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# Biological Reasons for the Neurotoxic Effects of MDMA ('Ecstasy') on the Developing Fetus

By Leah Schneeweiss

Leah Schneeweiss will be graduating with a BS/MS from Touro's PA program in Bay Shore, Long Island in Sept. 2017.

## Abstract

MDMA (3, 4-methylenedioxymethamphetamine) is an illicit, recreational drug known by many individuals as 'Ecstasy.' MDMA has gained popularity over the past decade and has become a drug of choice at dance parties and clubs because of the stimulating and hallucinogenic effects that it has on the central nervous system. Scientists have determined that MDMA causes neurotoxic damage to adults by harming the serotonergic system in the adult brain. Researchers discovered that embryos exposed to MDMA while in utero also suffer neurotoxic deficits, although not due to impairments in the embryos' serotonergic systems. These deficits arise because of the cortisol increase that is found in adults after ingestion of MDMA, which can be transmitted to a developing fetus and thereby lead to a reprogramming of the hypothalamic-pituitary-adrenal axis in the fetus. In addition, MDMA can cause changes in the norepinephrine and/or dopamine systems in a developing fetus and thus create lasting neurological damage. MDMA-induced elevation of Atg5, a protein involved in autophagy, leads to teratogenesis in a developing fetus by inhibiting neuronal growth and differentiation. In another vein, 3, 4-Dihydroxymethamphetamine (HHMA) and malondialdehyde (MDA), two main metabolites of MDMA, have toxic effects on an embryo and are another mechanism via which Ecstasy can cause impairments in the fetal brain. While these and other hypotheses are currently under much investigation, scientists are approaching this topic with the understanding that it is most probably an interplay of many biological changes that result from fetal exposure to MDMA that together create the neurological defects observed in these fetuses. The various aspects of MDMA and the damage it can have on a fetus have been researched by the author using the Touro database and various links to journals and articles that this database provided.

## Introduction

MDMA, known scientifically as 3, 4-methylenedioxymethamphetamine, is an amphetamine derivative drug increasing in popularity amongst teenagers and young adults (Broening, et al., 2001). Amphetamines are a class of molecules that have stimulating effects on the central nervous system (CNS). MDMA is known by recreational users as 'Ecstasy' because it has stimulating and hallucinogenic effects on the CNS while engendering immediate feelings of ecstasy and openness upon ingestion (Singer, et al., 2012).

Studies show that adults taking MDMA have a decrease in serotonin (5-HT) in the brain, a reduction in 5-hydroxyindoleacetic acid (5-HIAA), a main metabolite of serotonin, and a reduction in tryptophan hydroxylase (TPH), an enzyme involved in the synthesis of serotonin (Broening, et al., 2001). This serotonergic reduction is harmful to the exposed adult. Interestingly, though the effects of MDMA on adults have been well researched, few studies have been conducted on the effects of MDMA on prenatally exposed children and on the reasons for these effects. Due to its popularity amongst teenagers and young adults, it has become increasingly prevalent to find developing fetuses exposed to MDMA while in utero. Scientists are determining the long term neurological effects of Ecstasy-exposed fetuses by conducting post parturition studies on both rats and children that have been prenatally exposed to MDMA. Some long term neurotoxic effects include sequential and spatial learning delays (Broening, et al., 2001) milestone delays at 4 months of age, and poorer mental development index scorings at 12 months of age (Singer, et al., 2012). The question stands as to why these and

other neurotoxic effects develop in both rats and children that have been exposed to MDMA in utero. Scientists are hypothesizing numerous reasons for these effects, including serotonin (5-HT) reduction (Broening, et al., 2001), elevated levels of cortisol (Parrott, et al., 2014), changes in the norepinephrine (NE) system (Thompson, et al., 2011) and in the dopamine (DA) system (Thompson, et al., 2009), an increase in autophagy protein 5 (Atg5) (Chae, et al., 2009), and embryotoxicity due to MDMA metabolites (Barenys, et al., 2012). This paper explores various venues theorized to be the cause of the cognitive and neuronal impairment observed in Ecstasy-exposed fetuses.

## Methods

Research on the topic of the biological reasons for the neurotoxic effects of MDMA on the developing fetus was compiled from various sources found in the Touro database. Information was obtained regarding general usage of MDMA as well as the observations noted in children of women who ingested MDMA while pregnant. Finally, data about various experiments performed on rats was obtained in order to gain insight into possible biological causes for the neurotoxic deficits noted in MDMA exposed fetuses. The information was arranged into a comprehensive order and edited by the author.

