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Relationship Between Facial Flushing and Blood Acetaldehyde Levels After Alcohol Intake

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MIZOI, Y., I. IJIRI, Y. TATSUNO, T. KIJIMA, S. FUJIWARA, J. ADACHI AND S. HISHIDA. *Relationship between facial flushing and blood acetaldehyde levels after alcohol intake.* PHARMAC. BIOCHEM. BEHAV. 10(2) 303–311, 1979.—Normal subjects were divided into two groups, i.e., those showing, and those not showing, facial flushing after consuming a small amount of alcohol. In the flushing group, increases of pulse rate, facial skin temperature and carotid arterial pressure and blood flow rate, as well as changes of digital plethysmogram and electrocardiogram, were found together with a conspicuous rise in blood acetaldehyde levels after the drinking. However, significant change of the signs as mentioned above and elevation of blood acetaldehyde did not occur in the non-flushing group. The maximum blood alcohol levels and the rate of alcohol elimination showed no difference between these two groups. Furthermore, urinary excretions of epinephrine and norepinephrine increased in the flushing cases after the drinking.

Blood acetaldehyde level Facial flushing Pulse rate Skin temperature Digital plethysmogram Electrocardiogram Carotid arterial blood flow Urinary epinephrine and norepinephrine

COMPARED with other drugs, the qualitative and quantitative reactions that occur in the human body to alcohol intake vary vastly from man to man. Many people, on intake of an adequate amount of alcohol, get into a stage in which general hot feeling, euphoria, talkativeness and excitation occur. As they drink more, they usually get into the stage of severe toxic symptoms and signs such as disturbance in gait, emotional fluctuation, vomiting and disturbance in consciousness. There are, on the other hand, not a few people who, even on drinking a small amount of alcohol, present marked facial flushing, and fall into drunken sickness, feeling palpitation and a chest distress. Others, even with a small amount of alcohol, present ataxia associated with marked euphoria, while some contrarily do not present any changes in the face or ataxia even with a relatively large amount of alcohol.

Individual difference in the metabolic pathway of alcohol, interactions between the metabolism of alcohol and of other substances, and individual difference in the sensitivity of the living body may be considered responsible for such a wide variability in the response to alcohol. It appears to involve complex problems such as whether these causes are congenital or acquired ones, or whether some pathologic factors are involved.

The involvement of acetaldehyde may be considered one of the possible causes for the above-mentioned individual variability of symptoms and signs of alcohol drinking. Acetaldehyde is produced by the oxidation of alcohol, but because it is usually oxidized rapidly to acetate, its toxicity does not manifest itself. In the disulfiram-alcohol reaction [21], however, the blood level of acetaldehyde is markedly increased, associated with facial flushing, elevation of skin temperature, and increase in pulse rate and ventilation. It was shown by Asmussen *et al.* [6] that these manifestations evolve even on slow intravenous infusion of acetaldehyde. These symptoms and signs may be considered to result from the production of sympathomimetic effects by acetaldehyde, and reports of experiments on animals indicate that acetaldehyde increases the blood and urine levels of catecholamines [3, 23, 34]. Since the clinical observation of increased urinary excretion of catecholamines following the administration of alcohol [35], many authors have described the relations of alcohol to the urinary excretion of

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catecholamines [1, 4, 7, 17, 36]. The possible involvement not only of acetaldehyde but also of catecholamines in the symptoms and signs following the intake of alcohol must be considered.

In the present work, a study has been made of individual variability in facial flushing, facial skin temperature, pulse rate and peripheral blood flow, alcohol and acetaldehyde levels in the blood, and their relations to the urinary excretion of catecholamines, in subjects drinking a small amount of alcohol.

METHOD

Experimental Procedures

Healthy subjects kept without breakfast on the day of experiment, were each made to drink 200 ml (200–1000 ml in Experiment 3) of *sake* (Japanese rice wine, with 16 v/v% alcoholic content), together with 30 g of "*okaki*" (a rice cracker), between 10:30 and 10:40 a.m. (10:40–11:20 in Experiment 3) and then kept at rest on a sofa (lying in a supine position in Experiment 3). The room temperature was maintained at 24–26°C. They were allowed to eat a light meal (lunch) following blood sampling 2 hr after the start of the drinking.

