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Short Communication

‘Candyflipping’: Synergistic discriminative effect of LSD and MDMA

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Abstract

The co-administration of D-lysergic acid diethylamide (LSD; ‘Acid’) and 3,4-methylenedioxymethamphetamine (MDMA; ‘Ecstasy’; ‘XTC’), has reached a prevalence that has allowed for the street terminology ‘candyflipping’ to describe the combination. Internet sites indicate a significant enhancement of central effects with their simultaneous use. In this preliminary observation, male Fawn-Hooded rats were trained to discriminate 1.5 mg/kg MDMA and were, subsequently, tested with doses of MDMA (0.15 mg/kg) or LSD (0.04 mg/kg) that each produced a saline-like response. Co-administration of these doses of MDMA and LSD synergized to produce a maximal MDMA-like response. The possible mechanism for synergistic action upon central serotonergic neurons is discussed to explain the observed effect. © 1998 Elsevier Science B.V.

Keywords: Drug discrimination; MDMA; LSD (D-lysergic acid diethylamide); Candyflipping; Synergism; (Rat)

1. Introduction

‘Candyflipping’ is the ‘street’ term for the co-administration of D-lysergic acid diethylamide (LSD) and 3,4-methylenedioxymethamphetamine (MDMA). The scientific literature on the effects of using these two Drug Enforcement Agency (DEA) classified Schedule I drugs is understandably limited. Nonetheless, a recent report indicates that on one college campus of a private American university, LSD was used by 17% of the students, whereas MDMA was used by 24%, making co-use a very distinct probability (Cuomo et al., 1994). A recent scientific publication employed the innovative concept of using select computer Internet news groups to request and receive interviews with users of hallucinogenic drugs (Bonson et al., 1996). In all, a total of 33 individuals, ranging in age from 15 to 37, participated in this study by completing a structured interview. Thus, the Internet has become a source capable of eliciting information that would not readily be reported by more traditional means. It is probably for this same reason that much of the information regarding the co-use of LSD and MDMA, in fact, comes from the Internet and, in what may be a departure from normal citation literature, these World Wide Web pages will be cited (http://www sites). This information may be seen to be of suspicious scientific merit yet this source may allow for extensive subjective and unsolicited information to permit insights into the popular trends in the drug culture. Having stated these caveats, the co-administration of MDMA with LSD has been suggested to ‘‘go very well together. (Co-administration of) LSD and MDMA is commonly known as XL or candyflipping. Most prefer quite low doses of LSD’’ (http://www.damicon.fi, 1996). Since MDMA has been cited as significantly enhancing (‘though sometimes distorting’) the senses, MDMA users can produce ‘a powerful, synergistic effect’ in which ‘the combination (is) extremely powerful’. When the ‘‘Ex (sic) takes effect, the visual characteristics of the scene begin to change and... emotional reactions to objects and people strongly cast their appearance. There was a definite combination of the MDMA ‘everything is beautiful look’ and the Acid’s power to ‘warp’ the actual appearance of things’’ (http://www.hyperreal.com, 1994). Beyond these subjective recollections, there have been a few published reports regarding the co-use of LSD and MDMA especially as they are used at ‘rave’ parties and concerts (Miller and Gold, 1994; Millman and Beeder, 1994).

Recent research in this laboratory has indicated that the Fawn-Hooded rat, a strain of rat with a serotonergic deficiency in the brain (Gudelsky et al., 1985), is able, like the Sprague–Dawley rat (Glennon et al., 1986; Schechter,

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1987; Oberlander and Nichols, 1988; Glennon and Misenheimer, 1989), to discriminate the interoceptive cues produced by MDMA (Schechter, 1997b). In both this latter work and another recent assessment of the discriminative effects of MDMA (Baker et al., 1995), the administration of LSD substituted for the drug used in the training of the animals, i.e. MDMA. Further evidence suggests that not all Fawn-Hooded rats may have the same degree of central serotonin deficiency (Overstreet and Rezvani, 1996). It was the purpose of the present experimentation to use Fawn-Hooded animals trained to discriminate 1.5 mg/kg MDMA from its vehicle in a drug discrimination paradigm and to test them with a saline-like dose of both MDMA and LSD alone and after co-administration to indicate the possibility of increased discriminative effects of MDMA.