## Discussion

One strong hypothesis as to how Ecstasy induces long term brain damage in a fetus is that MDMA-exposed fetuses are harmed due to a decrease in 5-HT in the brain. This hypothesis is based on the established fact that MDMA causes serotonergic reductions in the adult brain. In a study done on Sprague-Dawley

rats, researchers in the University Of Cincinnati College Of Medicine sought to determine whether the effects of MDMA on exposed fetuses are indeed caused by a 5-HT reduction. Sprague Dawley rats were mated and their litters were reduced to 8 pups, 4 males and 4 females, with parturition day termed P0. The rats were divided into 2 groups. One group received two subcutaneous injections of MDMA daily on P1-P10 while the second group received similar MDMA injections on P11-P20. These intervals of P1-P10 and P11-P20 correspond to early and late third trimester development in humans, respectively.

Between P60 and P80, the rats were tested in various assigns. The results of the tests illustrated that the rats in the P11-P20 group had significant decreases in sequential learning, spatial learning, and memory abilities, while those in the P1-P10 group did not show significant decreases in any of these areas. Neither group showed a significant decrease in cued learning. These tests demonstrate that the neurotoxic effects that MDMA has on a developing fetus are more likely to occur when MDMA is taken during late third trimester development and that these effects are long term, as seen from the presence of the impairments in rats that had already reached adulthood.

The researchers sought to determine whether these cognitive impairments in the rats were due to serotonergic decreases in the rat brains. In order to investigate this hypothesis, the rats were decapitated on P105 and their brains were dissected. Reductions in 5-HT in the hippocampus were found for both the P1-P10 and P11-P20 groups, findings that do not correlate with the cognitive impairments seen only in the P11-P20 groups. In addition, the frontal cortex of the rats displayed 5-HT reductions only in the P11-P20 group, but these reductions were insignificant as seen with a correlation coefficient between these reductions and the spatial learning deficits exhibited by the rats that did not approach significance. Therefore, while this study shows that MDMA has long term negative effects on spatial and sequential learning and memory, it also illustrates that these cognitive deficits are not due to serotonergic reductions. The cause of fetal brain damage by MDMA must be via a mechanism other than the 5-HT reduction that causes MDMA induced damage in the adult brain (Broening, et al., 2001).

This idea that prenatal MDMA exposure and the long term damage that it causes is not due to 5-HT reduction can be supported by the mechanism via which MDMA causes 5-HT reduction in the adult brain. Studies indicate that MDMA metabolites form free radicals upon further metabolism and thereby damage serotonergic neurons. This is supported by the presence of malondialdehyde in rat brains after exposure to MDMA. Malondialdehyde is an end product of lipid peroxidation, the process during which lipids in cell membranes are broken down

via free radicals. Because free radicals are hard to measure due to their short half-lives, the by-products of these radicals known as TBARS (thiobarbituric acid reacting substances) are used to measure the damage induced by the free radicals. The TBARS Assay is a test that reacts thiobarbituric acid with malondialdehyde in order to quantify the amount of free radicals found in a specimen. This reaction yields a florescent product that indicates the presence of free radicals. Thus, a high yield of malondialdehyde from a TBARS Assay found in adult rats exposed to MDMA indicates the presence of free radicals in these rats. Another indication of the presence of free radicals in rats exposed to MDMA is that 5-HT reduction is prevented from occurring in MDMA-exposed rats that are injected with alpha-phenyl-N-tert-butyl nitron (PBN), a free radical scavenger. This indicates that the 5-HT reduction occurring in adult rats may be happening in part because of free radicals. A study exposing both neonate and adult rats to MDMA showed no significant increase in the presence of malondialdehyde in the hippocampus and cortex of the neonate rats while the adults' brain cortices did demonstrate a significant increase in malondialdehyde (Figure 1). Free radicals cause the serotonergic reduction in adult rats, and it can be inferred that cognitive defects found in adult humans exposed to MDMA are caused by this 5-HT

Figure 1

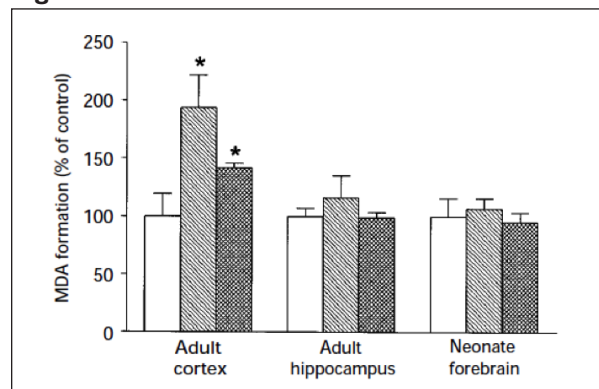


Figure 1 - Formation of thiobarbituric acid reacting substances (TBARS) in the hippocampus and cortex of adult rats and cortex of neonate rats 3 h (hatched columns) and 6 h (cross-hatched columns) after MDMA (40 mg kg<sup>-1</sup>, i.p.) administration. Results show % change in brain malondialdehyde (MDA) formation compared to saline-injected control animals (open columns), as mean±s.e.mean, n=8± 10. \*Significantly different from saline (Colado, et al., 1997).

