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Effects of (±) 3,4-methylene–dioxymethamphetamine (ecstasy) on dopamine system function in humans

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Abstract

Twelve (±) 3,4-methylenedioxymethamphetamine (MDMA) users, who did not show other drug dependencies or prolonged alcohol abuse (group A), and 12 control subjects (group B) were included in the study. Prolactin (PRL) and growth hormone (GH) responses to the dopaminergic agonist bromocriptine (BROM) and psychometric measures were evaluated 3 weeks after MDMA discontinuation. PRL decreased both in A and B subjects after BROM suppression, without any significant difference between the two groups. PRL responses to BROM in MDMA users were in the normal range. In contrast, GH responses to BROM stimulation were found significantly reduced in ecstasy users, in comparison with control subjects ($P < 0.001$; $F = 6.26$). MDMA users showed higher scores on the Novelty Seeking (NS) scale at the Three dimensional Personality Questionnaire (TPQ), on direct aggressiveness subscale at Buss Durkee Hostility Inventory (BDHI), on subscale D (depression) at Minnesota Multiphasic Personality Inventory (MMPI 2) and on Hamilton Depression Rating Scale (HDRS) than control subjects. PRL areas under the curves (AUCs) showed a significant inverse correlation with NS scores both in A and B subjects. GH AUCs directly correlated with NS scores in healthy subjects, but not in MDMA users. No other psychometric measure correlated with hormonal responses. GH AUCs were inversely correlated with the measures of MDMA exposure ($r = -0.48$; $P < 0.01$). Lower GH response to BROM in A subjects (MDMA users) could reflect reduced D2 receptor sensitivity in the hypothalamus, possibly due to increased intrasynaptic dopamine concentration. Although the hypothesis of dopaminergic changes associated with a premorbid condition cannot be completely excluded, the inverse correlation between DA receptors sensitivity and the extent of ecstasy exposure may suggest a direct pharmacological action of MDMA on brain dopamine function in humans.

Keywords: MDMA (ecstasy); Dopamine; Prolactin; Growth hormone; Bromocriptine; Depression; Aggressiveness; Novelty seeking

1. Introduction

A consistent association between ecstasy exposure and long lasting serotonin (5-HT) system impairment has been demonstrated in humans [20,28,37,38] with selective changes in global and regional brain 5-HT transporter binding [38]. On the other side, the role for dopamine in mediating the effects of MDMA and the possible persistent changes induced by ecstasy on dopaminergic system have not yet been examined extensively in humans.

A variety of studies in experimental animals indicate that repeated exposure to MDMA is able to induce a consistent dysfunction in the dopaminergic system [14,29,36]. Changes in dopaminergic neurotransmission in the nucleus accumbens of the rat have been reported after MDMA exposure [42]. MDMA acute administration seems to be able to increase DA release in experimental animals [17,26]. Accordingly, Shankaran and Gudelsky observed increased levels of extracellular DA in the hippocampus of the animals, as acute ecstasy effect [45,48], with enhanced release of DA from the noradrenergic neurons.

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Among long-term effects of sub-chronic MDMA treatment in the rat, 5-HT and noradrenaline (NE) levels were found decreased, whereas DA levels were increased 4 weeks after ecstasy exposure, with monoamine transmitter levels outlasting cessation of drug intake [35]. Augmentation of DA was hypothesized to be attributable to reduced 5-HT and NE, and not primarily to ecstasy action.

On the other hand, MDMA has previously been shown to produce conditioned place-preference among rats, being the release of dopamine critical to ecstasy ability to establish a conditioned behavior [4].

The potential effects of MDMA on central dopamine system in humans have been evaluated indirectly, by measuring the capacity of dopaminergic antagonists, such as haloperidol, to influence ecstasy-induced psychological changes in healthy volunteers [33]: haloperidol was found to attenuate positive and mania-like mood, without reducing other subjective effects. The same authors evidenced that DA does not seem to contribute to the physiological effects of MDMA: in fact cardiovascular changes induced by MDMA in normal subjects were not influenced by haloperidol pretreatment.

Although obtained in an isolated case, recent findings evidenced that the striatal levels of DA in the brain of a chronic ecstasy user were within the normal range [29], suggesting that MDMA may be able to induce more a functional impairment of DA system than an overt neurotoxicity on nervous pathways.

For these reasons we decided to investigate dopaminergic function in ecstasy users measuring the endocrine responses to acute administration of bromocriptine (BROM) (a specific D-2 receptor agonist): the challenge evaluated BROM capacity to stimulate growth hormone (GH) and inhibit prolactin (PRL) responses to BROM as expression of D2 receptors sensitivity. Based on the evidence in the animals, we expected that dopamine system dysfunction may involve receptor sensitivity in humans also [47]. In the present study, the correlation between the extent of ecstasy exposure and hormonal findings in response to the dopaminergic agonist was measured, to evaluate whether the possible changes in D2 receptors sensitivity reflect a direct pharmacological action of ecstasy or, in contrast, a pre-existing biological brain dysfunction.

