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A DEVELOPMENTAL COMPARISON OF THE NEUROBEHAVIORAL EFFECTS OF ECSTASY (MDMA)

Brian J. Piper

Neuroscience and Behavior Program, University of Massachusetts, Amherst, MA

Abstract

The entactogen $\pm$ 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) is a popular recreational drug among college, high school, and, occasionally, middle school students. Preclinical research examining the acute and long-term effects of MDMA has predominately been conducted in reproductively mature subjects but there has been increasing interest in adolescent and *in utero* exposure. This review examines the acute and long-term responses to MDMA during perinatal, adolescent, and adult periods. The ability of MDMA to alter core body temperature emerges gradually during ontogeny while a reduction in body weight is evident at all ages. Learning and working-memory are also altered independent of the developmental stage of exposure. Current evidence suggests adults are more sensitive to the long-term serotonin depletions following MDMA but younger ages also exhibit substantial and rapid neuroplasticity. Sexually dimorphic MDMA responses have been identified for the acute hyperthermic and motoric effects of MDMA with pubescent males being especially susceptible. Several physiological, behavioral, and neurochemical MDMA issues requiring further study are also outlined.

Keywords

$\pm$ 3; 4-methylenedioxymethamphetamine; Adolescence; Anxiety; Depression; Learning; Serotonin

The phenylethylamine $\pm$ 3,4-methylenedioxymethamphetamine (MDMA) is a popular recreational drug best known as ecstasy. MDMA has several other street names including Adam, baby slits, chocolate chips, clarity, doctor, essence, kleenex, and roll [77]. Although ecstasy has some similarities with both stimulants and hallucinogens, MDMA is an entactogen. Entactogen means “touching within” based on the drug’s subjective effects [110]. MDMA also causes long term changes in several markers of the integrity of the serotonin (5-HT) neurotransmitter system [58]. There have been several excellent recent reviews on MDMA toxicology, pharmacokinetics, pharmacodynamics, and neurobehavioral consequences [30, 37,113,157], but none have systematically addressed the intricate effects of MDMA during development.

Ecstasy use is not restricted to limited subpopulations, that is fans of techno music and “raves” [173] or male homosexuals [73,81], as MDMA has expanded into the general population [124,148,170] and especially young people [52,78,170,172]. Over one hundred pregnant women in Toronto called a substance abuse helpline between 1998 and 2000 to inquire

Corresponding Author: Brian J. Piper, Neuroscience and Behavior Program, University of Massachusetts, Amherst, MA 01003-7710, Tel: (413) 545-3333 Fax: (413) 545-0996, bpiper@nsm.umass.edu

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about the potential teratogenic effects of MDMA [64]. Approximately the same number of women in the United Kingdom reported using ecstasy in the 1990's, often with other drugs, during pregnancy [91]. Self-reported ecstasy consumption has been documented as early as age 10 [38]. Many (11.7%) high school seniors in 2001 had tried ecstasy in the United States [67]. According to a 2005 report, 8–9% of teenagers (aged 15–16) in some schools in Ireland, the United Kingdom, and the Netherlands had taken ecstasy [44]. A national survey in Australia conducted in 2001 revealed that 5% of teenagers and 10% of young adults had used ecstasy at least once in the preceding year [40]. Although self-reported substance use is an imperfect measure, the conclusion that ecstasy use is prevalent is generally supported by other indices of drug use including arrests [123], drug seizures [143], hair analyses [69], emergency room records [53,98,114], and coroner's reports [138].

Several drugs are known to have different effects at different ages of exposure. Neurodevelopmental processes including the formation of neurons and glia, cell proliferation, migration, synaptogenesis, myelination, and apoptosis are modified by xenobiotics [134]. The acute physiological response to a substance may be atypical in an immature organism. Between birth and adulthood, there are also many parameters that change that influence pharmacokinetics including the water and lipid content of the body, liver and brain size as a proportion of total body weight, blood flow to the central nervous system, the binding capacity of plasma proteins that drugs adhere to, and renal function [54]. Studies of amphetamines have identified critical periods during ontogeny that are more easily disrupted relative to adult exposure [122,159]. However, the embryo may appear less sensitive than the adult. This can result from age dependent modulation of pharmacodynamics (e.g. lower number of neurotransmitter receptors at earlier ages). The tremendous plasticity of the developing nervous system could mask the long-term effects of a drug. Overall, the many quantitative and qualitative differences between the mature and immature beings can limit any prediction of equivalent responses across ages. As will be shown, age differentially modulates the biochemical and behavioral consequences of MDMA. The following sections will provide a brief historical perspective on this drug and then contrast the pharmacokinetics and pharmacodynamics of MDMA at prenatal, adolescent, and adult ages using measures where comparative information is available. In addition, although epidemiological evidence indicates that infants are infrequently exposed to MDMA, some laboratories consider the preweanling rat to be analogous to third trimester human [160]. Therefore, evidence from this period of drug treatment will also be described as the goal of this paper is to describe whether there are age differences in MDMA responsivity, and, when present, to identify the mechanisms mediating the variability in vulnerability across the lifespan. As animal investigators have adopted various treatment regimens, (i.e. single or multiple doses per day, different inter-dose intervals) the amount of MDMA administered will be listed as the mg/kg/day. Note that because of species differences in lifespan, the age of non-human subjects will typically be listed for each investigation.

