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Anti-Muricide Mechanisms of Chlorpromazine and Imipramine in OB Rats: Adrenoceptors and Hypothalamic Functions

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HARA, C., S. WATANABE AND S. UEKI. *Anti-muricide mechanisms of chlorpromazine and imipramine in OB rats: Adrenoceptors and hypothalamic functions.* PHARMACOL BIOCHEM BEHAV 21(2) 267–272, 1984.—Chlorpromazine (CPZ) microinjected into the posterior part of the lateral hypothalamus (p-LH) and the lateral preoptic area (l-POA) of OB rats shows anti-muricide and cataleptogenic effects as well as a drowsy pattern in cortical EEG, while imipramine (IMP) injected into p-LH shows anti-muricide and cataleptogenic effects without change of cortical EEG. The present study examined the effects of drugs injected into p-LH and l-POA on muricide, catalepsy and cortical and limbic EEG. CPZ (20, 50 μg) suppressed muricide and induced catalepsy and an EEG drowsy pattern in the two regions. The effects of CPZ in p-LH were similar to those of propranolol (PRO). In l-POA, the anti-muricide effect of CPZ was similar to that of phenoxybenzamine, whereas the cataleptogenic and EEG effects were similar to those of PRO. IMP (10, 20 μg) in p-LH showed anti-muricide and cataleptogenic effects and induced a slight drowsy pattern in limbic EEG. The effects were similar to those of atropine. Lidocaine did not show any effects in the two regions. The cataleptogenic effects of CPZ and IMP did not appear related with the anti-muricide effects. The results suggest that the anti-muricide effect of CPZ in the hypothalamus depends on its adrenoceptor blockage, while that of IMP relates to its anticholinergic effect. In addition, β-receptors in the hypothalamus appear related to the arousal system and dopaminergic functions.

Adrenoceptors Psychotropic drugs Atropine Muricide Catalepsy EEG Hypothalamus Limbic area Microinjection

THE mode and site of actions of psychotropic drugs in the brain remain unclear in spite of the development of biochemical tools. One of the reasons is that the interactions between the drugs and physiological functions of the brain are not well understood since; the activities of drugs have been evaluated primarily by observing animal behavior.

To elucidate the site and mode of actions of psychotropic drugs in the brain, we have previously examined the effects of the drugs on muricide of olfactory bulbectomized rats (OB rats) by microinjecting the drugs into the hypothalamus [8]. The results were as follows: (1) Inhibition of muricide was found when chlorpromazine (CPZ) was injected into the lateral preoptic area (l-POA) and the posterior part of the lateral hypothalamus (p-LH), and by chlordiazepoxide (CDP) when injected in the mammillary body. Inhibition of muricide was observed following injection of antidepressants (amitriptyline, imipramine) in the p-LH. (2) The effects of CPZ and CDP were based on their sedative properties (e.g., EEG drowsiness). (3) The effects of the antidepressants appeared related to EEG and behavioral arousal. Thus, the results suggested that anti-muricide actions of psychotropic drugs are related to the physiolocigal functions in the hypothalamus. The pharmacological mechanisms, however, remain unclear.

It has been suggested that the noradrenergic (NE) system in the brain plays an inhibitory role in the occurrence of muricide in OB rats [17,31]. The distribution of α-adrenergic, β-adrenergic and dopaminergic (DA) receptors in discrete regions of the hypothalamus have been analyzed by radiologic binding assays [10]. For aggressive behavior, however, the interaction between the location of receptors and physiological functions of the hypothalamus is unknown.

Therefore, the pharmacological mechanisms for the

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anti-muricide actions of CPZ and imipramine (IMP) in the hypothalamus were examined with NE receptor antagonists in the present study.

METHOD

Animals

Male Wistar-King A strain rats (200–250 g) from the Kyushu University Institute of Laboratory Animals were used as subjects. The animals were housed in groups of 4 animals each for at least 1 week prior to olfactory bulbectomy. They were maintained in an air conditioned room with 12:12 LD cycle (lights on 07:00–19:00) and given food and water ad lib. On the day before olfactory bulbectomy and continuing throughout the experimental period, the animals were individually housed in cages (23×20×20 cm).

