REVIEW ARTICLE

MDMA and heightened cortisol: a neurohormonal perspective on the pregnancy outcomes of mothers used 'Ecstasy' during pregnancy

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Objective   The illicit recreational drug 3,4-methylenedioxymethamphetamine (MDMA) or Ecstasy has strong neurohormonal effects. When taken by recreational users at dance clubs and raves, it can generate an 800% increase in the stress hormone cortisol, whereas drug-free users show chronically raised levels of cortisol. The aim here is to critically debate this neurohormonal influence for the children of pregnant MDMA-using mothers.
Methods   High levels of cortisol are known to be damaging for neuropsychobiological well-being in adult humans. MDMA can damage foetal development in laboratory animals, and the prospective Drugs and Infancy Study was established to monitor the effects of MDMA taken recreationally by pregnant women.
Results   The Drugs and Infancy Study revealed that young mothers, who took MDMA during the first trimester of pregnancy, gave birth to babies with significant gross psychomotor retardation . These mothers would have experienced high levels of cortisol due to Ecstasy/MDMA use, and since cortisol can cross the placenta, this is likely to have also occurred in the foetus.
Conclusions   In terms of causation, the developmental problems may reflect a combination of neurotransmitter and neurohormonal effects on the hypothalamic–pituitary–adrenal axis, with serotonergic activity being influenced by the high levels of cortisol. Copyright © 2014 John Wiley & Sons, Ltd.

KEY WORDS—Ecstasy; MDMA; cortisol; stress; hormone; pregnancy

MDMA: A BRIEF INTRODUCTION TO 'ECSTASY'

3,4-Methylenedioxymethamphetamine (MDMA) or 'Ecstasy' is used as an illicit recreational drug, by minority subgroups of adolescents and young adults (Parrott, 2001; Singer *et al.*, 2004). MDMA is a ring-substituted methamphetamine derivative with many similarities to the parent compound. It has a particular affinity for the serotonin transporter (SERT) and can release up to 80% of available serotonin, but like methamphetamine, it also stimulates the release of dopamine and other neurotransmitters (Ricaurte *et al.*, 2000; Green *et al.*, 2003). MDMA is a powerful central nervous system stimulant, which can lead to psycho-physiological overstimulation and various aspects of the serotonin syndrome (Parrott, 2002). Its acute effects typically include euphoria, although it can also lead to feelings of anxiety and mental confusion (Cohen, 1998; Parrott *et al.*, 2011; Kirkpatrick *et al.*, 2012). In recreational users at dance clubs, its use often leads to overheating and physical exhaustion (Suy *et al.*, 1999; Morefield *et al.*, 2009; Parrott, 2012a), with occasional medical complications, which can prove fatal if not treated rapidly (Hall and Henry, 2006; Schifano *et al.*, 2006; Greene *et al.*, 2009).

In laboratory animals, MDMA is a serotonergic neurotoxin (Ricaurte *et al.*, 1985, 2000), with the extent of neuronal damage heightened by environmental conditions, which necessitate further energy expenditure (Huether *et al.*, 1997; Malberg and Seiden, 1998; Sanchez *et al.*, 2004; Puerta *et al.*, 2009). In abstinent recreational users, neuroimaging procedures such as positron emission tomography and functional magnetic resonance imaging have revealed lower levels of the SERT across all regions of the cerebral cortex, with the degree of serotonin loss correlating with lifetime

Ecstasy/MDMA usage (Reneman *et al.*, 2006; Cowan, 2007; Kish *et al.*, 2010; Erritizoe *et al.*, 2011). The functional problems of drug-free recreational users can include memory loss, impaired cognitive awareness, reduced problem solving skills, lower social intelligence and various forms of psychiatric distress (Schifano *et al.*, 1998; Topp *et al.*, 1999; Fox *et al.*, 2001, 2002; Parrott *et al.*, 2001; Roiser and Sahakian, 2004; Singer *et al.*, 2004; Soar *et al.*, 2004; Parrott, 2006, 2012b, 2013a, 2013b; Reay *et al.*, 2006; Zakzanis and Campbell, 2006; McCann and Ricaurte, 2007; Montgomery *et al.*, 2010; Brière *et al.*, 2012; Benningfield and Cowan, 2013). Abstinent Ecstasy/MDMA users also report feeling significantly more stressed in their daily lives than non-user controls (Scholey *et al.*, 2011) and feel less calm when undertaking a standard laboratory stress task (Wetherell *et al.*, 2012).