1.0 History

MDMA was first synthesized by Anton Kollisch at a German pharmaceutical company almost one-hundred years ago [7]. Merck filed a patent application for MDMA in 1912 which was granted two years later [116]. MDMA was a chemical intermediate in the synthesis of hydrastinin, an astringent to control bleeding. (A popular, although inaccurate, misconception is that MDMA was developed as an appetite suppressant [77]). The U.S. Army Chemical Center conducted toxicological studies in the 1950's which were declassified and published two-decades later [62]. Shortly thereafter, members of the mental health community began to explore the use of MDMA, known to therapists as "Adam", as an adjunct to psychotherapy. Hundreds of sessions were conducted with Adam and the drug subsequently gained recognition among some clinicians for the treatment of depression, physical and psychological pain, and

relationship problems [42,59]. Proponents of MDMA for psychotherapeutic purposes have made some advances recently and studies are ongoing to determine whether MDMA is beneficial for veterans with post-traumatic stress disorder and for terminally ill cancer patients with anxiety [41,163].

Great Britain listed MDMA and other substituted amines as Class A substances in 1977. Eight years later, the U.S. government classified MDMA as a Schedule I drug following a report that administration of a chemically similar compound to rats caused a profile of chemical changes that was interpreted as indicative of 5-HT neurotoxicity [131]. MDMA has acute and long-term effects on 5-HT in several species including several non-human primates (baboons, marmosets, squirrel, rhesus, and cynomolgous monkeys), pigeons, rabbits, guinea-pigs, rats, and some mouse strains [58,100,113,130,145]. Recent investigations have begun to determine that humans may exhibit similar alterations in 5-HT and serotonergic mediated function due to repeated ecstasy use [61,66,72,113]. As ecstasy is typically used recreationally with other substances, researchers have begun to determine how MDMA interacts with alcohol [21], caffeine [95], LSD [137], marijuana [107] and methamphetamine [24–26] in adults.

2.0 Pharmacokinetics

A substantial amount is known about MDMA absorption, distribution, and elimination in mature animals and humans [37,87]. At least fourteen metabolites are produced *in vivo* from MDMA [58]. Interestingly, direct administration of MDMA into the rat brain does not cause enduring neurochemical changes [43] suggesting that peripheral metabolism is necessary and that one or more metabolites cause neurotoxic effects. The identity of the presumed “neurotoxic metabolite” is uncertain as it has been difficult to identify a single metabolite with the same neurochemical profile as MDMA [68]. Due to this complexity, many investigators have focused their efforts on quantifying the levels of MDMA and its primary demethylated metabolite, methylenedioxymphetamine (MDA). The half-life of 20 mg/kg of MDMA to adult rats was two-hours with only slight differences between the R and S enantiomers [47]. Using the same species and dose as in [47], large age dependent differences were identified in rats at Postnatal Day (PD) 1 and PD 10 with half-lives of 2.8 and 4.0 hours, respectively [165]. Unfortunately, the route of administration was i.v. in [47] and s.c. in [165] so the differences in the rates of elimination are not readily comparable. Administration of MDMA to the rat dam on E14 resulted in fetal elimination profiles and peak concentrations [20] very similar to those obtained on PD 1 [165].

Some investigators argue that because the new born rat is more immature than the new born human, the neonatal rat is equivalent neurodevelopmentally to a third trimester human fetus. Although this justification for postnatal rodent dosing certainly has some merit, MDMA disposition following *in utero* exposure and direct rat pup administration are likely to be quite different which is likely a substantial consideration for extensively metabolized drugs. Even sophisticated mathematical techniques to approximate dose equivalencies across species [22] do not address developmental factors. Further study using the same MDMA dose and route of administration across a range of ages in both sexes and measuring the neurotoxic MDMA metabolite levels in plasma, brain, and, if feasible, urine, would greatly enhance our understanding of how different development periods differ in their susceptibility to the consequences of MDMA.

3.0 Acute Responses

Age modulates the short (hours) and long (weeks to months) term effects of MDMA. Persistent consequences of ecstasy that occur after MDMA has been eliminated from the body are the topic of section 4.0. The alterations in temperature and motor activity have been the most frequently assessed acute effects but some evidence is also available about other parameters.

3.1 Physiological

The effect of MDMA on core body temperature emerges gradually during ontogeny while a reduction in body weight is evident at all ages (Table 1).

