Published in final edited form as:

Neurotoxicol Teratol. 2010 ; 32(2): 152–157. doi:10.1016/j.ntt.2009.08.012.

Glucose and corticosterone changes in developing and adult rats following exposure to ($\pm$)-3,4-methylenedioxymethamphetamine or 5-methoxydiisopropyltryptamine

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Abstract

The use of the club drugs 3,4-methylenedioxymethamphetamine (MDMA) and 5-methoxy-*n,n*-diisopropyltryptamine (Foxy) is of growing concern, especially as many of the effects, particularly during development, are unknown. The effects of these drugs upon homeostasis may be important since both are known to stimulate the hypothalamic-pituitary-adrenal axis. The purpose of this experiment was to examine alterations in rats in corticosterone and glucose following an acute exposure to these drugs at different stages of development: preweaning, adolescence, and adulthood. Both MDMA and Foxy increased corticosterone levels significantly at all ages examined, while glucose was elevated at all stages except at the adolescent time point (postnatal day 28). For both measures, there were no differences between the sexes with either drug. The data indicate that an acute exposure to these drugs alters CORT and glucose levels at all ages tested, raising the possibility that these changes may have effects on behavioral and cognitive function, as we and others have previously demonstrated.

Keywords

Corticosterone; glucose; 3,4-methylenedioxymethamphetamine; 5-methoxydiisopropyltryptamine; stress hyporesponsive period

1. Introduction

The use of club drugs, such as in “rave” venues, has remained widespread for years. The most recent Monitoring the Future survey noted that while use of one such drug, $\pm$ 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy), held steady, its perceived risk amongst

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

young people has declined, indicating that students are unfamiliar with the hazards of Ecstasy use [30]. Some of these club drugs, such as MDMA, have been well-studied in terms of their neurotoxic and/or other adverse effects [24]. In addition, the use of hallucinogenic tryptamines is on the rise. One such drug is 5-methoxy-*n,n*-diisopropyltryptamine (Foxy, Foxy Methoxy). Foxy has hallucinogenic properties similar to psilocybin and was classified as a Schedule I drug in September 2004 [64]. While relatively unknown in mainstream culture, Foxy use is growing in spite of prohibitions on its sale and consumption [63].

Given the popularity of these drugs, the consequences of their use are of interest. Despite the extensive literature noting the damaging effects of MDMA, its use remains popular. MDMA users exhibit cognitive abnormalities, including increases in impulsivity [27,48] and long-term deficits in decision-making ability and/or verbal memory [27,for review see 31,62]. Several studies have demonstrated that MDMA use results in deficits in serotonergic function. In particular, MDMA users exhibit decreased levels of serotonin (5-HT) transporter (SERT), even after abstinence from the drug [33,36,62], and this loss has been correlated with the effects of the drug on memory [36]. Imaging studies show that MDMA users have decreased metabolic function as measured by glucose uptake compared to controls [42]. Furthermore, MDMA use has been implicated in an elevated stress response, as indicated by elevated cortisol and ACTH levels in humans users [21,26,35,44].

Numerous studies in animals have demonstrated the ability of MDMA to deplete 5-HT and its metabolite, 5-HIAA [12,24,46], and to block SERT, thus preventing the reuptake of 5-HT. Animal experiments have further established the role of MDMA use on learning and memory, especially in terms of its developmental effects. Our and other laboratories have demonstrated that MDMA exposure results in deficits in learning and memory in both adults [1,39,56] and in animals exposed to the drug during critical stages of early development [8,10,58,66].