DRUGS AND INFANCY STUDY: PROSPECTIVE EFFECTS OF MDMA IN PREGNANCY

Animal laboratory research has shown that MDMA can damage foetal development. A review of the preclinical literature has implicated MDMA exposure, in the period equivalent to the first or third trimester, with deficits in long-term memory, learning and loco-motor activity (Skelton *et al.*, 2008). These preclinical findings raise concerns about the potentially damaging effects in pregnant women. The Drugs and Infancy Study (DAISY) was undertaken to empirically investigate this question. We prospectively monitored 28 women who took MDMA during pregnancy and compared them with a polydrug control group of 68 women who took other psychoactive drugs while pregnant. The drug usage patterns for these mothers have been summarised by Moore *et al.* (2010), the birth and 4-month child outcome findings are described by Singer *et al.* (2012a), the 12-month child profiles by Singer *et al.* (2012b) and the 24-month outcomes by Singer *et al.* (2013). The main finding was a significant delay in psychomotor development in the children of Ecstasy/MDMA-using mothers (Table 1). This was found at the 4, 12 and 24-month assessment batteries, and the degree of psychomotor deficit was positively associated with greater MDMA usage during the first trimester (Singer *et al.*, 2012a, 2012b). Two European medical studies found a higher incidence of congenital malformations, in the births of mothers who had used MDMA while pregnant (van Tonningen-van Driel *et al.*, 1999; McElhatton *et al.*, 1999; Table 1).

In terms of causation, one potential explanation for the psychomotor differences is MDMA-induced 'serotonergic neurotoxicity' in the developing neonatal brain. In support of this serotonergic explanation, Jacobs and Fornal (1995) noted in a serotonin review that one of the functions it modulated was gross psychomotor control. However, cortisol may also be involved, as recreational Ecstasy/MDMA users can show pronounced changes in this core neurohormone. Reynolds (2013) reported that high levels of cortisol could have a range of adverse effects during human pregnancy, although psychobiological problems in the emergent children were also noted in an earlier review (Van den Bergh *et al.*, 2005). Hence, cortisol may have some directly damaging effects on foetal development in humans. Furthermore, as cortisol is known to influence serotonin activity (Chaouloff, 2000), it may also contribute indirectly to serotonergic neurotoxicity.

CORTISOL AND MDMA

Selye (1956) revealed the crucial role of cortisol for homeostasis and psychophysiological stability. Under conditions of high energy demand, the capacity for metabolic stability could be overloaded, and the general adaptation syndrome was initiated. This comprised an integrated set of neurohormonal and physiological reactions, including cortisol release, which helped to provide the additional metabolic resources necessary for continued functioning (Lovallo, 1997). Selye's research was primarily focused on physical stressors, such as hot and cold environments, anoxia at high altitudes and marathon running. The physical nature of biological stress is particularly relevant here, as MDMA is typically taken under physically demanding conditions. Dance clubs are often overcrowded, with high ambient temperatures, and dancing can be both energetic and prolonged. Suy *et al.* (1999) described one large Dutch rave, where most visits to the paramedic centre involved Ecstasy/MDMA users who were feeling overheated or physically exhausted. After rest, cooling and fluid replacement, many returned to the dance floor.

In placebo-controlled laboratory studies, MDMA can generate a dose-related increase in core body temperature in humans (Freedman *et al.*, 2005; see summary table in Parrott, a). Dance clubbers may demonstrate even greater increases in body temperatures, with group mean peak changes of over $1.0\,°C$, although these thermal effects can be variable (Parrott and Young, 2005; Parrott *et al.*, 2006, 2007; Morefield *et al.*, 2009). As this recreational drug is typically used in physically stressful conditions (Suy *et al.*, 1999; Parrott, 2004), it is probably the combined effects of sympathomimetic drug and environmental co-stimulation, which make MDMA damaging for human psychobiology (Parrott, 2002, 2004, 2006). For instance, Darvesh and Gudelsky (2005) noted that 'MDMA produces a dysregulation of energy metabolism

Table 1. Overview of human studies into the effects of recreational Ecstasy/3,4-methylenedioxymethamphetamine (MDMA) taken during pregnancy on birth outcomes