3.1.1 Temperature—Emergency medical personnel occasionally encounter patients that consumed ecstasy and are running a fever over 43 °C [58]. Accordingly, the capacity of MDMA to increase core temperature has been a primary research focus of many laboratories. Ecstasy does not cause uni-directional temperature changes as MDMA is a poikilothermic substance that elicits temperature dysregulation that is dependent on the ambient temperature. More specifically, MDMA administration in a cool environment causes hypothermia while dosing at warmer temperatures induces hyperthermia [56,86]. The core temperature response at intermediate temperatures (20–23 °C) is bidirectional in rats [14,118,121]. In contrast, recent evidence suggests that MDMA induces unidirectional temperature changes (hyperthermia) in rhesus monkeys [158] and possibly also humans [49]. Newborn mammals are very sensitive to decreases in the ambient temperature but can engage in nonshivering thermogenesis to produce some heat from brown adipose tissue. Uncoupling proteins found in the inner mitochondrial membrane produce heat by separating ATP synthesis from oxidation [5]. Adult mice lacking uncoupling protein-3 exhibited a substantially blunted hyperthermic response to MDMA [102].

The effects of single, large doses (up to 40 mg/kg) of MDMA on thermal homeostasis were compared in neonatal (PD 10), adolescent (PD 40), and young-adult (PD 70) rats by [10]. It is important to note that a single 50 mg/kg dose is lethal for fifty percent of adult rats [62]. MDMA treatment in a hot environment (33 °C) did not significantly alter rectal temperature in neonates but evoked an intense, prolonged, and potentially life-threatening, hyperthermia among adolescents and adults. Additional study using a more moderate MDMA dose (20 mg/kg/day) at intermediate ambient temperatures showed that adolescents are less sensitive than adults to pyrexia [120,121]. Twenty mg/kg was administered twice per day to pregnant rats on gestational day (GD) 14 to 17. The first MDMA treatment caused hyperthermia but the dams rapidly developed tolerance to this response [28]. A gradually diminishing temperature dysregulation in rat dams was also seen by [76]. The development of thermal tolerance is not unique to females or to pregnancy as a blunted temperature dysregulation also occurs in adolescents [118] and adults [25,142]. The mechanism(s) responsible for tolerance, especially at different ages, is presently unclear as, in addition to the activation of uncoupling proteins by norepinephrine and thyroid hormones [103], dopamine, serotonin, and several cytokines mediate the core temperature response to MDMA [58].

3.1.2 Weight—Ecstasy users frequently lament the weight loss that accompanies chronic use [113]. The rapid increase in body mass from birth through young-adulthood might be anticipated to influence the sensitivity of this measure to MDMA treatments. Although weight data is commonly obtained in animal studies, the simplicity of measurement belies the numerous factors that can change this index. MDMA alters several physiological processes including reducing food [71] and, to a lesser extent, water intake [39,50]. MDMA also increases urination and defecation [8]. Elevated salivation has also been documented following MDMA [146] which, in combination with increased grooming, aids in thermoregulation. Further, rats increase their respiratory rate after MDMA which causes substantial evaporative water loss [56]. The additive effect of increased urination and defecation is evident by examining the large short-term weight reduction that occurs immediately following adult exposure [8,121]. Similarly, adolescent rats lost over ten grams, 8% of pre-drug weight, only hours after MDMA treatments [121]. The molecular mechanisms of MDMA induced weight loss are incompletely understood but are quite likely to involve systemic norepinephrine release by this sympathomimetic and binding to alpha1 or beta3 adrenergic receptors followed by activation

of uncoupling proteins. Uncoupling proteins can reduce body weight by decreasing fat stores and increasing muscle breakdown [103].

Body weight exhibits dose dependent reductions at all exposure ages tested [1,11,50,71,75, 76,99,118,119,121,166,167]. Intermittent MDMA (20 mg/kg/day) delivery every fifth day from PD 35 to 60 to rats reduced the rate of weight gain [118,119]. MDMA (30 mg/kg/day, administered subcutaneously) on GD 14 to 20 decreased the weight gain for the dam and the offspring were lighter at birth [76]. Oral MDMA administration (10 mg/kg/day) every other day from GD 6 to 18 slightly, but significantly, attenuated maternal weight gain during pregnancy while the offspring were unaffected [147]. Similarly, a single MDMA dose (8–32 mg/kg) administered directly to the egg did not alter the weight of newly hatched chickens [12]. Perinatal exposure (PD 1–4, 20 mg/kg/day), decreased weight gain in male and female rat pups [99]. Treatments (10–40 mg/kg/day) during a longer period (PD 1–10 or 11–20) attenuated the body mass such that there were still small (5–10%) deficits in adulthood (PD 82) [11]. Importantly, as will also be discussed later, [166] determined that the amount of weight loss caused by MDMA was inadequate to affect learning and memory.

