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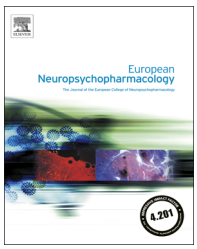

Increased cortisol levels in hair of recent Ecstasy/MDMA users

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Abstract
Previous research has revealed an acute 8-fold increase in salivary cortisol following self-administrated Ecstasy/MDMA in dance clubbers. It is currently not known to what extent repeated usage impacts upon activity of the hypothalamic-pituitary-adrenal axis over a more prolonged period of time. This study investigated the integrated cortisol levels in 3-month hair samples from recent Ecstasy/MDMA users and non-user controls. One hundred and one unpaid participants (53 males, 48 females; mean age 21.75 years) completed the University of East London recreational drug use questionnaire, modified to cover the past 3-months of usage. They comprised 32 light recent Ecstasy/MDMA users (1–4 times in last 3 months), 23 recent heavy MDMA users (+5 times in last 3 months), and 54 non-user controls. Volunteers provided 3 cm hair samples for cortisol analysis. Hair cortisol levels were observed to be significantly higher in recent heavy MDMA users (mean= 55.0±80.1 pg/mg), compared to recent light MDMA users (19.4±16.0 pg/mg; $p=0.015$), and to non-users (13.8±6.1 pg/mg; $p<0.001$). Hence the regular use of Ecstasy/MDMA was associated with almost 4-fold raised hair cortisol levels, in comparison with non-user controls. The present results are consistent with the bio-energetic stress model for Ecstasy/MDMA, which predicts that repeated stimulant drug use may increase cortisol production acutely, and result in greater deposits of the hormone in hair. These data may also help explain the neurocognitive, psychiatric, and other psychobiological problems of some abstinent users. Future study design and directions for research concerning the psychoneuroendocrinological impact of MDMA are also discussed.

1. Introduction

The amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) is associated with a wide range of central nervous system effects, particularly through its indirect

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agonistic actions on the serotonergic and dopaminergic systems (Green et al., 2003). MDMA is most widely known for its euphoriant properties, when it is used as an illicit recreational drug under the street name of 'Ecstasy' (Schifano, 2000; Parrott, 2004a, 2013a). The activating effects of MDMA are not limited to positive moods, since negative moods such as anxiety can also be increased (Kirkpatrick et al., 2012; Parrott et al., 2011). The regular use of Ecstasy/MDMA is associated with a range of neurocognitive and other psychological problems, including deficits in memory, higher executive processing, sleep and psychiatric well-being (Fox et al., 2002; Laws and Kokkalis, 2007; McCann et al., 2008; Montgomery et al., 2010; Parrott, 2012a, 2013b; Zakzanis and Campbell, 2006).

MDMA also stimulates the hypothalamic-pituitary-adrenal (HPA) axis, with increased secretion of the glucocorticoid hormone cortisol (Mas et al., 1999; Pacifici et al., 2001; Harris et al., 2002). Following acute doses of MDMA in the laboratory, the increase in cortisol can range from 100% to 150% over baseline, depending on factors such as dosage level (Harris et al., 2002), and repeated administration (Farré et al., 2004). Stronger endocrine changes have been reported in real world studies of recreational drug users. In two independent studies, the acute use of Ecstasy/MDMA in combination with dancing and partying induced an almost 8-fold acute increase in salivary cortisol levels (Parrott et al., 2007, 2008). Importantly, no significant increases in cortisol were observed in either study on the control weekends, when participants went partying as usual, but without taking Ecstasy/MDMA. The marked cortisol increase in Ecstasy/MDMA-using party-goers may result from the combination of drug and environmental stimulation, with dance clubs typically involving loud music, crowding, and physical exertion (Parrott, 2004b).

Although the short-term neuroendocrine effects of MDMA are well established, the longer-term effects of repeated drug use on HPA axis activity and cortisol remain unclear. Initial evidence suggests that drug-free Ecstasy users exhibit altered baseline and stress-responsive cortisol secretion (Gerra et al., 2003). Until recently, the measurement of chronic cortisol levels was limited to blood, saliva, or urine samples, ideally taken repeatedly at several time points (Evans et al., 2012; Hellhammer et al., 2007). Cortisol in hair provides a methodological advance, since it generates a cumulative index of hormone secretion over several months (Stalder and Kirschbaum, 2012). The underlying theory is that the hormone is incorporated into the growing hair, and that the hair cortisol index may provide a valid (Broderick et al., 2004; Kirschbaum et al., 2009; Thomson et al., 2010; Manenschijn et al., 2011), and reliable (Stalder et al., 2012b) measure of longer-term neurohormonal secretion. In the current study we utilised this novel procedure, to investigate the links between Ecstasy/MDMA use and cortisol secretion over the previous 3 months. Our prediction was that more frequent and repeated Ecstasy/MDMA usage would lead to higher levels of cortisol in the hair.

2. Experimental procedures

2.1. Participant characteristics

One-hundred and one participants (53 males, 48 females, mean ± SD age: 21.75 ± 4.23 years) were recruited via advertisements concerning MDMA usage. Study inclusion was restricted to participants who had hair longer than 3 cm at the posterior vertex region of the scalp, and who did not suffer from any chronic medical or psychiatric conditions. Participants were divided into three subgroups depending on their self-reported Ecstasy/MDMA usage over the prior three months. Recent light users comprised 27 participants (18 male, 9 female, mean ± SD age: 21.15 ± 1.09 years) who had consumed MDMA between one and four times in the past 3-months. Recent heavy users comprised 23 participants (8 male, 15 female, mean ± SD age: 21.48 ± 0.89 years) who had consumed MDMA more than five times in the past 3-months. The control group

Table 1 Recent 3-month drug consumption: self-reported by recent light MDMA users, recent heavy MDMA users, and non-user controls (modified University of East London Recreational Drug Usage Questionnaire; Parrott et al, 2001).

	Non-user controls		Recent light users		Recent heavy users	
	Number of users	Times used (S.D.)	Number of users	Times used (S.D.)	Number of users	Times used (S.D.)
MDMA	0	0 (0)	32	2.7 (1.1)	23	7.5 (2.4)
Amphetamine	1	1 (0)	7	5 (4.97)	1	3 (0)
Cocaine (Nasal)	2	5.5 (66.3)	12	9.4 (16.5)	11	1.9 (1.2)
Cocaine (Crack)	0	0 (0)	0	0 (0)	0	0 (0)
LSD	1	1 (0)	1	1 (0)	1	1 (0)
Mephedrone	7	8.4 (6.6)	12	11.6 (16.9)	6	1.5 (0.8)
Opiate	0	0 (0)	1	90 (0)	1	1 (0)
Barbiturate	2	1.5 (2.1)	2	1.5 (0.7)	2	3.5 (3.5)
Magic Mushrooms	0	0 (0)	1	1 (0)	1	1 (0)
Steroids	0	0 (0)	0	0 (0)	0	0 (0)
Solvents	0	0 (0)	0	0 (0)	0	0 (0)
Poppers	1	1 (0)	2	1(0)	4	1(0)
Ketamine	0	0 (0)	2	3 (2.8)	2	1.5 (0.7)
Tobacco/day	19	7.5 (4.7)	27	6.7 (3.8)	13	6.6 (4.4)
Alcohol/week	54	13.4 (11.8)	32	19.7 (12.6)	23	19.7 (9.)
Cannabis/month	20	19.6 (11.2)	27	18.5 (10.5)	18	14.1 (12.3)