Study	Summary of methods and main findings
McElhatton et al. (1999)	'Prospective follow-up of 136 babies exposed to ecstasy in utero indicated that the drug may be associated with a significantly increased risk of congenital defects'. Cardiovascular anomalies and musculoskeletal anomalies were predominant.
Van Tonningen-van Driel et al. (1999)	Monitored 43 case studies of Ecstasy/MDMA exposure early in pregnancy, in the Netherlands. One incidence of a congenital cardiac abnormality. Authors concluded that 'The sample size was too small to draw conclusions'.
Singer et al. (2012a)	DAISY of 96 women in the UK, with 28 MDMA exposed and 68 control group mothers. Prospectively monitored from early pregnancy to 2 years post-partum. This report covers the neonatal findings 4 months post-partum. 'MDMA exposed infants… had poorer motor quality and lower milestone attainment at 4 months, with a dose-response relationship to amount of MDMA exposure'.
Singer et al. (2012b)	Infants from DAISY study 12 months post-partum. Standard assessments for cognitive, language and psychomotor functioning. It was found that 'Amount of prenatal MDMA exposure predicted poorer infant mental and motor development at 12 months in a dose-dependent manner'.
Singer et al. (2013)	DAISY study at 24 months post-partum, with significant psychomotor problems still present In overall terms: 'Prenatal MDMA exposure predicts poorer motor outcomes from 4 months to 2 years of age. Given the widespread recreational use of MDMA (Ecstasy), pregnant women should be cautioned about possible developmental effects in offspring'.

which contributes to the mechanism of MDMA induced neurotoxicity'.

The effects of acute MDMA on cortisol have been investigated in several placebo-controlled laboratory studies. Mas et al. (1999) found a significant increases in cortisol after 75 and 125-mg oral MDMA. Similar increases in cortisol were noted by Pacifici et al. (1999, 2001). In percentage terms, Harris et al. (2002) reported that 0.5 mg/kg MDMA led to a cortisol increase over baseline of around 100%, whereas the higher dose of 1.5 mg/kg led to percentage increase of 150% over baseline. In their MDMA review, Dumont and Verkes (2006) concluded that acute drug administration led to a robust cortisol increase. Cortisol is also heightened after recreational Ecstasy/MDMA self-administration in dance clubs or house parties (Table 1). In the work of Parrott et al. (2008), Ecstasy/MDMA users were assessed on successive weekends when partying on-drug as usual and when partying while abstaining from MDMA. Saliva samples confirmed MDMA presence during the on-drug weekend and its absence during the abstinence weekend (Parrott et al., 2008). The combination of dance clubbing and recreational Ecstasy/MDMA led to a group mean 800% increase in saliva cortisol, significantly higher than both baseline and clubbing during abstinence (Table 2). In a related study, experienced Ecstasy users were assessed at a 'house party', where self-reported Ecstasy/MDMA use ranged from 2 to 9 tablets per individual (Parrott et al., 2007). Cortisol levels were again increased by 800% after 4 h on self-administered Ecstasy/MDMA, whereas cortisol levels while partying without MDMA were statistically unchanged (Table 2).

In chronic terms, abstinent recreational Ecstasy/MDMA users also show significant neurohormonal changes. Gerra et al. (1998) found a reduced cortisol response to a d-fenfluramine challenge in drug-free recreational MDMA users. This was empirically replicated in a follow-up study by the same group (Gerra et al., 2000). Verkes et al. (2001) also found a significant reduction in cortisol responses to a d-fenfluramine challenge, in both moderate and heavy abstinent Ecstasy/MDMA users. Gerra et al. (2003) further noted that baseline cortisol levels were significantly lower in abstinent Ecstasy users; they also demonstrated a reduced cortisol response to a psychosocial stressor. The authors concluded that there was empirical evidence for 'hypothalamic–pituitary–adrenal (HPA) basal hyperactivation and reduced responsiveness to stress, which may represent a complex neuroendocrine dysfunction associated with MDMA use'. More recently, hair samples from +100 participants in Wales were analysed at Dresden University for cumulative 3-month cortisol levels (Parrott et al., 2012). Recent light Ecstasy/MDMA users (1–4 occasions in the past 3 months) had a group mean 50% elevation of cortisol levels, compared with non-user controls. Recent heavier Ecstasy/MDMA users (+5 occasions in past 3 months) displayed a group mean 400% increase in hair cortisol. They also displayed poorer cognitive performance, with fewer words recalled, and more self-rated memory problems (Table 3). This is consistent with empirical evidence that high levels of cortisol are associated with various neurocognitive deficits, including poorer memory across all stages of the lifespan (Lupien et al., 2005). Furthermore, these high 3-month cortisol values suggest that regular Ecstasy/MDMA users experience both HPA axis overactivity and enduring psychobiological stress.

