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RAPID COMMUNICATION

Ibotenic Acid Lesions of Medial Prefrontal Cortex Augment Swim-Stress-Induced Locomotion

GEORGE E. JASKIW[1] AND DANIEL R. WEINBERGER

Clinical Brain Disorders Branch, National Institutes of Mental Health Intramural Research Program, NIMH Research Center, Washington, DC 20032

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JASKIW, G. E. AND D. R. WEINBERGER. *Ibotenic acid lesions of medial prefrontal cortex augment swim-stress-induced locomotion.* PHARMACOL BIOCHEM BEHAV 41(3) 607–609, 1992.—Locomotor activity of rats with sham or ibotenic acid lesions of the medial prefrontal cortex (MPFC) was assessed after animals were exposed to a 15-min swim or control stress. Swim-stress-induced locomotor activity was augmented in the MPFC-lesioned rats. These and other data suggest that lesions of the MPFC are followed by an exaggeration of the normal behavioral response to stress. Dysregulation of dopamine transmission in the basal ganglia may be involved.

Prefrontal cortex Ibotenic acid Stress Swim Locomotion Dopamine Rat

THE rat medial prefrontal cortex (MPFC) is both stress sensitive (2,3,5,17) and modulates nigrostriatal and mesolimbic dopamine (DA) transmission (9,10,14,16). Insofar as basal ganglia DA systems have been implicated in the regulation of motor behaviors (4,13), it is not surprising that both we and others have reported motor disturbances in MPFC-lesioned rats exposed to aversive conditions (1,6,10,12). Most data suggest that the MPFC exerts a predominantly inhibitory influence on both subcortical DA transmission and on locomotor exploration (9,10,14,16). Rats with nonspecific ablative MPFC lesions typically demonstrate increased levels of locomotor activity [for review, see (8)]. However, we have found that axon-sparing ibotenic acid (IA) lesions of the MPFC potentiate the *hypo*motility induced by the anxiogenic β-carboline FG 7142 (10). It is conceivable that differences in lesioning technique account for the ostensibly discrepant results. An alternative explanation is that the behavioral influence of the MPFC is critically context dependent and that MPFC lesions produce motor hyperreactivity rather than hyperactivity per se (6,12). Accordingly, under testing conditions that normally increase locomotion, IA lesions of the MPFC should potentiate hypermotility. To test this hypothesis, we exposed MPFC-lesioned rats to swim stress, a condition that increases subsequent locomotor activity in intact animals.

METHOD

Male Sprague-Dawley rats (Zivic-Miller Labs) weighing 220–250 g were housed three to a cage in a room with a 12 L:12 D cycle and with unlimited access to food and water. Anesthesia was induced by ketamine (70 mg/kg) and xylazine (6 mg/kg). IA (Sigma Chemical Co.) (5 μg/0.5 μl over 2.5 min) or vehicle (0.1 M phosphate-buffered saline) for SHAM operates was stereotaxically administered bilaterally through 26-ga cannulae at the coordinates: AP + 3.5 mm, ML ± 0.7 mm, and VD − 3.5 mm relative to bregma (15). The cannulae remained in place for 5 min after the end of the infusion. Seven days later, six rats with IA injections were anesthetized with chloral hydrate 300 mg/kg, IP, and perfused with a 4% buffered formalin solution. After immersion in a 30% sucrose solution, cryostat sections were prepared and stained with cresyl violet.

Four months postoperatively, rats were randomly assigned to swim stress (STRESS), or control (CONT) stress exposure. There were thus four groups in total, SHAM/CONT, IA/CONT, SHAM/STRESS, and IA/STRESS (n = 10–12/group). After overnight acclimatization to the testing area, animals were placed in Plexiglas cylinders (height 30 cm, diameter 30 cm) that contained either sawdust (2 cm deep) or water (21–24°C, 23 cm deep). Neither the tail nor the hindfeet

[1] Requests for reprints should be addressed to Dr. George E. Jaskiw, Rm. B68, Hanna Pavilion, 2040 Abington Road, Cleveland, OH 44106.

of the animal could reach bottom unless the head was also submerged.

