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BRIEF COMMUNICATION

Effects of Idebenone, a Cerebral Metabolism Activator, on Muricidal Behavior in Rats With Raphe Lesions

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MIYAMOTO, M. AND A. NAGAOKA. *Effects of idebenone, a cerebral metabolism activator, on muricidal behavior in rats with raphe lesions.* PHARMACOL BIOCHEM BEHAV **27**(2) 351–353, 1987.—The effects of idebenone, a cerebral metabolism activator, on mouse-killing behavior (muricide) in rats with lesions of the midbrain raphe nuclei were studied. Single administration of idebenone (30 and 100 mg/kg, IP) inhibited the muricidal behavior in the raphe-lesioned rats in a dose-dependent manner. Idebenone also suppressed muricide in the olfactory bulbectomized rats, although the effect was less marked than that shown in the raphe-lesioned rats. In addition, the antimuricidal effect of idebenone was augmented with repeated administration. These results support previous findings that idebenone has an activating action on central serotonergic neurons in rats and in patients with cerebrovascular dementia, and suggest that idebenone may improve some of the depressive symptoms often observed in patients with cerebrovascular lesions and other forms of brain disturbance.

Idebenone Mouse-killing behavior (muricide) Raphe-lesioned rats Olfactory bulbectomized rats Imipramine

IDEBENONE, a cerebral metabolism activator, has been shown to exert an anti-anoxic action in mice [12] and an inhibitory action on spontaneous or cerebral ischemia-induced stroke in stroke-prone spontaneously hypertensive rats [14,15]. Idebenone ameliorates memory impairment in animal models produced in various ways, such as cerebral embolization [5,6], cerebral ischemia [24] and lesioning of the basal forebrain [10,11]. These effects of idebenone might be due to the improvement of the brain energy metabolism through stimulation of ATP formation and reduction of non-respiratory oxygen consumption in brain mitochondria [19]. Recently, it has been demonstrated neurochemically that idebenone has an accelerating effect on the turnover of serotonin (5-HT) in rats and human patients with cerebrovascular dementia [4,16]. In the present study, the effect of idebenone on muricidal behavior in both midbrain raphe-lesioned rats [3,22] and olfactory bulbectomized (OB) rats [8, 9, 21] was investigated.

METHOD

Male Wistar rats weighing 190–230 g, 7 weeks old, were anesthetized with sodium pentobarbital (50 mg/kg, IP) and fixed to a David Kopf stereotaxic apparatus. Midbrain dorsal and medial raphe lesions were respectively produced by passing an anodal DC current (1 mA, 20 sec) through an electrode implanted at an angle of 10° to the mid-sagittal plane according to the atlas of König and Klippel [7]; the coordinates of the dorsal and medial raphe nuclei were A 0.2, L 0.0, H −1.0 and A 0.2, L 0.0, H −2.5, respectively. In another experiment, male Wistar rats weighing 250–320 g, 8–9 weeks old were used, and under pentobarbital anesthesia the bilateral olfactory bulbs were removed by suction. All rats were housed in individual cages (14×27×12 cm) and given free access to food and water in a temperature- and light-controlled room (24±1°C; 12-hr light/dark cycle with lights on at 7:00 a.m.) throughout the experimental period. For experiments, only rats showing stable muricidal behavior were used from 2 weeks after lesioning.

In the muricide test, the number of rats showing a muricidal response within 5 min after introduction of a mouse into the rat home cage was determined. 6-(10-Hydroxydecyl)-2, 3,-dimethoxy-5-methyl-1,4-benzoquinone (idebenone) was suspended in 5% gum arabic solution, and imipramine hydrochloride (Tofranil®, Ciba-Geigy) was dissolved in physiological saline. Drugs were given intraperitoneally at a volume of 0.2 ml per 100 g body weight, control rats being given an equal volume of saline. In a chronic administration study,

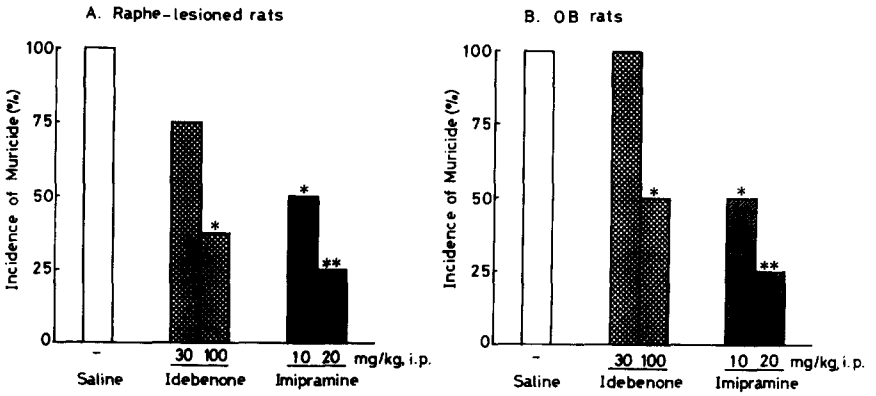

FIG. 1. Effects of idebenone and imipramine on muricide in raphe-lesioned rats (A) and olfactory bulbectomized (OB) rats (B). Eight rats were used in each group. Drugs were given 30 min before the test. *$p<0.05$, **$p<0.01$, compared with the saline control.

