Effects of Adrenergic Blockers on the Inhibition of Muricide by Chronic Administration of Desipramine in Olfactory Bulbectomized Rats

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Mouse-killing behavior (muricide) of olfactory bulbectomized rat (Ob rat) is selectively suppressed by tricyclic antidepressants (1, 2) and electroconvulsive shock (ECS) (3), and this muricide suppression is potentiated by chronic treatment (4). However, brain mechanisms of this potentiation remain unknown. Muricide inhibition by single administration of desipramine (DMI) and ECS is antagonized by phenoxybenzamine, but unaffected by sotalol and propranolol (2). These facts have suggested that muricide inhibition induced by antidepressants and ECS resulted from the activation of a mechanism mediated by adrenergic alpha-receptors. The present experiment was therefore designed to investigate the effects of alpha- and beta-adrenergic blockers on muricide inhibition produced by chronic administration of DMI.

Eighty-five male Wistar King A rats supplied by the Kyushu University Institute of Experimental Animals were used. Body weights at the initiation of experiment ranged from 250 to 300 g. Before olfactory bulbectomy, all rats underwent one muricide test. Only rats not showing muricide (68 rats) were selected for the experiment. The olfactory bulbs were removed bilaterally by suction as described previously (1-4). Immediately after olfactory bulbectomy, isolated housing was commenced. Only rats displaying muricide within 7 days after olfactory bulbectomy (52 rats) were used in the following experiment. Throughout the experimental period, both the animal quarters and experimental room were maintained at a controlled temperature of 23±2°C. Illumination was provided on a 12 hr light-dark cycle (07:00-19:00, light period), and food and water were supplied ad lib.

Muricide tests were performed immediately before and 1 hr after the drug treatment, since in the previous report (2), we demonstrated that the time of the peak effect of DMI was 1 hr after administration. Muricide was assessed as positive if the rat killed a mouse within 3 min after introducing it into the rat’s home cage. The following drugs were used in this study: desipramine hydrochloride (DMI) (Pertfran, Ciba-Geigy), phenoxybenzamine hydrochloride (Dibenzyline, Tokyo Kasei), propranolol hydrochloride (Inderal, Sumitomo). All of the drugs were dissolved in physiological saline and were subcutaneously given at a volume of 0.1 ml per 100 g rat body weight. Blockers were administered simultaneously with DMI. Chronic treatments of DMI, blockers and DMI+blockers were conducted once daily at 13:00-14:00 for 21 consecutive days. On days 7 and 14 after the cessation of chronic treatment, DMI, blockers and DMI+blockers were administered again, and muricide tests were conducted.

Muricide was inhibited by about 30% 1 hr after the first administration of DMI at 10 mg/kg s.c. (Fig. 1), and this inhibitory effect was gradually increased by chronic administration. Muricide was inhibited by about 80% 1 hr after administration on day 6, and this level was maintained thereafter.

Muricide was hardly inhibited by chronic
administration of phenoxybenzamine at 10 mg/kg s.c., alone. When 10 mg/kg phenoxybenzamine was chronically administered concomitantly with DMI at 10 mg/kg s.c., DMI-induced muricide inhibition was partially antagonized (Fig. 1A).

Muricide was inhibited by single and chronic administration of propranolol at 20 mg/kg s.c., alone. Concomitant administration of 20 mg/kg propranolol with 10 mg/kg DMI produced a higher degree of muricide inhibition as with the administration of DMI alone (Fig. 1B). Moreover, remarkable muscle relaxation and ataxia were seen concurrently with muricide inhibition. Chronic administration of propranolol alone did not inhibit muricide on days 14 to 21, but propranolol could not antagonize the DMI-induced muricide inhibition. Single administration of propranolol at 10 mg/kg s.c., which caused neither muscle relaxation nor ataxia, did not antagonize the DMI-induced muricide inhibition (2).

On days 7 and 14 after the cessation of drug administration, muricide was almost completely recovered. DMI at 10 mg/kg s.c. caused muricide inhibition, and this effect was antagonized by phenoxybenzamine at 10 mg/kg s.c., but potentiated by propranolol at 20 mg/kg s.c.

Muricide in OB rats was inhibited by DMI, and this inhibition was potentiated by chronic

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**Fig. 1.** Effects of phenoxybenzamine (A) and propranolol (B) on muricide inhibition induced by the chronic administration of desipramine (DMI) in OB rats. Muricide was tested 1 hr after drug administration. Blockers were administered simultaneously with DMI. Chronic administration was conducted once daily for 21 days (between arrows). Significant difference from the values of animals tested with DMI-alone (Fisher's exact probability test). Abscissa: incidence of muricide (%). Numbers in parentheses designate the number of animals used.
treatment. This potentiation induced by chronic administration of DMI was partially reduced by phenoxybenzamine, but enhanced by propranolol. We have demonstrated that muricide inhibition induced by single treatment of DMI was antagonized by phenoxybenzamine, but unaffected by sotalol and propranolol (2). The present result and our previous report indicate that the potentiation of muricide inhibition induced by chronic administration of DMI is produced by activating the alpha receptor mediated mechanism. Phenoxybenzamine at 10 mg/kg s.c. possesses an antiserotonergic action as well, but this action may not be involved in its ability to antagonize the DMI-induced muricide inhibition, since we suggested that the brain serotonergic system was unlikely to play an important role in the muricide of OB rats (5).

Recently we reported that muricide inhibition by ECS was antagonized by phenoxybenzamine, but unaffected by sotalol (3). In the meanwhile, the “behavioral despair” model is thought to be useful for evaluating antidepressant drugs. Kitada et al. reported that the duration of immobility in forced swimming rats was reduced by antidepressants, and this reduction was antagonized by phenoxybenzamine (6). Although this model completely differs in behavior from muricide, it is worth mentioning that both models are likewise inhibited by antidepressants through the alpha-adrenergic mechanism in the brain.

These reports and our present result, therefore, supported that the muricide of OB rats would be a good animal model for the study of antidepressants, and the mechanism mediated by brain noradrenergic alpha-receptor plays an important role in muricide inhibition by single and chronic administration of DMI.

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References