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RAPID COMMUNICATION

Ibotenic Acid Lesions of the Medial Prefrontal Cortex Potentiate FG-7142-Induced Attenuation of Exploratory Activity in the Rat

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JASKIW, G. E. AND D. R. WEINBERGER. *Ibotenic acid lesions of the medial prefrontal cortex potentiate FG-7142-induced attenuation of exploratory activity in the rat.* PHARMACOL BIOCHEM BEHAV **36**(3) 695–697, 1990.—Six weeks after induction of bilateral sham or ibotenic acid lesions of the medial prefrontal cortex (MPFC), groups of rats were injected with the anxiogenic β-carboline FG-7142 (15 mg/kg IP) or vehicle (VEH) before exposure to a novel open field. The attenuation of exploratory activity by FG-7142 was markedly enhanced in the MPFC-lesioned rats. The results suggest that the behavioral effects of MPFC lesions may be amplified under stressful conditions. Secondly, the inhibition of exploratory activity by FG-7142 does not depend on its action within the MPFC.

Prefrontal cortex Ibotenic acid Stress FG-7142 Locomotion Exploration

RATS with lesions of the medial prefrontal cortex (MPFC) display a variety of abnormalities in complex motor sequences, particularly those subserving neuropsychological tasks (8). In contrast, discrete MPFC lesions rarely induce changes in gross locomotor activity. Such disturbances have been noted, however, in MPFC-lesioned rats exposed to certain stresses, such as food deprivation (11) or a novel environment (5). These conditions have also been associated with enhanced dopamine turnover in the MPFC (1,17). The reactivity of MPFC dopamine systems to these and other aversive stimuli (3,14) suggests that the mesocortical DA system and the MPFC play a critical role in the response to stress, perhaps by mediating cognitive aspects of a coping mechanism (2). Accordingly, we postulated that while MPFC dysfunction might not alter locomotor activity under usual testing conditions, an abnormal locomotor response would be elicited in MPFC-lesioned rats tested during exposure to stressful conditions which normally activate the mesocortical DA system. Insofar as it would impair coping mechanisms, the MPFC lesion would be expressed as an amplification of the stress dependent locomotor response seen in intact rats. To test these hypotheses, the exploratory activity of rats with ibotenic acid (IA) lesions of the MPFC was evaluated following administration of FG-7142, an anxiogenic β-carboline which enhances dopamine turnover in the MPFC (16) and which inhibits exploratory behavior (4).

METHOD

Male Sprague-Dawley rats (Zivic-Miller Labs) weighing 220–250 g were housed 4 to a cage in a room with a 12-hour light/12-hour dark cycle and with unlimited access to food and water. Anesthesia was induced by Ketamine (70 mg/kg) and xylazine (6 mg/kg). Ibotenic acid (Sigma Chemical Co.) (5 μg/0.5 μl over 2.5 min) or an equal volume of vehicle (0.1 M phosphate-buffered saline) was stereotaxically administered bilaterally through 26-gauge cannulae at the coordinates: AP +3.5 mm, ML ±0.7 mm and VD −3.5 mm relative to bregma (10). The cannulae remained in place for 5 min after the end of the infusion.

Six rats with IA injections were randomly selected 7 days after the lesion, anesthetized with chloral hydrate 300 mg/kg IP, and perfused with a 4% buffered formalin solution. After immersion in

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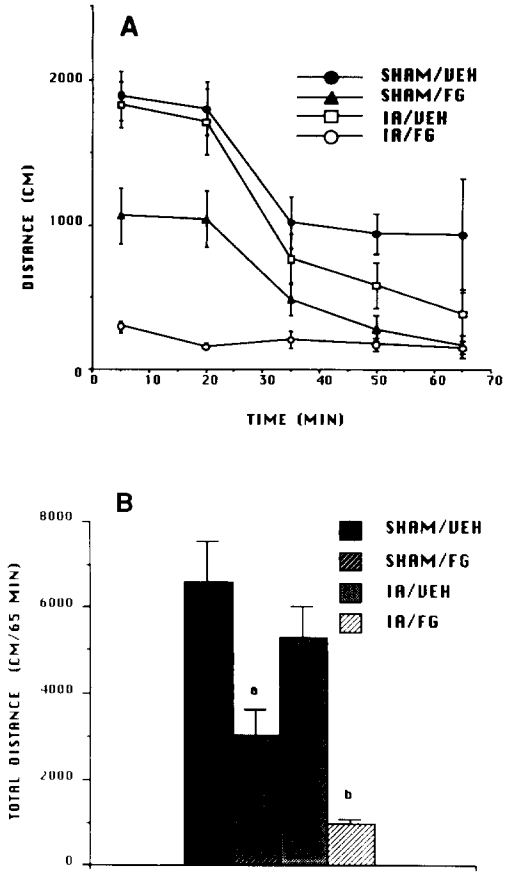