Procedure

After adaptation for 24 hr to the individual cage, a muricide test was performed by putting a white male mouse into the cage. Only animals which did not show muricide within 30 min after introduction were selected and subjected to olfactory bulbectomy. The olfactory bulbs of these animals were bilaterally removed by suctioning under pentobarbital anesthesia (45 mg/kg, IP). The animals which showed muricide within 2 weeks after the olfactory bulbectomy and killed a mouse within 1 min were subjected to the surgery for the EEG electrode and guide-cannula implantations. Each rat was chronically implanted three electrodes and two guide-cannulas into the brain under pentobarbital anesthesia. The bipolar electrode for EEG recording was connected to a twisted pair of stainless steel wires (0.2 mm in diameter) and insulated except for the terminal 0.5 mm. The electrode was implanted into the frontal cortex, dorsal hippocampus (A: 3.4, L: 2.2, H: +2.5) and amygdaloid complex (A: 4.8, L: 3.5, H: −3.5) according to the stereotaxic coordinates of the de Groot brain atlas [5]. Each electrode was connected to the pins of a small socket.

The guide-cannula was constructed of a stainless steel cannula of 0.7 mm in diameter and 15 mm in total length. The cannula was bilaterally implanted into the lateral preoptic area (l-POA, A: 7.6, L: 2.5, H: −1.3) and the posterior part of the lateral hypothalamus (p-LH, A: 5.0, L: 1.3, H: −2.0) according to the atlas. The electrodes, cannulas and socket were fixed to the skull with dental cement together with two screws driven into the skull. EEG was recorded with a polygraph (NIPPON KODEN).

For five days after the implantation surgery, the animals were handled daily in the same manner as the manipulation during the drug injection. Ten days after the surgery, a muricide test of 1 min duration was performed again. Animals which showed muricide within 1 min were selected and used in the drug injection experiment. The drug test was performed in the observation box (20×20×25 cm) which was placed in a sealed box. Behavioral observations were made through the window of the box. Animals were adapted to the observation box for at least 1 hr.

In the drug test, all drug solutions were bilaterally injected through an injection cannula with an injection volume of 1 μl over a period of 1 min. In the case of repeating drug injection in the same animal, the interval between injections was more than 2 days. On the experimental day, the animals were bilaterally injected with saline 1 hr before the drug test. At 3, 5, 10 and 15 min after saline treatment, the muricide test was repeated. Only animals in which muricide was not inhibited by saline were used in the drug test. The procedure for the drug test was the same as that for the saline treatment. EEG was successively recorded after drug treatment. When muricide was inhibited within 15 min after the drug injection, muricide test and EEG recording were successively performed at intervals of 30 min until the reappearance of muricide.

Catalepsy was tested just after each muricide test. The presence of catalepsy was determined if animals retained for 30 sec the imposed abnormal position placing both frontal limbs over the horizontal bar. Because of the possibility of the disruption of the effectiveness of the drugs on muricide by repeating drug injection, the drugs having a positive effect on muricide were occasionally retested in the same animal during the experimental period. When the drugs ceased to inhibit muricide, the animals were withdrawn from the experiment. Consequently, each animal was not always administered all of the drugs used in this study.

At the termination of the experiment, the locations of the cannulas and electrode tips were verified histologically. The data from animals in which the cannula was not located at appropriate regions were discarded.

Drugs

Drugs used in the present study and their abbreviations were as follows: (1) chlorpromazine hydrochloride (CPZ), (2) imipramine hydrochloride (IMP), (3) phenoxybenzamine hydrochloride (PHE), (4) dl-propranolol hydrochloride (PRO), (5) atropine sulfate (At) and (6) 3% lidocaine hydrochloride (LID). Doses used in the present study were determined in previous reports [8,15]. Doses were expressed in quantity in salt form. The drugs were dissolved in distilled water, and the proper quantity of sodium chloride was added to make an isotonic solution. The drugs were treated in random order.

Data Analysis

The statistical evaluation was based on the Fisher exact test [22] to compare between drug and saline treated animals.

RESULTS

Table 1 shows the incidence of rats showing muricide suppression, catalepsy and drowsiness in the cortical, amygdaloid and hippocampal EEG when drugs were injected into p-LH and l-POA. EEG drowsiness in the cortex and amygdala were judged by appearance of high-voltage slow waves, and that in the hippocampus was done by desynchronization of hippocampal θ-waves. In p-LH, muricide was inhibited by CPZ (20, 50 μg), IMP (10, 20 μg), PRO (20 μg) and At (10 μg), while in l-POA it was inhibited by CPZ (20, 50 μg) and PHE (10 μg).