Determination of Blood Alcohol

Blood samples were collected from the median cubital vein of each subject at 30 min and 1, 2, 3, 4 and 5 hr after the drinking to determine alcohol levels in the blood. A 0.5 ml portion of each sample was delivered into an 18 ml vial tightly closed with a rubber stopper and an aluminum cap; 0.5 ml of 0.8 per mil n-propanol was added to the vial as an internal standard solution; the vial was incubated at 55°C for 30 min; and gas chromatography was performed on 0.5 ml of the head space gas. The peak area was calculated with the digital integrator.

Determination of Blood Acetaldehyde

Blood acetaldehyde levels were determined by the same gas chromatographic procedure as the blood alcohol levels, except that 0.5 ml of 0.02 per mil n-propanol in physiologic saline solution was used as internal standard and the incubation period was 20 rather than 30 min.

Determination of Urinary Catecholamines

Each subject was made to void immediately before the drinking; urine was collected during the 5 hr after the start of the drinking and assayed for epinephrine and norepinephrine. On the day preceding the experiment with alcohol, each subject was made to drink 200 ml of water under the same conditions as for the experiment with alcohol; urine was collected as a control sample during the following 5 hr. A modification of the method of von Euler and Floding [13] was used for the assay. The recovery rate of epinephrine was 94.3 ± 8.9%, and that of norepinephrine, 87.3 ± 3.1%.

Skin Temperature

The forehead skin temperature was determined by a thermister-type digital thermometer with a sensitivity of 0.1°C.

TABLE 1

AVERAGES AND STANDARD DEVIATIONS OF β_{60} (MG/ML/HR), r AND RATE OF ALCOHOL ELIMINATION (MG/KG/HR) IN THE NON-FLUSHING, SLIGHTLY FLUSHING AND HIGHLY FLUSHING GROUPS FOLLOWING INTAKE OF 200 ML *SAKE*

Group		β_{60} (1–4 hr)	r	Elimination (1–4 hr)
Non-Flushing		0.13	0.79	100
	± SD	0.02	0.13	11
Slightly Flushing		0.13	0.86	106
	± SD	0.02	0.14	19
Highly Flushing		0.12	0.83	102
	± SD	0.02	0.21	20

Pulse Wave

The pulse waves in the left index fingertip were recorded photoplethysmographically.

Blood Flow Rate and Arterial Pressure

The blood flow rate in the common carotid artery was measured on the skin surface of the left lateral region of the neck with the ultrasonic blood flowmeter (Nihon Kohden, Model EUD-3B), and the arterial pressure in the common carotid artery was measured by attaching a transducer (Nihon Kohden, Model TF-111S) to the right lateral region of the neck.

Estimation of the Degrees of Facial Flushing

Those who presented marked facial flushing and sometimes showed in addition flushing of the neck, anterior chest region, upper and lower extremities, after the drinking were assigned to the highly flushing group; those who showed flushing only around the eyelids, to the slightly flushing group; and those who showed no changes in the face, to the non-flushing group.

RESULTS

Experiment 1: Degrees of Facial Flushing, Blood Alcohol Level, and Alcohol Elimination Rate Following Drinking

Twenty-eight, including 2 women, out of 75 subjects were assigned to the highly flushing group; 16 (including 1 woman), to the slightly flushing group; and 31 (including 2 women), to the non-flushing group.

Mean ages in the highly and slightly flushing groups and the non-flushing one were 24.1, 22.3 and 23.3 years, and their mean body weights were 60.5, 59.7 and 64.3 kg, respectively.

Although the blood alcohol level varied from subject to subject, the mean level in each group reached a maximum 30 min after the start of the drinking, which was 0.44 mg/ml in the non-flushing group, 0.45 mg/ml in the slightly flushing group and 0.47 mg/ml in the highly flushing group. The alcohol disappeared from the blood in all three groups in 5 hr. Table 1 shows the averages and standard deviations of Widmark's factor β_{60}, factor r [43] and rate of alcohol elimination in the three groups. No significant differences were detected

TABLE 2

BLOOD ALCOHOL AND ACETALDEHYDE (AcH) LEVELS AND THE RATE OF INCREASE IN PULSE RATE AFTER INTAKE OF 200 ML *SAKE*

	Before	30 min	1 hr	2 hr	3 hr	4 hr
Non-Flushing Group N=15						
Blood alcohol (mg/ml)	0	0.47	0.44	0.32	0.17	0.04
± SD		0.14	0.08	0.08	0.07	0.03
Blood AcH (μg/ml)	0	0.101	0.071	0.040	0.026	0.018
± SD		0.080	0.063	0.052	0.038	0.028
Increase of pulse rate (%)		5	4	4	7	8
Flushing Group N=11						
Blood alcohol (mg/ml)	0	0.47	0.44	0.29	0.14	0.03
± SD		0.12	0.15	0.09	0.10	0.03
Blood AcH (μg/ml)	0	0.508	0.571	0.425	0.394	0.226
± SD		0.279	0.103	0.163	0.166	0.150
Increase of pulse rate (%)		43	39	21	27	16

