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Lack of Evidence for the Involvement of Catecholaminergic Mechanisms in the Behavioral Anti-Methamphetamine Effect of L-Histidine in the Mouse

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ITOH, Y , R OISHI, M NISHIBORI, K SAEKI, K FURUNO, T FUKUDA AND Y ARAKI *Lack of evidence for the involvement of catecholaminergic mechanisms in the behavioral anti-methamphetamine effect of L-histidine in the mouse* PHARMACOL BIOCHEM BEHAV **24**(3) 571–574, 1986 —The effects of L-histidine (HIS) on the hypermotility and the changes in brain monoamine dynamics induced by methamphetamine (MAMP) were examined in mice HIS (1000 mg/kg) completely inhibited the hypermotility induced by MAMP (1 mg/kg) MAMP (1 mg/kg) significantly increased the dopamine level and decreased the 3,4-dihydroxyphenylacetic acid level MAMP (5 and 10 mg/kg) also produced changes in the levels of noradrenaline, serotonin and their metabolites HIS administered alone caused no significant changes in the levels of these amines and metabolites, nor did it affect MAMP-induced alterations in monoamine dynamics These results suggest that catecholaminergic mechanisms are not involved in the behavioral anti-MAMP action of HIS

L-histidine Methamphetamine Motor activity Dopamine Noradrenaline Serotonin HPLC Electrochemical detection

HISTAMINE (HA) acts as a neurotransmitter in the brain [4, 19, 21], yet details on the physiologically related functions are not well understood We reported that L-histidine (HIS) inhibits the methamphetamine (MAMP)-induced increase in locomotor activity measured by an open-field apparatus in mice and this effect seems to be mediated by the activation of histaminergic neurons [6] However, the significance of the histaminergic system in the control of behavior, including those induced by MAMP, remains obscure Joshi *et al* [7] observed that HIS (850 and 1000 mg/kg, IP) antagonized the MAMP (5–7 mg/kg, IP)-induced but not the apomorphine (0 5–1 5 mg/kg, SC)-induced stereotypy in mice and suggested that HIS inhibits the dopamine (DA) release enhanced by MAMP Although behavioral effects of MAMP such as hypermotility and stereotypy are mainly due to its effect on the dopaminergic system [3,11], noradrenaline (NA) [13] and serotonin (5-HT) [2] neurons are also involved in the behavioral actions of MAMP There is apparently no documentation on the influence of the histaminergic system on MAMP-induced alterations in the central monoamine dynamics Since we could confirm, using an automated activity meter, the inhibitory effect of HIS on the MAMP-induced hypermotility previously observed in an open-field apparatus, the influence of HIS at a dose effective in the behavioral anti-MAMP action on the MAMP-induced changes in brain monoamine dynamics was investigated For this purpose, we simultaneously determined the levels of DA, NA, 5-HT and their metabolites, in the same brain samples, using high performance liquid chromatography with electrochemical detection (HPLC-ED)

METHOD

Subjects

Male dd-Y mice weighing 30–35 g (Shizuoka Laboratory Animal Center, Hamamatsu, Japan) were housed in an environmentally controlled room maintained at 22±1°C Animals were given food and water ad lib All experiments were performed between 10 00 a m –2 00 p m

Drugs

L-Histidine hydrochloride (HIS, Nakarai Chemicals Co , Kyoto, Japan) and methamphetamine hydrochloride (MAMP, Dainippon Pharmaceutical Co , Osaka, Japan) were dissolved in saline HIS (1000 mg/kg, IP) or saline was administered 1 hr before the IP injection of MAMP or saline

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All drugs were injected in a volume of 0 1 ml/10 g body weight

Locomotor Activity

Locomotor Activity was measured for 5 min before and 30, 60 and 90 min after MAMP administration, using a Natsumex activity meter (KN-70H, Natsume Seisakusho Co , Tokyo, Japan)