In either p-LH or l-POA, inhibition of muricide by CPZ was accompanied by catalepsy and drowsiness in the cortical EEG. When muricide was inhibited by CPZ, the rats became sedated without ataxia as reported by the preceding study [8]. The anti-muricide effect of CPZ appeared to be dose-dependent, but the cataleptogenic effect did not. A typical EEG record from a rat with 20 μg of CPZ in p-LH is shown in Fig. 1. The duration of muricide suppression by CPZ was comparable to that of drowsiness in the cortical EEG, but not of catalepsy. In the effect on the limbic EEG, there was a difference between 20 μg and 50 μg. In l-POA, a drowsy pattern of the hippocampal EEG was elicited by the two

TABLE 1

INCIDENCE OF RATS SHOWING MURICIDE SUPPRESSION, CATALEPSY AND EEG DROWSINESS

Drugs	Dose (μg)	Anti-muricide effect	Cataleptogenic effect	EEG drowsiness FC	AM	HP
		The posterior part of the lateral hypothalamus				
saline		0/8	0/8	0/8	0/8	0/8
chlorpromazine	50	7/7‡	6/7‡	5/7†	0/7	5/7†
	20	8/11†	9/11‡	8/11†	6/11†	4/11
imipramine	20	5/5‡	3/5*	1/5	2/5	3/5*
	10	5/8*	4/8*	1/8	3/8	3/8
phenoxybenzamine	10	2/8	0/8	1/8	0/8	1/8
propranolol	20	12/13‡	11/13‡	9/13†	5/13	4/13
atropine	10	4/5†	1/5	1/5	2/5	3/5*
	5	1/3	0/3	0/3	1/3	1/3
3% lidocaine		0/9	1/9	3/9	0/9	0/9
		The lateral preoptic area				
saline		0/7	0/7	0/7	0/7	0/7
chlorpromazine	50	6/7†	7/7‡	5/7†	4/7*	4/7*
	20	3/6*	5/6†	3/6*	1/6	3/6*
phenoxybenzamine	10	3/5*	0/5	0/5	0/5	0/5
propranolol	20	2/7	5/7†	4/7*	1/7	5/7†
3% lidocaine		2/6	0/6	2/6	1/6	2/6

*$p<0.05$, †$p<0.01$, ‡$p<0.001$: significantly different from saline (Fisher exact probability test, one-tailed).

EEG drowsiness of cortical and amygdaloid EEG were judged by high voltage slow waves and/or spindle burst, and that of hippocampal EEG was done by desynchronization of hippocampal theta waves. FC: frontal cortex, AM: amygdala, HP: hippocampus.

doses, and that of the amygdaloid EEG was only by the 50 μg dose (Table 1). In p-LH, 20 μg induced drowsiness of the amygdaloid EEG, and 50 μg showed the arousal pattern (Table 1). In the hippocampal EEG, 50 μg, but not 20 μg, induced drowsiness (Table 1).

The anti-muricide effect of IMP was examined in p-LH. IMP (10, 20 μg) inhibited muricide, and induced catalepsy and EEG arousal (Table 1). Twenty μg of IMP induced a drowsy pattern in only the hippocampal EEG. The anti-muricide effect, but not the cataleptogenic effect, was dose-dependent. The anti-muricide effect did not always accompany the cataleptogenic effect. Rather, the anti-muricide effect was coincided with EEG arousal. When muricide was inhibited by IMP, the rats exhibited exploratory behavior (e.g., rearing, sniffing and locomotion).

PHE, an α-adrenoceptor antagonist, inhibited muricide in only l-POA (Table 1). The inhibition was not accompanied by catalepsy and EEG drowsiness. In contrast to PHE, PRO, a β-adrenoceptor antagonist, inhibited muricide in only p-LH treatments (Table 1). The effect was accompanied by catalepsy and drowsiness in the crotical EEG similar to CPZ. The limbic EEG, however, did not show drowsy pattern with PRO treatment. When injected into l-POA, PRO did not inhibit muricide in spite of inducing a drowsy pattern in the cortical and hippocampal EEG. A typical EEG record from a rat injected with 20 μg of PRO into p-LH is shown in Fig. 2. Muricide suppression, catalepsy and a drowsy pattern in the cortical EEG were found at 5 and 10 min after the treatment simultaneously.