reduction. In contrast, neonatal rats and, by inference, humans prenatally exposed to MDMA, have cognitive impairments that cannot be attributed to 5-HT reductions (Colado, et al., 1997). Other factors must be explored to lend reason for these long term neurotoxic effects.

Another possible cause for the cognitive deficits recognized in children prenatally exposed to MDMA is elevated levels of

## Biological Reasons for the Neurotoxic Effects of MDMA

cortisol caused by ingestion of Ecstasy. As noted, MDMA has been shown to cause impairments in long term memory, learning, and locomotor activity in children exposed to this drug in utero. Researchers hypothesize that these impairments may be due to the increase in cortisol that is present. Individuals ingesting Ecstasy display higher levels of cortisol in comparison to drug-free individuals with baseline cortisol levels. In addition, increased cortisol levels may be damaging to fetal development. Therefore, if the Ecstasy user is a pregnant woman, her MDMA usage may put her fetus at risk (Parrott, et al., 2014).

Cortisol is a glucocorticoid steroid hormone produced by the adrenal cortex in response to bodily stress and/or low blood glucose levels. The body releases this hormone in order to provide additional metabolic resources that enable an individual to function properly while under stress. The hypothalamic-pituitary-adrenal (HPA) axis is a systemic interaction of endocrine glands that utilize a negative feedback mechanism in order to control the hormonal activities of the adrenal cortices (Mosby's Medical Dictionary, 2009).

In a recent study performed on MDMA users, light usage of MDMA (ingestion of MDMA 1-4 times within the past 3 months) led to a mean increase of 50% in cortisol levels, in contrast with a control group of MDMA-free individuals. Heavier Ecstasy users (ingestion of MDMA 5+ times within the past 3 months) were noted to have a mean increase of 400% in their cortisol levels in comparison with a control group. While these statistics definitely illustrate radical increases in cortisol levels in MDMA users, a 10% increase of maternal cortisol leads to a mere 1% increase in fetal cortisol. This is due to the placental glucocorticoid barrier that prevents most of the cortisol from reaching the fetus. However, while a small increase in maternal cortisol levels may not cause damage to a fetus, a 400% increase in maternal cortisol can possibly have long term deleterious effects on the child.

According to the scientific review by Parrott, et al. (2014), "... HPA basal hyperactivation... may represent a complex neuro-endocrine dysfunction associated with MDMA use." They imply that elevated cortisol levels caused by MDMA ingestion may lead to HPA axis impairments, specifically in a developing fetus. This idea is supported by a study on the effects of maternal stress on a fetus, because researchers have found that similar to ingestion of MDMA, an increase in a mother's stress level causes more cortisol to be produced, and this hormone is then passed to the fetus via the placenta. As noted, although most of the cortisol is prevented from reaching the fetus due to the placental glucocorticoid barrier, about 1/10th of the cortisol will still reach the fetus. This hormone may then reprogram the HPA axis activity of the developing fetus which can cause long

term damaging effects on the child. Studies illustrate that the negative effects of stress on the developing fetus include poorer attention spans, sleeping, feeding, and activity problems, greater impulsivity, and a higher pervasiveness of Attention Deficit Hyperactivity Disorder (ADHD). Because ingestion of MDMA causes an increase in cortisol in the same way that maternal stress does and because cortisol has been shown to cross the placental barrier, researchers infer that it is the elevated cortisol levels found in MDMA users that are responsible for the neurotoxic deficits found in Ecstasy-exposed fetuses and that the long term effects of MDMA may mirror the effects of maternal stress on a fetus.

It is interesting to note that increased cortisol levels can be seen in an individual for up to 3 months after he/she has stopped using MDMA. Thus, it follows that a woman who stops MDMA usage prior to pregnancy may still be liable to inflict lasting damage to her fetus unless she has had several months of drug abstinence prior to conception (Parrott, et al., 2014).

