Differential Effects of Electroconvulsive Shock on Four Models of Experimentally-Induced Aggression in Rats

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Abstract—The effects of electroconvulsive shock (ECS) on the hyperemotionality and muricide in olfactory bulbectomized rats (OB rat) were compared with those in spontaneous killer rats (SP rat), raphe lesioned rats (Raphe rat) and J9-tetrahydrocannabinol treated rats (THC rat). Single and chronic treatment of ECS inhibited the muricide and attack response to a rod, but did not affect the struggle response to handling and flight response to air blowing. Muricide was markedly inhibited by ECS in OB and SP rats, and was moderately inhibited in THC rats, while it was slightly inhibited in Raphe rats. The present result indicates that muricide of OB rats is a useful model for evaluating antidepressant drugs as this behavior is markedly inhibited by ECS in OB rats. Furthermore, it is suggested that the effect of ECS on muricide is different depending upon the methods to induce muricide, although muricide itself seems to be behaviorally similar.

Hyperemotionality including muricide can be induced in rats by olfactory bulbectomy (1) and this hyperemotionality is suppressed by antipsychotic and antianxiety drugs (2). Muricide is markedly inhibited by antidepressant drugs without causing muscle relaxation and ataxia, while hyperemotionality is almost unaffected (3, 4). Muricide induced by isolated housing and olfactory bulbectomy is also suppressed by electroconvulsive shock (ECS) (5, 6), which is an excellent form of therapy for depression (7, 8). However, no experiments concerning the effects of ECS on the hyperemotionality have been reported. The present first study was designed to elucidate whether ECS specifically suppresses muricide without affecting other manifestations of hyperemotionality or not.

We previously reported that hyperemotionality induced in rats by midbrain raphe lesions or J9-tetrahydrocannabinol (THC) administration was different from that induced by olfactory bulbectomy with respect to the type of aggressive behavior (9, 10) and the effects of antidepressants (11, 12). The second study was therefore designed to demonstrate whether the effect of ECS on muricide is different in 4 aggression models induced by various methods.

Materials and Methods

Animals: A total of 136 male Wistar King A rats supplied by the Kyushu University Institute of Laboratory Animals, weighing 190–250 g at the beginning of the experiment, were employed. Rats which showed muricide were determined as spontaneous killer rats (SP rat, n=26). The remaining rats which did not show muricide were used for the other 3 aggression models.

All animals were housed in individual cages (17 x 17 x 21 cm) with food and water ad lib and maintained under standardized conditions of temperature (22–25°C) and light (07:00–19:00) throughout the experiment.

Surgical procedure: All surgical procedures were performed under anesthesia with pentobarbital sodium 40 mg/kg, i.p. Bilateral olfactory bulbectomy was performed by suction of the olfactory bulbs through a hole made in the skull (OB rat, n=30). Lesions of the midbrain raphe nuclei were carried out by inserting an insulated, monopolar stainless
steel wire electrode (tip diameter, 0.4 mm; uninsulated length, 0.5 mm) as an anodal electrode, according to the rat brain atlas of König and Klippel (13), and applying a direct current of 3 mA for 15 sec (Raphe rat, n=35).

Measurement of hyperemotionality and muricide: Hyperemotionality was measured by scoring the following 4 responses to given stimuli: (1) air blowing onto the back (startle response), (2) a rod presented in front of the mouth (attack response), (3) pinching the tail by a forceps (flight response) and (4) handling with a gloved hand (struggle response). These responses, except for muricide, were graded as follows: score 0, no reaction; score 1, slight; score 2, moderate; score 3, marked; score 4, extreme response. The number of rats which exhibited muricide within 3 min after introducing a mouse into the rat's home cage was measured.

Histology: After termination of the behavioral experiment, OB and Raphe rats were sacrificed, and the heads were perfused with saline and 10% formalin. Thereafter, 50–60 μm sections of the brains were prepared and stained with cresyl violet to verify the site and extent of OB lesion and raphe lesion in OB and Raphe rats, respectively.

Statistical analysis: Results were evaluated statistically by means of the two-tailed Mann-Whitney test and Fisher's exact probability test.

Procedure: Rats exhibiting muricide within 10 days after OB or raphe lesions or after the administration of 6 mg/kg THC, i.p. were subjected to the treatment of ECS. The apparatus described by Woodbury and Davenport (14) with some modifications was used for the treatment of ECS. Rats were given a constant current of 60 Hz, 150 mA, 200 msec through both eyes of the rat via corneal electrodes, and control animals were given no current.

OB rats were tested for hyperemotionality and muricide in an individual cage and Raphe, SP and THC rats were tested for muricide only. Following single ECS treatment, the emotional responses of rats were consecutively scored at 0.5, 1, 2, 4, 8 and 24 hr after ECS. In rats given chronic treatment of ECS, identical ECS was given once daily for 10 days, and the emotional responses were tested immediately before and 1 hr after each ECS.

Results

Effect of ECS on muricide and hyperemotionality of OB rats: Muricide was significantly suppressed by ECS in comparison with control rats at 30 min (69.2%, P<0.005), and the inhibition of this muricide lasted for 8 hr (Fig. 1A).

Figure 1B shows the daily incidence of muricide upon chronic treatment before and 1 hr after ECS. The inhibition of muricide (77%) was maintained on day 3 after ECS, but it was decreased to about 50% on day 10 after ECS. Muricide suppression at 24 hr after ECS increased to about 70% by the 3rd and 4th ECS and about 60% by the 5th to 9th ECS. Muricide suppression, however, recovered almost 7 days after cessation of chronic ECS treatment.

