RELATIONSHIP BETWEEN 4'-TETRAHYDROCANNABINOL-INDUCED MOUSE KILLING BEHAVIOR ON THE RAT AND THE METABOLISM OF MONOAMINES IN THE BRAIN, PARTICULARLY THE Olfactory BULB

Hirohito SHIOMI, Hajime NAKAHARA, Mitsuru SEGAWA and Hiroshi TAKAGI
Department of Pharmacology, Faculty of Pharmaceutical Sciences, Kyoto University, Kyoto 606, Japan
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THC-induced muricide behavior (muricide) in rats (1). The neural mechanism underlying this abnormal behavior is not clearly understood, although some workers have shown that the metabolism of noradrenaline (NA) or serotonin (5HT) in rat brain is influenced by a single administration of THC (2, 3). Bilateral ablations of the olfactory bulb (OB) of the rat were shown to induce muricide (4), suggesting that the OB plays an important role in the manifestation of muricide. Effects of THC on the metabolism of monoamines in the OB have apparently not been reported, although there are numerous papers on THC and the metabolism of monoamines in the whole brain.

The present experiments were performed to investigate the relationship between the THC-induced muricide and the changes in the metabolism of monoamines in the various regions of rat brain, particularly the OB and the diencephalon.

Male Sprague Dawley rats, weighing 90 to 130 g, were isolated in individual cages, 18 x 25 x 15 (cm) with wire mesh wall, and food and water were withdrawn for 24 hr prior to THC administration. THC was suspended in 1% Tween 80-saline suspension and given i.p. in a dose of 20 mg/kg. In preliminary experiments, a maximal manifestation of the muricide was seen with a 20 mg/kg dose of THC. Sixty to 90 min after the THC injection, 60% of rats showed muricide behavior. In some experiments, the rats were divided...
into two groups, muricidal and non-muricidal group. Muricidal rats were defined as those which killed a mouse that was introduced in the rat home cage within 10 min. Rats were decapitated and the various regions of brain; the OB, cerebral cortex, hippocampus, striatum, diencephalon and the mesencephalon + pons + medulla oblongata, were rapidly divided. NA and normetanephrine (NM) contents of the tissue samples were fluorimetrically determined by methods described by Anton and Sayre (5), and Anton and Sayre (6), respectively. 5HT and 5-hydroxyindoleacetic acid (5HIAA) were determined by the method of Curzon and Green (7).

In preliminary experiments, an administration of THC (20 mg/kg, i.p.) resulted in a significant increase in NA contents in both the OB and diencephalon but no significant increase in the other regions of the brain in the muricidal rats as compared with those of the control rats. Therefore, further determinations of NA metabolism of THC-treated muricidal and non-muricidal rats were made in the OB and the diencephalon. As shown in Fig. 1, THC-treated muricidal rats showed a 39% increase in NA content and a 34% decrease in

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**Fig. 1.** Effects of THC on NA and NM contents in the olfactory bulb and the diencephalon of the rat. NA and NM contents were determined 60 to 90 min after the administration of THC (20 mg/kg, i.p.). The controls were isolated and food and water were withdrawn for 24 hr. Each value was determined from 7 to 9 observations. Bars indicate s.e. mean. C: control, M(+): Muricide, M(-): non-muricide. *Significant difference (p<0.05) as compared with control. *Significant difference (p<0.05) when compared between muricidal and non-muricidal group.

**Fig. 2.** Effects of THC on 5HT and 5HIAA contents in the olfactory bulb and the diencephalon of the rat. 5HT and 5HIAA contents were determined 60 to 90 min after the administration of THC (20 mg/kg, i.p.). The controls were isolated and food and water were withdrawn for 24 hr. Each value was determined from 6 to 8 observations. Bars indicate s.e. mean. C: control, M(+): muricide, M(-): non-muricide. *Significant difference (p<0.05) as compared with control. *Significant difference (p<0.05) when compared between muricidal and non-muricidal group.
NM content as compared with those of the control rats. However, significant changes were not seen in either NA or NM contents in the THC-treated non-muricidal rats. In the diencephalon, NA and NM contents were significantly increased and decreased, respectively, in both the muricidal and non-muricidal rats treated with THC but the difference between the two groups was not significant.

Significant increases in 5HT contents were seen in both the diencephalon and the hippocampus of the THC-treated muricidal rats. The 5HIAA contents in the muricidal rats were significantly increased in both the diencephalon and the OB as compared with the control. With regard to the OB and the diencephalon, a further investigation on changes in 5HT metabolism between muricidal and non-muricidal rats treated with THC was carried out. As shown in Fig. 2, a marked decrease in 5HIAA content was observed in muricidal rats and there was an evident decrease in both 5HT and 5HIAA contents in the non-muricidal rats. In the diencephalon, a significant increase in 5HT content of muricidal rats and a significant increase in 5HIAA contents of both muricidal and non-muricidal rats were observed. However, when the muricidal and non-muricidal rats were compared, the difference was significant only regarding the 5HT level of the OB.

These results indicate that there is a distinct difference in the monoamine metabolism between muricidal and non-muricidal rats treated with THC as observed in the noradrenergic system of the OB. In contrast, the noradrenergic system of the diencephalon and the serotonergic systems of both the OB and the diencephalon showed essentially no difference in metabolism between muricidal and non-muricidal rats. Effects of a single administration of THC on the metabolism of catecholamine in the brain have been extensively studied, but the results were acceleration (2, 8), retardation (9), or no influence (10) on the turnover of catecholamine in the rat brain. In addition, Holtzman et al. (11) reported the bidirectional action of THC, according to the doses used. The content of NM can be taken as an index of the activity of the noradrenergic neurons, since NM is considered to be formed by catechol-O-methyl transferase from NA after its neuronal release (12). Therefore, the present results indicate that THC produces a selective decrease in the activity of noradrenergic system in the OB and the diencephalon of the muricidal rats and that the effect is closely related to the induction of the muricide. The decrease in the activity of noradrenergic system in the OB may thus play an important role in muricide, since noradrenergic neuronal activity in the OB of non-muricidal rats was not decreased.

With regard to the effect of THC on the serotonergic system, decrease in the 5HIAA content in the OB and increase in the 5HIAA content in the diencephalon were observed in both the muricidal and non-muricidal rats. Changes in the 5HT metabolism in the OB suggest that THC produces inhibition of the synthesis and release of 5HT as this compound does not depress monoamine oxidase activity (3). Segawa et al. (13, 14) reported that increase in brain 5HIAA content after THC administration is due to a blockade of elimination of 5HIAA from the brain, that is, a probenecid-like effect and that THC actually decreases the central serotonergic neuron activity. Likewise, the present data on the diencephalon may indicate a similar phenomenon. Regarding the serotonergic system, there was no
difference in the 5HIAA content between the muricidal and non-muricidal rats, thereby suggesting that the serotonergic systems in these regions do not play an important role in the generation of the muricide. However, this does not rule out the possibility that 5HT does play a role in other brain regions, in the generation of the muricide (15). Since THC-induced muricide can be inhibited by pretreatment with 5HTP or DOPA (Ueki et al., personal communication), the generation of the muricide may be due to both the general decrease in the central 5HT neuron activity and the selective decrease in the NA neuron activity in the OB and diencephalon, particularly in the former.

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