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Urinary Excretion of *p*-Hydroxylated Methamphetamine Metabolites in Man. II. Effect of Alcohol Intake on Methamphetamine Metabolism

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SHIMOSATO, K. *Urinary excretion of* p-*hydroxylated methamphetamine metabolites in man. II. Effect of alcohol intake on methamphetamine metabolism.* PHARMACOL BIOCHEM BEHAV **29**(4) 733–740, 1988.—The effect of drinking alcoholic beverages on methamphetamine metabolism was investigated in man. The subjects, 97 males and 9 females, were divided into three groups by evaluation of their urinary pH; i.e., acidic, subacidic and neutral groups. The subjects in each group were further divided into ethanol-positive subjects and ethanol-negative subjects, depending on the presence or absence of ethanol in their urine. Gas chromatographic analysis showed the urinary concentrations of methamphetamine in the ethanol-positive subjects to be higher than those in the ethanol-negative subjects in both the acidic and subacidic urinary pH groups. Liquid chromatography, on the other hand, showed the urinary concentrations of *p*-hydroxymethamphetamine and *p*-hydroxyamphetamine for the ethanol-positive subjects to be lower than those for the ethanol-negative subjects in all three groups. The relative proportions of *p*-hydroxylated metabolites to unchanged methamphetamine in urine, therefore, were severely reduced in the ethanol-positive subjects. These results suggest that drinking alcoholic beverages probably results in a suppression of methamphetamine metabolism in man.

Methamphetamine *p*-Hydroxymethamphetamine *p*-Hydroxyamphetamine Ethanol
Methamphetamine metabolism Man

AT least two major pathways each have been recognized for the metabolisms of methamphetamine (MAP) and amphetamine (AMP) in man [9, 14, 28] and in animals [9, 10, 14, 25, 26]. In the case of MAP, they are *p*-hydroxylation of the aromatic ring and *N*-demethylation of the side chain, and for AMP, they are *p*-hydroxylation of the aromatic ring and deamination of the side chain. Many investigations in animals have shown that various drugs influence the metabolism of amphetamines and that thereby the urinary metabolite profiles of the amines are altered [12,21]. It has been reported, for instance, that in rats pretreated with desipramine the levels of AMP were not only higher than those of control animals but also declined at a slower rate [30]. These phenomena have been explained by observations of urinary metabolite profiles indicating that pretreatment with this antidepressant drug caused an almost complete inhibition of the *p*-hydroxylation and a slight inhibition of the deamination of AMP [20]. In addition, other investigations in animals have shown that simultaneous administrations of ethanol produced higher concentrations of AMP in the brain and the blood of test animals than in those of controls [16,31], that the excretion of unchanged AMP in urine increased and that of *p*-hydroxyamphetamine was decreased following doses of ethanol [11, 12, 15]. Thus the urinary metabolite profiles of AMP and MAP seem to be useful for investigation of the metabolism of these amines. Recently we found in man that the urinary concentrations of MAP, *p*-hydroxymethamphetamine (OH-MAP), and *p*-hydroxyamphetamine (OH-AMP) varied widely and that the relative proportions of the metabolites to unchanged MAP in urine were scattered widely over the percentage scale [28].

In the present investigation the author studied the effect of alcohol intake on MAP metabolism in man by means of determination of the urinary concentrations of MAP and its metabolites. Additional analyses were carried out to compare the relative proportions of metabolites to unchanged MAP in order to exclude any effect of drinking on urine output.

METHOD

Subjects

Urine samples of MAP addicts were provided for this investigation by the Criminal Science Laboratory of the Okayama Prefectural Police Headquarters. The subjects, 97 males and 9 females, were divided into three groups by evaluation of their urinary pH; i.e., acidic, subacidic and neutral groups, with ranges of urinary pH between 5.0–5.7, 5.8–6.4 and 6.5–7.6, respectively. The subjects in each group

TABLE 1

THE MEANS AND THE STANDARD DEVIATIONS OF AGES, MAP DOSES AND URINE COLLECTION TIMES AFTER THE LAST INJECTION OF MAP IN ADDICTS INCLUDED IN THE PRESENT INVESTIGATION