In addition, since dopamine system changes have been demonstrated to be associated with temperament traits [13,21] and psychiatric diseases such as depression [31] and antisocial personality disorder [19,48], we also investigated in ecstasy users the possible relationship between dopamine receptors sensitivity and the psychometric measures concerning novelty seeking temperament, depressive and aggressive traits.

2. Methods

2.1. Subjects

Twelve male MDMA users (group A), aged 18–29 years ($M \pm SD = 23.41 \pm 5.93$ years), with a history of at least 50 occasions of drug use ($M \pm SD = 53.2 \pm 33$; range from 22 to 86) prior to drug interruption entered the study. All the subjects gave informed consent. The subjects included in the study used MDMA only during the weekend nights, one to two pills every night. In the Italian illicit market, the variability of MDMA concentration is from 25 to 125 mg [3]. The duration of MDMA use was from 8 to 30 months ($M \pm SD = 18.8 \pm 8$). Demographic data and characteristics of MDMA use are included in Table 1.

All the subjects were studied 3 weeks after their last dose of ecstasy. In the last month before MDMA discontinuation, the urine controls for amphetamines, metamphetamines, morphine, methadone, cannabis, cocaine, barbiturates and alcohol were performed three times a week.

Urine controls were found positive for MDMA, before discontinuation, in all MDMA users. Urine controls were occasionally positive for cannabis in five subjects. Heroin metabolites were found in two subjects in single urine controls together with ecstasy. One subject showed a single urine sample positive for cocaine. The use of other illicit drugs, apart from MDMA, was occasional: cannabis was found only in 4 out of 12 urine controls in four subjects and in two urine controls in another subject. Heroin and cocaine metabolites were found in a single urine sample.

Previous prolonged consumption and/or dependence on other drugs of abuse and psychotropic agents, or continuous excessive alcohol intake, were excluded, utilizing a structured interview. Many subjects were excluded after the first contact because of their previous long lasting use of other drugs. Most of the subjects included in the study reported occasional use of cannabis and cocaine or abuse of alcohol (two or three times) in the last 6 months. Three subjects had used heroin daily for a few months, respectively, 2, 4 and 5 years before the study. In the following years they spontaneously stopped the continuous use of heroin. In

Table 1
Demographics and characteristics of MDMA use (means ± SE)

	Age (years)	Height (cm)	Weight (kg)
MDMA subjects (15)	22.7 ± 2.8	173.6 ± 10.3	67.9 ± 9.6
Control subjects (15)	24.3 ± 5.6	175.4 ± 13.4	74.5 ± 10.8
Number of exposures	53.2 ± 33		Range: 22–86
Duration of use	18.8 ± 8 months		Range: 8–30
Frequency of use	5.7 ± 3.7 per month		Range: 3.5–10.0

the last 6 months they reported one to two episodes of heroin use.

Information about MDMA and/or other drugs use was obtained in several ways including: self-report during the first clinical evaluation; an MDMA questionnaire that asked about duration, frequency, doses and time of last dose; a questionnaire concerning other drugs and alcohol; a double interview with the family to correct for possible denial; and direct medical evaluation.

The subjects had contacted one of the investigators at the Drug Addiction Service in Parma (Az. USL) seeking initial information about MDMA [4], or treatment [2]; the other subjects [6] had contacted the center through a teacher or one of the parents. Seven subjects were students, three subjects were workers and two were unemployed. Six of the seven students showed academic underachievement. Ten of the 12 subjects were still living in their parents' home, and their socio-economic status was medium or high. Two subjects did not report relationships problems in the family, and six (50%) had conflictual relationships with family members. All MDMA users included in the study spent their weekend nights in disco-clubs and manifested a preference for techno-music or progressive music. Seven subjects among the MDMA users showed a weight loss within 10% of their ideal weight that was recovered in the 3 weeks after MDMA discontinuation.

The subjects were admitted to a long-term psychosocial rehabilitation program, and, if two-times-a-week analyses for urine metabolites of the main substances of abuse excluded their consumption in the first 3 weeks after admission, they were included in the study.

Criteria for exclusion also included severe chronic liver (transaminases >50 U/L and gamma-globulines $>20\%$ g/dl) or renal (creatinine clearance: 100–120 mg/l/min) diseases or other chronic physical disorders, significant weight loss ($>10\%$) or obesity, endocrinopathies, and immunodeficiencies (the subjects were HIV-negative).

Twelve healthy male volunteers (group B), matched for age (20–30 years; $M \pm SD = 24.30 \pm 5.62$ years) and demographic/cultural data, were recruited from the hospital staff and the high school of Parma as controls. The controls never used psychoactive drugs or abused alcohol: urine controls for 4 weeks and a double interview with the parents confirmed the self-report data. Exclusion criteria were the same as for subjects.

2.2. Personality assessment

DSM-IV clinical evaluation and psychometric measures were performed 3 weeks after MDMA discontinuation and repeated after 12 months of abstinence from MDMA at the end of the study. Following the same schedule, control subjects were retested after 12 months. Axis I and II disorders were evaluated by a trained psychiatrist utilizing the Structured Clinical Interview (SCID) for Axis I disorders [46] (Italian Version: Intervista Clinica Strutturata per il DSM-III-R, Fava et al., 1993, Organizzazioni Speciali, Florence) and the Structured Interview for DSM-IV Personality Disorders (SIDP) for Axis II disorders [5] (Italian Version: Maggini and Piccini, Draft Ed., 1994).