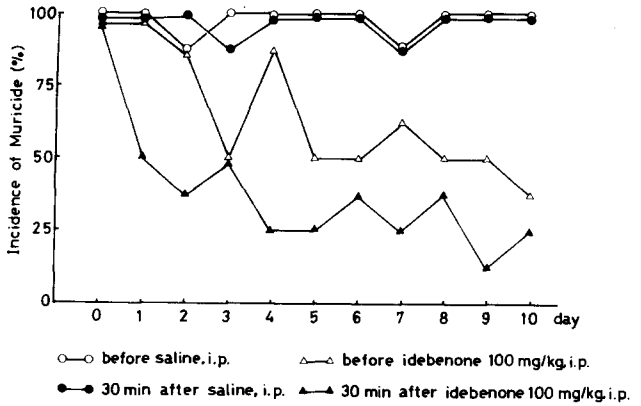

FIG. 2. Effects of chronic administration of idebenone on muricide in raphe-lesioned rats. Idebenone was given once daily for 10 days. Muricide test was performed just before and 30 min after daily administration of idebenone. Eight rats were used in each group.

idebenone was injected once daily (9:00–10:00 a.m.) for 10 consecutive days. Statistical comparisons between different treatments were made using the Fisher exact probability test.

RESULTS

Idebenone (30 and 100 mg/kg, IP) inhibited the muricidal behavior induced by the midbrain raphe lesions in a dose-dependent manner (Fig. 1A), the inhibition rates at 30 min after the administration being 25% and 62.5%, respectively. The time to peak effect was 0.5–1 hr after dosing, the effect gradually becoming attenuated thereafter and disappearing completely at 24 hr after administration. Idebenone also suppressed the muricide shown by OB rats, although the effect was less potent than that produced in the raphe-lesioned rats (Fig. 1B). On the other hand, imipramine (10 and 20 mg/kg, IP) markedly and equally inhibited both types of muricide. However, idebenone and imipramine did not significantly affect other forms of hyperemotional behavior such as attack and struggle responses of OB rats, suggesting that these drugs do not produce any significant muscle relaxation or sedative effect at the doses used in the present study.

The antimuricidal effect observed when idebenone was given repeatedly to rats with lesions of the midbrain raphe is shown in Fig. 2. The antimuricidal effect of idebenone was gradually augmented with repeated administration, the incidence of muricide being inhibited by 62.5% to 87.5% at 0.5 hr after the administration on days 4 to 10. Moreover, on days 5 to 10, about 50% of the rats did not exhibit muricide even in the test carried out just before administration.

DISCUSSION

Lesions of both the dorsal and medial raphe nuclei, which contain cell bodies projecting both ascending and descending 5-HT fibers, induce marked aggressive responses in rats, including muricide [3,22]. P-Chlorophenylalanine, an inhibitor of 5-HT synthesis, also produces aggression in rats [18]. Muricidal behavior in raphe-lesioned rats is markedly suppressed by L-5-hydroxytryptophan, and clomipramine which inhibits 5-HT uptake rather than norepinephrine [20,23]. These findings suggest that muricidal behavior in rats with raphe lesions is closely related to dysfunction of the 5-HT system in the brain. In the present study, idebenone suppressed the muricide shown by raphe-lesioned and OB rats, the effect being more potent in the former. The antimuricidal action of idebenone was augmented by chronic administration, as has been previously observed when antidepressants are given repeatedly [20]. Narumi *et al.* [16] have demonstrated that idebenone accelerates the turnover of 5-HT in the rat brain, on the basis of findings that idebenone produced an increase in 5-hydroxyindole acetic acid (5-HIAA), a metabolite of 5-HT, in various brain regions, and enhanced 5-HT release from brain slices. Thus, the antimuricidal action of idebenone may be related to activation of the 5-HT system in the brain. Furthermore, it has been shown that activation of the 5-HT system causes mood elevation in both healthy humans [2,17] and depressive patients [1,13]. In a clinical trial, chronic administration of idebenone improved the psychiatric symptoms associated with the acceleration of 5-HT turnover in patients with cerebrovascular dementia [4].

From these findings, it is suggested that idebenone may be beneficial for improving the depressive symptoms often observed in patients with cerebrovascular lesions and other forms of brain disturbance.

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