A study researching the connection between elevated cortisol levels and memory problems supports the idea that elevated cortisol levels may be the cause of long term damage in MDMA-exposed fetuses, specifically in the area of memory impairment. Researchers tested healthy individuals with a mean age of 61.8 years to determine if memory problems are linked to elevated cortisol levels. This study used a special testing method in order to control for any stress that would develop in the subjects because of the inherent knowledge of their memory loss. The study demonstrated that women with memory complaints had significantly higher levels of cortisol than women without memory complaints, although no such difference was seen in men. In addition, individuals who complained of memory issues also had increased activity of their HPA axes (Wolf, et al., 2004). Similar to the adults in this study, fetuses exposed to MDMA also had elevated cortisol levels and hyperactivity of their HPA axes (Parrott, et al., 2014). In a similar vein, a study performed on cocaine dependent individuals served to analyze the cause for the learning and memory dysfunctions observed in these drug addicts. Researchers determined that cocaine dependent individuals have higher levels of cortisol than individuals in a 'cocaine-free' control group, and this increase was associated with the poorer learning and memory skills observed in these individuals (Fox, et al., 2009). Thus, it can be inferred that the memory impairments noted in children prenatally exposed to MDMA may be caused by the elevated cortisol levels that these fetuses are exposed to.

Another hormone that may be linked to the damage induced by MDMA in the developing fetus is norepinephrine (NE). NE is a noradrenergic hormone and neurotransmitter made from

dopamine (DA) by the enzyme dopamine beta hydroxylase (DBH). It is released from the adrenal medulla into the bloodstream and acts as a systemic hormone, and it is also released from noradrenergic neurons in the locus ceruleus of the brain where it acts as a neurotransmitter. Scientists have found that a correlation exists between prenatal exposure to MDMA in rats and changes in the structure and function of the NE system in these prenatally exposed rats. NE system dysfunction has been associated with exaggerated behavioral responses to new stimuli as well as a decrease in habituation to these stimuli, impairments which are attributed to attentional processing deficits. Because researchers have observed these behaviors in prenatally exposed rats, they infer that the damage induced by MDMA exposure to a developing fetus may be linked to abnormal wiring of the fetus's NE system (Thompson, et al., 2011).

In order to test this hypothesis, pregnant Sprague-Dawley rats were randomly assigned to two groups. One group was injected with 15mg/kg of MDMA twice a day at 8 hour intervals, a dose consistent with the typical MDMA dosage taken for human consumption, while the other group received subcutaneous injections of saline two times a day at corresponding 8 hour intervals. These injections were administered from embryonic day 14 (E14) to embryonic day 21 (E21). The pups were born on E21 and the first day after parturition was termed postnatal day 1 (P1). The litters were reduced to 4 males and 4 females for the MDMA group and 5 males and 5 females for the saline group. The pups were anesthetized on P21 and their brains were removed and cut into specific sections for observational analysis.

Among the different areas of the brain that were analyzed, three sections of the rostral hippocampus, CA1, CA2, and CA3, were scrutinized for NE abnormalities. This section of the brain was studied because it receives noradrenergic innervation from the locus ceruleus and because it is involved in spatial memory and responses to novelty, abilities that have been found lacking in MDMA exposed fetuses. The rats prenatally exposed to MDMA exhibited a 32.1% increase in DBH fiber density in the CA1 region of the hippocampus in comparison with the control group. In addition, norepinephrine transporter (NET), a molecule that regulates NE signaling by clearing NE from the synaptic cleft, increased in MDMA rats by 39.3% in the CA1 region and 32.1% in the CA3 region. In spite of these increases, the rostral hippocampus displayed no elevation in NE levels and levels of 3-methoxy-4-hydroxyphenolglycol (MHPG), a main metabolite of NE. The locus ceruleus displayed no increase in DBH fibers, and NET binding did not increase in this area. However, in the prelimbic (Cg3) region of the prefrontal cortex, there was a 69.2% increase in DBH neurites. This was accompanied by a 15% increase in NE in the prefrontal cortex as a whole, although there was no increase in NET binding or MHPG levels in the

prefrontal cortex.

These findings suggest that MDMA can cause NE system dysfunction in the developing fetus. As an example, the increase in NET binding observed in the CA1 and CA3 regions of the hippocampus illustrate that MDMA caused more NE to continue to be present in these areas even after exposure, or that the high levels of NE found in the hippocampus during MDMA exposure led to a sustained increase in NET binding in these areas as a form of systemic regulation. Because NE in the CA1 region of the hippocampus plays a big role in communication signaling between the hippocampus and entorhinal cortex, NE abnormalities in this region may lead to communication deficits which in turn may lead to impairments in spatial learning and working memory. In fact, as illustrated in other studies previously mentioned, these deficits have been found in rats exposed to MDMA while in utero. Also, as mentioned previously, NE increases have been related to exaggerated responses to novelty and attentional processing impairments. These deficits also correlate with a study that observed that rats exposed to MDMA while in utero had increased levels of responsivity to a new cage at P21, an increase that persisted into adulthood as far as P61-P62. Therefore, it can be theorized that NE system changes caused by rat embryonic exposure to MDMA, and, by inference, NE system changes caused by human fetal exposure to MDMA, lead to many of the impairments observed in children prenatally exposed to MDMA. Changes in the noradrenergic system that develop in the fetus as a result of MDMA exposure have direct links to the deficits noted in these children post-parturition.