The SCID excluded Axis I disorders among MDMA users and controls. The evaluation with SIDP for Axis II disorders found four subjects with open personality disorders out of 12: three subjects had borderline personality disorder, and one had avoidant personality disorder. Another two subjects showed symptoms partially corresponding to avoidant personality disorder criteria, and one subject to antisocial personality disorder, but not the complete clinical picture of this Axis II disorder. No Axis II disorders were in evidence among control subjects. Although major depression was not diagnosed among MDMA users, 10 subjects showed dysphoria and mood changes in the weeks following MDMA discontinuation; six subjects reported tiredness and fatigue; and two subjects had subtle cognitive impairment and confusion episodes. Nine subjects among the MDMA users showed novelty seeking behavior as a characteristic of their life style.

Personality was also investigated by the Minnesota Multiphasic Personality Inventory (MMPI 2) [23]. This test was compared with the DSM structured interviews in order to investigate the possible differences in personality analysis with the self-administered methods. Character and quantification of aggressiveness (defined as direct, indirect or verbal; irritability; negativism; resentment; suspiciousness; guilt; and total score) were analyzed by the Buss–Durkee Hostility Inventory (BDHI) [9] in the Italian version, "Questionario per la Tipizzazione della Aggressività" (QTA) [10]. QTA raw scores, in accordance with Castrogiovanni, have been used for the total score and for the single subscales scores. Depression was monitored by Hamilton Rating Scale (HRS-D) at 21 items [22]. All the subjects were given the Three dimensional Personality Questionnaire (TPQ) [12] to investigate temperamental aspects, particularly "harm avoidant," "novelty seeking," and "reward dependent".

2.3. Neuroendocrine challenge

BROM challenges (a D2 receptor agonist) were performed 3 weeks after MDMA discontinuation. Controls were also tested utilizing BROM 4 weeks after they were contacted.

Subjects and controls took no prescribed medication for at least 3 weeks before the challenge sections, followed a low monoamine diet and avoided smoking during the last 12 h prior to the neuroendocrine tests.

The BROM challenge was done with a catheter inserted at 9:00 a.m. into an antecubital vein, kept patent by saline infusion. At 10:00 a.m., 5 mg of BROM (Parlodel, Sandoz, Italy) were administered orally. Blood specimen for GH and PRL assays were drawn into EDTA-containing tubes immediately before the BROM administration, and 15, 30, 60, 90 and 120 min afterwards. Blood was immediately centrifuged, and plasma stored at −20 °C until assayed. PRL concentration were measured radioimmunologically with the commercial kits of Sorin (Italy). GH concentrations were measured with a method of chemiluminescence with the commercial kits of Medical System (Italy).

The sensitivity of the method for GH was 0.5 ng/ml and for PRL 1 ng/ml; the inter-assay variability for GH was 7.3% and the intra-assay variability 4.9%; and for PRL inter-assay variability was 4% and intra-assay 7%.

2.4. Statistical analysis

Student t-test was performed to assess the normality of distribution of the data: no ''outliers'' were included in the results.

The responses of PRL and GH to the dopaminergic stimulus in A and B subjects groups were analyzed statistically by one-way ANOVA and by two-way ANOVA for repeated measures, to evaluate the effects of time, group and time × group. Co-varied ANOVA and Pearson correlation were also utilized, and Bonferroni correction of the P-values was employed.

Psychometric measures were correlated with endocrine responses (areas under curves: AUCs). The AUCs were calculated with the Sibson Rule method: AUCs had positive values when over the basal levels ($T = 0$) and negative values when under the basal levels ($T = 0$).

The responses to the neuroendocrine challenges (GH and PRL AUCs) were correlated with time and number of exposures to MDMA (use extent).

3. Results

Psychological data (mean score ± SE) obtained by the MMPI II, BDHI, HDRS and TPQ at 3 weeks of abstinence are reported in Table 2. MDMA users (A subjects) showed significantly higher scores than control subjects (B subjects) at MMPI subscale D ($df = 22$; $t = 3.3$; $P < 0.01$). No other significant difference between MDMA users and controls was evidenced at MMPI test.

In comparison with control subjects, MDMA users showed significantly higher scores on the BDHI direct aggressiveness subscale ($df = 22$; $t = 3.8$; $P < 0.001$), on the BDHI guilt subscale ($df = 22$; $t = 4.7$; $P < 0.001$), on the HDRS ($df = 22$; $t = 4.1$; $P < 0.005$) and on the novelty seeking TPQ subscale ($df = 22$; $t = 4.7$; $P < 0.001$).

3.1. Hormonal basal levels

No significant differences were found between basal values of PRL in MDMA users and controls (MDMA = ng/ml 5.67 ± 0.8 vs. controls = 4.49 ± 0.9). Similarly, GH basal values did not show significant differences between subjects and controls (MDMA = ng/ml 1.56 ± 0.56 vs. controls = 1.88 ± 0.4).

3.2. BROM challenge

Mean AUCs ± SE of PRL and GH in response to BROM test are reported in Table 3, with the results of one-way two-groups ANOVA on the AUCs values.