TABLE 3

URINARY EXCRETIONS OF EPINEPHRINE (EP) AND NOREPINEPHRINE (NE) AND MAXIMUM BLOOD ACETALDEHYDE (AcH) LEVELS IN CONTROL AND ALCOHOL EXPERIMENTS

	Non-Flushing Group N=15	Flushing Group N=11
Age (Range)	25.9 (20–45)	25 (20–33)
EP (μg/hr) ± SD		
Control	0.60 ± 0.20*	0.65 ± 0.21†
Alcohol	0.60 ± 0.19*	1.08 ± 0.40†
NE (μg/hr) ± SD		
Control	1.48 ± 0.50*	1.47 ± 0.41‡
Alcohol	1.50 ± 0.54*	2.57 ± 0.77‡
Maximum Blood AcH (μg/ml) ± SD		
Before	0.0	0.0
After alcohol	0.103 ± 0.088	0.693 ± 0.124

*Not significant; †$p<0.01$; ‡$p<0.001$ by t-test.

by the t-test which was made on any of these parameters among the three groups.

Experiment 2: Relationship Between Physiological Responses to Alcohol, Blood Acetaldehyde Level, and Urinary Excretion of Catecholamines

Eleven out of the subjects who presented marked facial flushing, and 15 who showed no facial flushing in the preceding experiment were selected as subjects.

Facial flushing after the drinking. The 11 subjects of the flushing group all presented also severe facial flushing in this experiment for about 30–60 min after the start of the drinking, and normal facial color returned in 3–4 hr.

Relationship between blood alcohol and acetaldehyde levels and pulse rate. The blood alcohol and acetaldehyde levels and the rate of increase in pulse rate in the flushing and non-flushing groups are shown in Table 2. As observed in the preceding experiment, there was no difference in the blood alcohol level between the two groups. The blood acetaldehyde level of the non-flushing group scarcely increased and remained 0–0.31 μg/ml, while that of the flushing group was markedly increased and reached to the maxima 0.48–0.95 μg/ml between 0.5 and 2 hr after the drinking. The pulse rate in the non-flushing group virtually did not increase, while the rate in the flushing group strikingly increased 30–60 min after the drinking.

Urinary excretion of catecholamines. The urinary excretions of epinephrine and norepinephrine and the maximum blood acetaldehyde levels in the non-flushing and flushing groups in the control experiment and the experiment with alcohol are shown in Table 3. The urinary epinephrine and norepinephrine in the control experiment varied considerably from subject to subject, but no difference was noted in the mean excretion of either catecholamine between the non-flushing and flushing groups. In the alcohol experiment, the excretion of both catecholamines presented no significant difference in the non-flushing group, but a significant increase in the flushing one.

Alterations in skin temperature, pulse rate, pulse waves of fingertip and electrocardiogram. In all the flushing subjects, the forehead skin temperature rose by 1.0–2.5°C at 30 min after the start of the drinking, dropped as the flushing faded, and returned mostly to the same pre-drinking level by 3–4 hr after the drinking. The temperature was scarcely found to rise in the non-flushing subjects. The blood pressure did not vary markedly in either group.

In Fig. 1(a) are shown the findings in a typical case where palpitation was complained of, 30 min after the start of the drinking, associated with flushing not only in the face but all over the body, and where the blood pressure remained unchanged, but the blood acetaldehyde level, pulse rate, skin