It is worth mentioning that the results of the MDMA exposure are noted on P21, and that this corresponds to the early teenage years in humans. Thus, NE system changes and the resulting impairments can be effective in this time period. These systemic deficits may be the cause of the impulsivity and 'search for novelty' that is present amongst many young adults that often leads to substance abuse or reckless behavior (Thompson, et al., 2011). Perhaps the mothers ingesting MDMA while pregnant are unknowingly setting the stage for substance abuse in their children many years down the line.

In a similar study, scientists determined that fetal rat exposure to MDMA affects the fetus's dopamine (DA) system. These effects can be seen by a five-fold increase in dopamine neuron fibers in the prefrontal cortex of the rat brain as well as by smaller increases in DA fiber density in the striatum and nucleus accumbens of rats exposed to MDMA while in utero. DA has many pathways in the brain, one of which is the mesocortical tract, a pathway that transports DA from the ventral tegmentum to the frontal cortex. The pathway is known to

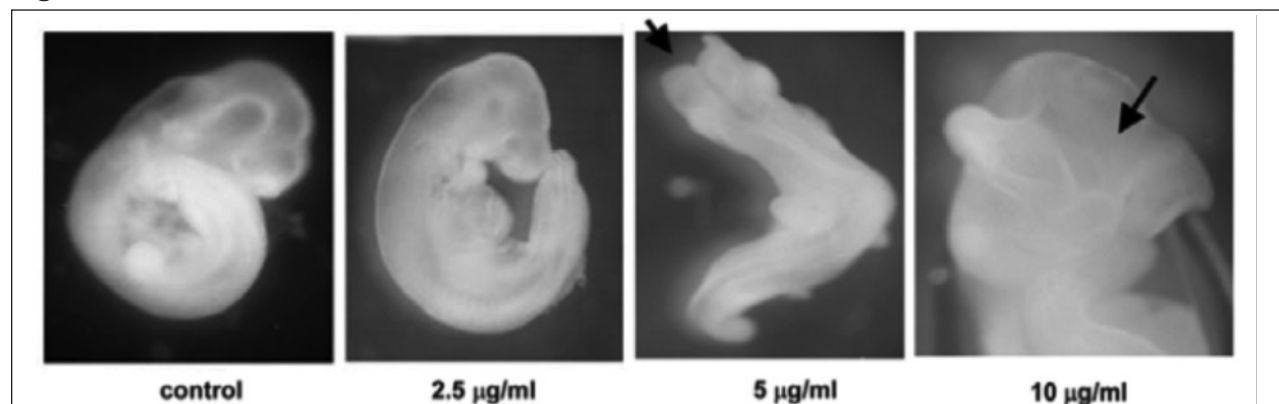
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influence exploratory behaviors, impulsivity, and a search for novelty. When this system is impaired, the results can cause hyperactivity and are sometimes linked to behavioral issues such as ADHD. Because changes in the DA system of both humans and rats is associated with decreased habituation to novelty and increased locomotor activity, this study sought to discover whether the changes in the DA system noted in the rats exposed to MDMA could be correlated with significant changes in these particular behavioral areas (Thompson, et al., 2010).

The study tested Sprague Dawley rats that were injected with MDMA on embryonic day 14-20, as well as a group of 'control' rats, and measured their behavior on postnatal day 21. Many

packaging unneeded cytoplasm and organelles into vesicles known as autophagosomes in preparation for degradation so that the cell can recycle these particles. After an isolation membrane elongates and surrounds unneeded cellular particles, an autophagosome is formed which fuses with a lysosome, eventually leading to the catalytic breakdown of the extraneous cellular particles. Seven proteins known as autophagy-related proteins regulate this process. These proteins are grouped into two distinct categories – the Atg12 system (comprised of Atg 5, 7, 10, and 12) which involves regulating the elongation of the autophagosome isolation membrane, and the Atg8 system (comprised of Atg 3,4,7, and 8), a system involved in regulating the attachment of the phospholipids in the autophagosome

