ELSEVIER

European Journal of Pharmacology 283 (1995) R5–R7

ejp

Rapid communication

Fenfluramine's appetite suppression and serotonin neurotoxicity are separable

Una D. McCann [a], Jie Yuan [b], George A. Ricaurte [b,*]

[a] *Section on Anxiety and Affective Disorders, Biological Psychiatry Branch, National Institute on Mental Health, Building 10 – 3N212, 9000 Rockville Pike, Bethesda, MD 20892, USA*

[b] *Department of Neurology, 5501 Bayview Boulevard, Johns Hopkins Medical Institutions, Baltimore, MD 21224, USA*

Received 1 August 1995; accepted 4 August 1995

Abstract

To determine whether fenfluramine's anorectic and neurotoxic effects could be dissociated, rats were treated with fenfluramine or the serotonin transporter blocker fluoxetine, alone or in combination. Fenfluramine alone produced anorexia, weight loss and lasting depletions of brain serotonin axon markers. Fluoxetine prevented fenfluramine-induced long-term serotonergic deficits, yet did not diminish fenfluramine's acute anorectic effects. These findings indicate that fenfluramine's anorectic and neurotoxic actions are distinct and separable.

Keywords: Fenfluramine; Neurotoxicity; Appetite

(±)-3,4-Methylenedioxymethamphetamine (MDMA, 'ecstasy') is a synthetic amphetamine derivative that is used recreationally and is known to damage brain serotonin neurons in rats (Commins et al., 1987), monkeys (Ricaurte et al., 1992) and, possibly, humans (McCann et al., 1994). MDMA users report that, when they take MDMA in combination with the serotonin transporter blocker fluoxetine, they still experience MDMA's unique reinforcing subjective effects (McCann and Ricaurte, 1993). For reasons we have detailed elsewhere (McCann and Ricaurte, 1993), these reports strongly suggest that MDMA's behavioral and neurotoxic effects may be separable. The present study sought to determine whether the anorectic and neurotoxic effects of fenfluramine, a structurally related amphetamine, might also be separated through the use of fluoxetine. Despite extensive evidence that fenfluramine has high neurotoxic potential toward brain serotonin neurons in animals (Schuster et al., 1986; Ricaurte et al., 1991), fenfluramine continues to be the most widely prescribed appetite suppressant in Europe.

Male Sprague-Dawley rats (Harlan, Madison, WI, USA; $n = 34$) weighing 200–225 g were housed individually in a temperature-controlled room (22 ± 1°C) on a 12:12 h light/dark cycle (light from 6 a.m. to 6 p.m.), with free access to food (Purina rodent chow) and water. Animals received drugs (or vehicle) orogastrically by means of gavage twice daily (09.00 and 17.00 h) for 6 consecutive days. There were four treatment groups: (1) fenfluramine 5 mg/kg ($n = 9$); (2) fluoxetine 5 mg/kg ($n = 8$); (3) fenfluramine 5 mg/kg plus fluoxetine 5 mg/kg ($n = 9$) or; (4) equal volumes of vehicle (water) ($n = 8$). Daily weights were obtained using an electronic scale with a 0.1 g accuracy, at baseline, during drug treatment and for 2 weeks following drug treatment. The amount of food ingested was calculated daily. Two weeks following drug treatment, the effects of various treatments on regional brain content of serotonin and 5-hydroxyindoleacetic acid (5-HIAA) were determined as previously described (Ricaurte et al., 1992). Food intake and body weight data were analyzed by two-way analysis of variance (ANOVA) for repeated measures, with treatment as the between-subjects factor and time as the within-subjects factor. When appropriate, group means at individual time points were compared by a one-way ANOVA, and post-hoc comparisons were performed by the Bonferroni test. Regional brain serotonin data were analyzed by one-way ANOVA, also with post-hoc Bonferroni tests.

* Corresponding author. Tel. (410) 550-0993, fax (410) 550-2005.