Assay of Brain Momoamines and Their Metabolites

Mice were decapitated and the whole brain excluding the cerebellum was removed and immediately homogenized with 3 ml of 0 4 N perchloric acid containing 0 1% L-cysteine and 300 ng of epinine as an internal standard After centrifugation, a 20-μl aliquot of the supernatant was injected onto HPLC for the determination of DA, 3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-HT and 5-hydroxyindoleacetic acid (5-HIAA), according to the method of Magnussen *et al* [10] with a slight modification For the determination of NA and its metabolites, we used the method of Oishi *et al* [15] Briefly, NA in the remaining supernatant was adsorbed on 50 mg of alumina at pH 8 3, and eluted with 0 5 ml of 1 M formic acid after washing the alumina with redistilled water After centrifugation, a 20-μl aliquot was injected onto HPLC To the residual solution after alumina adsorption were added 4 g of K_2HPO_4 and 0 5 ml of 1 M borate buffer, pH 10 5 Normetanephrine (NM) and 3-methoxy-4-hydroxyphenyl glycol (MHPG) were twice extracted by shaking with 9 ml of ethylacetate The ethylacetate layer was evaporated and the residue was dissolved in 0 5 ml of 1 M formic acid A 100-μl aliquot was injected onto HPLC The HPLC-ED system consisted of a pump (L-4000S, Yanagimoto Mfg Co , Kyoto, Japan), a Yanapack ODS-H reversed phase column (250×4 mm, i d , 5 μm) and a thin layer voltammetric detector (VMD-101)

The concentration of NA and its metabolites were determined by comparing the peak heights from the brain samples with those from the standard mixtures extracted using the same procedure The recovery of the authentic NA, MHPG and NM was 85, 94 and 63%, respectively Other metabolites of NA were difficult to separate from interfering substances in brain samples using the present condition

Statistics

Data analyses were performed by the two-tailed Student's *t*-test for the biochemical data and Mann-Whitney U-test for the behavioral data

RESULTS

MAMP (1 mg/kg) significantly increased locomotor activity and its maximum effect was observed 60 min after the injection (Fig 1) HIS (1000 mg/kg) alone did not show any influence on the spontaneous locomotor activity, however, HIS completely inhibited the MAMP-induced hypermotility

As shown in Fig 2, MAMP (1 mg/kg) significantly increased the DA level and the maximal effect was observed 60 min after the MAMP injection The DOPAC and HVA levels were lowered by MAMP The decrease in the DOPAC level reached the maximum 30 min after, significant changes being observed up to 120 min after The decrease in the HVA level was significant only 120 min after MAMP had no significant effect on the levels of NA, 5-HT and their metabolites at any

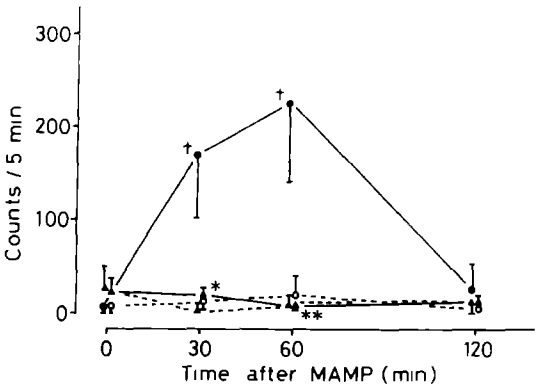

FIG 1 Effect of L-histidine (HIS) on methamphetamine (MAMP)-induced hypermotility in mice HIS (1000 mg/kg) was administered IP 1 hr before the MAMP injection (1 mg/kg, IP) Each point represents the mean±S E M of 6 animals ○——○ saline—saline treated group, △——△ HIS—saline treated group, ●——● saline—MAMP treated group, ▲——▲ HIS—MAMP treated group Data were analyzed by Mann-Whitney U-test †$p<0$ 05 as compared with saline—saline treated group *$p<0$ 05 **$p<0$ 01 as compared with saline—MAMP treated group

times tested No significant differences were observed in the levels of all these substances between the groups pretreated with HIS (1000 mg/kg) and saline HIS (1000 mg/kg) administered alone caused no alterations in the steady-state levels of these amines and metabolites, nor did it have any influence on the MAMP-induced changes in DA dynamics MAMP at higher doses (5 and 10 mg/kg) produced changes in the dynamics of not only DA but also NA and 5-HT (Fig 3) While the DA level was still elevated at both MAMP doses, the DOPAC level decreased dose-dependently The HVA level increased at 10 mg/kg of MAMP The NA level decreased and NM level increased at these MAMP doses There were no significant changes in the MHPG and 5-HT levels The 5-HIAA level decreased dose-dependently The pretreatment with HIS had no influence on the changes in monoamine dynamics induced by higher doses of MAMP, except for those in the 5-HIAA level

DISCUSSION

As for the effect of MAMP on DA metabolism, the present findings are generally consistent with those obtained by Kuzenski [8], in the rat striatum MAMP elevated the DA level and this may be due to an increase in the DA synthesis, since amphetamine is considered to release DA from an unbound cytoplasmic pool [8] and which regulates the DA synthesis through a feedback inhibition on tyrosine hydroxylase The dose-dependent decrease in the DOPAC level might be associated with blockade of the presynaptic neuronal re-uptake of DA and/or monoamine oxidase inhibition However, the latter possibility seems unlikely, since the HVA level increased at 10 mg/kg of MAMP, in contrast to the DOPAC depletion Compared with doses of MAMP effective in altering DA metabolism, larger doses of this compound are required to produce changes in the NA metabolism This suggests that the dopaminergic system is more sensitive to the MAMP action than is the noradrenergic system The NA level decreased after the administration of 5 and 10 mg/kg of MAMP, in good agreement with the results of other investigators [14,18] Although amphetamine re-

