Pharmacology Biochemistry & Behavior, Vol. 21, pp. 667–669, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

BRIEF COMMUNICATION

The Effects of the β-Carboline FG 7142, on Intracranial Self-Stimulation in the Rat

SHARON PELLOW, L. J. HERBERG* AND SANDRA E. FILE

*MRC Neuropharmacology Research Group, Department of Pharmacology, The School of Pharmacy University of London, 29-39 Brunswick Square, London WC1N 1AX and *Experimental Psychology Laboratory, Institute of Neurology, Queen Square, London WC1N 3BG*

Received 23 January 1984

PELLOW, S., L. J. HERBERG AND S. E. FILE. *The effects of the β-carboline, FG 7142, on intracranial self-stimulation in the rat.* PHARMACOL BIOCHEM BEHAV 21(4) 667–669, 1984.—The effects of FG 7142 were examined, alone and in combination with chlordiazepoxide, on self-stimulation of the mid-lateral hypothalamus. Rewarding stimuli were delivered according to a 10-sec variable-interval schedule of reinforcement. FG 7142 (1–20 mg/kg) produced a dose-related depression in responding, and chlordiazepoxide (5 mg/kg) enhanced it. When these two drugs were given together, response rates did not differ significantly from control rates.

Self-stimulation FG 7142 Chlordiazepoxide β-carboline Benzodiazepine

LOW doses of benzodiazepines may enhance responding for intracranial stimulation in the lateral hypothalamus [1,9], particularly in sites where stimulation has rewarding as well as aversive properties [10] or when reinforcement is delivered on a variable interval schedule [5]. In the latter study, Herberg and Williams showed that low doses of chlordiazepoxide (2.5–5 mg/kg) facilitated responding, whereas high doses (50–90 mg/kg) depressed it. The facilitatory effects were enhanced by picrotoxin and by pentylenetetrazol, even though the latter agents depressed self-stimulation when given alone, and antagonised the effects of benzodiazepines in other pharmacological tests [2,14]. We were therefore interested in investigating the effects on self-stimulation of other drugs that can antagonise the behavioural effects of benzodiazepines: particularly those thought to do so via an action at the benzodiazepine binding sites.

FG 7142 β-carboline-3-carboxylate methyl amide), like other alkyl-β-carboline-3-carboxylates, has high affinity for benzodiazepine binding sites in the CNS [7] and possesses intrinsic activity opposite in direction to that of benzodiazepines: it is anxiogenic [4,13] and proconvulsant with audiogenic seizures [7]. The present study investigated the actions of FG 7142 alone and in combination with chlordiazepoxide. The doses chosen had previously been found to be effective in behavioural tests [4,13] and the dose of chlordiazepoxide was that shown to be optimal for enhancing the rate of variable-interval self-stimulation [5].

METHOD

Male Lister hooded rats (Bantin and Kingman Ltd.) weighing 200–300 g at time of surgery were individually housed with free access to food and water. Twisted bipolar stainless steel electrodes (0.25 mm diameter, Plastic Products Inc., Roanoke, VA) were stereotaxically implanted under halothane anesthesia in the mid-lateral hypothalamus 1.0 mm posterior to Bregma, 1.3 mm to the left of the midline and 9.0 mm below the skull surface [11]. Electrode placements were determined from enlarged photographic projections of unstained 50-μm frozen sections at the end of the investigation.

FG 7142 (Ferrosan) was suspended in distilled water with a drop of Tween 20, and dispersed by ultrasound. Chlordiazepoxide hydrochloride (Roche Products) was dissolved in distilled water. Control injections consisted of distilled water, with or without a drop of Tween 20, as appropriate. Drugs were injected intraperitoneally in a volume of 2 ml/kg.

Rats were allowed to recover from surgery for a week, and trained to operate a pedal for a 0.5-sec 50-Hz sinewave, constant-current reinforcing train available on a variable-interval schedule of 10-sec mean duration. The stimulating current for each rat was fixed at the lowest intensity that elicited uninterrupted responding in preliminary trials in which intensities were decremented in approximately decilog steps, between 50 and 10 μA r.m.s. Response rates in different rats ranged between 15 and 30 lever-presses/min.

During test sessions, animals were allowed to respond for 45 min, of which the last 30 min provided a pre-injection baseline. The rat was then injected, and allowed to self-stimulate for a further 60 min. For further procedural details, see [5]. Response rates were recorded automatically at 5-min intervals in a digital printout. Drug effects were determined from the rate recorded during the second 15-min period after injection, during which, as in previous studies [5] drug effects were maximal. Response rates were expressed as a percentage of the pre-injection baseline, and compared with the corresponding rate after control injections.

Experiment 1 was a dose-response study of FG 7142 acting alone. In Experiment 2 the effects of an active dose of FG 7142 were investigated in combination with a dose of chlordiazepoxide that enhanced responding. Doses were administered in a pre-determined random order and are detailed in the results. Each rat was tested 8 times, at 2-day intervals.

RESULTS

Analysis of variance for the second 15-min period after injection showed that FG 7142 had a significant effect on self-stimulation (Friedman $\chi^2=23.33$, $p<0.0001$). Posthoc analysis by Wilcoxon tests showed that all doses of FG 7142 (1, 5, 10 and 20 mg/kg) significantly reduced self-stimulation ($p<0.05$, see Fig. 1A). Wilcoxon tests showed that chlordiazepoxide (5 mg/kg) produced a significant enhancement of self-stimulation ($p<0.05$) compared with controls, and that chlordiazepoxide (5 mg/kg) significantly reversed the reduction in self-stimulation produced by FG 7142 (5 mg/kg, $p<0.05$, see Fig. 1A).