The effect of At on muricide was examined in p-LH. Ten μg of At inhibited muricide without inducing catalepsy and EEG change with the exception of the hippocampal EEG (Table 1). The hippocampal EEG showed drowsy pattern at that dosage. Rats, for which muricide was inhibited by At, displayed the exploratory behavior similar to IMP.

Table 2 illustrates comparison between effects of CPZ and IMP and those of other drugs on muricide and catalepsy in the same animals. In p-LH treatments, rats showing muricide suppression and catalepsy by either CPZ or PRO were the same (Rat No. C-31, C-50). Muricide suppression by IMP and by At were found in the same animals (Rat No. C-30, C-31, C-50, C-52). In l-POA, muricide suppression by CPZ and that by PHE were found in the same animals (Rat No. C-19, C-22, C-53, C-56). Catalepsy by CPZ and that by PRO were found in the same animals (Rat No. C-19, C-22, C-53).

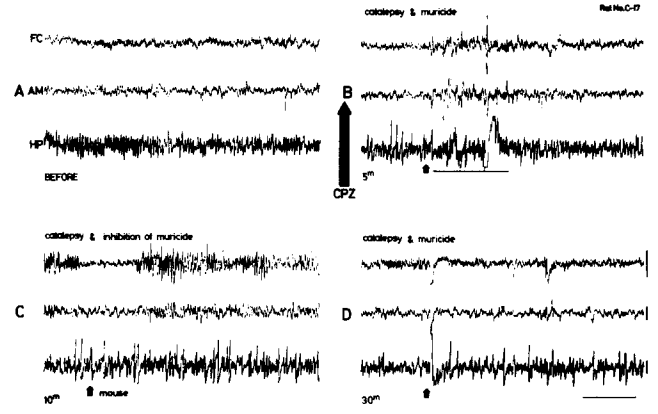

FIG. 1. Effects of chlorpromazine (CPZ, 20 μg) injected into the posterior part of the lateral hypothalamus (p-LH) on the cortical, amygdaloid and hippocampal EEG. A: EEG just after muricide in the saline treatment. B: EEG at 5 min after the CPZ treatment. The rat revealed catalepsy, though muricide was not inhibited. In the underlined-period, the rat killed a mouse without exerting EEG drowsiness. C: EEG at 10 min after the treatment. EEG of the frontal cortex and hippocampus showed drowsiness. The rat revealed both catalepsy and loss of muricide. D: EEG just after muricide at 30 min after the treatment when muricide reappeared. In spite of reappearance of muricide, the rat revealed catalepsy. FC: EEG from the frontal cortex. AM:EEG from the amygdaloid complex. Vertical bar, 200 μV; horizontal bar, 3 sec.

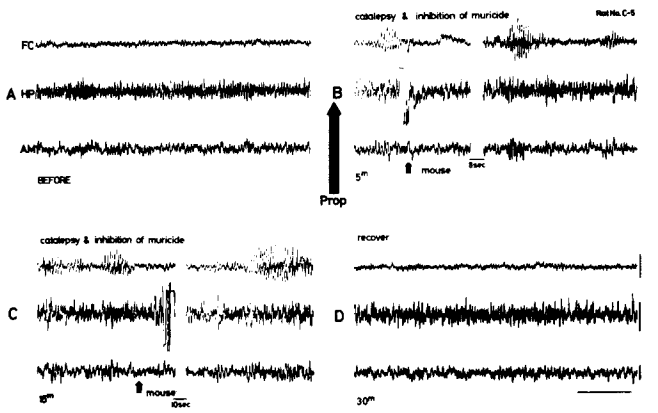

FIG. 2. Effect of propranolol (Prop, 20 μg) injected into p-LH on EEG. A: EEG just after muricide in the saline treatment. B and C: EEG at 5 min and 15 min after the Prop treatment. EEG showed the drowsy pattern. The rat revealed catalepsy and loss of muricide. D: EEG just after muricide at 30 min after the treatment when muricide reappeared. See Fig. 1 legend for abbreviations.

Inhibition of muricide by LID was found in l-POA at only 3 min after the treatment (Rat No. C-19).