Group	Urinary pH	Ethanol	N	Age	Dose (mg)*	Time After Inject (hr)*	n*
Acidic	5.0–5.7	Negative	21 (1)†	35 (12)	41 (10)	30.04 (28.61)	13
		Positive	9	37 (8)	44 (19)	44.10 (40.73)	5
Subacidic	5.8–6.4	Negative	36 (5)†	32 (12)	47 (27)	30.46 (28.72)	22
		Positive	12	33 (9)	53 (27)	38.63 (32.08)	7
Neutral	6.5–7.6	Negative	21 (3)†	34 (11)	49 (20)	57.55 (41.91)	10
		Positive	7	42 (7)	54 (29)	46.80 (33.25)	5

*Column n refers to the number of the latter two parameters.
†The number of female addicts.

in whose urine ethanol was detected were referred to as ethanol-positive subjects and those in whom it was undetected were considered to be ethanol-negative subjects.

Table 1 summarizes the means of ages, MAP doses and duration times between urine collection and the last injection of MAP of the above-mentioned subjects. The data regarding the MAP doses and the duration times between urine collection and the last injection of MAP were obtained from each police station on a voluntary basis so that the number of subjects for these two pieces of data were less than the number in each group. Statistical analyses revealed that there were no significant differences as to any of these parameters in each group.

Determination of Methamphetamine and Its Metabolites

The apparatus and conditions employed for gas chromatography (GC) and high-performance liquid chromatography (HPLC) have been described previously [27]. The urine samples, 1 ml each, were used for both the GC analysis of MAP and AMP and the HPLC analysis of the free form of OH-MAP and OH-AMP. Two ml of water was added to each sample, and then the extraction procedure was employed. For the HPLC analysis of the total *p*-hydroxylated metabolites, which included both the free and conjugated forms of the metabolites, 0.1 ml each of the urine samples was hydrolyzed with equal volumes of 12 N HCl at 60°C for 4 hr [28]. After hydrolyzing, 3 ml of water was added to each sample and they were neutralized with NaOH solution. Subsequently, the extraction procedure was employed with these hydrolyzed samples.

Details of the extraction procedure have been described elsewhere [27]. Each urine sample was passed through a solid phase extraction column, Bond-Elut® C_{18} (Analytichem International, Harbor, CA, USA). After washing with water, 30% methanol, and acetonitrile, respectively, the substances were eluted with acidified acetonitrile. For the HPLC analysis of the *p*-hydroxylated metabolites, 50 μl of acetic acid was added to the eluate from each sample, and then it was evaporated under a stream of nitrogen. The residue was dissolved in 100 μl of 0.1 N perchloric acid and 5 μl of the aliquot was injected into the HPLC column. For the GC analysis of MAP and AMP, the residue was dissolved in 100 μl of ethyl acetate, after which 200 μl of trifluoroacetic anhydride was added to it. Each sample was incubated at 56°C for 30 min. After the reaction, the samples were again evaporated to dryness under a stream of nitrogen. Then each sample was dissolved in 100 μl of ethyl acetate, and 1 μl of the aliquot was injected into the GC system.

Detection of Ethanol in Urine

The urine samples, 0.2 ml each, were mixed with 0.8 ml of 0.5 N perchloric acid in 10 ml vials and sealed with rubber stoppers. The vials were incubated at 65°C for 30 min. After the incubation, 1 ml of head space gas from the vial was injected into a Shimadzu GC-9A equipped with a flame ionization detector and a digital integrator (Shimadzu, Chromatopac C-R2A, Kyoto, Japan). The column packing for GC was Chromosorb 101 (60–80 mesh) in a glass column (3.2 mm i.d.×2.1 m). The running conditions were: column temperature, 130°C; detector temperature, 160°C; carrier gas (nitrogen) flow rate, 60 ml/min.

This analysis revealed that the mean concentration of ethanol in urine was 0.30±0.14 (SEM) mg/ml in the ethanol-positive subjects.

Data Analysis

Differences between groups were tested using Student's *t*-test.

