similar to the effect of DAT blockers on AMPH-induced DA release in the NAC (12). This suggests that AMPH may release DA in the PFC primarily through NETs. Since the NET does have a higher affinity for DA than for NE (6), it is plausible that the NET is primarily responsible for the increase in extracellular PFC DA levels by AMPH. Indeed, it is believed that MDMA (methylenedioxymethamphetamine) releases DA via the NET in the hippocampus, another brain region with a high NE to DA ratio (13). Since

AMPH released more NE in the PFC than METH did, this could mean that AMPH interacts with the NE terminal to a greater extent than METH does, resulting in a greater release of both NE and DA from the NE terminal. Thus, when the NET is blocked with desipramine, AMPH is prevented from releasing DA from the NE terminal, and the amount of DA released by AMPH is significantly decreased. Since the NAC has low levels of NETs, the difference between METH and AMPH to interact with the NET would not be expected to lead to significant differences in efficacy to raise NAC DA levels, thereby explaining the observed differences between the PFC and the NAC.

METH released less NE than AMPH did, suggesting that METH has less effect on the NE terminal, releasing less NE and DA from the NE terminal than AMPH does. Since desipramine did not antagonize the METH-induced release of DA, it is possible that METH may instead release DA from the DA terminal. However, under normal conditions, while NET is unblocked, this DA would be cleared away from the extracellular space by the NET. The net result would be a small increase in extracellular DA levels by METH. When NET is blocked with desipramine, the DA released by METH from the DA terminal may be more apparent, as it is no longer removed by the NET. This suggests that METH is capable of releasing DA from the DA terminal to a greater extent than is AMPH; otherwise, when the NET was blocked with desipramine, AMPH would still release large amounts of DA from the DA terminal and a decrease in AMPH-

induced DA release would not have been observed. Because AMPH and METH have similar effects on DA in the NAC, it is possible that the DAT is expressed differently or functions differently in the PFC than in the NAC (14,15,16). Furthermore, in one study it was found that AMPH was not transported into the terminal by the DA transporter in the cortex as it was in the striatum (16). The transport of AMPH into the terminal is a key step in the reverse transport of DA. Although, the ability of METH to be transported into the terminal by the DA transporter has not been examined, if METH, but not AMPH, were able to enter the PFC DA terminal then this would explain the present results.

An alternative explanation for the increase in DA release by METH after desipramine treatment is that METH normally releases little DA and NE from the NE terminal, but the NE or 5-HT released by desipramine synergistically interacted with the glutamate (GLU) released by METH to cause an increase in DA release. The PFC projects to and controls the activity of DA neurons in the ventral tegmental area (17). Both NE and 5-HT have been shown to excite PFC projection neurons, and this effect may rely on GLU (18,19). We have previously shown that METH, but not AMPH, stimulates GLU release in the PFC (2). Therefore, the DA released by METH in the presence of desipramine may represent the synergistic combination of transporter-released DA by METH and impulse-dependent DA release through polysynaptic activation.

The effect of desipramine on serotonin

Another interesting result was the effect of desipramine on DA and 5-HT release. Desipramine was found to raise extracellular DA levels, consistent with previous results (8). However, this appears to be the first study to also examine the effects of desipramine on DOPAC and HVA. If desipramine raised DA levels by blocking DA uptake through the NET, as previously assumed, then there should be an accompanying decrease in DOPAC and HVA. Also, the time course for the increase in DA was very slow, suggesting that this was instead an indirect effect of desipramine. The increase in 5-HT by desipramine was more immediate. There is substantial evidence indicating that 5-HT increases DA release in the PFC, by acting at presynaptic heteroreceptors (20). Therefore, while DA uptake blockade may contribute to the increase in DA levels caused by desipramine, this effect may mostly be secondary to an increase in 5-HT.