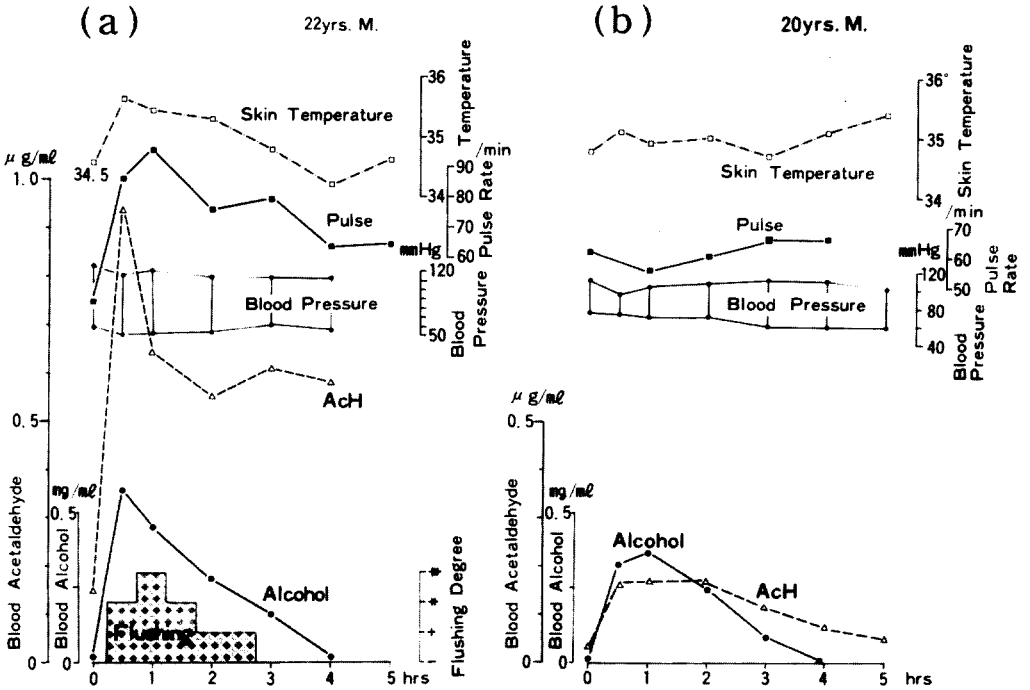

FIG. 1. Time course of changes of blood alcohol and acetaldehyde levels, degrees of facial flushing, skin temperature, pulse rate and blood pressure following intake of 200 ml *sake* in flushing (a) and non-flushing (b) subjects.

temperature, urinary excretions of epinephrine and norepinephrine were all increased. No symptoms and signs of drunken sickness evolved, however. In Fig. 1(b) are shown the findings in the case of a student with little experience of drinking, where no facial flushing occurred, but where mild dizziness was complained of 2 hr after the drinking, and a mild headache 3 hr after the drinking, but both of these complaints disappeared 4 hr after the drinking. The blood acetaldehyde level scarcely increased. The blood pressure remained unchanged nor were the skin temperature, pulse rate and urinary excretions of epinephrine and norepinephrine increased.

In all the flushing subjects, a marked incisura appeared in the fingertip plethysmogram 30 min after the drinking, but the normal pattern gradually returned thereafter as the blood acetaldehyde level decreased. In Fig. 2(a) are shown alterations in the pulse wave pattern of one flushing subject. The coefficient of incisura 30 min after the drinking was 0.23, with the incisura disappearing along with the fading of the flushing and a decrease in pulse rate. In Fig. 2(b) are shown the pulse wave patterns of one non-flushing subject. No alterations occurred either in the pulse rate or the pulse wave pattern of this subject. The pulse wave pattern did not alter in any other non-flushing subject.

In many flushing subjects, the electrocardiogram pattern showed an increase in heart rate and a depression of T waves. On the other hand, no depression or very slight depression of T waves, if any, was observed in the non-flushing subjects.

Experiment 3: Alterations in the Blood Flow Rate and Arterial Pressure in the Common Carotid Arteries After Drinking

Sixteen normal subjects aged 20–30 were given *sake*. The mean blood flow rate in the common carotid artery was increased by not less than 25%, 30–60 min after the start of the drinking in 5 out of 16 subjects, the increase being associated with marked facial flushing and increases in pulse rate in all of them, while the facial color remained unchanged or only slight facial flushing occurred in the other subjects. In the subjects presenting marked flushing, the blood flow rate pattern became diphasic, along with an increase in arterial pressure, while no alterations occurred in the non-flushing subjects. In Fig. 3(a) and (b) are shown the recordings in typical cases where flushing occurred and not, respectively. The wave patterns of the arterial pressure and blood flow rate changed in the former case after the drinking, but not in the latter case.