DISCUSSION

The purpose of the present study is to elucidate pharmacological and physiological mechanisms on anti-muricide actions of CPZ and IMP in the hypothalamus of OB rats. The present study showed that CPZ in l-POA and p-LH simultaneously elicited inhibition of muricide, catalepsy and drowsiness of the cortical and limbic EEG, whereas IMP in p-LH induced inhibition of muricide and catalepsy without showing drowsiness of the cortical EEG (Table 1). The results were in agreement with those in a preceding study [8].

Regarding the pharmacological mechanism of anti-muricide action of CPZ, the interesting observation is that PHE, but not PRO, inhibited muricide in l-POA, while PRO, but not PHE, did it in p-LH (Table 1). Various types of aggressive reaction are suppressed by adrenergic receptor antagonists such as PHE, phentolamine and PRO [1, 13, 14]. The mode and site of actions of the antagonists, however, are unclear. On the other hand, l-POA and p-LH are known to be implicated in predatory aggression [3, 9, 18, 23, 29]. Recently, Leibowitz *et al.* [10] reported the distribution of α-adrenergic, β-adrenergic and DA receptors in discrete hypothalamic areas of rats, though they did not examine l-POA. In the present study, the cannula tips in p-LH were located along the medial forebrain bundle which is regarded as a β-adrenergic radioligand binding site by Leibowitz *et al.* [10]. Therefore, muricide of OB rats may relate to α-receptors in the l-POA, and to β-receptors in the p-LH. On the other hand, inhibition of muricide by PRO in the p-LH accompanied catalepsy and EEG drowsiness. The onset and duration of the inhibition was in accordance with those of EEG drowsiness. In the l-POA, PRO elicited catalepsy and EEG drowsiness without inhibiting muricide, whereas PHE inhibited muricide without inducing catalepsy and EEG drowsiness. Therefore, the results of the present study may suggest that inhibition of muricide by PRO attributes to its sedative property, while the effect by PHE is selective on muricide.

On the other hand, CPZ is known to have an α-adrenergic receptor blocking action, but not a β-adrenergic blocking action [16]. However, a central action of CPZ was suggested to relate to α-receptors as well as β-receptors [4]. Moreover, a number of studies have reported a central action of CPZ closely related to the β-adrenergic blocking action [28]. In the present study, a mode of anti-muricide action of CPZ in p-LH was the same as that of PRO (Table 1). Moreover, results of rats showing inhibition of muricide and catalepsy by CPZ and rats showing inhibition by PRO were the same (Table 2). On the other hand, PRO is known to possess sedative and anticonvulsant properties [11,14]. The effects are considered to be associated with β_2-receptor blockade or the membrane stabilizing effect in the brain [11]. A common pharmacological property of both CPZ and PRO is the membrane stabilizing effect and the suppressing effect on DA neurons [2, 16, 20]. However, since LID did not show any effects in the present study, the membrane stabilizing effect is not responsible for the anti-muricide factors. On the other hand, PRO elicited catalepsy in both l-POA and p-LH. This supports the hypothesis of a suppressing effect of PRO on DA functions. However, the onset and duration of catalepsy were different from those of anti-muricide action. Therefore, the anti-muricide action of CPZ in p-LH is considered to be based on β-adrenergic receptor blockade.

On the other hand, inhibition of muricide by CPZ in l-POA is considered to depend on α-adrenergic receptor blockade, because the results of rats showing muricide suppression by CPZ and rats showing suppression by PHE are the same (Table 2). The effects of CPZ on catalepsy and EEG were similar to PRO. The onset and duration of EEG drowsiness were different from those of catalepsy, but not

TABLE 2

COMPARISON BETWEEN DRUG EFFECTS WITHIN THE SAME RATS

		Drugs (μg)											
		CPZ (50)		PHE (10)		PRO (20)		3% LID		IMP (29)		At (10)	
Position	Rat No.	AM	CA	AM	CA	AM	CA	AM	CA	AM	CA	AM	CA
p-LH	C-30	−	−	−	−	−	−	−	−	+	−	+	−
	C-31	+	+	−	−	+	+	−	−	+	+	+	−
	C-50	+	+	−	−	+	+	−	−	+	−	+	−
	C-52	+	−	−	−	+	−	−	−	+	−	+	−
l-POA	C-19	+	+	+	−	−	+	+*	−				
	C-22	+	+	+	−	−	+	−	−				
	C-53	−	+	−	−	−	+	−	−				
	C-56	+	+	+	−	+	−	−	−				

*Muricide-suppression was found only at 3 min after the drug treatment. +: positive, −: negative.