2. Materials and methods

2.1. Discrimination training to 1.5 mg / kg MDMA

The subjects used in this study were 10 Fawn-Hooded male rats previously trained to discriminate the interoceptive cueing properties of 1.5 mg/kg MDMA from its saline vehicle 20 min after intraperitoneal (i.p.) administration. The training and maintenance procedure, as well as the dose-response relationship of MDMA and LSD, can be found in a previous publication (Schechter, 1997b). The results of this study indicated that the allegedly serotonin deficient Fawn-Hooded rats discriminated MDMA with the same sensitivity as did Sprague–Dawley rats. This had previously been found using a second serotonergic drug, fenfluramine (Schechter, 1997a). Essentially, the MDMA-trained rats were trained to discriminate 1.5 mg/kg MDMA from its saline vehicle. The first lever to accumulate ten responses was considered the 'selected lever', and the animals were required to maintain eight correct lever selections according to the state imposed on that daily maintenance session over ten consecutive days. After the correct lever was pressed 10 times, the animal was reinforced on the FR 10 schedule; 40 additional food pellets on the FR 10 schedule were provided to allow for continued training.

2.2. Generalization to lower doses of MDMA and LSD done alone and together

Interspersed between test/training maintenance with 1.5 mg/kg MDMA or saline sessions were test sessions in which the animal received either a low dose of MDMA (0.15 mg/kg) or a low dose of LSD (0.04 mg/kg) or both drugs administered at the same time. The dose of MDMA was selected based upon dose-response data after administration of 0.0315–2.0 mg/kg MDMA. The LSD dose was, likewise, chosen from generalization tests in the same animals employing 0.02–0.12 mg/kg. At 20 min post-administration, the animals were placed in the experimental chamber and allowed to accumulate ten presses on one of the levers. From the time that they pressed the lever for the first time to the time that the FR 10 was attained on the 'selected' lever, time (in s) was measured with a stop watch. Upon 10 presses on either of the levers, the animal was immediately removed from the experimental space without receiving reinforcement.

2.3. Measurements and statistical analysis

The measurements taken during both maintenance and test sessions included the quantal measurement, which is the number of rats tested that accumulated ten selections first (i.e., 'selected' this lever) on the MDMA-appropriate lever. A second measurement involved the total number of responses made on both the selected and nonselected levers, i.e. the number of responses on the MDMA lever divided by the total number of responses made on the MDMA plus saline-appropriate lever $\times 100$. This is the quantitative measurement and indicates the magnitude, as well as the direction, of lever selection. Lastly, the number of seconds to fulfill the FR 10 criterion was measured. Differences in the quantitative measures were tested for statistical significance by *t*-test between treatments.

2.4. Drugs

Both D,L-MDMA hydrochloride and D-LSD tartrate were received from the National Institute on Drug Abuse. Solutions were made daily by dissolving in 0.9% saline vehicle and injected i.p. at a constant volume of 1 mg/kg.

3. Results

The results of maintenance day testing with saline indicated that the animals chose the MDMA-correct lever on 4.8% of all tests or, to look at it a different way, 95.2% first lever selections were made on the saline-correct lever after saline administration. In contrast, maintenance day testing with 1.5 mg/kg MDMA allowed for 92.9% of all MDMA lever selections made during these interspersed maintenance day trials. These are represented by the hatched bars in Fig. 1 designated 'saline' and 'MDMA', respectively. The open bar represents the quantitative measurement, whereas the striped bar indicates, by virtue of the representation on the right *y*-axis, the percent of mean time required to reach the FR 10 selection as a percent of that seen with MDMA. Thus, for saline, the percent mean time required to reach FR10 was 90.8 ± 23.7 s or approximately 102.9% more time when compared to the mean time after MDMA testing (88.2 ± 5.5 s). In the second set of bars referring to MDMA during training sessions, the