Figure 4 shows the time course of changes of the findings in the same subjects as Fig. 3. In the flushing case, the mean arterial pressure in the common carotid artery was 1.30 g/cm^2 before, and 3.65 g/cm^2 2 hr after the drinking, and the mean blood flow rate was 6.41 cm/sec before, and 9.38 cm/sec after the drinking; thus, both parameters were markedly increased after the drinking. In the non-flushing case, however, the arterial pressure was 1.38 g/cm^2 before, and 1.25 g/cm^2 1 hr after the drinking, and the mean blood flow rate was 6.39 cm/sec and 7.76 cm/sec; thus, neither parameter was markedly increased. In the former (the flushing case), 200 ml of *sake* was administered, and in the latter (the non-flushing case), 400 ml; however, the blood acetaldehyde levels were higher in the former.

DISCUSSION

Alcohol has been reported to produce peripheral vasodilatation [5, 8, 16, 18, 19, 25]. On the other hand, there are also many reports, indicating that an adequate amount of alcohol

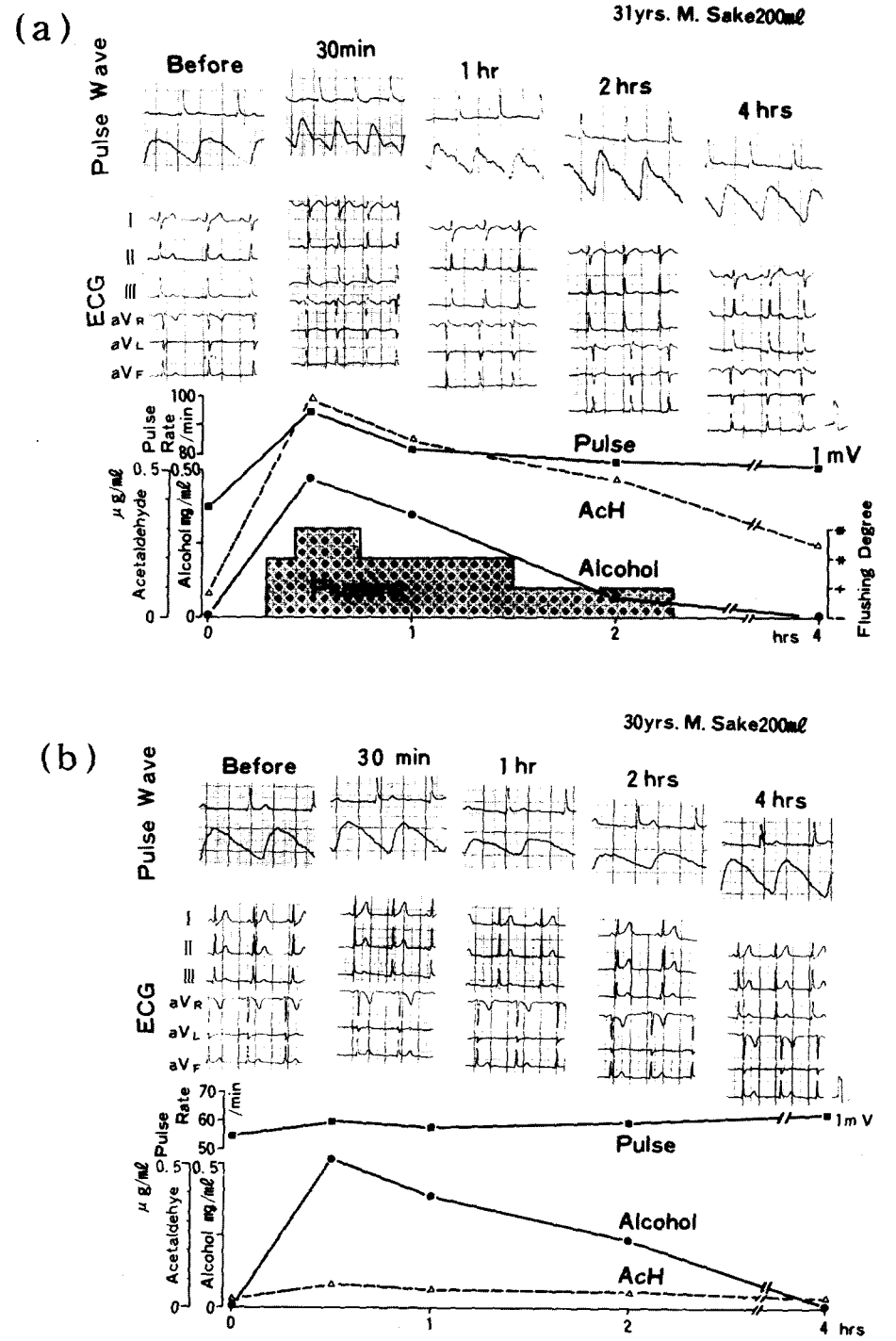

FIG. 2. Time course of changes of blood alcohol and acetaldehyde levels, degrees of facial flushing, pulse wave of fingertip and electrocardiogram following intake of 200 ml *sake* in flushing (a) and non-flushing (b) subjects.