RESULTS

Urinary Concentration of Methamphetamine in Ethanol-Positive and Ethanol-Negative Subjects

The effect of drinking on the urinary concentrations of MAP was investigated in each urinary pH group (Table 2). Generally, it was observed that in comparison with the ethanol-negative subjects, the ethanol-positive subjects showed higher concentrations of urine. In the acidic group, the mean concentrations for the ethanol-positive and ethanol-negative subjects were 37.6±8.2 (SEM) and 24.6±4.5 μg/ml urine, respectively. In the subacidic group, the mean concentration of the positive subjects was significantly higher than that of the negative ones (37.2±7.1 and 22.2±3.2 μg/ml, respectively). Furthermore, in the neutral group, the mean concentrations for the positive and negative subjects were estimated to be 22.9±5.3 and 18.8±4.4 μg/ml, respectively.

No clear-cut effects of urinary pH on the urinary excretion of the unchanged MAP were observed in the pH 5.0 to

TABLE 2

EFFECT OF DRINKING ON THE CONCENTRATION OF MAP EXCRETED IN URINE OF ADDICTS

Group	Ethanol	Concentration ±SEM (μg/ml)
Acidic	Negative	24.6 ± 4.5
	Positive	37.6 ± 8.2
Subacidic	Negative	22.2 ± 3.2
	Positive	37.2 ± 7.1*
Neutral	Negative	18.8 ± 4.4
	Positive	22.9 ± 5.3

Asterisk (*) denotes the significance of difference ($p<0.05$) versus the negative subjects in the subacidic group.

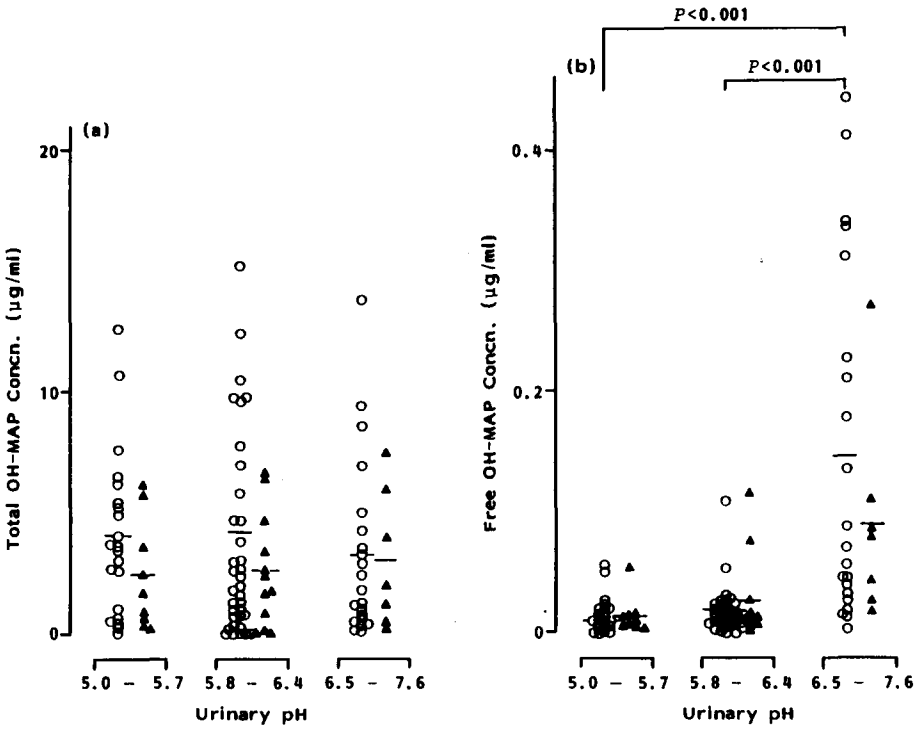

FIG. 1. Effect of drinking on the concentration of OH-MAP excreted in urine. Panels (a) and (b) represent the distribution of the total and free forms of OH-MAP concentrations, respectively, for ethanol-positive subjects (▲) and ethanol-negative subjects (○) in each group. Each horizontal bar indicates the mean value in each class. Each p value refers to the significance of difference between two classes.

7.6 range in either the ethanol-positive or ethanol-negative subjects.

Urinary Concentration of p*-Hydroxylated Metabolites in Ethanol-Positive and Ethanol-Negative Subjects*

The distributions of total (free plus conjugated) OH-MAP concentrations were compared between the ethanol-positive and ethanol-negative subjects (Fig. 1a). Generally, in contrast with the distribution for the unchanged MAP, the urinary concentrations of the metabolite for the ethanol-positive subjects fell as compared with those for the ethanol-negative subjects. In the acidic group, the mean concentrations for the ethanol-positive and ethanol-negative subjects were 2.423±0.760 and 4.066±0.728 μg/ml urine, respectively. In the subacidic group, the means were estimated to be 2.648±0.653 μg/ml for the positive subjects and 4.210±0.858 μg/ml for the negative ones.