3.1.3 Serotonin Syndrome—The overt symptoms of the serotonin syndrome are stereotyped motor behaviors that occur following excessive 5-HT release. The syndrome is expressed in a species typical fashion and in the rat it is characterized by head-weaving, forepaw treading, and low body posture [146]. Individual syndrome elements exhibit unique developmental profiles. For example, the headweaving and forepaw treading responses to a 5-HT_{1A} agonist in rats are expressed at adult-like levels at weanling but hindlimb abduction decreases around puberty [35].

Although the syndrome has been documented following prepubescent MDMA exposure [48, 118], direct comparisons using the same treatment regimen at different ages has yet to be conducted. Adult rats (PD 100) responded to a single 10 mg/kg dose, administered i.p., with a robust syndrome where all components were clearly visible [120]. In contrast, forepaw treading was minimal after four subcutaneous 10 mg/kg treatments to young adults [121]. Adolescents (PD 35) displayed some headweaving responses whereas forepaw treading activity was inconsistently observed after four 5 mg/kg doses [118]. Overall, although different dosing regimens were employed, the general conclusion from these studies is that sensitivity to 5-HT mediated stereotypies following MDMA may increase with age.

3.1.4 Sexual Response—As MDMA is colloquially known as ecstasy, it may not be surprising that adult humans report that the drug modifies the sexual experience [42,175]. Serotonin is important for male reproductive development [4], and MDMA depletes 5-HT [58]. Therefore, the acute and long-term effects of MDMA on genital morphology and function might be promising areas of study. Unfortunately, our knowledge of this topic is very preliminary. Sperm plugs were found in the locomotor chambers after MDMA treatment (6 mg/kg) to adult rats and, evidently, MDMA induced spontaneous ejaculation [8]. Periadolescent rats (PD 35) exhibit penile discharge following MDMA, although much less commonly than older ages. This sexual response could be occurring because MDMA appears to activate norepinephrine receptors in the vas deferens [79,126] although central factors are also likely to be involved.

3.2 Behavioral

3.2.1 Motor Activity—MDMA, like other amphetamines, increases locomotion in adults [50,55]. Amphetamine induced hyperactivity in mice emerges at weanling [80]. Interestingly, direct administration of MDMA, or amphetamine, to the chicken embryo five days prior to hatching induced an acute reduction in motility [13]. Young rats (PD 28) also exhibit an acute

elevation in motor-activity, particularly horizontal activity, following MDMA [16,17]. This motor response has yet to be thoroughly characterized after perinatal exposure. Rat pups that received MDMA on PD 1–4 show a general increase in limb movements, but at this age, these do not result in locomotion (unpublished observations).

3.2.2 Anxiety—Anxiety is a frequently used term with a wide range of operational definitions for different ages and species. Interconnections among the anatomical structures mediating affective behavior continue formation into young-adulthood [33]. Adult humans who had never before used ecstasy showed a small, but significant, elevation in self-reported anxiety following MDMA administration in a hospital setting [156]. Young-adult mice exhibited a dose dependent reduction in open-arm entries of the elevated plus maze, a pattern of behavior suggestive of greater anxiety [85]. Rats had more anxiety-like behavior in the plus maze and emergence tests but less in the social-interaction assessment [108]. Finally, newborn rats vocalize when separated from their mother and drugs with anxiolytic properties in humans also limit isolation calls [9,155]. MDMA induced a substantial reduction in these vocalizations [168]. Further preclinical research with several ages and a single reliable measure of anxiety-like behavior might be helpful to clarify these disparate outcomes.

3.3 MDMA Re-Exposure

Subjects with a MDMA history are re-exposed or “challenged” with the same substance to determine if the physiological response to MDMA has changed. This may reveal a diminished or an enhanced effect (i.e. tolerance or sensitization). The stereotypy and locomotor responses increased in adult rats that received MDMA every other day for two-weeks [146]. Using the same species and age, an augmented hyperthermia was identified with daily treatments, also for two weeks by [34]. A locomotor sensitization two weeks after an escalating MDMA regimen was reported [127,128]. In contrast, the serotonin syndrome and pyrexia was substantially reduced one week after a rat MDMA binge [142].

Intermittent MDMA exposure every five days beginning on PD 35 (adolescence) lead to a reduction in the temperature dysregulation and headweaving stereotypy by PD 60 [118]. Prior embryonic experience modified the behavioral response to a second MDMA treatment in newly hatched chickens [13]. An alteration in the physiological response to a MDMA challenge can be extremely long-lasting or possibly even permanent. A single MDMA dose administered to adults (PD 100) caused a heightened temperature dysregulation and 5-HT syndrome among rats that received MDMA perinatally (PD 1–4) [120]. There are divergent outcomes across age although it is not clear if these result from developmental factors or differences between studies in the drug dose and MDMA free or “washout” periods.

4.0 Long-term Behavioral Consequences

The behavioral effects of MDMA (Table 2) are not limited to the period immediately after drug exposure as changes have also been documented weeks to months after MDMA [16,17,24–27,92,93,118,119,155,159,166,168].