Figure 2 shows the effect of single treatment of ECS on the hyperemotionality of OB rats. The score of attack response was significantly inhibited at 30 min (P<0.002), 1 hr (P<0.002), 2 hr (P<0.002) and 8 hr (P<0.02). On the other hand, the startle, flight and struggle responses were almost unaffected by single treatment of ECS (Fig. 2B, C, D).

Figure 3 shows the effect of chronic treatment of ECS on the hyperemotionality of OB rats. The score of the attack response was significantly decreased 1 hr (P<0.005) after ECS, and this inhibitory effect was maintained throughout chronic treatment. However, the score of the startle response was significantly increased on day 6 after chronic ECS, and this effect was maintained thereafter. The struggle and flight response were unaffected by either single or chronic treatment of ECS.

In the second experiment, we examined the effects of ECS on muricide in other 3 aggression models; i.e., SP rat, Raphe rat and THC rat. The muricide of SP rats was significantly depressed by single treatment of ECS (Fig. 4B), and the potency and the time course of muricide inhibition were the same as those in OB rats (Fig. 4A). In Raphe rats, muricide was slightly inhibited by single
Fig. 1. Effects of single (A) and chronic (B) ECS treatment on muricide in OB rat. Ordinate, incidence of muricide. Abscissa, time (A) and day (B). ECS treatment was given once daily for 10 successive days. Muricide tests were conducted immediately before (open) and 1 hr (closed) after daily ECS treatment. ***P<0.001, **P<0.01, *P<0.05: significant difference vs. the control untreated group.

Fig. 2. Effects of single ECS treatment on the attack response (A), startle response (B), flight response (C) and struggle response (D) in OB rat. Ordinate, scores of emotional responses. ***P<0.001, **P<0.01, *P<0.05: significant difference vs. the control untreated group.
Fig. 3. Effects of chronic ECS treatment on the attack response (A), startle response (B), flight response (C) and struggle response (D) in OB rat. Hyperemotionality tests were conducted immediately before (open) and 1 hr (closed) after daily ECS treatment. ***P<0.001, **P<0.01, *P<0.05: significant difference vs. the control untreated group.

Fig. 4. Effects of single ECS treatment on muricide in olfactory bulbectomized rat (A), spontaneous killer rat (B), raphe lesioned rat (C) and J9-tetrahydrocannabinol injected rat (D). Ordinate, incidence of muricide. Abscissa, time after ECS. ***P<0.001, *P<0.05: significant difference vs. the control untreated group.
treatment of ECS at 30 min (P<0.05) and 1 hr (P<0.05). Muricide of THC rats was moderately suppressed by ECS treatment, and the incidence of muricide was approximately 50% at 0.5, 1, 2 and 4 hr (P<0.05) after ECS.

Discussion

The effects of ECS on the hyperemotionality and muricide in OB rats, and those on muricide in SP rats, Raphe rats and THC rats were investigated. Single and chronic treatment of ECS inhibited not only muricide but also the attack response in OB rats. We previously reported that imipramine suppressed the muricide and attack response of OB rats without affecting the response to stimuli (2). From our present and previous studies, it is suggested that imipramine and ECS inhibit offensive aggression such as the muricide and attack response, but do not affect defensive aggression such as the flight and struggle responses. Furthermore, it is suggested that the muricide and attack response in OB rats are a useful model for evaluating antidepressant drugs since these behaviors are inhibited not only by antidepressants (2, 4) but also by ECS (6).

Muricide was markedly inhibited by ECS in OB and SP rats, and moderately in THC rats, while it was slightly inhibited in Raphe rats. We have reported that hyperemotionality induced by various methods is different with respect to 1) the pattern and characteristics of hyperemotionality (9, 10), 2) potency of antidepressants inhibiting muricide (2, 11, 12), 3) inhibitory effect on muricide of electrical stimulation of the locus coeruleus (15) and 4) the functional role of the medial amygdala in muricide (16). Furthermore, the present study suggests that the effect of ECS treatment on muricide is different depending upon the methods to induce muricide, although muricide itself seems to be behaviorally similar.

Studies have shown that muricide induced by OB lesions is markedly inhibited by desipramine (11), which is known to have a potent blocking activity on noradrenaline uptake at synapses (17), and electrical stimulation of the locus coeruleus (15). These facts suggest that mechanisms eliciting muricide inhibition by ECS in OB rats involve the central noradrenaline system. We previously reported that muricide inhibition induced by ECS and desipramine in OB rats was antagonized by phenoxybenzamine (6, 18), and thus this muricide inhibition was mediated by α-receptors in the central noradrenergic system. When the noradrenaline turnover rate was increased by single and chronic treatments with ECS and antidepressants, subsensitivity reportedly occurs only in the β-receptor (19, 20), but not in the α-, serotonin and dopamine receptors (19, 21). As stated above, suppression of muricide was not attenuated by repeated ECS treatment in this experiment.

At present, we have no clear explanation why the muricide of Raphe rats is only slightly inhibited by ECS treatment. However, we previously reported that the muricide of Raphe rats was slightly inhibited by locus coeruleus stimulation (15), and it was preferentially inhibited by chlorimipramine (11) possessing the blocking activity on serotonin uptake at synapses (17). Therefore, the mechanism of muricide inhibition by ECS and antidepressants in Raphe rats may be involved in the central serotonergic system but not in the catecholaminergic system.

The turnover rate of noradrenaline and serotonin in the brain is increased by ECS treatment (22, 23); however, it can be assumed that the noradrenergic function enhanced by ECS treatment plays an inhibitory role in the muricide of OB rats, but not of Raphe rats. Although precise mechanisms should be further clarified, the present studies demonstrated that the effect of ECS on muricide is different in each of the 4 aggression models.

References