0014-2999/95/$09.50 © 1995 Elsevier Science B.V. All rights reserved
SSDI 0014-2999(95)00482-3

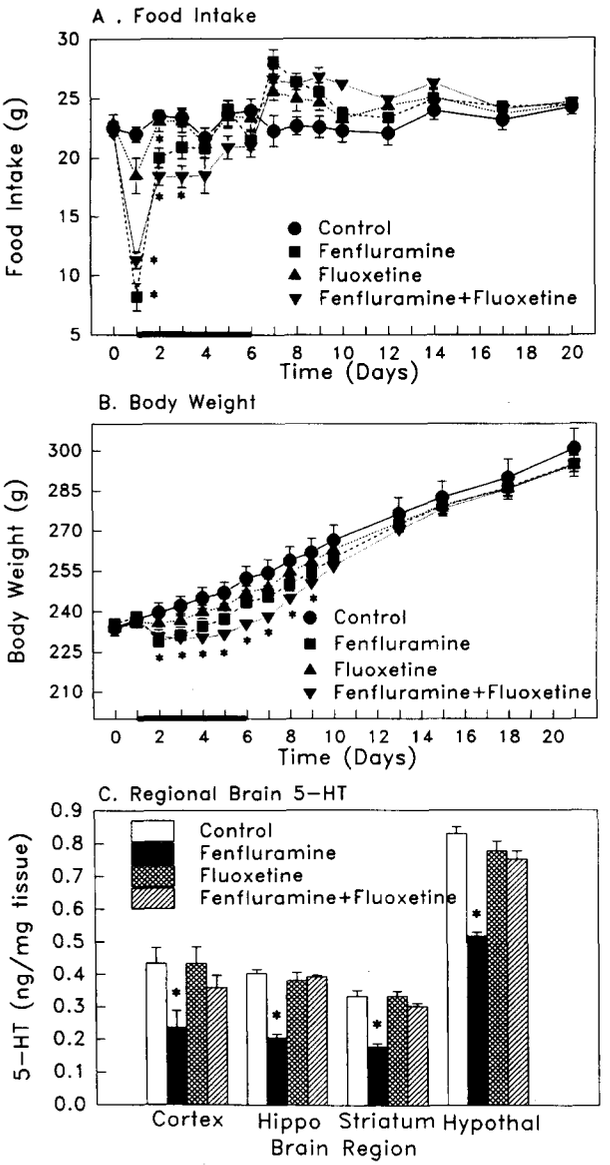

Fig. 1. Effects of fenfluramine and fluoxetine, administered alone or in combination, on rat (A) food intake, (B) body weight and (C) regional brain serotonin. Food intake and body weight were measured throughout the study; regional brain serotonin levels were determined 2 weeks after termination of drug treatment. Drugs were administered orogastrically by means of gavage twice daily (09.00 and 17.00 h) for 6 consecutive days, as indicated by the bar overlying the abscissa. Each drug was administered at a dose of 5 mg/kg. Control animals received equivalent volumes of the vehicle (water), also by gavage. Results are the means ± S.E.M. ($n = 8$ or 9 per group). For food intake, ANOVA revealed a significant group by time interaction, with post-hoc tests revealing significant effects of treatment with fenfluramine (·) on treatment days 1 and 2, and significant effects of treatment with fenfluramine plus fluoxetine (▼) on treatment days 1, 2 and 3. For body weight, ANOVA also revealed a significant group by time interaction, with post-hoc tests revealing significant effects of treatment with fenfluramine (■) on treatment days 2–5, and significant effects of treatment with fenfluramine plus fluoxetine (▼) on treatment days 2–9. For regional brain serotonin, ANOVA revealed a significant main effect of treatment with post-hoc tests showing significant effects of fenfluramine (■), but no significant effects of treatment with fenfluramine plus fluoxetine, or fluoxetine alone. $^{*}P < 0.05$ compared to control.