Contrary to what is known about MDMA, little is known about the effects of Foxy. In humans, Foxy elicits visual and auditory hallucinations, flashbacks, agitation, and at higher doses rhabdomyolysis, renal failure, tachycardia, myoclonus and seizure activity, and even death in rare cases [2,29,34,38,40,55,61,72]. Foxy is commonly used to enhance sexual pleasure, and it has been suggested that Foxy may be especially detrimental to users infected with HIV [34]. In animal studies, Foxy also affects the serotonergic system as a SERT inhibitor [59] and via the 5-HT_{2A} receptor [20], although the mechanism of action is poorly understood. Data from our laboratory show that Foxy alters 5-HT turnover but does not affect 5-HT or dopamine (DA) levels in adult rats [67]. Following a single-day exposure to Foxy, adult rats exhibited hypoactivity and performed poorly in the Cincinnati water maze (CWM), a putative test of path integration [67]. Furthermore, Foxy induced an increase in the head-twitch response in mice [20]. Rats exposed to Foxy during development demonstrated deficits in response learning [13], spatial learning in the Morris water maze (MWM), and exaggerated hyperactivity following a methamphetamine challenge in adulthood [57].

Despite the literature examining the serotonergic effects of MDMA and Foxy, little is known of their effects on neuroendocrine systems, especially in regards to the output of the hypothalamic-pituitary-adrenal (HPA) axis. MDMA is known to increase corticosterone (CORT) release in adult rats [4,41] as well as during development [53,70]. Our laboratory found that in adult male rats, a single day administration of Foxy resulted in increased basal CORT levels, as well as significantly increased adrenal weights 72 h after drug administration [67]. However, it is not known how acute administration of Foxy or MDMA affects CORT and glucose levels at various stages of development. Alterations in glucocorticoids such as CORT are known to alter energy metabolism and glucose homeostasis [3,50]. Given the importance of these entities in terms of maintaining homeostasis and directing neuronal

development, the purpose of this experiment was to examine and compare the acute effects of MDMA and Foxy on CORT and glucose levels in rats at different ages.

2. Methods

2.1 Subjects

Sprague-Dawley CD (IGS) male and female rats (175–200 g) from Charles Rivers Laboratories (Raleigh, NC) were habituated to the vivarium in a temperature- ($19 \pm 1^\circ\text{C}$) and humidity-controlled room with a 14:10 h light:dark cycle (lights on 600 h) for at least 2 weeks following arrival. Following acclimation, male and female rats were paired in hanging wire cages for breeding. Food and water were available *ad libitum* throughout. Detection of a sperm plug was designated embryonic day 0 (E0). Females were removed and placed in individual, polycarbonate cages ($46 \times 24 \times 20$ cm) with woodchip bedding on E1. Birth was designated postnatal day 0 (P0). On P1, litters were culled to 10–12 pups. If a litter was not large enough, pups from other litters sharing the same birth date were fostered to achieve a litter size of at least 10. In litters raised to adulthood, offspring were separated from their mother on P28 and housed in same-sex pairs. The ages tested were P1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 28, and 60. A random numbers table was used to determine the day of experimentation and treatment used. All procedures were approved by the Cincinnati Children's Research Foundation's Animal Care and Use Committee and the vivarium was fully accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care.

2.2 Drug Administration

The drugs, 5-methoxy-*n,n*-diisopropyltryptamine-HCl (expressed as freebase) and $\pm$ 3,4-methylenedioxymethamphetamine-HCl (expressed as freebase), were obtained from Research Triangle Institute (Research Triangle Park, NC; >95% purity). On the day of experimentation, animals were weighed and received a single subcutaneous injection of 20 mg/kg Foxy (72.3 $\mu\text{mol/kg}$; Foxy group), 20 mg/kg MDMA (103.5 $\mu\text{mol/kg}$; MDMA group), or isotonic saline (SAL group). The MDMA dose was based on previous studies showing that 20 mg/kg/dose of MDMA is well-tolerated in pups and effective in producing later learning deficits [8,69]. The Foxy dose was based on the highest effective dose in an adult behavioral study that induced learning deficits and alterations in CORT [67]. Injections were administered in the dorsum in a volume of 3 ml/kg. Only for the later time points (P28 and 60) were male and female data separated. At these times, one male and female pair from each litter was injected with one of the compounds. Animals were returned to the home cage following the injection. Only one pair of animals was used from each litter per day, and these rats were removed at approximately the same time in order to minimize the number of daily disturbances to the litter. Temperatures were not recorded in this study as animals were sacrificed within 30 min of drug administration. Although administration of MDMA is known to cause hyperthermia in adult rodents [7,25, 54] at 60 min following drug exposure, it has little or no effect in neonates [7]. Foxy is known to cause an initial drop in body temperature in adult rats (~ 3 h) followed by a delayed (24–48 h) hyperthermic response [67].