Table 2. Cortisol levels for two studies of recreational Ecstasy/3,4-methylenedioxymethamphetamine (MDMA) users before, during and after dance clubbing or partying (means and standard errors)

Study 1	Pre-drug baseline	1-h post-drug	2.5-h post-drug	48-h post-drug	72-h post-drug
On MDMA	0.3 + −0.3	0.9 + −0.5***	2.2 + −1.1***	0.5 + −0.7	0.4 + −0.5
Abstinence	0.2 + −0.1	0.2 + −0.2	0.4 + −0.4	0.4 + −0.4	0.2 + −0.2
Study 2	Pre-drug baseline	2-h post-drug	4-h post-drug	6-h post-drug	24-h post −drug
On MDMA	0.3 + −0.1	1.0 + −0.7*	2.3 + -0.3***	1.5 + −0.9**	0.7 + −0.6+
Abstinence	0.3 + −0.3	0.4 + −0.3	0.3 + −0.2	0.5 + −0.8	0.4 + −0.5

Each participant was assessed on self-administered MDMA, and off-MDMA, over counterbalanced weekends at the same dance club. Significance levels represent comparisons with pre-drug baseline (studies 1 and 2 after Parrott et al., 2007, 2008).
Paired comparisons with pre-drug baseline.
*$p < 0.05$.
**$p < 0.01$.
***$p < 0.001$.

Table 3. Cortisol levels and cognitive assessments for recent light Ecstasy/3,4-methylenedioxymethamphetamine (MDMA) users, recent heavy Ecstasy/MDMA users, and non-users controls

	Non-user controls (no MDMA usage)	Recent light users (1–4 MDMA times)	Recent heavy users (5+ MDMA times)
Cortisol (3-month hair)	13.78 (6.09)	19.37 (15.96)	55.01 (80.13)*
Hassles (self-rated)	4.63 (3.58)	5.25 (4.75)	7.48 (3.64)*
Cognitive failures (self-rated)	4.87 (4.22)	5.97 (5.26)	8.17 (4.14)*
Memory problems (self-rated)	4.26 (3.94)	5.72 (5.5)	7.91 (4.24)*
Rivermead: delayed word recall	6.83 (3.48)	4.25 (3.24)*	4.91 (1.98)*

Drug usage and cortisol hair sampling from the previous 3-months (after Parrott et al., 2012).

The mothers in our DAISY, who were also regular users of Ecstasy/MDMA, may therefore have experienced similar high levels of cortisol and stress.

CORTISOL DURING PREGNANCY AND FOETAL DEVELOPMENT

Any increase in maternal cortisol may be an adverse impact on the developing foetus. Cortisol is involved in the neurohormonal stress, and increased levels of maternal stress during pregnancy are associated with many sub-optimal developmental outcomes. In animal studies, the offspring of prenatally stressed mothers show increased anxiety and reduced attention span (Schneider et al., 2001). They also show differences in brain structure, including changes in hippocampal volume and other areas (Coe et al., 2003). In human infants, heightened stress during pregnancy is associated with several adverse physical effects, including low birth-weight, reduced head circumference, low Agpar scores and other short-term/long-term developmental issues. Reviews of the literature (Van den Bergh et al., 2005) have concluded that ante-natal stress can lead to significant long-term regulation problems in human infants. This can be manifest at cognitive, behavioural and emotional levels, with infants showing higher reactivity in interactions with their mothers, poorer attention, lower maternally-reported language ability, sleeping, feeding and activity problems, and higher ratings for irritability and being difficult. When the children reach pre-school years, it has been found that those who were exposed to stress *in utero* showed poorer attention, greater hyperactivity, emotional problems and more behavioural difficulties. In the longer term, these children and adolescents may show greater impulsivity, reduced IQ and a greater prevalence of Attention Deficit Hyperactivity Disorder (Van den Bergh et al., 2005). Reynolds (2013) similarly noted that high levels of maternal cortisol were associated with adverse outcomes in their children, including behavioural disorders and altered brain structure.

The mechanisms underlying the transmission of the effects of stress from the mother to the developing infant are not fully understood, but one hypothesis is that maternal stress hormones and particularly glucocorticoids are transmitted across the placenta. Singh et al. (2012) noted that 'Maternal stress during pregnancy can raise endogenous levels of the natural glucocorticoid cortisol. A significant proportion of the cortisol is inactivated by the placental glucocorticoid barrier', although some cortisol still reaches the developing foetus. These neurohormones may then re-programme the HPA reactivity of the infant, with a range of subsequent adverse outcomes. There is debate about the extent to which core psychobiological processes

and specifically HPA re-programming may be responsible for these stress effects. However, there is certainly evidence that an increase in maternal cortisol level can lead to a corresponding, but not directly equivalent, increase in levels of foetal cortisol. One source of uncertainty is the extent to which this effect is large enough and immediate enough to explain all adverse psychobiological outcomes. Typically, an increase in maternal cortisol of 10% in the mother is associated with a corresponding increase across the placenta of around 1% in the infant, with this change occurring after a delay of around 10 min.