The cylinder sides were opaque and the top was partially covered by clear Plexiglas that prevented egress but allowed air entry. After 15 min of swim- or control-stress exposure, all animals were transferred to a dry cylinder with sawdust bedding for a 5-min recovery period, and were then placed in photocell activity monitors (Omnitech Electronics RXYZCM) (18). Locomotor activity was recorded for the first 5 min and for 3 subsequent 30-min intervals. Distance traveled was analyzed using a three-way analysis of variance (ANOVA) with STRESS (SWIM or CONT) and LESION status (IA or SHAM) as single factors and TIME as a repeated factor. Newman-Keuls tests were used for posthoc comparisons.

RESULTS

The lesioned area was marked by the absence of neurons as well as by occasional cavitation, and 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 (15). The corpus striatum and nucleus accumbens were not affected.

An overall ANOVA of all four time periods demonstrated significant main LESION, $F(4,37) = 3.05$, $p < 0.03$, STRESS, $F(4,37) = 41.5$, $p < 0.0001$, TIMES, $F(3,38) = 23.5$, $p < 0.0001$, and significant LESION × STRESS $F = 2.59$, $p < 0.05$, TIMES × STRESS, $F(3,38) = 56.8$, $p < 0.0001$, and TIMES × LESION × STRESS, $F = 3.5$, $p < 0.02$, interactions. The TIMES × LESION interaction was not significant, $F(3,38) = 1.42$, $p > 0.25$. The time periods were then subjected to individual ANOVA. During the first 5 min of testing, there was a strong STRESS effect, $F(3,40) = 51.64$, $p < 0.0001$, but no significant LESION, $F(3,40) = 2.83$, $p > 0.1$, or LESION × STRESS effects, $F(3,40) = 2.16$, $p > 0.15$. Both groups of swim-stressed rats were initially hypoactive compared to their sham-exposed counterparts (Fig. 1). During the first 30-min period, there was a significant STRESS effect, $F(3,40) = 23.02$, $p < 0.0001$, and both swim-stressed groups were hyperactive compared to unstressed controls; LESION, $F(3,40) = 0.13$, $p > 0.7$, and LESION × STRESS, $F(3,40) = 0.17$, $p > 0.7$, effects were not significant. During the second 30-min period, LESION, $F(3,40) = 10.1$, $p < 0.003$, STRESS, $F(3,40) = 69.95$, $p < 0.0001$, and LESION × STRESS, $F(3,40) = 5.13$, $p < 0.03$, effects were all significant. Both swim-stressed groups were more active than unstressed animals and the IA/STRESS rats were significantly more active than the SHAM/STRESS rats. During the third period, the significant LESION, $F(3,40) = 5.55$, $p < 0.02$, and STRESS, $F(3,40) = 47.2$, $p < 0.0001$, effects persisted and there was a strong trend towards a LESION × STRESS interaction, $F(3,40) = 3.91$, $p < 0.06$. Again, swim-stressed animals traveled a greater distance than unstressed groups, and the IA/STRESS group was the most active ($p < 0.05$).

DISCUSSION

As reported previously (8), the IA lesion deefferented the MPFC without encroaching on the basal ganglia. Immediately after exposure to swim stress, both SHAM and IA-lesioned animals were briefly hypoactive compared to unstressed controls. Over the subsequent 90 min, however, swim-stressed animals were more active than unstressed rats. Furthermore,