2.3 CORT and Glucose Assessment

Thirty min following drug administration, animals were transferred to an adjacent room and decapitated within 30 s of removal from the home cage. The 30 min time point was chosen based on previous data showing that CORT levels peak at approximately 30 min following MDMA administration [4,14]; the same has been found for blood glucose levels following MDMA treatment [23]. For CORT assessment, blood was collected in 12 $\times$ 75 mm polyethylene tubes containing 0.05 ml of 2% EDTA. Samples were centrifuged at 1300 RCF for 25 min at 4°C , and plasma was collected and stored at -80°C until assayed. Plasma samples, diluted 3:1 in supplied buffer, were assayed in duplicate using a commercially available EIA kit specific

for CORT (Immunodiagnostic Systems Inc., Fountain Hills, AZ). The limit of detection (LOD) for this assay was 0.55 ng/ml, and any sample that fell below this limit was automatically assigned the LOD value. For glucose level determination, a separate aliquot of whole blood was collected from the same animals, and glucose levels were assessed using a commercially available Precision Xtra blood glucose monitor (Abbott Laboratories, MediSense Products Inc., Bedford, MA). However, due to equipment malfunction, some glucose readings were not obtained. Thus, the final sample size per group was N = 5-10 (P1-19 rats); N = 7-8 (P28 rats), and N = 4-7 (P60 rats). A total of 23 litters were used.

2.4 Statistical Analysis

Data were analyzed using an analysis of variance (SAS Institute, Cary, NC) using mixed linear models (Proc Mixed). Main effects included treatment, age, and sex for the later time points. Litter effects were controlled using a completely randomized block design in which litter was the block factor. Proc Mixed calculates adjusted degrees of freedom using the Kenward-Rogers method, and therefore do not match those obtained from general linear model ANOVAs and can be fractional. Significance was considered at $p \leq 0.05$.

3. Results

3.1 Prewaning Effects (P1-19)

For CORT, there was a significant treatment main effect ($F(1,106)=132.27$, $p<0.0001$) and a treatment $\times$ day interaction ($F(9,106)=9.82$, $p<0.0001$) in MDMA-exposed pups. CORT was significantly increased by MDMA at all time points examined from P1-19 ($p<0.05$), although the increase was not uniform across ages compared with the SAL group (Fig. 1A). Foxy administration also resulted in a significant treatment main effect ($F(1,136)=57.99$, $p<0.0001$) and a treatment $\times$ day interaction ($F(9,136)=4.61$, $p<0.0001$) (Fig. 1B). Foxy significantly elevated CORT levels on P5-19 versus the SAL group ($p<0.05$).

For glucose, there was a treatment main effect of MDMA (Fig. 2A) ($F(1,91)=12.67$, $p<0.0006$), demonstrating that MDMA produced a slight increase in glucose levels compared to the SAL group. The treatment $\times$ day interaction was not significant. Foxy also had a treatment main effect upon glucose levels ($F(1,138)=52.83$, $p<0.0001$); the treatment $\times$ day interaction was not significant (Fig. 2B). Similar to MDMA, Foxy produced an increase in glucose levels, regardless of day, relative to the SAL group.

3.2 Adolescent Effects

For CORT, MDMA produced a treatment main effect ($F(1,21)=47.64$, $p<0.0001$), but no sex main effect or treatment $\times$ sex interaction. MDMA increased CORT levels at this age regardless of sex compared to the SAL group (Fig. 3A, right panel). Likewise, Foxy administration also resulted in significantly increased CORT levels at this age compared to the SAL group ($F(1,21)=55.66$, $p<0.0001$) (Fig. 3B, right panel). Neither a sex main effect nor a treatment $\times$ sex interaction was obtained for Foxy on CORT.

For glucose, neither MDMA nor Foxy produced alterations on P28 in males or females (Fig. 4A and B). There were no significant interactions between treatment and sex on glucose levels.