BROM reduced PRL values both in ecstasy users ($P < 0.001$, $F = 18.58$, $df = 55$) and controls ($P < 0.01$, $F = 4.08$, $df = 55$). In contrast GH was increased by BROM in B subjects ($P < 0.001$, $F = 34.9$, $df = 55$), but showed only a slight, not significant increase in A subjects (ecstasy users).

No significant difference was found in PRL AUCs after BROM administration between group A and B (ecstasy users and controls). Group A subjects showed significantly lower GH AUCs than B group subjects ($P < 0.05$, $t = 2.3$, $df = 22$) (Table 3).

ANOVA for repeated measures showed no significant effects of time, of diagnosis, and diagnosis per time in A and B PRL responses to BROM (Fig. 1).

Table 3
Mean AUCs ± SE of PRL and GH during bromocriptine challenge in control and ecstasy users

	GH AUCs after BROM	PRL AUCs after BROM
Controls	99.83 ± 33.31	−128.33 ± 54.89
MDMA	−42.83 ± 50.34	−191.66 ± 47.1

Table 2
Psychometric measures in MDMA users and control subjects including depression scale D at MMPI, direct and guilt subscales at Buss Durkee Hostility Inventory, Hamilton Rating Scale and Threedimensional Personality Questionnaire subscales

	MMPI D	BDHI direct	BDHI guilt	HDRS	TPQ NS[a]
MDMA users	62.6 ± 3.3	58.7 ± 3.3	60.6 ± 2.2	17.1 ± 3.1	25.3 ± 2.1
Control subjects	48.8 ± 1.8	43.7 ± 2.1	45.7 ± 2.3	5.1 ± 2.5	11.8 ± 1.1

[a] NS, Novelty seeking.

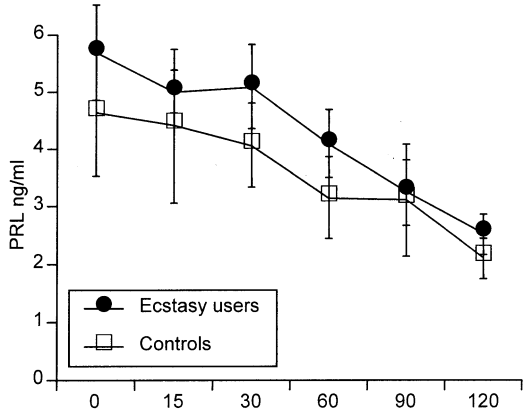

Fig. 1. Prolactin (PRL) response to bromocriptine stimulation (mean±SE) in ecstasy users (●---●) and healthy controls (○---○).

In the comparison between the GH responses to BROM of A and B subjects, ANOVA for repeated measures showed significant effects of time ($P < 0.05$, $F = 5.19$, df = 22), of diagnosis ($P < 0.001$, $F = 28.1$, df = 5) and diagnosis per time ($P < 0.001$, $F = 6.26$, df = 110) (Fig. 2).

Pearson's analysis revealed that PRL values obtained after BROM inhibition (AUCs) among MDMA users were negatively correlated with Novelty Seeking scores at TPQ both in ecstasy users ($r = 0.67$, $P < 0.01$) and in controls ($r = 0.51$, $P < 0.005$) (Fig. 3 upper and lower panels). GH values after BROM were directly correlated with NS scores at TPQ in normal subjects ($r = -0.47$, $P < 0.01$), but not among ecstasy users (Fig. 4 upper and lower panels).

No correlation was found between PRL and GH AUCs and HRDS, MMPI, BDHI subscales scores.

GH AUCs were inversely correlated with the measures of MDMA exposure ($r = -0.48$, $P = 0.01$). In contrast, PRL responses seem to be unaffected by ecstasy exposure: no correlation was found between PRL AUCs and MDMA exposure extent.

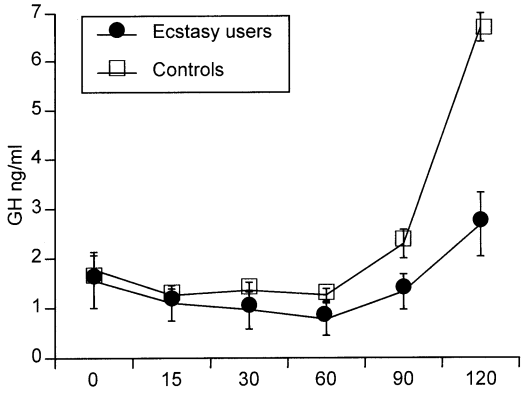

Fig. 2. Growth hormone (GH) response to bromocriptine stimulation (mean±SE) in ecstasy users (●---●) and healthy controls (○---○).