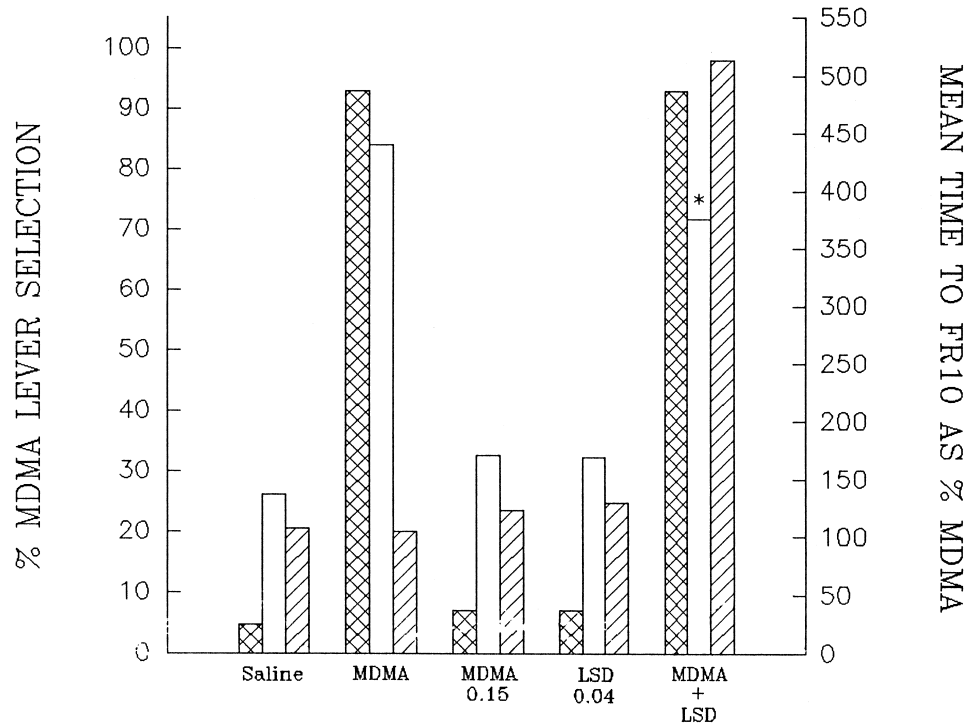

Fig. 1. Effect of 0.15 mg/kg MDMA and/or 0.04 mg/kg LSD on male Fawn-Hooded rats ($n = 10$) trained to discriminate the stimulus properties of 1.5 mg/kg MDMA from its saline vehicle. Left ordinate: Percent of animals either selecting the MDMA-appropriate lever (cross-hatched bars) or the percent of responses made on both levers at the time that 10 responses accumulate on 1 lever; the quantitative measurement, as represented by open bars (see Section 2). Right ordinate: Mean time, in s, to attain FR 10 on one or the other lever as a percent of that seen with the training dose of MDMA, viz., 88.2 ± 5.5 s. Asterisk indicates significant difference ($P < 0.05$) from saline, 0.15 MDMA and 0.04 LSD quantitative measurement.

quantitative measurement was 84.1% of total responses and, by definition, the 88.2 s mean to attain the FR10 is (placed at) 100%.

The next column labeled '0.15 mg/kg MDMA' indicates that in two separate tests, once following an MDMA maintenance session and once following a saline maintenance session, the MDMA lever was selected on 7.1% of all trials; the quantitative measurement was 32.7% and the time to FR10 was 104.4 s or 118.3% of that seen with the higher dose of MDMA. Likewise, 0.04 mg/kg LSD produced the same quantal measurement of 7.1% and a very similar 32.4% quantitative measurement as did the 0.15 mg/kg MDMA results. Comparing the second (open) bar to the right *y*-axis indicates that 123.5% of the MDMA mean time after this dose was required to reach the FR10 selection. Thus, it appears that both 0.15 mg/kg MDMA and 0.04 mg/kg LSD produced saline-like responding when each of the three measurements, i.e. quantal, quantitative and response rate, are considered.