3.3 Adult Effects

For CORT, a treatment main effect was observed after MDMA exposure ($F(1,18)=48.67$, $p<0.0001$); however, there was no sex main effect or treatment $\times$ sex interaction (Fig. 5A). MDMA administration produced an increase in CORT compared to SAL administration. Foxy treatment also resulted in increased CORT levels compared to the SAL group ($F(1,18)=12.03$,

$p < 0.0027$) (Fig. 5B). There was no sex main effect or treatment $\times$ sex interaction for Foxy on CORT.

For glucose, MDMA treatment at P60 resulted in a treatment main effect ($F(1,9)=14.99$, $p < 0.004$) but no treatment $\times$ sex interaction ($F(1,9)=3.93$, $p < 0.08$). No sex main effect was exhibited either. Overall, MDMA produced an increase in glucose (Fig. 6A, right panel) compared to the SAL group. The trend for the interaction suggested that males exposed to MDMA had increased glucose levels relative to the SAL group males, whereas MDMA-treated females did not demonstrate such a tendency (Fig. 6A). For Foxy, there was a significant main effect of treatment ($F(1,9)=20.84$, $p < 0.002$) but no sex main effect (Fig. 6B). Foxy exposure produced an increase in glucose, regardless of sex, relative to SAL exposure. There was no significant interaction of treatment $\times$ sex on glucose after exposure to Foxy.

4. Discussion

Designer drugs such as MDMA and Foxy have become popular, but the effects these drugs have upon CORT and glucose at different ages are not established. This experiment examined the outcome of these drugs on CORT and glucose levels during postnatal development through early adulthood to identify such drug effects. During the neonatal period, Foxy and MDMA treatment resulted in elevated levels of glucose and CORT. Neither drug had any effect on glucose levels at P28, but both increased circulating CORT levels at this age. Significantly elevated CORT levels at P60 were also seen following exposure to both drugs. There were no significant sex effects or interactions between drug and sex at these later time points.

Exposure during early postnatal development (P1-19) in rats correlates with second to third trimester development of the human brain [5,9,47]. These days were selected for investigation because they overlap with the stress hyporesponsive period (SHRP), a period during which the response of the HPA axis is attenuated [19,51,65]. In rats, the SHRP is approximately from P4-14. The blunted response of the HPA axis during this period is thought to be protective for developing neurons against high levels of circulating glucocorticoids. Previous studies from our laboratory have shown that exposure to methamphetamine during this period of development results in increased CORT levels in the neonatal rat that has a U-shaped function with age, i.e., the increase in CORT was above saline-treated controls, but still followed the pattern of reduced responsiveness characteristic of the SHRP [52,53,68,71]. A similar U-shaped response was noted for both MDMA and Foxy in this study. This pattern in stimulant-induced CORT release indicates that these drugs produce an HPA axis response characteristic of a stress-like over-reactivity. Over-stimulation of the HPA axis may dysregulate mechanisms that normally prevent excess CORT release, and this in turn may affect glucocorticoid receptor maturation. MDMA treatment on a single day (P11), near the middle of the SHRP, induces increases in CORT levels for up to 24 h later [52,70], indicating that the drugs not only override the normal inhibitory control over CORT release, they also induce a prolongation of the response. Furthermore, following a 15 min forced swim, ACTH levels are more elevated in male adult rats exposed to MDMA from P11-20 compared to controls exposed to saline from P11-20 [69], suggesting that the early exposure altered the response of the HPA axis at later time points. Interestingly, these alterations in CORT release during development occur before the later emergence of MDMA- and Foxy-induced deficits in learning and memory [57,70], raising the possibility that CORT may be involved in the mode of action of these drugs on brain development. While these data are associative, they suggest that further investigation into the possible role of CORT increases on later learning is warranted.