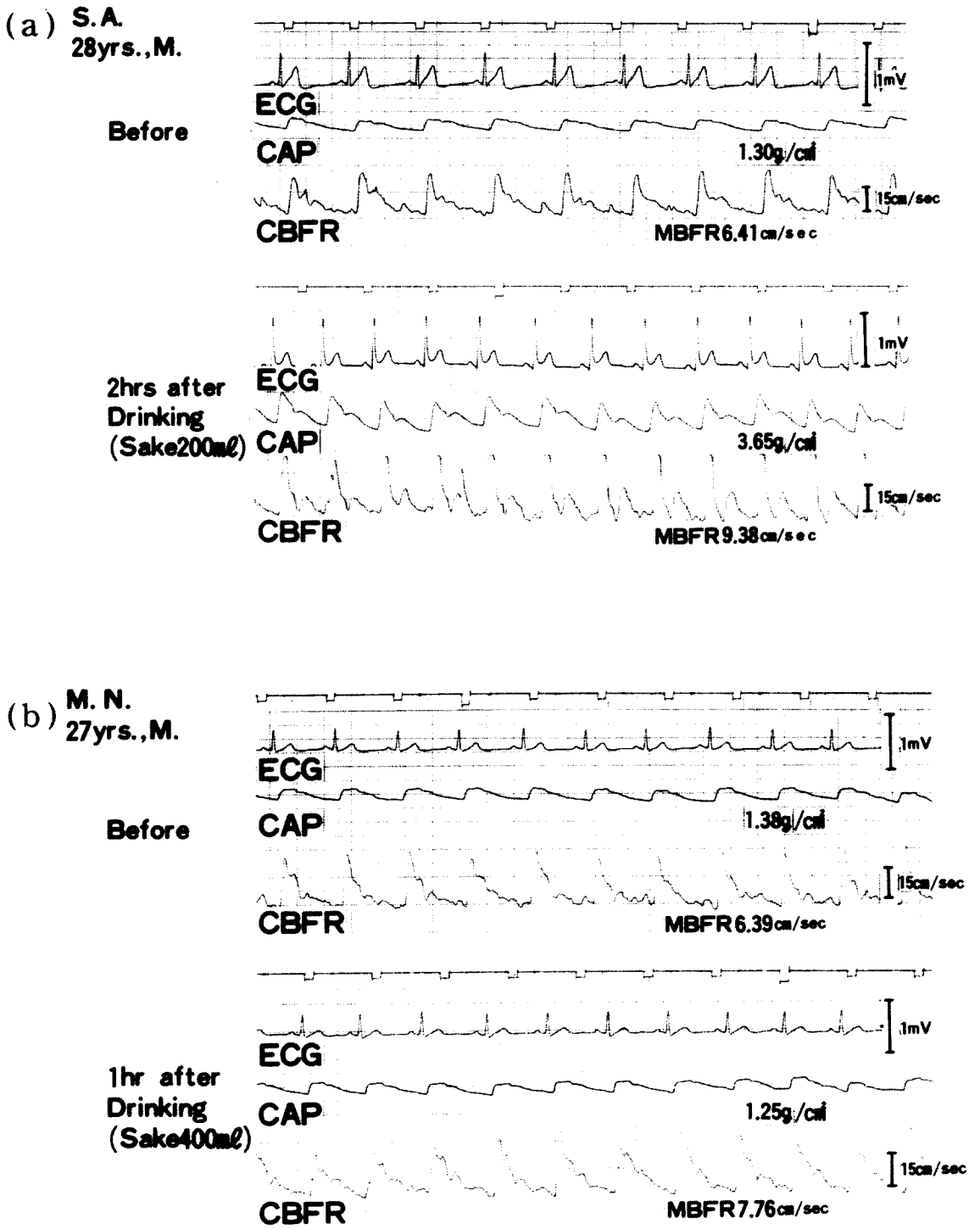

FIG. 3. Recordings of the electrocardiogram (ECG), and the arterial pressure (CAP) and blood flow rate (CBFR) in the common carotid arteries before and after drinking *sake* in flushing (a) and non-flushing (b) subjects. (MBFR: mean blood flow rate)