The right-most triad of bars represents the administration of 0.15 mg/kg MDMA at the same time as 0.04 mg/kg LSD. This shows a very different picture in that animals chose the MDMA-like correct lever on 92.9% of all responses; equal to that shown during interspersed MDMA maintenance trials. They pressed this lever 71.8% of all responses and required (again), referring to the right-most *y*-axis, approximately 522% as much time to reach the FR10 as they did after the MDMA maintenance administration, i.e. 460.4 s compared to 88.2 s. This is indicative of some behavioral disruption or performance deficit. Nonetheless, the MDMA-like response selection after co-administration was quantitatively equivalent to that seen after testing of the training dose of 1.5 mg/kg MDMA. Thus, it appears that 0.15 mg/kg MDMA plus 0.04 mg/kg LSD when testing in extinction (animals removed prior to receiving reinforcement after selecting one of the levers) produces additive effects when co-administered.

4. Discussion

The results of the present experimentation indicate that, in Fawn-Hooded animals, the additive effects of a sub-threshold discriminative dose of MDMA combined with a sub-threshold dose of LSD produce a large and significant increase in MDMA stimulus discrimination. The use of the Fawn-Hooded animals, who have been thought to have a serotonin dysfunction, have previously been found to have no difference in their discriminative sensitivity to either fenfluramine (Schechter, 1997b) or, in fact, MDMA (Schechter, 1997a) when compared to Sprague–Dawley rats. A recent study indicated that there were behavioral differences between two inbred strains of Fawn-Hooded

rats, casting some doubts on the established central serotonergic abnormalities in these animals and their possible difference in serotonergic-mediated behaviors (Overstreet and Rezvani, 1996).

Although the prevalence of concurrent use of LSD and MDMA remains conjectural, it is common enough to have generated a street name, i.e. 'candyflipping'. This combination is thought to allow for a heightening of each of the subjective effects of these two drugs and the present experimentation indicates that low doses of each do, in fact, synergize. In this case, a low dose of LSD added to a saline-like dose of MDMA produced a maximal MDMA-like discriminative response. This is suggested by the anecdote, again from the Internet (http://www.hyperreal.com, 1994): ''The acid, when taken in conjunction with the exctasy (sic), unless you take a lot of it, doesn't seem that much like acid at all. It extends and heightens the E buzz for a few more hours. I especially recommend it if you are particularly fond of acid... it acts as a safety buffer and allows you to go a lot further than you normally would.'' ''I candyflipped once and it was an incredible experience. The X gives its warm, loving glow to the acid trip and actually potentiates it a bit (the acid visuals seemed a bit different and stronger). Because of this potentiation, most people only take 10–20 mikes of the LSD.''

To return to a more scientific evaluation of exactly what might be happening in the brain, the effects of LSD have been suggested to require stimulation of the serotonin receptors. Studies indicate that pre-treatment with a specific blocker to these sites is effective in reversing the hallucinogenic effects caused by the ingestion of LSD or LSD-like drugs (Sadzot et al., 1989). Recent work indicates that MDMA acts by releasing central serotonin (Gudelsky and Nash, 1996) and the combination of increased synaptic serotonin, capable of acting on all receptor sites involved in the interoceptive cueing properties of both LSD and MDMA, may be the mode of synergistic action of this drug combination as found in these discriminating rats; this may also occur as in the subjective reports of human co-abusers. Continued work in this area would have animals trained to discriminate LSD and given lower doses than that used in their training to establish a saline-like dose. These animals can then be tested with a dose of MDMA that will be sub-threshold as well and a combination of these two low doses in LSD-trained animals may indicate the possibility of cross-generalization as to the additivity of these two drugs in this paradigm. In any case, the combined use of these two drugs undoubtedly, will continue; this practice may become even more prevalent as accessibility to the Internet expands. This is evidenced by the fact that it has recently been noted (http://www.damicon.fi, 1996) in an Internet 'reaction information' list of commonly encountered drug interactions that the combination of MDMA and LSD is 'not known for dangerous reactions!'

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