Tightly controlled glucose levels are required for homeostasis and are sensitive to perturbations that activate the HPA axis [6,16,37,43]. We have demonstrated that during early development, glucose levels are elevated after MDMA and Foxy exposure. While the increases were small,

there is evidence to suggest that brief hyperglycemia during the neonatal period is detrimental to physiological growth and metabolic function and can induce oxidative stress at later time points [15]. While it is not clear what effects hyperglycemia alone has on brain development at this stage, a recent study using older animals (180-200g) indicates that hyperglycemia can induce neural damage. Using a streptozotocin injection to induce a diabetic state, these researchers demonstrated that treated rats exhibited elevated levels of both lipid peroxidation and total lipids in the cerebral cortex as a result of hyperglycemia-induced oxidative stress [32]. While these measurements did not fall within the scope of the present study, nor were long-term glucose levels measured, there is evidence that hyperglycemia is detrimental to brain function. Thus, while MDMA and Foxy alter metabolic function during development, it is not clear whether or not these effects are associated with any of the long-term effects on CNS function.

At the one periadolescent age we tested (P28), neither drug significantly altered glucose levels. However, glucose was increased at P60 after exposure to either drug. It has been shown previously that acute MDMA results in increased cerebral glucose levels in the adult rat [18, 22,23,45] as well as in the periphery [23], although decreased cerebral glucose utilization is evident over time in MDMA-treated rats [22]. On the contrary, in Dark Agouti female rats, which are poor metabolizers of MDMA, exposure results in decreased blood glucose levels [60], implying that the pharmacology and metabolism of MDMA itself may play a role in glucose utilization. These data do not, however, indicate why adolescent rats are resistant to drug-induced hyperglycemia. The fact that there was no change in glucose levels at P28 most likely cannot be attributed directly to alterations in HPA axis function, as a 30 min restraint stress resulted in similarly elevated glucose levels in both P28 and P77 rats [49]. However, other possibilities exist, including altered 5-HT₂ receptor activation and temperature regulation [17], among others.

MDMA and Foxy treatment also increased CORT levels at P28 and at P60. As previously mentioned, several studies showed that MDMA and Foxy exposure results in elevated CORT levels in adult rats [4,41,67], however in many of these experiments, females were not tested. While no differential effect of sex was seen in this study, this factor should probably receive additional attention given that women use club drugs as commonly as men [11,28,73]. The data demonstrate for the first time that during development, MDMA and Foxy alter the CORT and glucose response in rats following a single injection of MDMA or Foxy and these alterations change as a function of age. Whether these drug-induced alterations in CORT and glucose are related to later neurocognitive and behavioral changes remains to be determined.

Acknowledgments

This research was supported by NIH project grant DA006733, training grant ES07051, and a fellowship from the Scottish Rite Foundation (NRH).

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Figure 1. Mean $\pm$ SEM plasma concentrations of CORT during the early developmental period. Effects are shown following administration of either 20 mg/kg of either MDMA (A) or Foxy (B) at ages P1-19. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. SAL.

Figure 2.

Glucose levels during the preweaning stage (P1-19). Mean $\pm$ SEM plasma concentrations of glucose following 20 mg/kg of either MDMA (A) or Foxy (B). Main treatment effects are displayed in the histograms. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. SAL.

Figure 3.

Corticosterone levels at P28 in treated and non-treated males and females. Mean $\pm$ SEM plasma concentrations following 20 mg/kg of either MDMA (A) or Foxy (B). Main treatment effects are displayed on the right. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. SAL.

Figure 4. Glucose levels at P28 in treated and non-treated males and females. Mean $\pm$ SEM plasma concentrations following 20 mg/kg of either MDMA (A) or Foxy (B). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. SAL.

Figure 5.

Corticosterone levels at P60 in treated and non-treated males and females. Mean $\pm$ SEM plasma concentrations of CORT following 20 mg/kg of either MDMA (A) or Foxy (B). Main treatment effects are displayed on the right for the CORT. * $p<0.05$; ** $p<0.01$; *** $p<0.001$ vs. SAL.

Figure 6.

Glucose levels at P60 in treated and non-treated males and females. Mean $\pm$ SEM plasma concentrations of glucose following 20 mg/kg of either MDMA (A) or Foxy (B). Overall treatment effects are displayed to the right of each treatment $\times$ sex interaction graph. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. SAL.