FIG. 1. (A) Time course of distance travelled over 65 minutes by the four groups (means ± SEM), starting 15 min after injection of either FG 7142 (15 mg/kg IP) or vehicle (VEH) (10% Tween 80). Rats received either sham or ibotenic acid (IA) lesions of the medial prefrontal cortex 6 weeks earlier. An ANOVA with lesion status, drug status and time as factors demonstrated significant drug as well as lesion × drug effects on distance travelled during the time of testing. The drug × time and lesion × drug × time interactions were also significant. (B) Total distance travelled over 65 minutes by the four groups (means ± SEM). Student-Newman-Keuls tests showed that IA lesioned rats which received FG 7142 (IA/FG) were markedly hypoactive with respect to all other groups (b: $p<0.05$). The exploratory activity of sham-lesioned, FG-7142-treated rats (SHAM/FG) was reduced relative to that of both groups (SHAM/VEH and IA/VEH) which received vehicle (a: $p<0.05$).

a 30% sucrose solution cryostat sections were prepared and stained with cresyl violet. Lesion sites were determined by comparison with the atlas of Paxinos and Watson (12).

Six weeks postoperatively rats were moved in their home cages to a room adjacent to the testing area and remained there for 20 hours. Testing was conducted between 12:00 a.m. and 2:30 p.m. over 4 consecutive days. Fifteen minutes after injection of either vehicle (VEH) (10% Tween 80 in distilled water) or FG-7142 (Research Biochemicals; 15 mg/kg IP), rats were placed in activity monitors (Omnitech Electronics Model RXYZCM 16) (15). Locomotor activity was recorded for the first 5 min and for the 4 subsequent 15-min intervals. Each rat was observed for 15 sec at 15-min intervals. Distance travelled was analysed using a three-way ANOVA with drug (FG-7142 or VEH) and lesion status (MPFC lesion or sham) as single factors and time as a repeated measure. Newman-Keuls tests were used for post hoc comparisons.

RESULTS

Neurons were absent from most of the area comprising the MPFC in animals with IA lesions. As in earlier studies (6), the area of neuronal loss extended rostrocaudally from the genu of the corpus callosum to just caudal to the rostral tip of the frontal pole, mediolaterally from the interhemispheric fissure to the forceps minor and ventrodorsally from the shoulder of cingulate area 1 to the lower border of cingulate area 3 (12). The corpus striatum and nucleus accumbens were not affected.

In rats with MPFC lesions, administration of FG-7142 abolished the initial phase of intense locomotor exploration (Fig. 1). There was a significant main drug effect, $F(5,24)=12.95$, $p<0.0001$, as well as a significant lesion × drug interaction (LSN × INJ, $F(5,24)=3.62$, $p<0.01$, in terms of distance travelled. The drug × time, $F(4,25)=8.60$, $p<0.0002$, and lesion × drug x time, $F(4,25)=4.55$, $p<0.01$, interactions were also significant (Fig. 1). Post hoc comparisons showed that FG-7142 administration markedly reduced the exploratory activity of IA-lesioned rats with respect to all other groups, and reduced the exploratory activity of sham-lesioned rats with respect to both the IA- and sham-lesioned rats which received a vehicle injection (Fig. 1).

DISCUSSION

In agreement with previous studies (4), FG-7142 inhibited exploratory locomotor activity in all animals. This effect was markedly enhanced in rats with IA lesions of the MPFC. While the mechanism for this effect of MPFC lesions is unknown, several possibilities can be discounted. Seizure activity, for instance, is unlikely. Though FG-7142 has been shown to be proconvulsant after repeated dosing (9), convulsions have not been observed following single doses in the range used here (4,16), nor were vocalizations or clonic movements observed in this experiment. Some studies suggest that enhanced mesocortical dopamine transmission may inhibit mesolimbic dopamine transmission and locomotor activity (10,13). Accordingly, it is conceivable that FG-7142 inhibits exploratory activity by enhancing dopamine release in the MPFC. Such a mechanism cannot, however, be invoked in rats in which IA lesions of the MPFC prevented transmission of information from the MPFC to other brain areas. It has been suggested that FG-7142 may influence ascending dopamine systems by interacting with γ-amino-butyric acid receptor sites within the substantia nigra (16) or within the corpus striatum (7). It is possible, therefore, that loss of MPFC projections to the substantia nigra or to subcortical dopamine terminal fields altered the behavioral response to FG-7142.

In earlier studies no gross disturbances in spontaneous exploratory activity were detected in rats tested 4 weeks after IA lesions of the MPFC (6). In this experiment, gross locomotor activity of IA-lesioned rats was significantly altered following the administration of FG-7142. Thus, as postulated, some behavioral sequelae of MPFC dysfunction can be elicited only under testing conditions which normally activate mesocortical dopamine systems.

In summary, our data suggest that FG-7142-induced attenuation of exploratory activity is not mediated primarily by the MPFC. Indeed, MPFC lesions amplify the acute behavioral effects of FG-7142. The data are consistent with the hypothesis that the primary role of the MPFC during exposure to aversive stimuli may be to coordinate cognitive coping processes rather than to mediate the experience of fear or anxiety (2). That certain testing conditions may amplify the sometimes subtle effects of prefrontal-cortical impairment should be considered in the investigation of neuropsychiatric syndromes where a prefrontal cortical deficit is suspected (18).

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