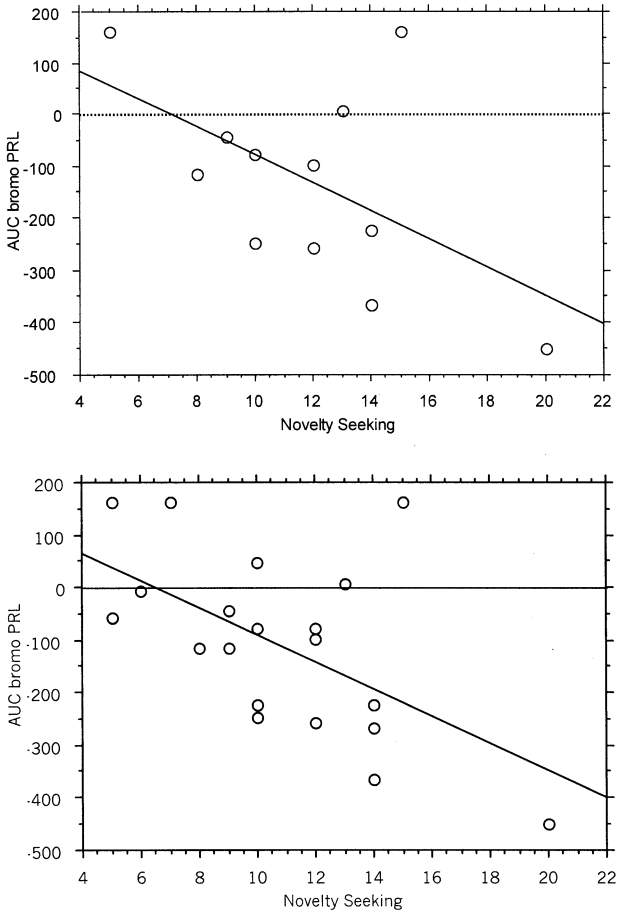

Fig. 3. Upper panel: correlation of Novelty Seeking TPQ scores with PRL AUCs during bromocriptine challenge in healthy subjects. Lower panel: correlation of Novelty Seeking TPQ scores with PRL AUCs during bromocriptine challenge in ecstasy users.

4. Discussion

The findings of the present study evidenced blunted GH responses to the dopaminergic agonist BROM in ecstasy users, in comparison with control subjects, indicating a dysfunction of dopaminergic pathways that are involved in the regulation of growth hormone releasing hormone (GHRH) and consequently of pituitary GH release [27]. The significantly reduced rise of GH plasma levels after D2 agonist administration might reflect a decrease of dopamine receptors sensitivity in the brain area that controls hypothalamic GHRH [15,34,40].

On the other side, BROM was able to suppress PRL secretion with significantly reduced PRL plasma levels after the neuroendocrine challenge, both in ecstasy users and controls. Normal PRL response to D2 receptors agonist may be interpreted as the expression of a well-preserved sensitivity to dopamine of PRL secreting pituitary cells [1,40] that appear unaffected by prolonged ecstasy use.

Although GH and PRL are both regulated by DA neurons, PRL suppression was intact in our subjects,

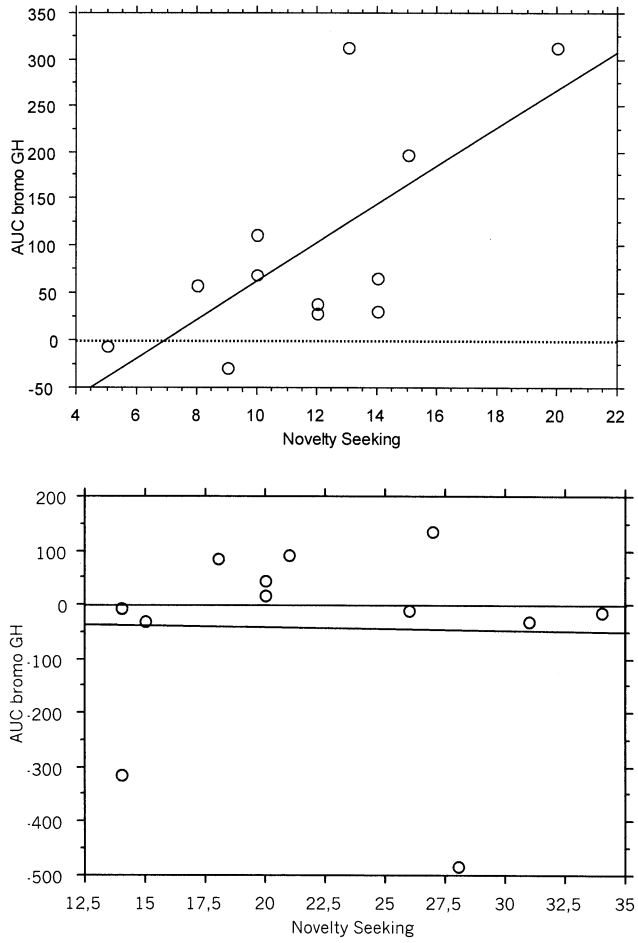

Fig. 4. Upper panel: correlation of Novelty Seeking TPQ scores with GH AUCs during bromocriptine challenge in healthy subjects. Lower panel: correlation of Novelty Seeking TPQ scores with GH AUCs during bromocriptine challenge in ecstasy users.

whereas GH secretion was diminished: this discrepancy was previously evidenced in different clinical conditions such as Huntington's chorea [11] and geriatric patients [25], suggesting the hypothesis of a different threshold in sensitivity changes of hypothalamus D2 receptors [41], in comparison with pituitary cells receptors.