There were no differences in the distribution patterns for free OH-MAP between the ethanol-positive and ethanol-negative subjects in any of the three groups (Fig. 1b). A statistical analysis revealed that the mean concentrations of the free metabolite in the neutral group were drastically higher than the means in both the acidic and subacidic

TABLE 3

EFFECT OF DRINKING ON THE CONCENTRATION OF OH-AMP EXCRETED IN URINE OF ADDICTS

Group	Ethanol	Concentration ±SEM (μg/ml) Total	Free
Acidic	Negative	0.251 ± 0.046	0.002 ± 0.001
	Positive	0.117 ± 0.047	0.001 ± 0.001
Subacidic	Negative	0.258 ± 0.045	0.003 ± 0.001
	Positive	0.146 ± 0.029*	0.004 ± 0.002
Neutral	Negative	0.223 ± 0.051	0.011 ± 0.003†‡
	Positive	0.160 ± 0.040	0.009 ± 0.003

Asterisk (*) denotes the significance of difference ($p<0.05$) versus the negative subjects in the subacidic group, and daggers († and ‡) denote the significance of difference ($p<0.01$ and $p<0.02$) versus the negative subjects in the acidic and subacidic groups, respectively.

TABLE 4

EFFECT OF DRINKING ON *N*-DEMETHYLATION OF MAP

Group	Ethanol	Relative proportion ± SEM (%) AMP/MAP	Total OH-AMP/ Total OH-MAP
Acidic	Negative	12.1 ± 2.4	7.0 ± 0.5
	Positive	5.7 ± 1.9*	3.6 ± 0.7†
Subacidic	Negative	12.2 ± 1.8	8.2 ± 0.8
	Positive	9.3 ± 1.9	6.6 ± 1.3
Neutral	Negative	12.9 ± 2.6	8.2 ± 1.0
	Positive	8.4 ± 3.5	10.5 ± 4.5

Symbols (* and †) denote the significance of difference ($p<0.05$ and $p<0.01$, respectively) versus the negative subjects in the acidic group.