The mechanism by which desipramine increased 5-HT levels remains unclear. The concentration of desipramine in the perfusate was 1 μ M, and the amount of desipramine delivered through the probe to the PFC by reverse dialysis would only be a small percentage (~10%) of that. Since desipramine has a very low affinity for the 5-HT transporter (21), this is most likely not a direct effect. Instead, the elevated NE produced by desipramine could act at presynaptic heteroreceptors to modify 5-HT release. However, the only documented presynaptic modulation of 5-HT by NE is a decrease in 5-HT release through α 2-adrenergic receptors (22). A multistep pathway, where NE alters the level of

another neurotransmitter which in turn modifies 5-HT release, may be involved. Alternatively, the PFC projects to the dorsal raphe and modifies the activity of 5-HT projection neurons (23). Desipramine may have induced an alteration in PFC activity, and consequently an increase in dorsal raphe output. The effects of desipramine on 5-HT levels could also be due to an effect independent of the NET. For example, desipramine has a high affinity for the 5HT_{1C} receptor (24,25).

These results suggest that AMPH releases PFC DA primarily through NET, while METH interacts minimally with NET. These results indicate that METH and AMPH, two similar drugs, have very different pharmacological profiles in the PFC, an area important in the psychopathology of drug addiction. These profiles suggest that different treatments may be needed for METH and AMPH addictions.

Acknowledgements

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Figure legends

Figure 1. Effects of METH (N=6), AMPH (N=6), and saline (N=6) on extracellular levels of NE (mean % of baseline \pm SEM). Twenty minute baseline samples indicated by B1-B6. Time of injection (0 min) indicated by arrow. * $p < 0.05$ METH and AMPH compared to saline at same time point, ★ $p < 0.05$ METH compared to AMPH at same time point.

Figure 2. Left. Effect of saline (N=6) on extracellular levels of DA (mean % of baseline \pm SEM). Twenty minute baseline samples indicated by B1-B6. Time of injection (0 min) indicated by arrow. Right. Effect of saline (N=6) on extracellular levels of DA (mean % of baseline \pm SEM) during perfusion with 1 μ M desipramine. Twenty minute baseline samples indicated by B1-B6. Time of desipramine perfusion (80 min prior to injection) indicated by bar. Time of injection (0 min) indicated by arrow. * $p < 0.05$ compared to baseline.

Figure 3. Effect of saline on DOPAC (left; N=6; mean % of baseline \pm SEM) and HVA (right; N=6; mean % of baseline \pm SEM) during 1 μ M desipramine perfusion. Twenty minute baseline samples indicated by B1-B6. Time of desipramine perfusion (80 min prior to injection) indicated by bar. Time of injection (0 min) indicated by arrow.

Figure 4. Left. Effect of desipramine on METH-induced changes in DA (mean % of baseline \pm SEM). METH (N=6) refers to METH with control aCSF. DES-METH (N=6) refers to METH with 1 μ M desipramine perfused 80 min prior to injection. Twenty minute baseline samples indicated by B1-B6. Time of injection (0 min) indicated by arrow. * $p < 0.05$ METH compared to DES-METH at same time point. Right. Effect of desipramine on AMPH induced changes in DA (mean % of baseline \pm SEM). AMPH (N=6) refers to AMPH with control aCSF. DES-AMPH (N=6) refers to AMPH with 1 μ M desipramine perfused 80 min prior to injection. Twenty minute baseline samples indicated by B1-B6. Time of injection (0 min) indicated by arrow. * $p < 0.05$ AMPH compared to DES-AMPH at same time point.

Figure 5. Effects of METH (N=6), AMPH (N=6), and saline (N=6) on DA (mean % of baseline \pm SEM) during 1 μ M desipramine perfusion. Twenty minute baseline samples indicated by B1-B6. Time of desipramine perfusion (80 min prior to injection) indicated by bar. Time of injection (0 min) indicated by arrow. * $p < 0.05$ METH compared to AMPH and saline at same time point.

