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Ecstasy (MDMA) mimics the post-orgasmic state: Impairment of sexual drive and function during acute MDMA-effects may be due to increased prolactin secretion

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Summary Methylenedioxymethamphetamine (MDMA or ''Ecstasy'') is a major stimulant drug of abuse worldwide. MDMA produces euphoria, enhances interpersonal communication and feelings of closeness with others. In contrast to the induced emotions of affection and sensual enhancement, clinical studies show that it impairs sexual drive and functioning. In drug-free humans, sexual stimulation with orgasm induces a pronounced secretion of prolactin, which may mediate the post-orgasmic state. The phenomenological features of the psychological state induced by MDMA show some similarities with features of the post-orgasmic state. In addition, MDMA also induces a prominent increase of prolactin plasma levels with a similar time kinetic compared to the post-orgasmic prolactin increase. Here, we present the hypothesis that the impairment of sexual parameters after MDMA may be mediated by increased prolactin.

Introduction

Methylenedioxymethamphetamine (MDMA or ''Ecstasy'') is a psychopharmacological agent with a unique spectrum of psychoactive effects and recently a major drug of abuse. MDMA induces a state of euphoria and minor perceptual changes combined with a subjective sense of being closer to other people and an ease to communicate [1]. Another specific effect is an increased desire for bodily contact with other people (''the hug drug'') [2].

MDMA (''Ecstasy'') and sexual function

In spite of its repeated mentioning as an aphrodisiac in the lay press, there is empirical and exper-

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imental evidence that MDMA impairs human sexual drive and behaviour. An early survey of MDMA users found a significant decrease of sexual activity, especially in initiating sexual activity [3]. Impairment in erectile function and ability to attain orgasm were also reported [3—5]. Although almost 50% of the subjects examined by Buffum and Moser [3] indicated that they felt more receptive for being sexual during the influence of MDMA, this effect was not paralleled by an increased interest in initiating sexual activity in either men or women. What most of the subjects reported as sexual receptivity seems to be mainly an increased emotional closeness. People may enjoy physical contact and feel love for others in the absence of a specific hunger for concrete sexual activity [6,7]. This is also confirmed by a group of Swiss psychotherapists who never came across a patient becoming sexually aroused while on MDMA despite conducting hundreds of group sessions [8]. These findings are in accord with those of earlier naturalistic studies of methylenedioxyamphetamine (a close chemical companion of MDMA) users [9,10]. ''Sexual relationships were possible as the drug waned, but during the height of the high people described a greater interest in a general, diffuse sensualism than in specific sexuality ... The desire to touch and pleasure in touching was specifically pan-sexual ... [10, p. 70]. From these studies and some additional anecdotal evidence [2,8] it can be concluded that MDMA provides a sensual rather than sexual experience.

Further evidence for an inhibitory effect of MDMA on sexual parameters derives from animal studies. Experiments in sexually vigorous male rats revealed that systemic administration of MDMA produced a transient disruption of the expression of male copulatory behaviour. In addition, in MDMA-treated male rats that did display copulatory behaviour, both the ejaculation latency and post-ejaculatory interval were dramatically lengthened when compared to placebo controls. One week after administration, copulatory behaviour in MDMA treated rats appeared unaffected despite a marked depletion of 5-HT and 5-HIAA content in the striatum, and hippocampus [11,12]. In contrast to MDMA the simple amphetamines like amphetamine and methamphetamine are known to stimulate sexual drive and performance [13,14].

MDMA and prolactin

Neuroendocrine studies examining the acute effects of MDMA or its pharmacological equivalent methylenedioxyethylamphetamine (MDEA) in humans demonstrate a dose-dependent increase of blood prolactin up to 300% [15—19]. Furthermore, MDMA significantly increased plasma cortisol and dehydroepiandrosterone [17] while plasma levels of human growth hormone remained unaffected [18,19].