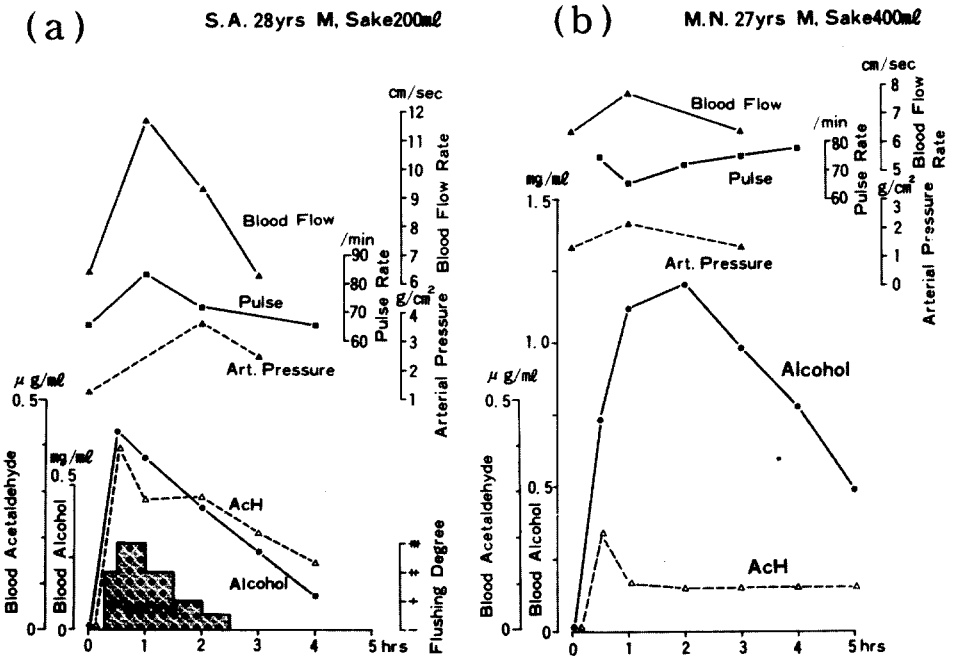

FIG. 4. Time course of changes of blood alcohol and acetaldehyde levels, pulse rate, and the carotid arterial pressure and blood flow rate of common carotid arteries in the same subjects as Fig. 3.

is either inert on, or only transiently and slightly increases, the heart rate, cardiac output and blood pressure [8, 9, 18, 20, 24, 30, 38]. The present study demonstrated that alcohol might be only partly responsible for the symptoms and signs that evolve after drinking, associated with vasodilatation, but acetaldehyde is responsible for the major part of the severe symptoms and signs. In his study on dogs, Handovsky [22] found the sympathomimetic actions of acetaldehyde such as acceleration of respiration and cardiac action, and a sharp rise in blood pressure; these effects of acetaldehyde have been confirmed by many authors [3, 10, 15, 29, 33, 39].

It was shown by Klingman and Goodall [26] as well as by von Wartburg *et al.* [41] that the urinary excretion of catecholamines increases in animals given alcohol. It was also disclosed by Walsh and Truitt [40] that alcohol only slightly increases the urinary excretion of norepinephrine in cats and rabbits, but that acetaldehyde markedly increases the excretion. Perman [34] and Akabane *et al.* [3] found that acetaldehyde increases the release of epinephrine and norepinephrine from the adrenal glands; and Nakanishi *et al.* [32] revealed that alcohol does not increase the release of epinephrine and norepinephrine from the same glands.

Some authors [1,5] report that the urinary excretion of catecholamine is increased when normal men drink alcohol, while others [7,17] find that the excretion does not vary. However, there are no published studies of the relationship between the urinary excretion of catecholamine and the blood acetaldehyde level. From the findings in our present study, it may be considered that the discrepancies between these reports are largely attributable to the difference in the blood acetaldehyde level, and individual or ethnic differences in the sensitivity to acetaldehyde. Wolff [44] reported that 83% of Japanese and Taiwanese adults responded to alcohol ingestion with a marked visible flush and with increased optical density of the earlobe, while only one of the 34 Caucasian adults showed visible flushing and only 2 had an increase on optical density of the earlobe comparable to that of the Oriental adults. Ewing *et al.* [14] described that 24 Oriental subjects showed higher blood acetaldehyde levels in response to alcohol ingestion than 24 Occidental ones, and that the former were significantly more sensitive to alcohol, responding with skin flushing, increased heart rate and a drop in blood pressure. Reed *et al.* [37] also showed that there is a difference in the blood acetaldehyde level as well as in the rate of alcohol metabolism between Caucasians, Chinese and Ojibwas. Zeiner [45] reported that the responses of the Caucasians to alcohol differ from those of the Tarahumara Indians.