4.1 Learning and Memory

Forebrain structures that are essential for cognitive function like the hippocampus and frontal cortex are highly sensitive to MDMA [58]. The serotonin system in these regions undergoes dynamic [23,51,115] and protracted development [104]. A deficit in learning and memory is a highly consistent finding of cross-sectional investigations with experienced adult ecstasy users [105,135]. McGregor and colleagues found that MDMA lowers the discrimination ratio in the novel object-recognition test with mature rats, particularly when the drug is administered in a hot environment [93,106]. A reduction in the discrimination ratio is suggestive of a deficit

in working-memory although other processes like habituation could be involved. Periadolescent MDMA treatments diminished the time spent exploring the objects, a gross index of attentional behavior [118], and decreased the discrimination ratio in this paradigm [119]. Neonatal MDMA (PD 11–20) diminished water maze learning and novel object exploration in adult-rats [27]. However, MDMA administration at earlier postnatal periods did not alter these endpoints [11,120]. Perhaps counter-intuitively, newborn rat offspring from mothers that received MDMA during pregnancy performed better on an olfactory discrimination task. Both male and female MDMA exposed pups took less time to identify familiar smells [147]. Importantly, Vorhees and colleagues have determined that cognitive deficits are not due to the MDMA induced reduction in weight gain by running an additional large litter vehicle treated group [166].

4.2 Depression

As drugs that increase 5-HT have some efficacy in treating affective disorders [45] and because MDMA causes 5-HT deficits [58], one might anticipate that the effects of MDMA on depression would be a major area of interest. Understanding of the biochemistry of depression is also important because serotonin reuptake inhibitors, a prevalent pharmacotherapy for adults, may not be appropriate for children and adolescents [169].

Among adults including heavy ecstasy users, inconsistent results have been obtained with some cross-sectional reports showing an elevation in depressive symptoms and other investigations showing no effects (reviewed in [105]). A large four-year longitudinal study (N=2,462) of adolescents and young-adults (age 14 to 24) assessed whether psychopathology preceded or followed ecstasy use. Major-depressive disorder was equally likely to occur prior to as after initial ecstasy consumption. However, dysthymia, a milder but more persistent form of depression, developed after using ecstasy [82]. MDMA increased immobility in the forced-swim test in adult rats when measured at least three months after drug treatments [93,152] but not at shorter intervals [26,141]. An increase in immobility is consistent with an elevation in depression-like behavior. Anhedonia, a loss of interest in previously pleasurable activities, is a core feature of major depressive disorder. Anhedonia-like behavior, as measured by a decrease in drinking preference for a sweetened solution, was observed in young-adulthood (PD 70) following prenatal exposure [51]. Adolescent ecstasy users reported more emotional neglect and physical abuse during childhood than non-users [144] and these stressors could increase the risk for mood disorders. Some ecstasy users may be self-medicating in an attempt to ameliorate symptoms of affective disorders although this possibility requires verification.

4.3 Anxiety

In addition to the acute changes following MDMA (described above), anxiety-like behavior may show enduring alterations subsequent to MDMA exposure. Adolescents and young-adults that consumed ecstasy were significantly more likely to suffer from a variety of anxiety problems including phobias, panic attacks, and generalized anxiety disorder. Anxiety concerns severe enough to meet psychiatric diagnostic criteria were more likely to follow, rather than precede, ecstasy use [82]. Alternatively, this report, although longitudinal, can not exclude the possibility that this self-selected population would have developed mental health issues even without ecstasy use.

Animal studies have used a variety of behavioral assessments of anxiety-like behavior. Results with the elevated plus maze have produced discrepant outcomes both between [17,60,65,96,106] and within [118,119] laboratories. There have been findings of an increase [60,106], decrease [96], or no appreciable change [17,65] in anxiety-like behavior in adult rats. A three day treatment regimen (PD 28–30) caused no significant effects when rats were assessed in early adulthood [16,17]. Repeated administration from PD 35 to 60, also in rats, resulted in

increased open-arm exploration [119] or hyperactivity [118] which appears to depend on the dosing regimen although the inherent unreliability of this test [32] could also be a factor. An anxiogenic pattern in the emergence test has been consistently identified several weeks after adult MDMA treatments to Wistar [26,60,93,107,152] but not Sprague-Dawley rats [118]. Possibly, these findings suggest there may be strain differences in either post-synaptic 5-HT receptors [17], or non-serotonergic mechanisms (described below) that mediate the behavioral toxicology of MDMA.

5.0 Long-term Neurochemical Consequences

The most consistently identified long-term effect following moderate to high dose MDMA exposure is a reduction in 5-HT levels but other parameters may also be affected. Indoleamine endpoints exhibit an increasing sensitivity with age (Table 3).