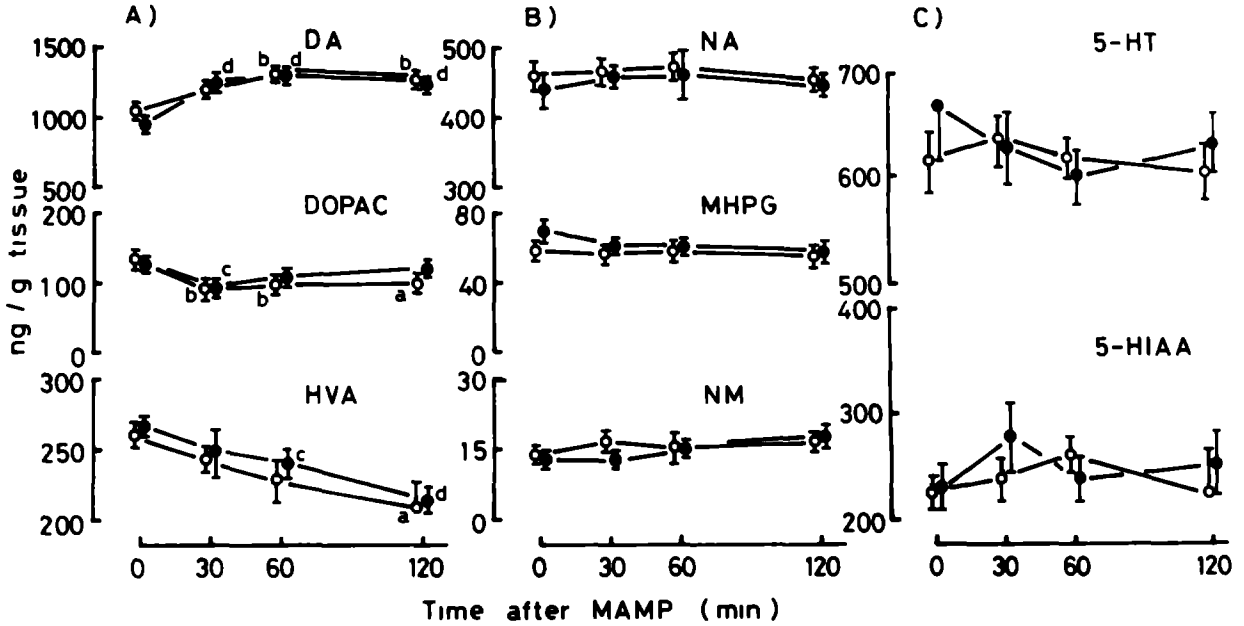

FIG 2 Time course of the effect of MAMP on dynamics of brain (A) dopamine (DA), (B) noradrenaline (NA) and (C) serotonin (5-HT) in histidine (HIS) treated mice HIS (1000 mg/kg) was administered IP 1 hr before the IP injection of MAMP (1 mg/kg) Each point represents the mean±S E M of 5 animals ○——○ saline treated group, ●——● HIS treated group Data were analyzed by Student's t-test a, $p<0$ 05, b, $p<0$ 01 as compared with the values at time 0 in saline treated group c, $p<0$ 05, d, $p<0$ 01 as compared with the values at time 0 in HIS treated group