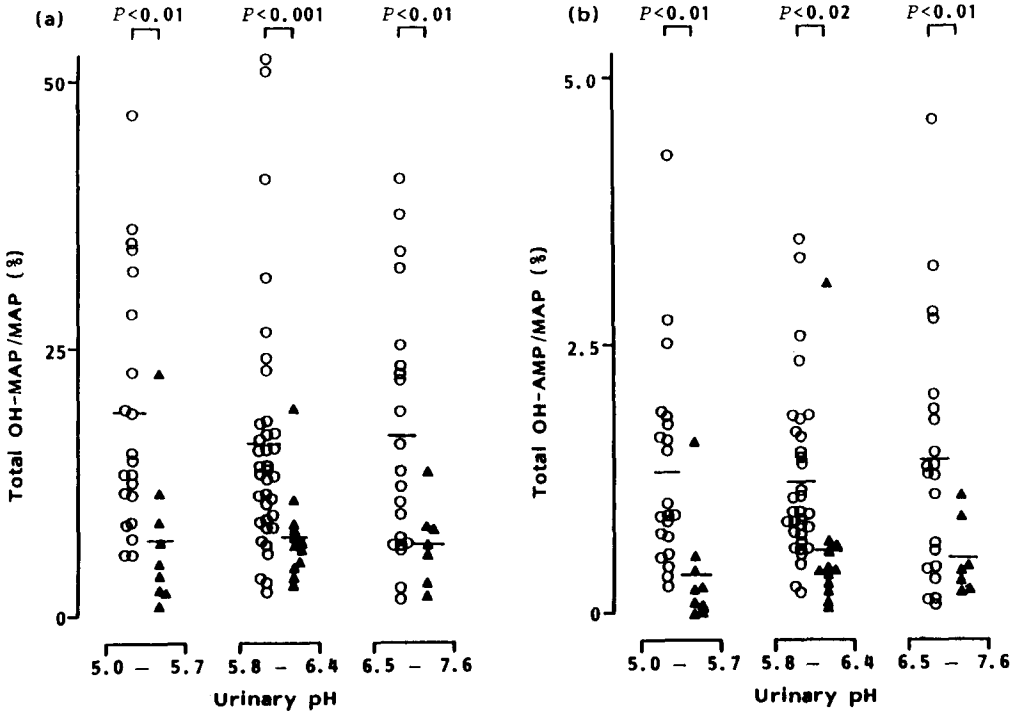

FIG. 2. Effect of drinking on *p*-hydroxylation of MAP and AMP. Panels (a) and (b) represent the distribution of the relative proportions of OH-MAP and OH-AMP, respectively, to MAP for ethanol-positive subjects (▲) and ethanol-negative subjects (○) in each group. Other details are described in the legend of Fig. 1.

groups. For example, the means in the ethanol-negative subjects were estimated to be 0.012±0.002, 0.017±0.003 and 0.147±0.032 μg/ml for the acidic, subacidic and neutral groups, respectively.

The mean concentrations of both total and free OH-AMP for the ethanol-positive and ethanol-negative subjects in each group are summarized in Table 3. The means of the total OH-AMP for the negative subjects ranged from 0.223 to 0.258 μg/ml and those for the positive ones from 0.117 to 0.160 μg/ml. These data showed that there were lower concentrations of total OH-AMP in the positive subjects than in the negative subjects, although the values were estimated to be only 5 to 7% of those for the total OH-MAP. In addition, as could be seen in the free OH-MAP, there was a great increase in the urinary excretion of the free OH-AMP in the neutral pH group.

Effect of Drinking on p*-Hydroxylation of Methamphetamine and Amphetamine*

Since ethanol has been reported to produce a stimulating

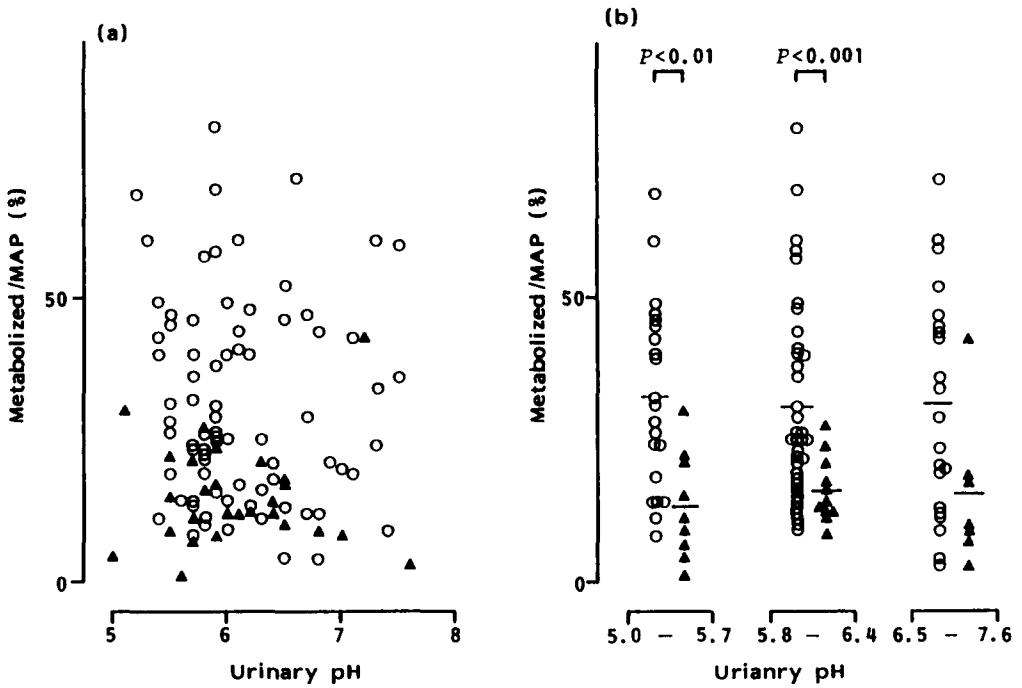

FIG. 3. Effect of drinking on metabolism of MAP. The left panel (a) represents the values of the relative proportion of the metabolized portion to unchanged MAP plotted against the urinary pH for ethanol-positive subjects (▲) and ethanol-negative subjects (○) and the right (b) represents the distribution of those in each group. Other details are described in the legend of Fig. 1.