**Figure 2**



*This diagram illustrates images of fetal brain development of various rat embryos that received specific doses of MDMA on gestational day 8.5. Note how the teratogenic effects pointed out by the arrows are in concordance with the higher dosages of MDMA (Chae, et al., 2009)*

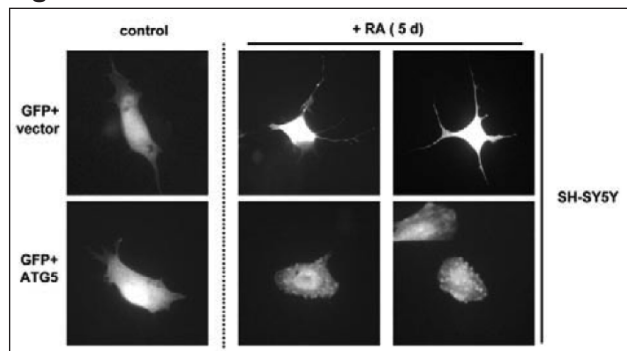
behavioral areas such as home cage locomotor activity, running wheel activity, gravitation towards a high fat diet, and cocaine self-administration levels where tested. However, the only areas of behavior that had significant results in comparison with the control group were the rats' decreased acclimation to new environments, increased perseverance to find a cued platform, and increased locomotion in the center of an open field which served as an indication of the rats' decreased levels of anxiety. Thus, the researchers hypothesized that the rats exposed to MDMA in utero had alterations in their dopamine systems, specifically in the mesocortical pathway. They conjectured that a possible cause for the decreased habituation to novelty and increased perseverance seen in the rats was caused by impairments that the MDMA wreaked on the fetal rats' developing DA systems (Thompson, et al., 2010).

Another study researching deficits found in fetuses exposed to MDMA explores impairments in neuronal differentiation that arise due to an increase in an autophagy-related protein 5 (Atg5). Autophagy is an intracellular process that involves

membrane (Chae, et al., 2009).

Defects in the autophagy system have been linked to various physiological impairments. In this study, researchers discovered that rats embryos injected with MDMA had elevated levels of Atg5. The study explanted rat embryos after 8.5 days of gestation and administered doses of 2.5, 5, and 10 micrograms of MDMA to the embryos. When the embryonic mRNA was sampled, it was noted that Atg5 expression had doubled after 48 hours of MDMA exposure and that extreme teratogenesis and fetal brain damage was observed in the rats (Figure 2). In order to determine if this brain damage occurred due to impairment of neuronal differentiation, human neuroblastoma SH-SY5Y cells were divided into two groups, a control group and a group injected with 10 micrograms of MDMA. The group of cells administered with MDMA illustrated an increase of 1.8 times the amount of Atg5 mRNA expression after 48 hours. Furthermore, when a sample of SH-SY5Y cells was induced with a green fluorescent protein vector (GFP), a protein used as a marker of genetic expression, in the presence of a plasmid encoding for Atg5, the cells did not express

Figure 3



This figure depicts the SH-SY5Y cells that were induced with GFP vector and retinoic acid for 5 days. The control group (top row) was imaged after 5 days while the test group (bottom row) was induced with Atg5 and also imaged after 5 days. Neurite extension and arborization is present and can be seen in the control group while no extension and arborization is present in the test group (Chae, et al., 2009).

any neurite extensions or arborizations (fine branching at the end of the neurite fiber). This was in the presence of retinoic acid, a metabolite of vitamin A that usually aids in growth and development. In contrast, a control group of SH-SY5Y cells induced with a GFP vector and retinoic acid in the absence of Atg5 exhibited extensive neurite extension and arborization (Figure 3). This demonstrates that an increase in Atg5 impairs neuronal growth and differentiation. Therefore, because an increase in Atg5 is found to impair the differentiation of SH-SY5Y neuroblastoma cells, it can be inferred that the teratogenesis observed in rats exposed to MDMA that is accompanied by an increase in Atg5 can be attributed to a similar mechanism of impairment of neuronal differentiation (Chae, et al., 2009).