5.1 Indoleamine

Serotonin is one of the earliest appearing neurotransmitters in the developing brain and is important for cellular proliferation, neuronal migration, neurite outgrowth, growth cone motility, and the differentiation of neuronal phenotypes [164,176]. Relatively high doses of MDMA to adults decrease 5-HT and the 5-HT metabolite 5-hydroxyindole acetic acid (5-HIAA). The density of SERT, as measured by either antibody or radioligand binding is similarly reduced in adults, [58,171 although see 161,162]. Moderate to high MDMA decreases 5-HT, 5-HIAA, and SERT levels following exposure at all ages studied [51,75,99,118,133, 141]. Table 3 outlines a pattern of increased susceptibility with age to indoleamine and SERT reductions following MDMA with the findings of [70] especially supporting this perspective. This group administered a high course MDMA treatment regimen (40 mg/kg/day $\times$ 4 days) to rats beginning either on GD 15, PD 10, 15, 20, 25, or 30 and measured radiolabeled paroxetine binding to SERT on PD 40. MDMA did not alter the affinity of paroxetine for SERT at any age but decreased SERT levels only when the exposure occurred after PD 20. Similar findings were also obtained with 5-HT by [2]. The absence of a hyperthermia at young ages does not appear to be responsible for the relative insensitivity of young organisms to MDMA. Increasing core body temperature by heating neonatal rats following MDMA administration did not increase the forebrain 5-HT or SERT reductions [99].

No development periods are immune from the neurochemical consequences of MDMA. Serotonin and 5-HIAA levels appear to triple at birth but this transient increase was temporarily blunted by prenatal MDMA [51]. There is considerable neuroplasticity in the 5-HT system in adulthood [6] but the response to an insult (i.e. MDMA) may be particularly rapid during development. The perinatal brain may also be differently sensitive than the mature brain. SERT is restricted to 5-HT neurons, specifically the axons, in adults but is expressed on 5-HT cell bodies and dendrites prenatally and SERT is found on non-serotonergic neurons during the early postnatal period [176]. Since SERT mediates MDMA induced neuron damage [58], the immature organism may uptake MDMA directly into the soma which could be deleterious not only for serotonergic but also non-serotonergic cells.

The neurochemical sequelae of low doses ($\leq$ 5 mg/kg in rats) of MDMA have been less extensively studied. Surprisingly, small, but significant, elevations in 5-HT (22.1%) and 5-HIAA (25.0%) were identified in the hypothalamus ten weeks after low doses (2 mg/kg $\times$ 4) of a combination of MDMA and methamphetamine to adult rats [24]. Similarly, early adolescent mice (PD 28) had significantly higher 5-HT in adulthood (PD 114) in the same region [109]. These findings of abnormal 5-HT levels in a structure essential for hormone regulation may have clinical implications for investigations using neuroendocrine challenge paradigms. Bi-directional dose dependent 5-HT and 5-HIAA levels alterations were identified two-weeks after MDMA treatments to male pubescent rats [74]. The 2 and 5 mg/kg doses

increased 5-HT in the forebrain by an average of 30.5% and 27.6%, respectively, relative to the control (Figure 1). The magnitude of the reduction in the 10 mg/kg group, 25.7%, is consistent with other studies at this age [48,118]. Bi-directional effects were also observed following oral MDMA treatments to female rhesus monkeys [3]. These findings of a high dose reduction and low dose increase in 5-HT are consistent with the predictions of a hormetic model [19] although further study with very low doses is necessary. Note that high 5-HT levels are not “good” as abnormal levels suggest a disruption in indoleamine homeostasis.

Non-unidirectional changes following MDMA have also been identified in 5-HT axon density. Immunocytochemistry of brains from adult squirrel monkeys that received MDMA seven years earlier revealed an overall 5-HT hypoinnervation in the neocortex and striatum but a hyperinnervation in the selected regions of the globus pallidus and thalamus [63]. Perinatal MDMA exposure (PD 1-4) resulted in significant SERT labeling reductions in the neocortex but an elevation in the striatum in middle aged (9 month old) rats [101]. Whether the regional differences in the 5-HT reorganization in these studies is due to differences in species, treatment paradigms, or the ages of exposure is not yet apparent.

5.2 Non-Indoleamine

MDMA is often described as a selective 5-HT neurotoxin [89] but this is an oversimplification. Non-serotonergic endpoints are also abnormal, particularly following developmental treatments.

5.2.1 Catecholamine—Dopamine levels are usually insensitive to adult MDMA exposure in many different species (except some mice strains: [58,130,145]). However, certain dosing regimens cause enduring reductions in rat forebrain dopamine and norepinephrine [31,88]. The spinal cord, a structure infrequently examined by MDMA investigators, had lower dopamine quantities in rats eighteen months after drug treatments [141]. Lower levels of dopamine metabolites were also detected in the caudate of squirrel monkeys and in the cerebral spinal fluid of women that used ecstasy [90,132]. Interestingly, either early or late neonatal (PD 1–10 or 11–20) MDMA caused subtle, yet significant, elevations in norepinephrine (7–15%) in the hippocampus of adult (PD 105) rats [11]. Even more striking, MDMA treatments to dams (GD 14 to 18) resulted in a five-fold increase in dopaminergic fiber density in the frontal cortex of offspring [76].