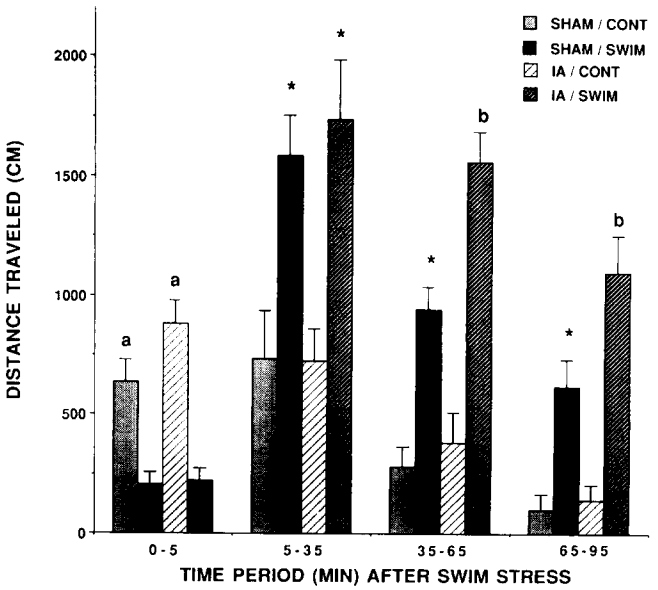

FIG. 1. Total distance (mean + SEM) traveled over 95 min of testing after a 15-min swim stress (SWIM) or control exposure (CONT) by rats with SHAM or ibotenic acid (IA) lesions of the MPFC. After an overall ANOVA of distance traveled over the entire testing period, individual time periods were subjected to ANOVA followed by Student-Newman-Keuls tests ($p < 0.05$). a > SWIM groups; * > CONT groups; b > all groups.

swim-stressed animals with IA lesions of the MPFC were more active than similarly stressed SHAM operates. The data suggest the MPFC lesion potentiated locomotion induced by the preceding swim stress.

In a series of studies, Holson and colleagues demonstrated that rats with aspiration lesions of the MPFC were hyperreactive to novel and aversive conditions (6). Others have reported that ablative frontal cortex lesions augment food-deprivation-induced increases in locomotor activity (1) and increase conditioned motor responding during food deprivation (12). We previously found that selective deefferentation of the MPFC potentiated the inhibition of exploratory activity induced by the anxiogenic β-carboline FG 7142 (10). While food deprivation, novel and aversive stimuli, and FG 7142 all activate mesocortical DA systems (2,5,17), the behavioral effects of MPFC lesions in animals exposed to such stressors are clearly not uniform. Along with the current data, such findings suggest that either nonspecific or axon-sparing MPFC lesions produce an exaggeration of context-dependent behavioral responses, and do not simply increase motor activity.

Swim stress increases mesocortical (3) and striatal DA activity (7) but its effect on mesolimbic DA systems has not to our knowledge been reported. The mechanism by which swim stress increases subsequent locomotor exploration is also not known. A simple carryover effect seems unlikely. Rats swim vigorously on introduction into a container of water, but demonstrate minimal movement by the end of a 15-min swim-stress exposure. Insofar as mesolimbic DA has been strongly implicated in the control of locomotion (4,13), our data could indicate that a similar degree of locomotor activation, and by inference a similar augmentation of mesolimbic DA transmission, occurs in sham and MPFC-lesioned rats immediately after a swim stress. While both groups reduce their locomotor

activity over the subsequent 90 min, the SHAM/SWIM animals do so to a greater extent, perhaps because an intact MPFC contributes to normalization of the stress-induced increase in mesolimbic DA transmission. The delayed "normalization" in MPFC-lesioned animals is noteworthy. Had the testing period been shorter, the differences between the groups would not have been evident. In an earlier study, we demonstrated that animals with MPFC lesions exposed to chronic low-level stress had changes in mesolimbic DA indices that endured beyond the stress period (9). Thus, the "cost" of an MPFC lesion may include longer periods of subcortical DA dysregulation, and perhaps concomitantly a longer aversive experience, after exposure to a situation requiring enhanced mesocortical activity.

In summary, IA lesions of the MPFC augmented the normal increase in locomotor activity seen after exposure to a swim stress. The results suggest that loss of the MPFC compromises mechanisms involved in attentuation of some stress-induced behaviors. The latter may reflect prolongation of subcortical DA dysregulation after an aversive experience in animals with impairment of the prefrontal cortex. Homologous mechanisms may be involved in the pathophysiology of schizophrenia (19).

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