Abbreviations: AM: anti-muricide effect, CA: cataleptogenic effect, CPZ: chlorpromazine, PHE: phenoxybenzamine, PRO: propranolol, LID: lidocaine, IMP: imipramine, At: atropine, p-LH: the posterior part of the lateral hypothalamus, l-POA: the lateral preoptic area.

muricide suppression. Therefore, it is assumed that the cataleptogenic effect of CPZ as well as PRO contributes to the DA-suppressing effect, and the EEG effect of CPZ is based on the β-adrenergic receptor blockade. Thus, anti-muricide action of CPZ is considered to be based on the two mechanisms as follows: (1) a selective inhibition by α-receptor blockade, and (2) a sedative property by β-receptor blockade.

Regarding the mechanism of anti-muricide action of IMP, the action in p-LH was accompanied by catalepsy, arousal pattern of the cortical and amygdaloid EEG, and slight drowsy pattern of the hippocampal EEG. Although the cataleptogenic effect appears to depend on its DA receptor blocking action [7], the effect is separate from the anti-muricide factors, because inhibition of muricide by IMP was not always accompanied by catalepsy (Table 2). The effects of IMP on muricide and EEG were similar to those of At injected into p-LH (Tables 1 and 2). On the other hand, the presence of a cholinoceptive component activating muricide in the hypothalamus is known [3,23]. Therefore, the anti-muricide action of IMP in p-LH may attribute to its anticholinergic property. Regarding the physiological mechanism, IMP as well as At, both in the peripheral and the intrahypothalamic administrations, elicited hyperactivity when muricide was inhibited as noticed in the preceding study [8]. On the other hand, anticholinergic drugs such as scopolamine and At are known to elicit hyperactivity [12, 19, 21]. Accordingly, the hyperactivity also appears to support the anticholinergic mechanism of IMP on muricide. Therefore, anti-muricide actions of IMP and At in p-LH may be based on hyperactivity resulting from their anticholinergic property. In the present study, IMP and At induced drowsiness of the hippocampal EEG when hyperactivity was elicited. On the other hand, hippocampal lesions increased spontaneous activity [24]. The critical site of anticholinergic drugs on the conditioned avoidance response has been suggested to be the subcortical area [12]. Therefore, if inhibition of muricide by IMP attributes to hyperactivity resulting from its anticholinergic property, the physiological mechanism will depend on the suppressing effect of the hypothalamo-hippocampal activating system by its anticholinergic effect as suggested by Dubinsky and Goldberg [6]. The mechanism will lead to a deficit of goal-oriented behavior or acute amnesia as suggested by Meyers *et al.* [12].

However, several reports [17, 25, 26, 31] have suggested that muricide of OB rats was regulated by NE neurons in the amygdala. Tricyclic antidepressants inhibited muricide dose-dependently when injected into the amygdala [27]. Moreover, the effect of antidepressants on muricide has been suggested to depend on their NE uptake blocking action [30]. Therefore, anti-muricide action of antidepressants administered peripherally appears to be implicated in NE uptake blockade in the amygdala. However, the reports described above do not inform induction of hyperactivity by the drugs. On the other hand, Yoshimura [32] reported specific inhibition of scopolamine (4, 8 mg/kg, IP) on muricide of OB rats, though there was no difference between killer and non-killer rats in choline acetyl transferase and acetylcholine esterase activities of the discrete brain areas. Scopolamine at doses over 1 mg/kg, IP and SC, is known to depress spontaneous activity and to elicit EEG drowsiness, and, moreover, to inhibit even food and water intakes [12,19]. At also induces the same effects as scopolamine, though there is some difference in potency between the two drugs [19]. Accordingly, there is a question about the selectivity of scopolamine on muricide in the Yoshimura's study because of using extremely large doses. His data may indicate that muricide of OB rats does not relate to a cholinergic component of the brain. On the other hand, the preceding study [8] showed that there was the difference of EEG effect between IMP and At in the peripheral administration. That is, At, but not IMP, elicited drowsiness of the cortical EEG. The event may be attributed to difference of pharmacological property between the two drugs. Thus, it remains unclear whether the specificity of antidepressants on muricide of OB rats is based on their NE uptake blocking effect or on their anticholinergic effect. To explain the specificity on muricide, further studies elucidating the interaction between the anti-muricide action and the effect on physiological functions in the brain are needed for antidepressants.

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