5.2.2 Other—A variety of other non-monoaminergic parameters are altered following MDMA. Silver staining is a general index of neurotoxicity and argyrophilic cell bodies were identified in the somatosensory cortex of sexually mature rats following an extremely high (160 mg/kg/day $\times$ 2 days) MDMA treatment regimen [31]. The neurochemical identity of these cell bodies is unknown but an investigation with a structurally similar drug suggests they may possibly be glutamatergic [125]. Similarly, Fluoro-Jade labeling occurs in the adult forebrain following a single (10 mg/kg) MDMA dose [139]. Fluoro-Jade is a validated histological measure of neurotoxicity [140]. Neonatal MDMA (PD 1–4) also doubled apoptosis in the rat striatum and hippocampus [101]. Since serotonergic and dopaminergic somas are not present in the structures previously described [45], the viability of non-monoaminergic neurons is challenged by MDMA.

6.0 Sex-Differences

More adolescent boys than girls try ecstasy [38,82,136] and this pattern typically continues into adulthood [78]. Women that received equivalent MDMA doses (on a mg/kg basis) as men in a research environment rated their acute subjective experiences, both positive and negative, as more intense than men. Possibly, females were either more perceptive or more willing to communicate their feelings. In contrast, men exhibited a greater MDMA induced increase in

systolic blood pressure [83]. Ecstasy related deaths, although infrequent relative to the total number of users, include a preponderance of men. Over two-hundred ecstasy-related fatalities were documented in England from coroner's reports from 1996 – 2002 with a ratio of men to women of 4:1 [138].

Animal studies in adults and adolescents have also identified a higher resistance to the consequences of MDMA among females. A large MDMA dose (80 mg/kg) was lethal in ninety percent of male mice versus less than one-third of females [18]. Similarly, male pubescent (PD 39) rats were shown to be much more sensitive to ecstasy in that MDMA doses that killed all males were non-fatal for most females. Males also showed greater hyperactivity and hyperthermia in response to non-lethal MDMA doses. However, adult female rats exhibited substantially more locomotor activation to MDMA than males [112]. Interestingly, there were no sex differences in the MDMA induced reduction in 5-HT or 5-HIAA in [74] which is consistent with a prior investigation [94]. It is not currently known if gender alters lethality at younger ages because, as previously described, neonatal rodents do not exhibit pyrexia and fatalities are seldom observed. Early developmental MDMA produces equivalent changes in body weight [76,99], tyrosine hydroxylase [75], brain derived neurotrophic factor [76], olfactory discrimination [147] and 5-HT [11,76] in males and females. There are also few consistently obtained sex differences following neonatal MDMA for spatial learning and memory [11,166].

Sexually dimorphic acute MDMA responses have been shown to be mediated by gonadal hormones although sex differences in pharmacokinetics are also likely to be important. Prepulse inhibition was inhibited by MDMA (2.5, 5, or 10 mg/kg) in males and females in the diestrous and metestrous phase of their estrous cycle. However, females in proestrous and diestrous showed no disruption in sensorimotor gating to MDMA [15]. Catechol-O-methyltransferase (COMT) is responsible for several methylation reactions in the metabolism of MDMA [37] and, perhaps not coincidentally, this ubiquitous enzyme has also been reported to be less active in women [97].

7.0 Conclusions

Developmental neuropharmacologists have established that the immature organisms responses to MDMA are quantitatively [70,99] and perhaps qualitatively [76] different from that of the adults. This accomplishment is an important contribution to the larger neurotoxicology and substance abuse fields but several challenges remain. First, the mechanisms that mediate this age dependent modulation of the biochemical sequelae of MDMA are far from understood. Pharmacokinetic differences have already been shown to mediate species [84] and sex [29] differences in MDMA neurotoxicity. The identity of the MDMA metabolite(s) responsible for SERT and 5-HT depletions has yet to be ascertained but it is quite possible that the production, distribution, or elimination of this chemical is modulated by age. Future pharmacodynamic avenues to continue to pursue will be how ontogeny influences free radical generation [28] and regulation in response to MDMA. Similarly, the dynamic changes in postsynaptic monoamine receptor levels are also likely contributors to the differential sensitivity to the physiological and behavioral effects of MDMA.

Second, although there is detailed epidemiological data in some countries about the patterns of ecstasy use among high school and middle school students [38,44,67], information on the prevalence of ecstasy use at other ages and among certain high risk groups, is inadequate. Some women report ecstasy use during pregnancy [64] and MDMA has been detected in meconium [117], albeit infrequently. Ecstasy use is not restricted to a single age group but, with the exception of a single report [145], there is no data about the consequences of MDMA during

middle-age or later periods. This is important to characterize because MDMA is being given to older people in an ongoing clinical trial [163].