effect on urinary output, it is conceivable that the values for the urinary concentrations of MAP and its metabolites could be misleading with regard to the real metabolic profile of the drug. Therefore, additional investigation was carried out to compare the relative proportions of metabolites to unchanged MAP between the ethanol-positive and ethanol-negative subjects. The distributions of the relative proportions of the total OH-MAP to MAP are shown in Fig. 2a. Generally, the ratios of the ethanol-positive subjects were significantly lower than those of the ethanol-negative subjects in each group. In the acidic group, although the ratio of the total OH-MAP to the unchanged drug excreted was 19.1±2.6% in the ethanol-negative subjects, the ratio fell to 7.1±2.3% in the ethanol-positive subjects. In the subacidic group, similarly, the ratio was 16.2±2.0% for the ethanol-negative subjects and 7.4±1.3% for the positive subjects. In addition, in the neutral group, the ratio for the ethanol-positive subjects (6.6±1.5%) was significantly less than that for the ethanol-negative subjects (17±2.6%).

Because *p*-hydroxylation is another pathway for the metabolism of AMP to OH-AMP, further comparisons of this metabolite were made (Fig. 2b). In the acidic group, while the urine of the negative subjects contained total OH-AMP with a relative ratio of 1.33±0.21% to the unchanged MAP, the urine of the ethanol-positive subjects had a ratio of only 0.36±0.17%. In the subacidic group, likewise, the ratio of the positive subjects was lower than that of the negative subjects (0.59±0.23 and 1.23±0.14%, respectively). Similar results were also obtained in the neutral group.

Effect of Drinking on N-*Demethylation of Methamphetamine*

The other major pathway for the metabolism of MAP involves *N*-demethylation of the side chain. Further investigation was carried out to determine the effect of drinking on *N*-demethylation by comparing the relative proportions of AMP to MAP between the ethanol-positive and ethanol-negative subjects (Table 4). As procurement of MAP and AMP has been legally restricted in Japan, it was not possible to obtain samples of AMP. Therefore the ratios were obtained from data for the peak area of the GC analysis. The urine of the ethanol-positive subjects contained demethylated metabolite AMP in relative ratios of from 5.7 to 9.3%, while the ratios of AMP in the urine of the negative subjects were in the range of from 12.1 to 12.9%. A significant difference was observed between the negative and positive subjects in the acidic group, while there was no difference in the other groups. Similar results were noted in the relative ratios of total OH-AMP to total OH-MAP, which were *p*-hydroxylated from AMP and MAP, respectively (Table 4).

Thus in all three groups the metabolized portion was lower in the ethanol-positive subjects than in the ethanol-negative subjects (Fig. 3).

Effect of Urinary pH on Excretion of Free Form of p-*Hydroxylated Metabolites*

Finally, the effect of urinary pH on the excretion of the metabolites was investigated. No distinctive effect of the urinary pH on the excretion of either AMP or the total *p*-hydroxylated metabolites was observed in either the ethanol-positive or ethanol-negative subjects from the data on relative proportions (Fig. 2 and Table 4). On the contrary, it was noted that the mean concentrations of both free OH-MAP and free OH-AMP in the neutral group significantly increased as compared with those of the other two groups (Fig. 1 and Table 3). Therefore the relative propor-