An additional area that can be explored in order to explain the neuronal impairments discovered in fetuses exposed to MDMA is the metabolites that MDMA forms upon ingestion. As stated previously, when MDMA enters the body, it is broken down into substances that are further metabolized into free radicals. This is supported by the presence of malondialdehyde (MDA) in rat brains after exposure to MDMA, because MDA is one of the end products of lipid peroxidation, a process during which lipids in cell membranes are broken down via free radicals. However, MDMA forms other metabolites aside from MDA, depending on which enzymes are present to break it down. Therefore, while the formation of the MDA metabolite accounts for the breakdown of 20-90% of MDMA ingested by rats, 3, 4-Dihydroxymethamphetamine (HHMA) is a metabolite of MDMA that is formed upon human consumption and accounts for 53-81% of MDMA metabolism in humans. The difference in MDMA metabolism that results in the formation of MDA or HHMA is very slight. Ortho-demethylation of MDMA, which occurs in humans, leads to the formation of HHMA, while

Figure 4

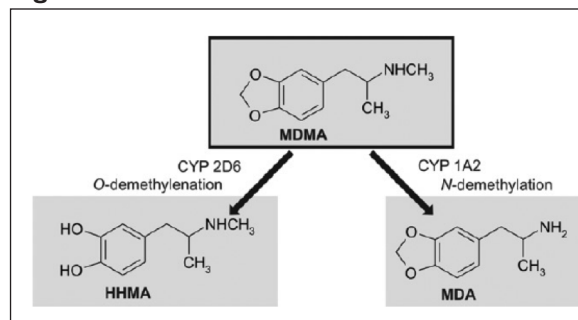


Figure 4 - This diagram illustrates the two main metabolic pathways of MDMA. O-demethylation produces HHMA and is the main pathway that occurs in humans while N-demethylation produces MDA and is the main metabolic pathway that occurs in rats (Barenys, et al., 2012).

N-demethylation, occurring in rats, leads to the formation of MDA (Figure 4). MDMA does metabolize into MDA in humans, as does MDMA metabolize into HHMA in rats, but only trace amounts of these metabolites are found in humans and rats, respectively (Barenys, et al., 2012).

Researchers have found that the presence of HHMA or MDA while a fetus is developing can lead to embryonic defects in the fetus. Scientists explanted embryos from Sprague Dawley rats after 9.5 days of gestation and injected various embryos with MDMA, MDA, and HHMA. The concentrations of the injections for each substance were 5, 15, 25, and 50 micrograms. They discovered that the embryos injected with 25 and 50 micrograms of MDMA had a decrease in crown-rump length (CRL), a measurement of the fetus from the top of the head (crown) to the bottom of the buttocks (rump). In addition, abnormal tissue formations, known as dysmorphogeneses, were observed in the rats injected with 50 micrograms of MDMA. These dysmorphogeneses displayed themselves as an opening in the superior frontal tissue of the head, termed an open cranial neural pore, an abnormal prominence in the inferior frontal part of the head, termed a protuberant nasal placode, and a disproportionately small forebrain in comparison with the midbrain and hindbrain (Barenys, et al., 2012).

Similarly, the embryos injected with doses of MDA displayed a decrease in their CRL after receiving a dose of 50 micrograms of MDA. These rats also exhibited dysmorphogeneses such as the posterior part of the embryonic trunk located behind the embryo instead of in front of it, termed an abnormal flexion, an abnormal caudal part of the embryo that was marked by a bend in the distal part of the embryo's trunk, abnormally shaped somites, and unusual narrowing of the otic vesicles that represented the formation of irregular ears (Barenys, et al., 2012).

The embryos injected with doses of HHMA also displayed

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similar anomalies. Interestingly, the group of embryos injected with 50 micrograms of HHMA died upon exposure to this concentration of metabolite. Therefore, the doses were modified to 10, 20, 30, and 40 micrograms of HHMA per group of embryos. At both 30 and 40 micrograms of HHMA, the CRL of the embryos significantly decreased. Additionally, dysmorphogeneses such as abnormal flexion, a protuberant nasal placode, and an abnormal yolk sac (an anomaly marked by a yolk sac that was not properly rounded or was missing vasculature) were noted in the embryos injected with 40 micrograms of HHMA (Barenys, et al., 2012).

This research indicates that MDMA severely damages a developing fetus due to the toxic metabolites that are formed upon MDMA ingestion. However, it must be addressed why the dysmorphogeneses noted in the fetuses exposed to MDMA differed from those noted in the fetuses exposed to MDA and HHMA. While some of the abnormalities such as a protuberant nasal placode and decreased CRL were seen in both the MDMA-exposed embryos and the MDA and/or HHMA-exposed embryos, there were anomalies noted in the MDA and HHMA-exposed embryos that were not found in the MDMA-exposed embryos. This presents a problem, because MDA and HHMA are metabolites of MDMA and therefore, all of the anomalies found in an embryo exposed to these metabolites should be found in an embryo exposed to MDMA. Perhaps this can be explained by the fact that MDMA forms many metabolites upon ingestion, aside from MDA and HHMA. It is possible that the 'other' metabolites of MDMA interact with one another and 'change' the irregularities noted in embryos exposed to MDA or HHMA to represent those seen in embryos exposed to MDMA.