Ecstasy capacity to partially affect dopamine system was evidenced also utilizing EEG techniques: comparison of the MDMA-specific EEG pattern with that of various 5-HT, DA, and NE agonists indicates that serotonin, NE, and, to a lesser degree, dopamine, contribute to the effects of MDMA on EEG, and possibly also on mood and behavior [18].

Accordingly, the pretreatment with dopamine D2 antagonist haloperidol has been reported to reduce MDMA-induced positive mood [33], indicating a possible action of ecstasy on the function of dopaminergic system in humans. Nevertheless, the same findings demonstrated that the stimulant-like properties of ecstasy were attenuated by ketanserin, a 5HT antagonist, and not by haloperidol, with the hypothesis that dopamine release induced by MDMA may be attributed partially to a 5-HT2-mediated mechanism [32].

Neurotoxic effect of MDMA was hypothesized to be associated with long-duration changes in both DA and 5HT neurotransmission in the nucleus accumbens by other authors [50]. Whether these long-duration changes in neurotransmission might be related to depression and other psychopathologies reported by some MDMA users remains to be determined.

In fact, patients with major depression were previously found to display a reduced sensitivity of central dopamine receptors compared to control subjects [44]. The same was true for those with eating disorders, who showed a sub-sensitivity of postsynaptic D2 receptors and possibly a presynaptic DA hypersecretion [7], and for alcoholic subjects investigated with both BROM and apomorphine [16,2,24,51,43].

Furthermore, a dysfunction in the brain reward cascade, which could be caused by certain genetic variants, especially in the DA system causing a hypodopaminergic trait, with compromised D2 receptors, has been described in drug-seeking behavior and might characterize our MDMA users [6]. Blunted GH responses to dopamine agonist stimulation were also found in obsessive–compulsive patients with a dysregulation of the dopaminergic system, which is possibly expressed in different ways in the various areas of the central nervous system [8].

Although our data need to be interpreted with great caution, because of the small sample, and inter-individual variability, dopamine receptor down-regulation, evidenced by blunted responses to BROM in ecstasy users, seems to be attributable to the direct pharmacological effect of ecstasy, being GH AUCs negatively correlated with the measures of MDMA exposure extent.

From a different point of view, the changes observed in dopaminergic sensitivity of ecstasy users may be interpreted in relationship more to personality traits preexisting to substance abuse, than to pharmacological effects of MDMA. Recent reports suggest that dopaminergic/noradrenergic system dysfunction may be associated with substance abuse and/or antisocial behavior [19] and higher heterogeneity of the striatal dopamine transporter (DAT) density has been found in impulsive violent offenders than in controls [30]. Accordingly, our results showed high outward directed aggressiveness in ecstasy users, in comparison with control subjects, possibly due to a personality trait marker.

Finally, dopamine receptors sensitivity could have been influenced by the deep derangement in serotonin function that was demonstrated in ecstasy users [38]. The stimulation of both 5-HT2A and 5-HT1A receptors may be important for the modulation of dopamine release in humans [49]: ecstasy neurotoxicity affecting

first serotonin function may have secondarily induced the changes in DA synaptic concentration.

Our data cannot exclude that the observed changes could be related to a variety of drugs used by the MDMA group, rather than MDMA. Nevertheless, the use of drugs other than ecstasy was occasional or short term in our subjects, differently from the sample of ecstasy users included in other studies [39], suggesting the comparison with a control group that did not abuse drugs.

In conclusion, although the changes in DA function appear related with MDMA exposure, the present findings cannot exclude that DA receptor reduced sensitivity observed in ecstasy users may be attributed to the genetic changes that have been reported in relationship with reward deficiency syndrome, impulsive–addictive behavior, aggressive or depressive trait, often preexisting to substance use disorders.

Further studies need to be performed to better understand the monoaminergic dysfunction of ecstasy users, its possible reversibility and the correlations with affective and behavioral features.