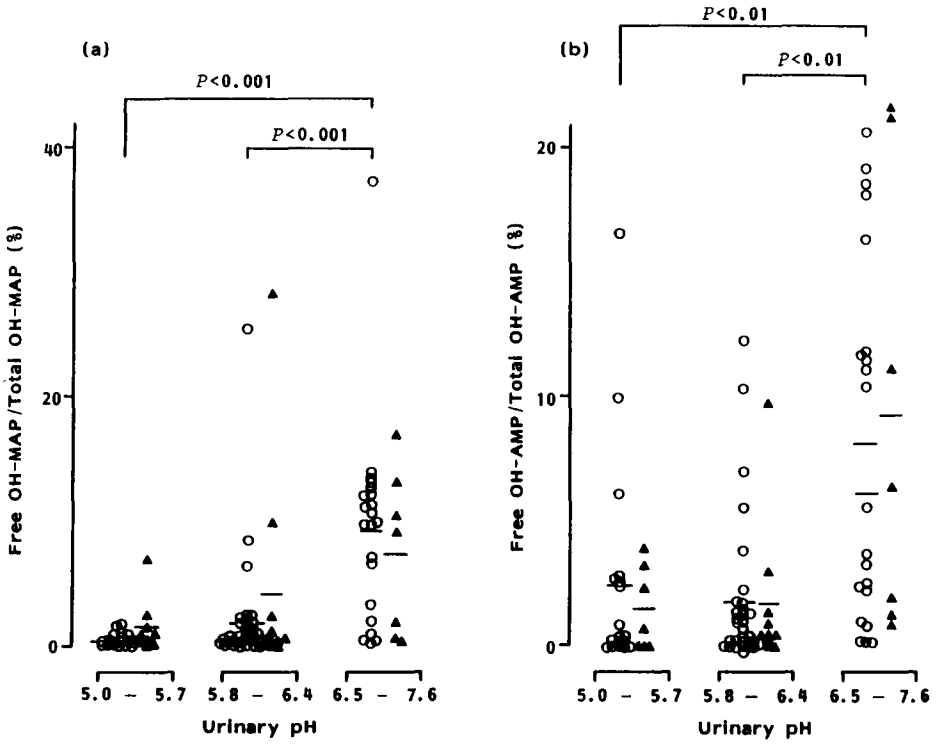

FIG. 4. Effect of the urinary pH on excretion of the free form of the *p*-hydroxylated metabolites in urine. Panels (a) and (b) represent the distribution of the relative proportions of the free form of OH-MAP and that of OH-AMP, respectively, for ethanol-positive subjects (▲) and ethanol-negative subjects (○) in each group. Other details are described in the legend of Fig. 1.

tions of the *p*-hydroxylated metabolites excreted as the free form to those excreted as the total (free plus conjugated) form were estimated for each urinary pH group (Fig. 4). In the case of OH-MAP, the ratio of the free to the total form for the ethanol-negative subjects was estimated to be 9.5±1.8% in the neutral group. This was statistically higher than the values for the negative subjects in the acidic and subacidic groups (0.4±0.1 and 1.9±0.8%, respectively). As for the OH-AMP, the ratio of 8.2±1.6% for the ethanol-negative subjects in the neutral group was also significantly larger than those in the acidic and the subacidic groups (2.4±1.0 and 1.8±0.6%, respectively). There was no difference in the ratios between the ethanol-positive and ethanol-negative subjects in any of the groups.

DISCUSSION

The present investigation has not only revealed that the urinary concentrations of unchanged MAP increased, but also that those of *p*-hydroxylated metabolites were reduced in subjects in whose urine ethanol was detected as compared to those in whom it was undetected. These findings are in line with observations that simultaneous administrations of ethanol have produced an increase in the urinary excretion of unchanged AMP as well as a reduction in that of OH-AMP in rats [11,12] and in mice [15]. In animals these phenomena have been explained in the following manner; ethanol inhibits *p*-hydroxylation of AMP and produces both higher levels of AMP and lower levels of OH-AMP in the brain and the blood [16,31] and thereby the urinary metabolite profile assumes the above-mentioned aspect. Therefore the present results also suggest that drinking alcoholic beverages causes an inhibition of the MAP metabolism in man.

In the present investigation the relative ratios have mainly been utilized for examination of the inhibiting effect of ethanol on the MAP metabolism in man. The reasons for this are as follows. There were wide variations in the urine samples employed in this investigation, in the MAP doses and in the duration times between urine collection and the last injection of this drug. Moreover, ingested ethanol has been revealed to increase urinary output in man [29], while it has also been reported that the urine flow rate has no effect on the urinary excretion rate of AMP and MAP [5,7]. With regard to these reports, drinking alcoholic beverages should increase urinary output and should dilute urinary MAP and its metabolites, thereby reducing the concentrations of these substances. Therefore the relative ratios have been considered more reliable in the present investigation than the urinary concentrations.