At baseline, the four treatment groups did not differ with regard to food intake (Fig. 1A) or body weight (Fig. 1B). Treatment with fenfluramine alone led to a sharp decline in food intake and weight on treatment days 1 and 2, respectively, with smaller, though persistent decreases observed on subsequent treatment days. The anorectic and weight-reducing effects of the fenfluramine/fluoxetine combination were equal to or greater than those of fenfluramine alone on all treatment days. Following drug discontinuation, rats in all three drug groups had a rebound increase in food intake above that observed at baseline, with concomitant increase in body weight. Increases in food intake after drug discontinuation lasted 2–5 days, dependent on treatment group. Two weeks after drug discontinuation, food intake and weight of animals among the four treatment groups did not differ significantly (Fig. 1A and B).

Two weeks after termination of the treatment period, rats treated with fenfluramine alone had significant decreases in regional brain serotonin (Fig. 1C), with parallel decreases in regional brain 5-HIAA (not shown). By contrast, identical measures performed in animals treated with fenfluramine plus fluoxetine were not different than those in animals treated with the vehicle or fluoxetine alone (Fig. 1C).

The present results strongly suggest that, at least in rats, fenfluramine's anorectic and neurotoxic effects are separable. Rats treated with the fenfluramine/fluoxetine mixture showed clear reductions in food intake (Fig. 1A) and body weight (Fig. 1B), yet had no alterations in brain measures indicative of serotonin neurotoxicity (Fig. 1C). Along with other recent findings (Raiteri et al., 1995), the present results also suggest that serotonin release may not be essential for fenfluramine's anorectic action, since fluoxetine is known to interfere with fenfluramine-induced serotonin release (Bonanno et al., 1994), yet does not block fenfluramine-induced hypophagia and weight loss (Fig. 1). It remains to be established whether fenfluramine, at clinically prescribed dosages, produces toxic effects on serotonin neurons in the human brain. Nonetheless, the present findings indicate that adjunctive use of fluoxetine (and perhaps other serotonin reuptake inhibitors) could be utilized to decrease the neurotoxic risks of fenfluramine in humans without adversely affecting (indeed, perhaps augmenting) fenfluramine's therapeutic appetite suppressant action.

Acknowledgements

This work was supported by National Institutes of Health Grants PHS R01 DA06275 and KO2 DA00206 to G.A.R., and by IRP support to U.D.M.

References

Bonanno, G., A. Fassio, P. Severi et al., 1994, Fenfluramine releases serotonin from human brain nerve endings by a dual mechanism, J. Neurochem. 63, 1163.

Commins, D., R. Virus, W. Woolverton et al., 1987, Biochemical and histological evidence that methylenedioxymethylamphetamine (MDMA) is toxic to neurons in the rat brain, J. Pharmacol. Exp. Ther. 241, 338.

McCann, U. and G. Ricaurte, 1993, Subjective and neurotoxic effects of (±)-3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') are separable: clinical evidence, J. Clin. Psychopharmacol. 13, 214.

McCann, U., A. Ridenour, Y. Shaham et al., 1994, Serotonin neurotoxicity after (±)-3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy'): a controlled study in humans, Neuropsychopharmacology 10, 129.

Raiteri, M., G. Bonanno and F. Vallebuona, 1995, In vitro and in vivo effects of *d*-fenfluramine: no apparent relation between 5-hydroxytryptamine release and hypophagia, J. Pharmacol. Exp. Ther. 273, 643.

Ricaurte, G., M. Molliver, M. Martello et al., 1991, Dexfenfluramine neurotoxicity in brains of non-human primates, Lancet 338, 1487.

Ricaurte, G., J. Katz, M. Martello et al., 1992, Lasting effects of 3,4-methylenedioxymethamphetamine on central serotonergic neurons in non-human primates, J. Pharmacol. Exp. Ther. 261, 616.

Schuster, C., M. Lewis and L. Seiden, 1986, Fenfluramine: neurotoxicity, Psychopharmacol. Bull. 22, 148.