Additionally, it is worth focusing on the fact that the HHMA killed the embryos that received injections of 50 micrograms while this did not occur to the embryos receiving injections of 50 micrograms of MDA. HHMA is the main metabolite of MDMA in humans, and this finding suggests that it is more toxic than MDA, the main metabolite of MDMA that is found in rats. Because many of the studies available today about MDMA and its harmful effects have used rats as their method of research, perhaps humans need to be extra cautious when ingesting MDMA. This is because the negative effects that MDMA has been shown to display in rats is probably greater in humans since HHMA is the main metabolite of MDMA in humans and appears to be a more toxic metabolite than MDA.

### Conclusion

MDMA is an illicit, amphetamine derivative drug known as 'Ecstasy' that causes harm to a developing fetus exposed to this drug while in utero. Scientists have confirmed that fetuses exposed to MDMA exhibit shorter attention spans, poorer

memory, decreased habituation to novelty, poorer mental development index scorings, and other neurological impairments. While researchers have determined the negative effects that MDMA has on a fetus, the biological reasons for these effects are still being researched extensively. Scientists have determined that these deficits are not due to 5-HT reductions in the brain. However, these defects may be caused by changes in the fetuses' cortisol levels, systemic NE or DA changes that are caused by exposure to MDMA, an increase in Atg5 that leads to inhibition of neuronal growth and differentiation, or the embryotoxic effects of HHMA and MDA, two main metabolites of MDMA. These explanations require further research to determine how they interrelate with one another. Additional studies can investigate the interactions of all of the systemic changes caused by fetal exposure to MDMA to explore how these interactions bring about the cognitive deficits noted in MDMA-exposed fetuses. While this area of research has yet to be explored, individuals should take note that the harmful effects of MDMA have already been determined with certainty and that consumption of this drug should be avoided.

### References

- Barenys M, Flick B, Boix N, et al. Effects of MDMA (ecstasy) and two of its metabolites on rat embryos in vitro. *Reproductive Toxicology*. 2012;34, 57-65.
- Broening HW, Morford LL, Inman-Wood SL, Fukumura M, Vorhees CV. 3, 4-Methylene-dioxymethamphetamine (ecstasy)-induced learning and memory impairments depend on the age of exposure during early development. *Journal of Neuroscience*. 2001;21(9):3228-3235.
- Chae M, Rhee G, Jang I, et al. Atg5 expression induced by MDMA (ecstasy), interferes with neuronal differentiation of neuroblastoma cells. *Molecules and Cells*. 2009;27, 571-575. doi/10.1007/s10059-009-0075-2.
- Colado MI, O'Shea E, Granados R, Misra A, Murray TK, Green AR. A study of the neurotoxic effect of MDMA ('ecstasy') on 5-HT neurons in the brains of mothers and neonates following administration of the drug during pregnancy. *British Journal of Pharmacology*. 1997;121, 827-833.
- Fox HC, Jackson ED, Sinha R. Elevated cortisol and learning and memory deficits in cocaine dependent individuals: Relationship to relapse outcomes. *Psychoneuroendocrinology*. 2009;34, 1198—1207.
- Mosby's Medical Dictionary. 2009 Hypothalamic-pituitary-adrenal axis. Available at: <http://medical-dictionary.thefreedictionary.com/hypothalamic-pituitary-adrenal+axis>. Accessed May, 2015.



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Parrott AC, Moore DG, Turner JJD, Goodwin J, Min MO, Singer LT. MDMA and heightened cortisol: a neurohormonal perspective on the pregnancy outcomes of mothers used 'Ecstasy' during pregnancy. *Hum. Psychopharmacol Clin Exp.* 2014;29: 1-7. doi: 10.1002/hup.2342.

Singer LT, Moore DG, Min MO, et al. One-year outcomes of prenatal exposure to MDMA and other recreational drugs. *Pediatrics.* 2012;130 (3). doi: 10.1542/peds.2012-0666.

Thompson VB, Heiman J, Chambers JB, et al. Long-term behavioral consequences of prenatal MDMA exposure. *Physiol Behav.* 2009;96(4-5): 593-601.

Thompson VB, Koprach JB, Chen EY, Kordower JH, Terpstra BT, Lipton JW. Prenatal exposure to MDMA alters noradrenergic neurodevelopment in the rat. *Neurotoxicology and Teratology.* 2011;34, 206-213.

Wolf OT, Dziobek I, McHugh P, et al. Subjective memory complaints in aging are associated with elevated cortisol levels. *Neurobiology of Aging.* 2005;26, 1357-1363.