Figure 6. Left. Effects of METH (N=6), AMPH (N=6), and saline (N=6) on extracellular levels of 5-HT (mean % of baseline \pm SEM) during 1 μ M

desipramine perfusion. Twenty minute baseline samples indicated by B1-B6. Time of desipramine perfusion (80 min prior to injection) indicated by bar. Time of injection (0 min) indicated by arrow. * $p < 0.05$ compared to baseline (main effect of time). Right. Effects of METH (N=6), AMPH (N=6), and saline (N=6) alone on 5-HT (mean % of baseline \pm SEM). Twenty minute baseline samples indicated by B1-B6. Time of injection (0 min) indicated by arrow.

Figure 1.

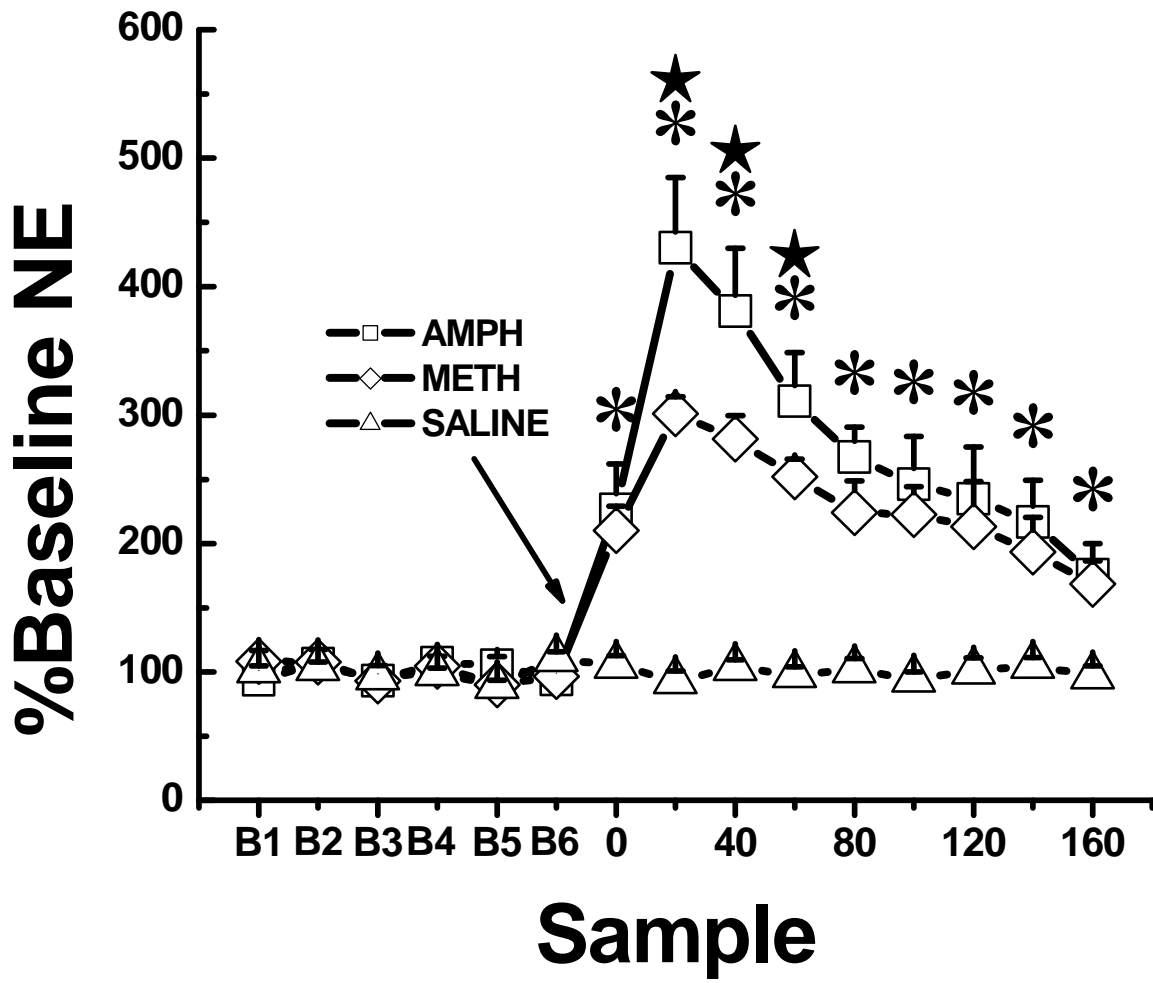


Figure 2.

