Psychopharmacology

10.1007/s00213-003-1653-1

Letter to the Editors

Hyperthermic and neurotoxic effect of 3,4-methylenedioxymethamphetamine (MDMA) in guinea pigs

Kathryn S. Saadat[1], J. Martin Elliott, M. Isabel Colado[2] and A. Richard Green[1, 3]

(1) Neuropharmacology Research Group, School of Pharmacy, De Montfort University, The Gateway, Leicester, LE1 9BH, UK

(2) Departamento de Farmacologia, Facultad de Medicina, Universidad Complutense, 28040 Madrid, Spain

(3) AstraZeneca R&D Charnwood, Bakewell Road, Loughborough, LE11 5RH, UK

A. Richard Green
Email: richard.green@astrazeneca.com

Received: 30 August 2003 **Accepted:** 8 September 2003 **Published online:** 9 December 2003

Without Abstract

The report (Ricaurte et al. *2002*) that frequent repeat dosing of primates with MDMA produced damage to dopaminergic neurones, in addition to the expected damage to serotonin nerve endings, has recently been withdrawn as a drug supply error had resulted in the animals being dosed with methamphetamine by mistake (Ricaurte et al. *2003*). Consequently, the view that MDMA is a selective serotonin neurotoxin has been reinforced. Essentially all studies of the neurotoxic effect of MDMA in rats have failed to detect damage to dopamine neurones (see Green et al. *2003*) and all studies on primates (both monkeys and humans) have similarly failed to demonstrate neurotoxic loss of dopamine or dopaminergic markers (see Green et al. *2003*). However, administration of MDMA to mice does result in neurotoxic damage to dopamine nerve endings (O'Shea et al. *2001*), with little evidence for serotonin loss except in selenium deficient animals (Sanchez et al. *2003*). It still, therefore, appears possible that MDMA might be capable of producing dopaminergic damage in other species, which would weaken the notion that it is primarily a selective neurotoxin of serotoninergic nerve endings. We have now briefly examined whether MDMA induces long-term dopamine loss in another small experimental animal, the guinea pig.

There appear to have only been two studies performed on the effect of MDMA in guinea pigs. Commins et al. (*1987*) gave two doses of MDMA (20 mg/kg) daily for 4 days and reported a major loss in striatal 5-HT content (71%) 14 days later and, crucially, a statistically significant loss (24%) of dopamine content. Battaglia et al (*1988*) confirmed the long-term MDMA-induced striatal 5-HT loss, but did not measure the dopamine concentration. Neither study examined whether there was an acute hyperthermic response following MDMA administration to guinea pigs. However, in rats there is general agreement that the induction of hyperthermia is a major, but not necessarily essential, factor in the degree of subsequent neurotoxic damage (Broening et al. *1995*; Malberg and Seiden *1998*; O'Shea et al. *1998*). We have now examined in guinea pigs both the acute hyperthermic response following MDMA administration and the striatal 5-HT and dopamine concentration 1 week following two different dosing regimes of MDMA.

Male guinea pigs (Hall, Burton on Trent, UK), weighing 350–425 g at the start of the experiment, were injected IP with either saline or MDMA using two different dose schedules (group I: 20 mg/kg×2 during 1 day; group II: 20 mg/kg twice daily for 3 days). Injections were given at 10.00 and 16.00 hours. Rectal temperature was measured in lightly restrained animals by use of a rectal probe with digital readout over 8 h on the first day (all groups) and for 4 h following the fifth injection (day 3) in saline-injected and group II.

Seven days following the final injection, all groups were killed and striatal 5-HT and dopamine were measured by HPLC with electrochemical detection (see O'Shea et al. *2001*).

The first injection of MDMA produced an acute hyperthermic response (Fig. 1), but the second dose failed to produce an increase in rectal temperature and there was no significant increase in rectal temperature following the fifth dose (Fig. 1, insert).

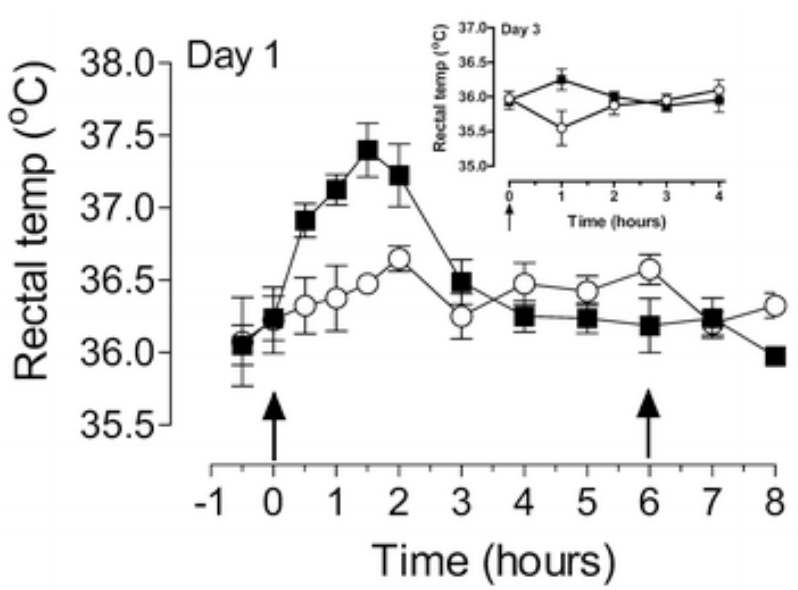

Fig. 1 The temperature response of guinea pigs following administration of MDMA (20 mg/kg IP). Main graph shows response of guinea pigs injected with either saline (○, *n*=4) or MDMA (■, *n*=8) on day 1. Time of injections shown by *arrows*. MDMA treated group different from saline group from 30 min to 180 min [$F(1,10)=10.63$, $P<0.01$], but not following the second injection. *Insert graph* shows the response of guinea pigs injected with either saline (○, *n*=4) or MDMA (■ *n*=4) on day 3 (fifth injection). Dosing time is shown by *arrow*. There was no statistically significant difference between the groups at any time