Third, it is important to stress that regular ecstasy users are not representative of the general population and cross sectional studies comparing an “ecstasy group” with controls are likely to reach erroneous conclusions resulting from group differences in polysubstance use, lifestyle factors including sleep and dietary habits, and pre-existing psychopathology. Due to impurities in entactogen composition [151], self-reported ecstasy use and hair analyses may be highly discrepant [69]. More longitudinal studies [57,82,174] in conjunction with rodent and especially non-human primate research using clinically relevant MDMA doses will allow a more accurate assessment of the public health risks of regular MDMA use. Fourth, selecting an MDMA dosing regimen to administer to a non-human animal that models human ecstasy consumption is complex and challenging for adult studies, and even more difficult for developmentalists. There is currently no uniformly accepted approach for interspecies dose comparisons [36] although there are advocates for allometric [22,58] or response scaling [161]. This profound issue has been under-appreciated by most preclinical MDMA investigators and more systematic attention is overdue.

Overall, this review shows that many developmental neurotoxicology laboratories have selected measures that are sensitive to adult MDMA exposure. This is certainly a reasonable starting point as this tactic has determined that the immature organism is less vulnerable to MDMA induced reductions in 5-HT and SERT because, in part, the neuroplasticity that is evident in the adult brain [6] may be even more pronounced in the developing organism. Age differences in temperature regulation [10], antioxidant enzymes [28], dopamine innervation [2], and, possibly, drug metabolism [165] could protect the immature organism from the indoleamine consequences of MDMA. Recent studies have moved beyond measuring only 5-HT and SERT and have targeted indices that may be even more relevant to the many ongoing neurodevelopmental events [75,76,101]. This approach will continue to be useful in determining how age modulates the physiological, neurobehavioral, and biochemical sequelae of MDMA.

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Figure 1.

Forebrain serotonin, expressed as a percent of the control, in male pubescent rats that received MDMA 13 days previously. The S.E.M. (not shown for clarity) ranged from 10.1% to 13.4% for the control. Adapted with permission from [74]. * $p < .005$ vs. 10 mg/kg.

Table 1
Comparison of the physiological effects of MDMA exposure at different developmental periods

	Prenatal	Neonatal	Adolescent	Adult	References
Temperature dysregulation	↑ ↑ ↑ (dam) ↓	0 ↑ ↓	↑ m, r ↓ m, r	↑ ↑ h, m, p, r ↓ h, r	10,28,58,99,121,150
Weight					1,11,50,71,75,76,101,113,118,119,121,166,167
Serotonin syndrome	NA	↑ r	↑ r ↓ r	↑ ↑ h, r ↓ p, r/0 r/↑ r	37,48,118,120,121
MDMA Challenge					27,113,120,121

↑ increase, ↓: decrease, 0: no change, Blank: not known; or NA: not applicable. Number of arrows designates relative magnitude of effect where age comparisons are possible. Species: h = human, m = mouse, p = non-human primate, or r = rat.

Table 2
Comparison of the behavioral effects of MDMA exposure at different developmental periods

	Prenatal	Neonatal	Adolescent	Adult	References
Anxiety (acute)	NA	↓ m, r		↓ r / ↑	85,108,156,168
Anxiety		↑ r	↓ r / 0 r	↓ v r / 0 v h, r / ↑ r	16,17,21,60,65,82,92,93,106,118
Depression		↑ r	↑ h	↑ h, r / 0 h, r	51,82,105,141,152-154
Learning and memory	↑ r	↓ r / 0 r	↓ h, r	↓ h, r	27,66,93,129,135,147

↑ increase, ↓ decrease, 0: no change, Blank: not known; or NA: not applicable. All measures are long-term unless otherwise specified. Number of arrows designates relative magnitude of effect.
Species: h = human, m = mouse, p = non-human primate, or r = rat.

Table 3
Comparison of the long-term neurochemical effects of MDMA exposure at different developmental periods

	Prenatal	Neonatal	Adolescent	Adult	References
5-HT	0 ↑/↓ r	↓ r	↓ ↓ r, m	↓ ↓ ↓ m, p, r	2,11,51,58,99,130,147,168
5-HIAA	0 ↑/↓ r	↓ r	↓ ↓ ↓ r	↓ ↓ ↓ h, p, r	48,51,58,76,147,168
SERT	0 ↑	↓ r	↓ ↓ ↓ h, r	↓ ↓ ↓ h, p, r	2,51,58,70,99,111,118,147,168

↑ : increase, ↓ : decrease, 0: no change, Blank: not known; or NA: not applicable. Number of arrows designates relative magnitude of effect. Species: h = human, m = mouse, p = non-human primate, or r = rat.