Investigation in rats has revealed that the excretion of OH-AMP during 0–3 hr after doses in controls was greatly reduced from 45% to 11% by the administration of 5 g/kg of ethanol. Even during 12–24 hr after doses, at which time the maximum blood ethanol level was 1.2 mg/100 ml, excretion of the metabolite was significantly reduced from the control value of 80% to 51% by this ethanol administration [12]. The present investigation has also revealed that the urine samples of the ethanol-negative subjects, collected at 30–57 hr after MAP doses, contained ratios of OH-MAP to MAP of 16–19%. Those of the ethanol-positive subjects, collected at

39–47 hr after doses, with an ethanol level of 0.30±0.14 mg/ml urine, had a ratio of 7%. It was further revealed that the urine of the former contained OH-AMP at ratios of 1.2–1.4% and that that of the latter had ratios of 0.1–0.3%. Therefore it was concluded that ethanol inhibits the *p*-hydroxylation of both MAP and AMP in man, although it remains unclear whether the ethanol-positive subjects drank alcoholic beverages simultaneously or not. The relative ratios of AMP to MAP also showed a suppression of the *N*-demethylation of MAP by ethanol ingestion, although no clear-cut evidence was obtained. Based on these results and those shown in Fig. 3, it can be concluded that a compensatory metabolism shift to *N*-demethylation did not occur even when *p*-hydroxylation was inhibited by ethanol.

In animals, it has been reported that excretion of the free form of OH-AMP is reduced by doses of ethanol, while the relative ratio to the conjugate remains unchanged [11,15]. However, the present investigation has shown that in man ethanol has no effect on either the relative ratios for the free form of *p*-hydroxylated metabolites or on the urinary concentrations of free metabolites. The reason for this discrepancy may lie in a difference in species specificity for the metabolism.

Chronic administration of ethanol has been shown to cause proliferation of the endoplasmic reticulum and increases in microsomal protein content and many of the constituents of the drug oxidizing system, consequently resulting in an increased microsomal drug-metabolizing ability [17,18]. On the other hand, as described above, ethanol inhibits the metabolism of MAP and AMP. The differential mechanism leading to ethanol inhibition of the metabolism of these drugs is as yet not well documented. To date the *p*-hydroxylation of AMP is known not to be one of the microsomal hydroxylations induced by phenobarbital but to be one inhibited by SKF 525-A, DPEA and Lilly 18947 [12]. Furthermore, ethanol inhibition is competitive at a low concentration of ethanol [31].

Many investigations have revealed that a low urinary pH results in the excretion of large amounts of unchanged MAP and AMP, while if the urine is alkaline only a small proportion of these drugs is excreted [1–3, 5–8, 13]. It has been observed that excretion of total OH-AMP is unaffected by the urinary pH [1–3, 13]. The present investigation was performed by dividing the subjects into three urinary pH groups based on these descriptions, and it has consequently been shown that the urinary pH has no distinctive effect on the urinary excretion of MAP or on the excretions of total OH-MAP and total OH-AMP in the pH 5.0 to 7.6 range. The reason for this discrepancy probably lies in the fact that other investigators have forcely produced alkaline urine with pH ranges of from 7.5 to 8.2 by administration of sodium bicarbonate, while in the present subjects the urinary pH was within a physiological range of from 5.0 to 7.6. The most striking effect of urinary pH was observed in the urinary metabolite profiles of free OH-MAP and free OH-AMP, there being accelerated excretion of these metabolites into neutral urine. These profiles can be explained by the theory of non-ionic diffusion of acids in the renal tubules [24], although the negative logarithm of the dissociation constant, pKa, of OH-AMP was assessed to be 10.7 [3,22].

There have been increasing reports that pretreatment with ethanol in animals potentiates the motor activity induced by MAP [19] and AMP [4,31]. Possible mechanisms of the ethanol potentiation of amphetamines-induced motor activity may underlie the ethanol inhibiting effect on the metabolism of amphetamines [31] and/or the ethanol inducing effect on the increase in the sensitivity of dopamine receptors in the brain [23]. Recently it has also been reported that psychosomatic disorders are more frequently manifested after MAP injections in persons who have a liking for alcoholic beverages than in persons who do not [32]. The results presented here strongly favor the possibility that the ethanol inhibiting effect on the metabolism may play an important role in the ethanol potentiation of the MAP manifested psychosomatic disorders in man.

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