Given that recreational MDMA leads to an 800% increase in cortisol 4 h after taking the drug and that regular users register a 400% increase over the 3-month period (Parrott *et al.*, 2008, 2012), there may be significant risks of heightened cortisol in the foetus of an Ecstasy/MDMA-using mother (Singer *et al.*, 2012a, 2012b). Furthermore, the 3-month data suggest that there may be a risk of increased cortisol for the developing foetus, in those mothers who quit using immediately before pregnancy. Sustained exposure is also more likely to have a detrimental impact than more fleeting exposures, although the strength of the acute neurohormonal reaction to MDMA should be noted. The main concern is that with regular recreational Ecstasy/MDMA usage, cortisol levels will be increased, both acutely and chronically. The adverse consequences of these neurohormonal changes for the developing foetus may be broadly similar to those found with other forms of maternal stress.

OVERVIEW: CORTISOL, MDMA AND PREGNANCY

The DAISY found that heavier recreational Ecstasy/MDMA use during the first trimester of pregnancy led to significant developmental differences in the emergent children (Singer *et al.*, 2012a, 2012b). The main area of difficulty was in gross psychomotor functioning, with the other assessed areas being unaffected. For the upper half of the sample whose infants demonstrated motor effects, MDMA usage averaged 3.3 ± 4.0 tablets per week in the month prior to pregnancy. The extent of the psychomotor differences was also associated with cumulative Ecstasy/MDMA usage during the first trimester. However, it is still not clear which underlying factors are causing these deficits. One potential explanation is serotonergic neurotoxicity. Neuroimaging studies have found that MDMA is associated with reduced levels of the SERT, whereas cumulative-lifetime drug usage correlates with the lower levels of SERT (McCann *et al.*, 2008; Kish *et al.*, 2010). This leads to the hypothesis that

the neonatal brain is being adversely affected, in a way similar to the mother's brain. Another potential explanation is neurohormonal, with heightened bio-energetic stress disrupting normal HPA axis activity and everyday homeostasis. This explanatory model for MDMA is outlined more fully by Parrott (2009), where it was noted that both high and low levels of cortisol can impair various neuropsychobiological functions, including memory, sleep, brain integrity and psychiatric well-being (Herbert *et al.*, 2007).

As outlined previously, Van den Bergh *et al.* (2005) reported that 'cortisol appears to cross the placenta'. Hence, high levels of cortisol in Ecstasy/MDMA-using mothers may have generated significant cortisol increases in the developing foetus (also: Singh *et al.*, 2012). The bio-energetic stress of recreational Ecstasy/MDMA in pregnant women may thus lead to bio-energetic stress, impaired homeostasis and developmental difficulties in the developing foetus. It should be emphasised that MDMA usage in the DAISY ceased almost entirely after the first trimester (Moore *et al.*, 2010), so that any increase in cortisol would largely be limited to that period. However, there may be some residual increases in cortisol, which continue into the next trimester. It should be noted that the neurotransmitter and neurohormonal explanations are not alternatives, but different aspects of the same underlying bio-energetic stress model. Serotonin and cortisol are closely interlinked (Chaouloff, 2000), with both being involved in neuropsychobiological integrity. Herbert *et al.* (2007) noted that 'Corticosteroids are an essential component of the body's homeostatic system'.

MDMA stimulates the release of cortisol in both the laboratory (Harris *et al.*, 2002) and at the dance clubs (Table 1). Hence, pregnant women who take Ecstasy/MDMA will experience profound changes in both cortisol and general neuropsychobiological integrity. Their homeostatic status may be impaired, and this will often occur at night when they would normally experience recuperating sleep. Cortisol is an important factor for acute bio-energetic stress, whereas in chronic terms, it can help explain the damaging effects of regular Ecstasy/MDMA usage. These neuropsychobiological effects may reflect a combination of factors, both hormonal and neural. Together they can produce an enduring period of homeostatic disruption and bio-energetic stress. Hence, it is not too surprising that child development can be adversely affected by recreational MDMA usage in the mother (Table 1).

A final issue raised by these findings is the importance of publicising the need for women to abstain from drug-taking if there is any possibility of pregnancy. There is also a need for several months of

abstinence beforehand, to facilitate a return to normal neurohormonal levels. This paper has focused on the adverse effects of Ecstasy/MDMA, but other stimulants such as cocaine and amphetamine are also damaging, as are psychoactive drugs such as cannabis, nicotine and alcohol. The HPA axis needs to be stable prior to conception and hence should not be disrupted by drug stressors. It is crucially important to protect the developing foetus from the potentially damaging effects of neurohormonal instability (Glover, 2011).

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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