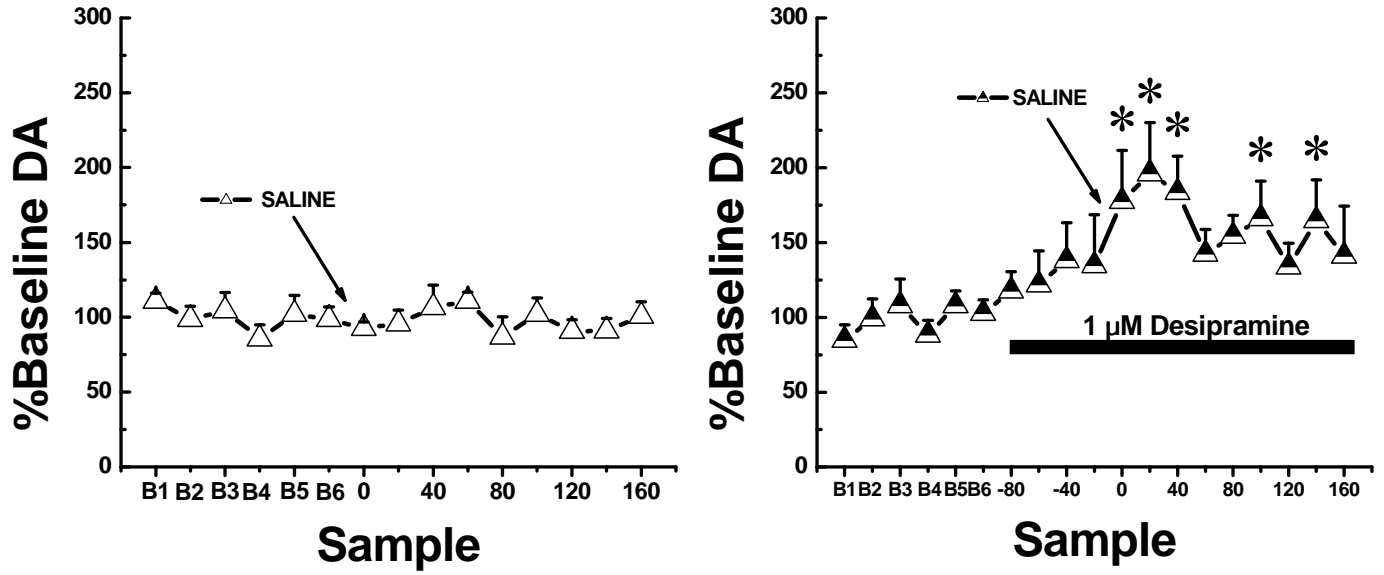


Figure 3.