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References

[1] Ayalon D, Eckstein N, Avidan S, Eshel A, L'Hermite M, Caufriez A, Spitz I, Zylber-Haran E. Dopaminergic regulation of prolactin secretion in the hyperprolactinemic syndrome. Gynecol Obstet Invest 1983;16:97–106.
[2] Balldin J, Berggren U, Lindstedt G, Sundkler A. Further neuroendocrine evidence for reduced D2 dopamine receptor function in alcoholism. Drug Alcohol Depend 1993;32:159–62.
[3] Bellomo RD. Aspetti di polizia scientifica. In: Atti del seminario studi sui derivati amfetaminici. Rome: Italian Ministry of Interior, 1995:43–8.
[4] Bilsky EJ, Montegut MJ, Nichols ML, Reid LD. CGS 10746B, a novel dopamine release inhibitor, blocks the establishment of cocaine and MDMA conditioned place preferences. Pharmacol Biochem Behav 1998;59:215–20.
[5] Black DW, Noyes R, Jr, Pfohl B, Goldstein RB, Blum N. Personality disorder in obsessive–compulsive volunteers, well comparison subjects, and their first-degree relatives. Am J Psychiatr 1993;150:1226–32.
[6] Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, Lubar JO, Chen TJ, Comings DE. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs 2000;32:1–112.
[7] Brambilla F, Bellodi L, Arancio C, Ronchi P, Limonta D. Central dopaminergic function in anorexia and bulimia nervosa: a psychoneuroendocrine approach. Psychoneuroendocrinology 2001;26:393–409.
[8] Brambilla F, Bellodi L, Perna G, Arancio C, Bertani A. Dopamine function in obsessive–compulsive disorder: growth hormone response to apomorphine stimulation. Biol Psychiatr 1997;42:889–97.
[9] Buss AH, Durkee A. An inventory for assessing different kinds of hostility. J Consult Psychol 1957;21:343–9.
[10] Castrogiovanni P, Maremmani I, Di Muro A. Aggressive behaviour and hostility in depression: clinical aspects. In: Placidi GF, Dell'Osso L, Nisticò G, Akiskal HS, editors. Recurrent mood disorders. Berlin Heidelberg: Springer–Verlag, 1993:51–65.
[11] Chalmers RJ, Johnson RH, Keogh HJ, Nanda RN. Growth hormone and prolactin response to bromocriptine in patients with Huntington's chorea. J Neurol Neurosurg Psychiatr 1978;41:135–9.
[12] Cloninger CR. A systematic method for clinical description and classification of personality variants. Arch Gen Psychiatr 1987;44:573–88.
[13] Cloninger CR. Neurogenetic adaptive mechanisms in alcoholism. Science 1987;236:410–6.
[14] Crespi D, Mennini T, Gobbi M. Carrier-dependent and Ca(2+)-dependent 5-HT and dopamine release induced by (+)-amphetamine, 3,4 methylendioxymethamphetamine, *p*-chloroamphetamine and (+)-fenfluramine. Br J Pharmacol 1997;121:1735–43.
[15] Cusimano G, Capriani C, Bonifati V, Meco G. Hypothalamo-pituitary function and dopamine dependence in untreated parkinsonian patients. Acta Neurol Scand 1991;83:145–50.
[16] Farren CK, Clare AW, Ziedonis D, Hammeedi FA, Dinan TG. Evidence for reduced dopamine D2 receptor sensitivity in postwithdrawal alcoholics. Alcohol Clin Exp Res Dec 1995;19(6):1520–4.
[17] Fischer HS, Zernig G, Schatz DS, Humpel C, Saria A. MDMA ('ecstasy') enhances basal acetylcholine release in brain slices of the rat striatum. Eur J Neurosci 2000;12:1385–90.
[18] Frei E, Gamma A, Pascual-Marqui R, Lehmann D, Hell D, Vollenweider FX. Localization of MDMA-induced brain activity in healthy volunteers using low resolution brain electromagnetic tomography (LORETA). Hum Brain Mapp 2001;14:152–65.
[19] Gabel S, Stadler J, Bjorn J, Shindledecker R. Homovanillic acid and dopamine-beta-hydroxylase in male youth: relationships with paternal substance abuse and antisocial behavior. Am J Drug Alcohol Abuse 1995;21:363–78.
[20] Gerra G, Zaimovic A, Ferri M, Zambelli U, Timpano M, Neri E, Marzocchi GF, Delsignore R, Brambilla F. Long-lasting effects of (+/−)3,4-methylenedioxymethamphetamine (ecstasy) on serotonin system function in humans. Biol Psychiatr 2000;47:127–36.
[21] Gerra G, Zaimovic A, Timpano M, Zambelli U, Delsignore R, Brambilla F. Neuroendocrine correlates of temperamental traits in humans. Psychoneuroendocrinology 2000;25:479–96.
[22] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatr 1960;23:56–62.
[23] Hathaway SR, McKinley JC. Minnesota Multifasic Personality Inventory -2. Manual. Minneapolis: University of Minnesota, 1989.
[24] Heinz A, Dettling M, Kuhn S, Dufeu P, Graf KJ, Kurten I, Rommelspacher H, Schmidt IG. Blunted growth hormone response is associated with early relapse in alcohol-dependent patients. Alcohol Clin Exp Res 1995;19:62–5.
[25] Hontela S, Nair NP, Rosenberg G, Schwartz G, Guyda H. Bromocriptine: effect on serum prolactin and growth hormone in psychogeriatric hospital patients. J Am Geriatr Soc 1978;26:49–52.
[26] Kalivas PW, Duffy P, White SR. MDMA elicits behavioral and neurochemical sensitization in rats. Neuropsychopharmacology 1998;18:469–79.
[27] Kimber J, Watson L, Mathias CJ. Neuroendocrine responses to levodopa in multiple system atrophy (MSA). Mov Disord 1999;14:981–7.