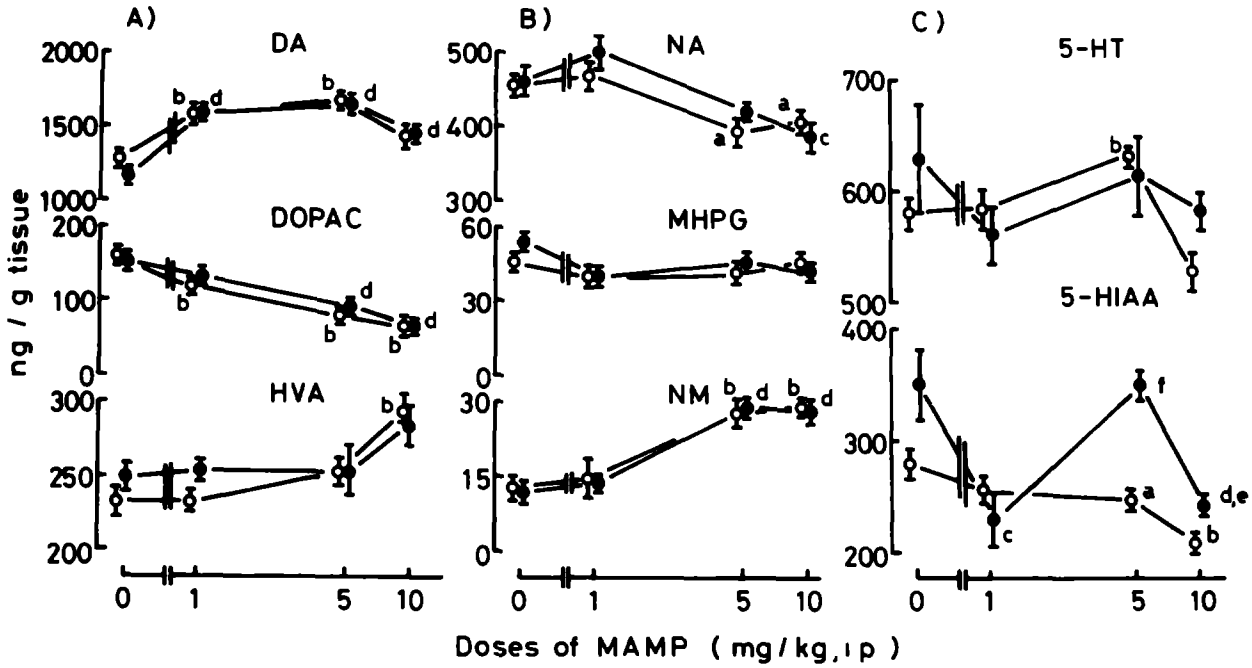

FIG 3 Effect of L-histidine (HIS) on methamphetamine (MAMP)-induced changes in the dynamics of brain (A) dopamine (DA), (B) noradrenaline (NA) and (C) serotonin (5-HT) HIS (1000 mg/kg) was administered IP 1 hr before the IP injection of MAMP Mice were decapitated 1 hr after the MAMP treatment Each point represents the mean±S E M of 5–7 animals ○——○ saline treated group, ●——● HIS treated group Data were analyzed by Student's t-test a, $p<0$ 05, b, $p<0$ 01 as compared with saline—saline (dose=0) treated group, c, $p<0$ 05, d, $p<0$ 01 as compared with HIS—saline (dose=0) treated group e, $p<0$ 05, f, $p<0$ 01 as compared with the corresponding saline—MAMP treated group

leases both DA and NA [3], the effects on these amine levels are quite the opposite This may be related to the different synthesis rates [1] or storage mechanisms [12] between DA and NA The release of NA by MAMP is also supported by marked elevation of NM level

The MHPG level did not change after the administration of MAMP in the present study Since MAMP inhibits the re-uptake of NA [5], the MHPG level might not increase after the MAMP treatment, despite the enhancement of NA release

In our study, MAMP caused a dose-dependent decrease in the 5-HIAA level, in good agreement with the data reported by Lokiec *et al* [9] However, we have no explanation for this action of MAMP The pretreatment with HIS reversed the decrease in the 5-HIAA level induced by 5 mg/kg of MAMP This reversal might be due to a release of 5-HT by HIS Such a view is supported by the data reported by Pilc and Nowak [17], that intracerebroventricularly injected HA reduced the 5-HT level and increased the 5-HIAA level in the rat hypothalamus However, in the present study, such an effect of HIS was not observed when administered in combination with 1 and 10 mg/kg of MAMP Thus, the changes in the 5-HIAA level cannot be explained clearly

Subramanian and Mulder [20] demonstrated that the release of ^{3}H-DA from rat striatal slices in the presence of a high concentration of K is reduced by preincubation with HA In our previous report [6], 1000 mg/kg of HIS produced in mice a clear inhibition of the MAMP-induced hypermotility as well as a significant elevation of brain telemethylhistamine which serves as an index of the brain histaminergic activity [16] Therefore, 1000 mg/kg of HIS seems sufficient to enhance the activity of histaminergic neurons

However, in the present experiment, such a treatment had no influence on the action of MAMP on the dynamic states of DA and NA despite the complete antagonism to the behavioral action of MAMP

In conclusion, we found no evidence for the influence on the MAMP-induced changes in the catecholamine dynamics after the administration of HIS

The proposal that behavioral anti-MAMP action of HIS might be due to its effect on the dopaminergic system was not supported as far as the present results were concerned