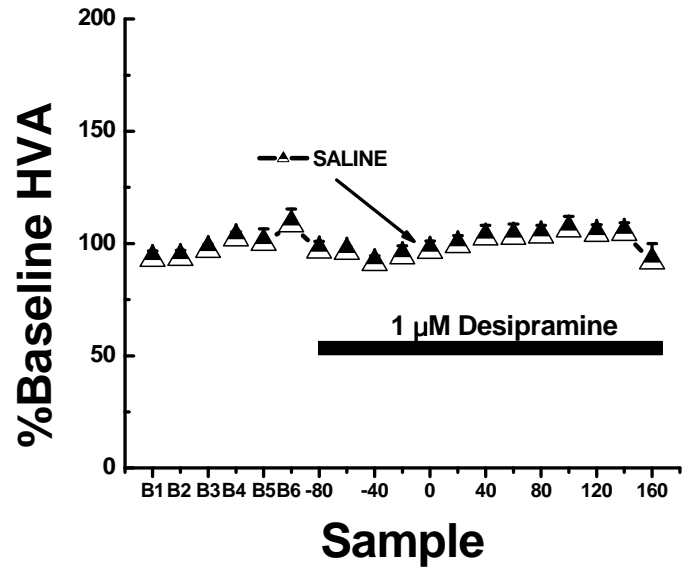
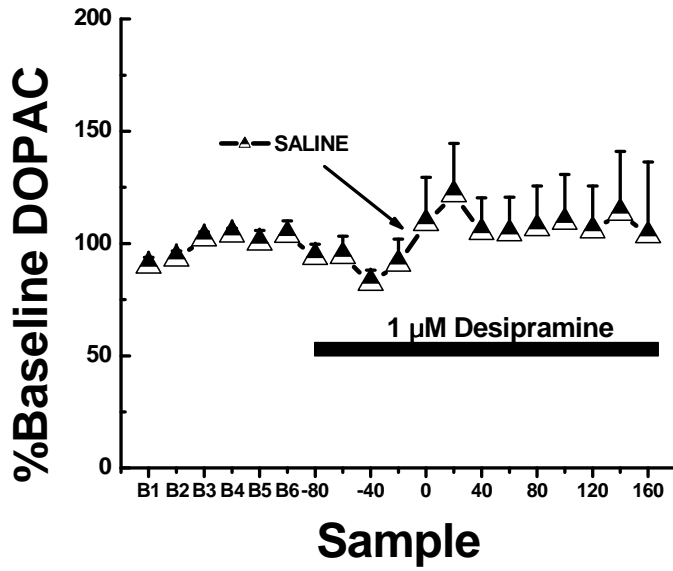


Figure 4.

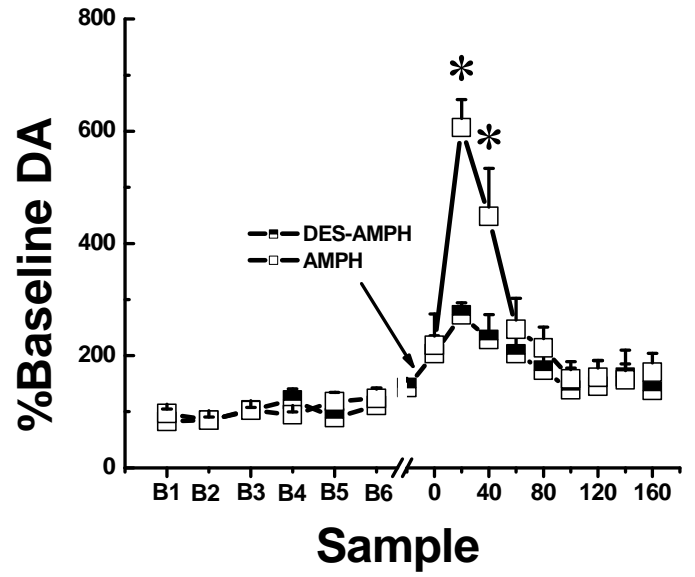
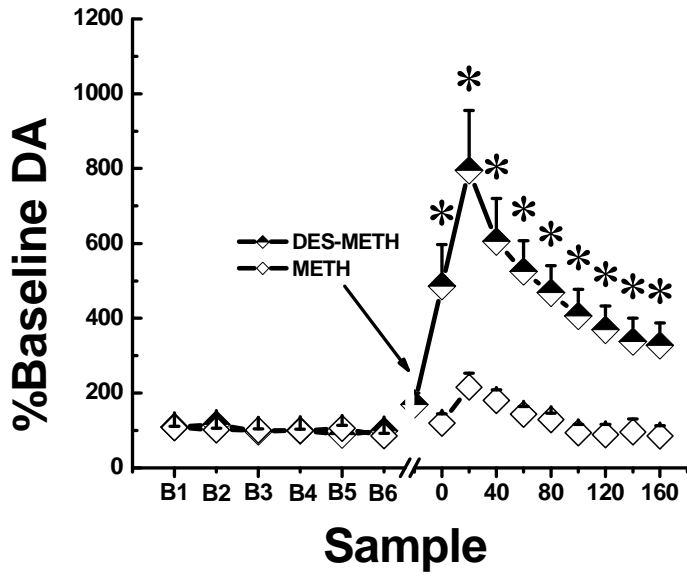


Figure 5.