The time course of prolactin increase follows closely the pharmacokinetics of MDMA or MDEA with significantly elevated prolactin plasma levels up to 4 h after ingestion of the drugs [15,18]. In contrast to MDMA methamphetamine does not alter prolactin levels [18] and d-amphetamine even reduces prolactin secretion in humans [20]. As mentioned above, methamphetamine and d-amphetamine are known to stimulate sexual drive and performance [13].

Sexual functioning, orgasm and prolactin

Recent neuroendocrine studies examining the effects of sexual arousal and orgasm in humans demonstrated a marked elevation of plasma prolactin in both males and females immediately after orgasm. Plasma prolactin concentrations remained elevated one hour following orgasm and were orgasm-dependent [21,22]. Plasma cortisol which is increased during acute effects of MDMA or MDEA remained unaffected during sexual arousal and orgasm in males and females [23]. As prolactin was shown to be a robust marker of orgasm, the authors suggested that prolactin may act as a peripheral neuroendocrine reproductive reflex (improving and facilitating fertility and conception) and/or as a feedback signal to neuronal systems that may mediate sexual arousability and satiation following orgasm [24]. This position is based on a wealth of data from both animal and human studies demonstrating a marked inhibitory effect of chronic hyperprolactinemia on appetitive and consummatory sexual parameters [24—27], with attenuation of inhibition following normalisation of circulating prolactin [28]. According to Krüger et al.'s theory [24] even acute increases in prolactin might contribute to a sexual satiation mechanism following orgasm via feedback to central nervous system structures. Specifically, neurons of the nigrostriatal, mesolimbic, and hypothalamic dopaminergic systems express a high density of prolactin receptors [29—31], and are known to play pivotal roles in the regulation of sexual arousal and behaviour [32,33]. Prolactin may be able to downregulate the dopaminergic activity in certain areas and

thereby modulate sexual arousability and satiation [24] (see Fig. 1).

MDMA induced prolactin secretion may impair sexual functioning

Here, we propose the hypothesis that the impairment of sexual drive and performance after MDMA-ingestion may be caused by the pronounced MDMA-induced secretion of prolactin leading to a psychophysical equivalent state of sexual satiation compared to the post-orgasmic period. According to these theories prolactin may mediate a feeling and physiological state of reduced sexual receptivity and lowered sexual drive. This is terminated approximately 30—60 min after orgasm and after 4—5 h following ingestion of MDMA/MDEA. The decrease of sexual performance during MDMA seems to correlate with the increase of prolactin levels which return to baseline after 4—5 h in accordance with normalisation of subjective psychotropic effects and reoccurrence of sexual drive and function (see Fig. 2).

MDMA is known to generate most of its psychophysical effects by a massive depletion of serotonin [1] which may imply a serotonergic mechanism of prolactin secretion [34,35]. One may assume that the impairment of sexual functioning after MDMA use is due to the release of serotonin, because serotonin, its precursors or the selective serotonin reuptake inhibitors (SSRIs) are known to generally inhibit sexual behaviour [27,33]. However, various factors limit the hypothesis of serotonin secretion being the causal factor of impaired sexual appetence and function after MDMA intake. First, there is a direct pharmacokinetic correlation, i.e., time-curve of the prolactin secretion induced by MDMA and the time-curve of impaired sexual functioning. Second, the MDMA-induced serotonin depletion lasts much longer than the sexual impairment. As mentioned above, MDMA also impairs sexual functioning in rats [11], with these effects correlating with the acute effects of MDMA. In contrast, the serotonin levels in the brain measured via reverse phase liquid chromatography coupled with electrochemical detection were elevated for more than one week [11]. Third, as described by phenomenological studies there is a strong similarity between the post-orgasmic state and the subjective state as typically induced by MDMA as shown in Table 1 [36,37]. Fourth, amphetamines such as d-amphetamine and methamphetamine also lead to serotonin re-

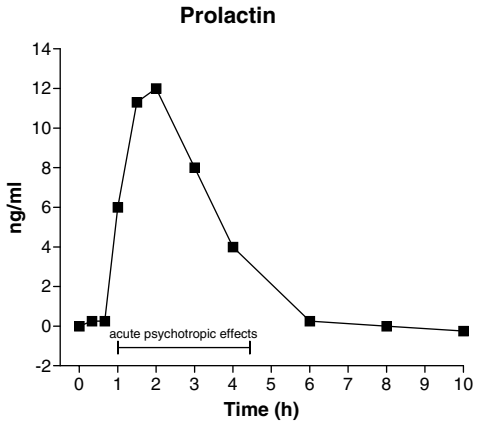

Figure 2 Mean plasma concentrations of prolactin following a dose of 100 mg MDMA p.o. in humans ($n = 9$) [modified from Ref. [15]].