One week after MDMA administration there was a major (72%) loss in striatal 5-HT and 5-HIAA concentration, and this loss was similar whether the rats were given two or six doses of MDMA. Neither dose regime resulted in a neurotoxic loss of striatal dopamine content, as indicated by the tissue concentration of dopamine and its major metabolites (Table 1).

Table 1 Striatal monoamine and metabolite concentrations in the striatum of guinea pigs 7 days after administration of MDMA. Results expressed as mean±SEM of four observations. All data shown in ng/g tissue

	Saline	MDMA (20 mg/kg×2)	MDMA (20 mg/kg×6)
5-HT	140±11	47±3*	40±2*
5-HIAA	112±10	46±8*	33±4*
Dopamine	10120±260	10070±671	10380±594
HVA	725±84	729±30	760±36
DOPAC	2006±280	2252±234	2062±101

*Different from saline group, $P<0.01$

Our study has resulted in two main findings. The first is that guinea pigs appear to be very susceptible to MDMA-induced neurotoxicity, since MDMA produced a much greater loss of striatal 5-HT than is generally seen in rats. However, even doses which produced a greater than 70% loss of 5-HT still failed to induce any neurotoxic loss of dopamine. Since we obtained a similar loss in striatal 5-HT content to that observed by Commins et al. (*1987*), we are not able to explain why we failed to confirm the loss in striatal dopamine that they reported. The second finding was that MDMA produces only a modest and transient hyperthermic response in guinea pigs. In rats, the expected peak response to a similar dose would be greater and the duration would be considerably longer. Thus it is difficult to conclude that in guinea pigs, the severity of the hyperthermic response is associated with the magnitude of the MDMA-induced damage to 5-HT nerve endings, an established association in rats (Broening et al. *1995*; Malberg and Seiden *1998*; O'Shea et al. *1998*).

These data strengthen the body of evidence suggesting that MDMA is a fairly selective serotonin neurotoxin. However, given the substantial evidence that neurotoxicity results from free radical formation (see Green et al. *2003*), it seems reasonable to propose that this selectivity may result from the relative ability of serotonin and dopamine neurones to inactivate free radicals and that particular conditions (for example, the degree of hyperthermia, the MDMA dosing schedule or the endogenous ability of the compromised tissue to inactivate free radicals: see Sanchez et al. *2001*) can result in damage in neurones that are not normally susceptible. The formation of species-specific neurotoxic metabolites might also play a role in determining the neurones damaged, and this should perhaps be the subject of further investigation.

References

Battaglia G, Brooks BP, Kulsakdinun C, De Souza EB (1988) Pharmacologic profile of MDMA (3,4-methylenedioxymethamphetamine) at various brain recognition sites. Eur J Pharmacol 149:159–163
ChemPort PubMed

Broening HW, Bowyer JF, Slikker Jr W (1995) Age-dependent sensitivity of rats to the long-term effects of the serotonergic neurotoxicant (±)-3,4-methylenedioxymethamphetamine (MDMA) correlates with the magnitude of the MDMA-induced thermal response. J Pharmacol Exp Ther 275:325–333
ChemPort PubMed

Commins DL, Vosmer G, Virus RM, Woolverton WL, Schuster CR, Seiden LS (1987) Biochemical and histological evidence that methylenedioxymethamphetamine (MDMA) is toxic to neurons in the rat brain. J Pharmacol Exp Ther 241:338–345
ChemPort PubMed

Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI (2003) The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacol Rev 55:463–508
crossref ChemPort PubMed

Malberg JE, Seiden LS (1998) Small changes in ambient temperature cause large changes in 3,4-methylenedioxymethamphetamine (MDMA)-induced serotonin neurotoxicity and core body temperature in the rat. J Neurosci 18:5086–5094
ChemPort PubMed

O'Shea E, Granados R, Esteban B, Colado MI, Green AR (1998) The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA ("ecstasy"). Neuropharmacology 37:919–926
crossref ChemPort PubMed

O'Shea E, Esteban B, Camarero J, Green AR, Colado MI (2001) Effect of GBR 12909 and fluoxetine on the acute and long term changes induced by MDMA ("ecstasy") on the 5-HT and dopamine concentrations in mouse brain. Neuropharmacology 40:65–74

Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD (2002) Severe dopaminergic neurotoxicity in primates after a single recreational dose regimen of MDMA ("Ecstasy"). Science (Wash) 297:2260–2263

Ricaurte GA, Yuan J, Hatzidimitriou G, Cord BJ, McCann UD (2003) Retraction. Science (Wash) 301:1479

Sanchez V, Camarero J, O'Shea E, Green AR, Colado MI (2003) Differential effect of dietary selenium on the long term neurotoxicity induced by MDMA in mice and rats. Neuropharmacology 44:449–461