Figure 1B shows the time-course of effects, over the 60-min test period, for the drug groups in Experiment 2. Wilcoxon tests showed that, at each 10-min period, animals receiving FG 7142 (5 mg/kg) had significantly reduced self-stimulation compared with controls ($p<0.05$). The stimulant effect of CDP (5 mg/kg) on self-stimulation was significant only within the third 10-min period ($p<0.05$). The combination of CDP with FG 7142 was not significantly different from control scores during the first 40 min, but was significantly reduced compared with controls during the final two 10-min periods ($p<0.05$).

Electrode placements were obtainable from five of the six rats, and were found to be in the area of the mid-lateral hypothalamus. There was no obvious correlation between electrode placement and drug effects.

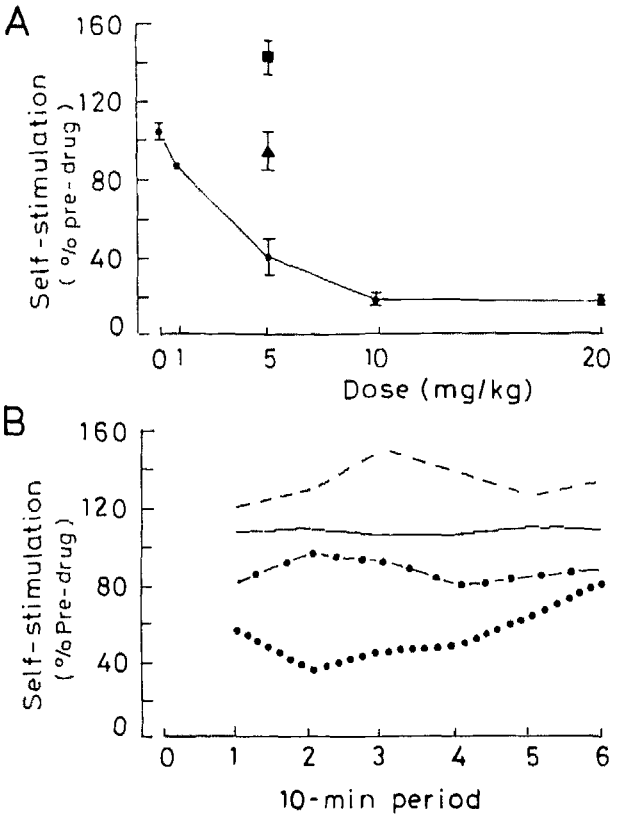

FIG. 1. (A) Mean (±S.E.M.) self-stimulation rate (VI 10 sec) in the second 15-min period after injection for control, FG 7142 (1–20 mg/kg), chlordiazepoxide (5 mg/kg) and the combination of FG 7142 (5 mg/kg) with chlordiazepoxide (5 mg/kg). ● FG 7142; ■ chlordiazepoxide; ▲ FG 7142 + chlordiazepoxide. (B) Mean self-stimulation rate (VI 10 sec) for each 10-min period after injection of control, FG 7142 (5 mg/kg), chlordiazepoxide (5 mg/kg) and the combination of chlordiazepoxide (5 mg/kg) with FG 7142 (5 mg/kg); ——— control; — — — chlordiazepoxide; ●●● FG 7142; ●—●—● FG 7142 + chlordiazepoxide.

DISCUSSION

The prolonged depression of self-stimulation by FG 7142, like its other intrinsic actions [4,13] is opposite in direction to the facilitatory effects of chlordiazepoxide on self-stimulation (this paper; [5]). The mechanism by which benzodiazepines enhance self-stimulation is not known: disinhibitory [9,10] or anxiolytic [5] mechanisms have been proposed, but other explanations are possible [6]. The opposite effect of FG 7142 is difficult to interpret, since it is always difficult to separate out the performance component from the reinforcement component in self-stimulation, and it is necessary to take into account results from other pharmacological test situations (see [8] for review). In the holeboard test in rats, which provides independent measures of locomotor activity and exploratory head-dipping, FG 7142 significantly reduced locomotor activity only at the 10 mg/kg dose, and not at 5 mg/kg [4]. The actual reduction was relatively small (down to 73% of control scores), and a mild reduction such as this seems unlikely to have decreased lever-pressing for self-stimulation, particularly since chlordiazepoxide enhanced responding for self-stimulation at a dose that reduced locomotor activity in covered circular bowls [5] and in the holeboard [3].

Another action of FG 7142 that might have contributed to decreased responding for intracranial stimulation is its proconvulsant action [7]; however, this effect was not observed with electroshock, against which high doses of FG 7142 were anticonvulsant [13]. In addition, responding for infrequent near-threshold currents on a VI-10 schedule ensured that seizures did not occur as they might have with a higher rate of reinforcement.

The depression of self-stimulation produced by FG 7142 (5 mg/kg) was reversed by a dose of chlordiazepoxide (5 mg/kg) which, alone, enhances self-stimulation. That these two drugs can reverse each other's action suggests that the effects of FG 7142 and of chlordiazepoxide on self-stimulation might be mediated via the benzodiazepine binding site, and in fact the benzodiazepine site also appears to mediate the opposite behavioural effects of benzodiazepines

and β-carbolines in other test situations (see [12] for review). That CDP can reverse the FG 7142 depression in self-stimulation even at time periods when it is having no significant stimulant effect alone suggests that this phenomenon is not merely a non-specific effect due to simple cancellation of stimulant and depressant actions.

ACKNOWLEDGEMENTS

We are grateful to Dr. C. Braestrup for the gift of FG 7142, to Dr. Margot Hamilton for technical advice, and to the MRC for equipment. SEF is a Wellcome Trust Senior Lecturer.

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