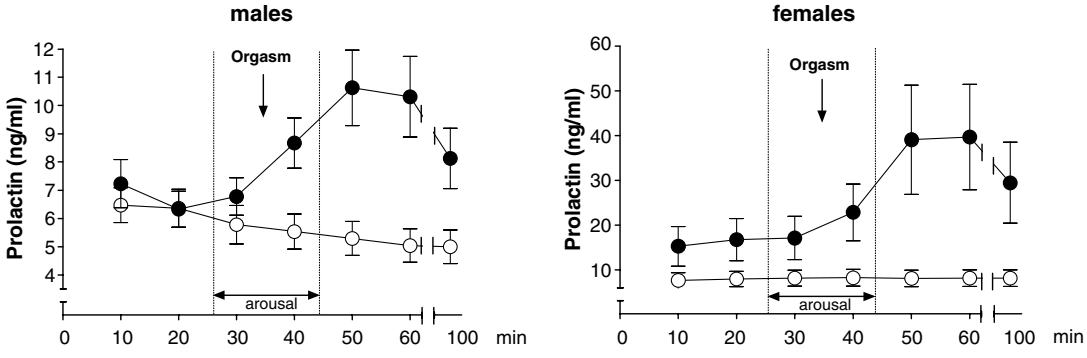

Figure 1 Mean (±SE) plasma prolactin concentrations following coitus in females and males during experimental (•) and control (○) sessions. Prolactin concentrations are divided into 10 minute intervals. The experimental session comprised viewing of an emotionally neutral documentary film (time 10, 20 min), pornographic film viewing and sexual arousal (30 min), coitus and orgasm (40 min), return to neutral film viewing (50, 60 min), and following a further rest period (100 min). Control session consisted of quiet viewing of an emotionally neutral documentary film throughout the session. Plasma prolactin was increased following coitus in both males and females, and remained elevated 1 h following orgasm. ($^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$ compared to control condition) [Ref. [22]].

Table 1 Comparison of some features of the typical MDMA-induced state and the post-orgasmic state.

Psychophysiological functions	MDMA-induced state	Post-orgasmic state
Physiological state	Deep relaxation[a]	Deep relaxation, light sedation
CNS arousal	Sympathetic arousal[a]	Decline of sympathetic arousal
Physiological functions	Heart rate + RR increased	Heart rate + RR increased
Neuroendocrine alterations	Prolactin + cortisol increased	Prolactin inreased
Vigilance	Heightened	Lowered (?)
Emotions	Intensified	Intensified
Anxiety level	Lowered	Lowered
Thinking	More imaginative	More imaginative
Associations	Loosened	Loosened
Body experience	Intensified	Intensified
Mind set	Opening up	Opening up

[a] The phenomenon of uncoupling of sympathetic arousal and a subjectively very calm state is well known from MDMA/MDEA research (cf. Ref. [18]).

lease, but induce a decrease of prolactin secretion, possibly due to a simultaneously increased dopaminergic tone [20]. Both amphetamines are known to stimulate sexual behaviour and functioning [13,14]. Thus, we assume that the inhibitory effects of MDMA on appetitive and consummatory sexual parameters in humans and animals may primarily be due to elevated prolactin levels.

Conclusion

In summary, several studies have demonstrated a marked increase of prolactin plasma levels after MDMA/MDEA consumption together with an impairment of sexual drive and function in humans. Clinical and experimental evidence suggest a possible role for prolactin in mediating a state of relaxation and sexual refractoriness after both orgasm and during the acute effects of MDMA/MDEA.

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