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REFERENCES

1 Bacopoulos, N G and R K Bhatnagar Correlation between tyrosine hydroxylase activity and catecholamine concentration or turnover in brain regions *J Neurochem* **29**, 639–643, 1977
2 Breese, G R , B R Cooper and R A Mueller Evidence for involvement of 5-hydroxytryptamine in the action of amphetamine *Br J Pharmacol* **52**· 307–314, 1974
3 Chiueh, C C and K E Moore Effects of α-methyltyrosine on d-amphetamine-induced release of endogenously synthesized and exogenously administered catecholamines from the cat brain in vivo *J Pharmacol Exp Ther* **190**: 100–108, 1974
4 Green J P , C L Johnson and H Weinstein Histamine as a neurotransmitter In *Psychopharmacology A Generation of Progress* edited by M A Lipton, A DiMascio and K F Killam New York Raven Press, 1978, pp 319–332
5 Heikkila, R E , H Orlansky, C Mytilineou and G Cohen Amphetamine, evaluation of d- and l-isomers as releasing agents and uptake inhibitors for ^{3}H-dopamine and ^{3}H-norepinephrine in slices of rat neostriatum and cerebral cortex *J Pharmacol Exp Ther* **194**, 47–56, 1975
6 Itoh, Y , M Nishibori, R Oishi and K Saeki Neuronal histamine inhibits the methamphetamine-induced locomotor hyperactivity in mice *Neurosci Lett* **48**, 305–309, 1984
7 Joshi, V V , J J Balsara, J H Jadhav and A G Chandorkar Effect of L-histidine and chlorcyclizine on apomorphine-induced climbing behaviour and methamphetamine stereotypy in mice *Eur J Pharmacol* **69**· 499–502, 1981
8 Kuzenski, R Biochemical actions of amphetamine and other stimulants In *Stimulants Neurochemical, Behavioral and Clinical Perspectives*, edited by I Creese New York Raven Press, 1983, pp 31–61
9 Lokiec, F , C Jacquot, J R Rapin and Y Cohen Effects of amphetamine on brain biogenic amines in isolated and aggregated rats *Eur J Pharmacol* **44**, 391–395, 1977
10 Magnussen, O , L B Nilsson and D Westerlund Simultaneous determination of dopamine, DOPAC and homovanillic acid Direct injection of supernatants from brain tissue homogenates in a liquid chromatography-electrochemical detection system *J Chromatogr* **221**· 237–247, 1980
11 Mckenzie, G M and J C Szerb The effect of dihydrophenylalanin, phenoprazine and dextroamphetamine on the in vivo release of dopamine from the caudate nucleus *J Pharmacol Exp Ther* **162**· 302–308, 1968
12 McMillen, B A and P A Shore The relative functional availability of brain noradrenaline and dopamine storage pools *J Pharm Pharmacol* **29**, 780–781, 1977
13 Mogilnicka, E and C Baestrup Noradrenergic influence on the stereotyped behavior induced by amphetamine, phenetylamine and apomorphine *J Pharm Pharmacol* **28**· 253–255, 1976
14 Moore, K E and E W Lariviere Effects of D-amphetamine and restraint on the content of norepinephrine and dopamine in rat brain *Biochem Pharmacol* **12**· 1283–1288, 1963
15 Oishi, R , S Mishima and H Kuriyama Determination of norepinephrine and its metabolites released from rat vas deferens using high performance liquid chromatography with electrochemical detection *Life Sci* **32**· 933–940, 1983
16 Oishi, R , M Nishibori and K Saeki Regional differences in the turnover of neuronal histamine in the rat brain *Life Sci* **34** 691–699, 1984
17 Pilc, A and J Z Nowak Influence of histamine on the serotonergic system of rat brain *Eur J Pharmacol* **55** 269–272, 1979
18 Sanan, S and M Vogt Effect of drugs on the noradrenaline content of brain and peripheral tissues and its significance *Br J Pharmacol* **18**· 109–127, 1962
19 Schwartz, J C , H Pollard and T T Quach Histamine as a neurotransmitter in mammalian brain neurochemical evidence *J Neurochem* **35**· 26–33, 1980
20 Subramanian, N and A H Mulder Modulation by histamine of the efflux of radiolabeled catecholamines from rat brain slices *Eur J Pharmacol* **43**: 143–152, 1977
21 Watanabe, T , Y Taguchi, S Shiosaka, J Tanaka, H Kubota Y Terano, M Tohyama and H Wada Distribution of the histaminergic neuron system of rats, a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker *Brain Res* **295**· 13–25 1984