[28] Kish SJ, Furukawa Y, Ang L, Vorce SP, Kalasinsky KS. Striatal serotonin is depleted in brain of a human MDMA (ecstasy) user. Neurology 2000;55:294–6.
[29] Koch S, Galloway MP. MDMA induced dopamine release in vivo: role of endogenous serotonin. J Neural Transm 1997;104:135–46.
[30] Kuikka JT, Tiihonen J, Bergstrom KA, Karhu J, Rasanen P, Eronen M. Abnormal structure of human striatal dopamine reuptake sites in habitually violent alcoholic offenders: a fractal analysis. Neurosci Lett 1998;253:195–7.
[31] Laasonen-Balk T, Kuikka J, Viinamaki H, Husso-Saastamoinen M, Lehtonen J, Tiihonen J. Striatal dopamine transporter density in major depression. Psychopharmacology (Berlin) 1999;144:282–5.
[32] Liechti ME, Geyer MA, Hell D, Vollenweider FX. Effects of MDMA (ecstasy) on prepulse inhibition and habituation of startle in humans after pretreatment with citalopram, haloperidol, or ketanserin. Neuropsychopharmacology 2001;24:240–52.
[33] Liechti ME, Vollenweider FX. The serotonin uptake inhibitor citalopram reduces acute cardiovascular and vegetative effects of 3,4-methylenedioxymethamphetamine ('Ecstasy') in healthy volunteers. J Psychopharmacol 2000;14:269–74.
[34] Maccario M, Grottoli S, Procopio M, Oleandri SE, Barberis A, Ciccarelli E, Camanni F, Ghigo E. Effect of bromocriptine on insulin, growth hormone and prolactin responses to arginine in obesity. J Endocrinol Invest 1996;19:219–23.
[35] Mayerhofer A, Kovar KA, Schmidt WJ. Changes in serotonin, dopamine and noradrenaline levels in striatum and nucleus accumbens after repeated administration of the abused drug MDMA in rats. Neurosci Lett 2001;308:99–102.
[36] Mann H, Ladenheim B, Hirata H, Moran TH, Cadet JL. Differential toxic effects of methamphetamine (METH) and methylenedioxymethamphetamine (MDMA) in multidrug-resistant (mdr1a) knockout mice. Brain Res 1997;769:340–6.
[37] McCann UD, Eligulashvili V, Mertl M, Murphy DL, Ricaurte GA. Altered neuroendocrine and behavioral responses to *m*-chlorophenylpiperazine in 3,4-methylenedioxymethamphetamine (MDMA) users. Psychopharmacology (Berlin) 1999;147:56–65.
[38] McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. Lancet 1998;352:1433–7.
[39] McCann UD, Ridenour A, Shaham Y, Ricaurte GA:. Serotonin neurotoxicity after (+/−)3,4-methylenedioxymethamphetamine (MDMA; "Ecstasy"): a controlled study in humans. Neuropsychopharmacology 1994;10:129–38.
[40] Muller EE, Nisticò G, Scapagnini U. Neurotransmitter and anterior pituitary function. New York: Academic Press, 1977.
[41] Muller EE, Rolla M, Ghigo E, Belliti D, Arvat E, Andreoni A, Torsello A, Locatelli V, Camanni F. Involvement of brain catecholamines and acetylcholine in growth hormone hypersecretory states. Pathophysiological, diagnostic and therapeutic implications. Drugs 1995;50:805–37.
[42] Obradovic T, Imel KM, White SR. Repeated exposure to methylenedioxymethamphetamine (MDMA) alters nucleus accumbens neuronal responses to dopamine and serotonin. Brain Res 1998;785:1–9.
[43] Schmidt LG, Dettling M, Graef KJ, Heinz A, Kuhn S, Podschus J, Rommelspacher H. Reduced dopaminergic function in alcoholics is related to severe dependence. Biol Psychiatr 1996;39:193–8.
[44] Schmidt K, Nolte-Zenker B, Patzer J, Bauer M, Schmidt LG, Hein A. Psychopathological correlates of reduced dopamine receptor sensitivity in depression, schizophrenia, and opiate and alcohol dependence. Pharmacopsychiatry 2001;34:66–72.
[45] Shankaran M, Gudelsky GA. Effect of 3,4-methylenedioxymethamphetamine (MDMA) on hippocampal dopamine and serotonin. Pharmacol Biochem Behav 1998;61:361–6.
[46] Spitzer RL, Williams JBW, Gibbon M, Firs MB. SCID III-R. First published by American Psychiatric Press: Washington, DC and London, England; 1990.
[47] Stanwood GD, Lucki I, McGonigle P. Differential regulation of dopamine D2 and D3 receptors by chronic drug treatments. J Pharmacol Exp Ther 2000;295:1232–40.
[48] Vanyukov MM, Moss HB, Kaplan BB, Kirillova GP, Tarter RE. Antisociality, substance dependence, and the DRD5 gene: a preliminary study. Am J Med Genet 2000;96:654–8.
[49] Vollenweider FX, Vontobel P, Hell D, Leenders KL. 5-HT modulation of dopamine release in basal ganglia in psilocybin-induced psychosis in man—a PET study with [11C]raclopride. Neuropsychopharmacology 1999;20:424–33.
[50] White SR, Obradovic T, Imel KM, Wheaton MJ. The effects of methylenedioxymethamphetamine (MDMA, "Ecstasy") on monoaminergic neurotransmission in the central nervous system. Prog Neurobiol 1996;49:455–79.
[51] Wiesbeck GA, Mauerer C, Thome J, Jakob F, Boening J. Alcohol dependence, family history, and D2 dopamine receptor function as neuroendocrinologically assessed with apomorphine. Drug Alcohol Depend 1995;40:49–53.