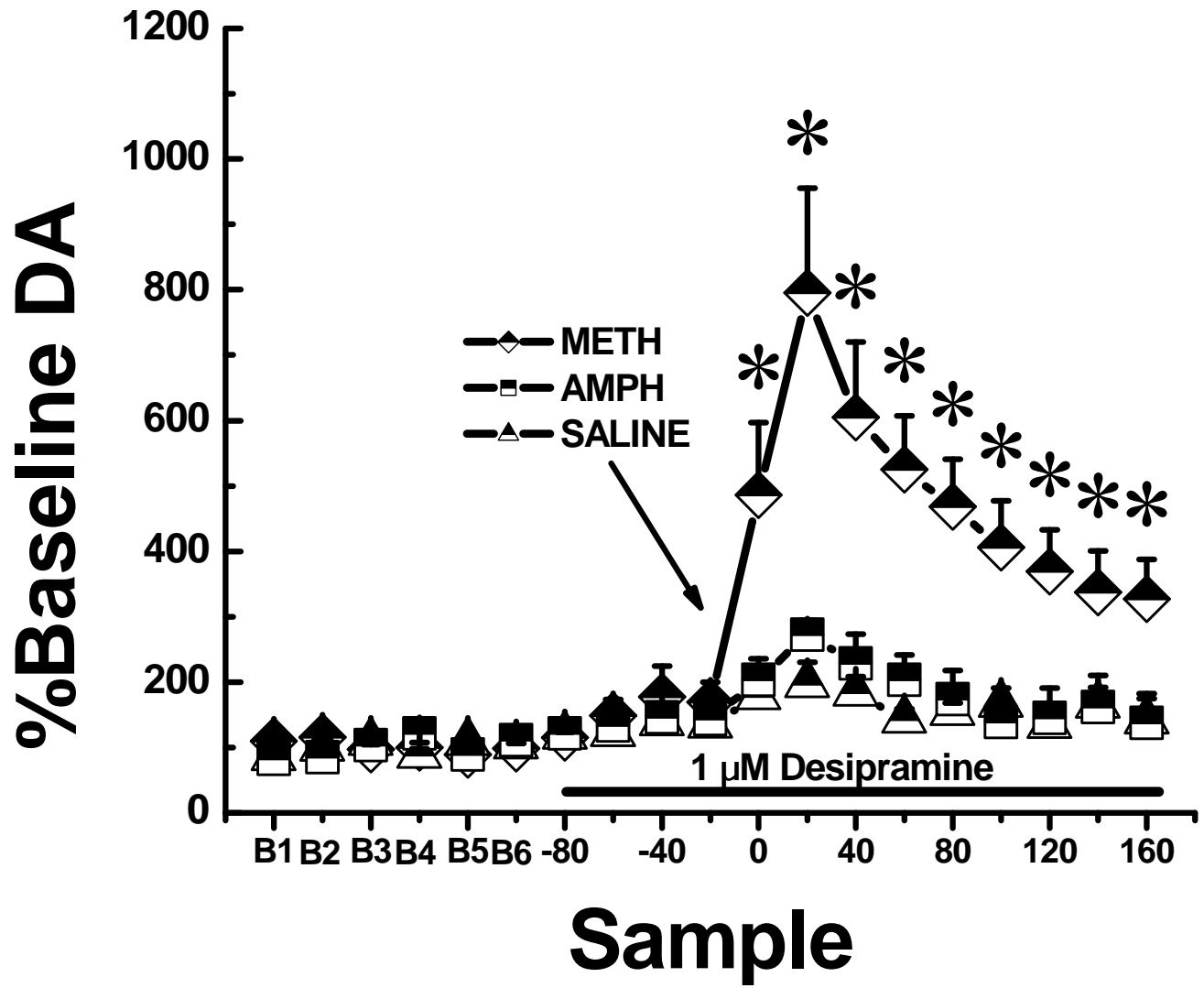


Figure 6.