All the experiments in our present study were made on Japanese only; and the slightly and highly flushing subjects accounted for 21% (16 subjects) and 37% (28) of a total of 75 subjects selected for the first experiment. However, care was exercised in our experiments so as to include more flushing subjects. For this reason, the actual population of flushing people in the Japanese may be considered to be slightly less than the figures given above. In the highly flushing subjects are included subjects with alcohol intolerant constitutions who readily presented dysphoric symptoms, e.g., severe palpitation, pounding in the head, nauseous feeling, and increased pulse rate; such people may be estimated as accounting for about 10% of the Japanese [28]. These symptoms are similar to the manifestations of disulfiram-alcohol reaction, and the fact suggests that at least high blood acetaldehyde levels are related with the evolvement of these symptoms and signs. However, the problem as to whether the constitution giving rise to such symptoms and signs is under genetic influence or not has not been thor-

oughly solved as yet; therefore, this problem could not be speculated on in the present study. Von Wartburg [42] proposed the hypothesis that individual differences in the response to alcohol are governed by the genetic polymorphisms seen in the human liver alcohol dehydrogenase. On the other hand, individual difference of the blood acetaldehyde level might be correlated with the activity of aldehyde dehydrogenase in liver, because it has been suggested that acetaldehyde metabolism during ethanol oxidation is regulated by the activity of liver aldehyde dehydrogenase [12], and it has been shown that in rat after ethanol administration, the acetaldehyde concentrations in blood and liver of the strain with low preference for ethanol are higher than in the ethanol-preferring strain [11] and that the ethanol-avoiding rat strain has higher alcohol dehydrogenase and lower aldehyde dehydrogenase activities than rats of the ethanol-preferring strain [27]. It may be, therefore, anticipated that studies on the response to alcohol will include a greater genetical aspect in the future.

It remains yet to be studied whether the increased urinary excretion of catecholamines results directly from the increased blood acetaldehyde levels or not, and why facial flushing is related with the increased urinary catecholamines.

For the last, it might be added that there is a great difference between the human blood acetaldehyde levels reported by Ewing *et al.* [14] and Reed *et al.* [37] and those obtained in the present study, because the spontaneous formation of acetaldehyde resulting from hemolysis or deproteinization of the blood sample was avoided in our procedure [31].

REFERENCES

1. Abelin, I., C. Herren and W. Berli. Über die erregende Wirkung des Alkohols auf den Adrenalin- und Noradrenalin-haushalt des menschlichen Organismus. *Helv. Med. Acta.* **25:** 591–600, 1958.
2. Abramson, D. I., H. Zazeela and N. Schkloven. The vasodilating action of various therapeutic procedures which are used in the treatment of peripheral vascular disease. *Am. Heart J.* **21:** 756–766, 1941.
3. Akabane, J., S. Nakanishi, H. Kohei, R. Matsumura and H. Ogata. Studies on sympathomimetic action on acetaldehyde . I. Experiments with blood pressure and nictitating membrane responses. *Jap. J. Pharmac.* **14:** 295–307, 1964.
4. Akabane, J., S. Nakanishi, H. Kohei, S. Asakawa, R. Matsumura, H. Ogata and T. Miyazawa. Studies on sympathomimetic action of acetaldehyde. II. Secretory response of the adrenal medulla to acetaldehyde: Experiments with the perfused cat adrenals. *Jap. J. Pharmac.* **15:** 217–222, 1965.
5. Anton, A. H. Ethanol and urinary catecholamines in man. *Clin. Pharmac. Ther.* **6:** 462–469, 1965.
6. Asmussen, E., J. Hald and V. Larsen. The pharmacological action of acetaldehyde on human organism. *Acta pharmac. Toxicol.* **4:** 311–320, 1948.
7. Davis, V. E., H. Brown, J. A. Huff and J. L. Cashaw. Ethanol-induced alterations of norepinephrine metabolism in man. *J. Lab. Clin. Med.* **69:** 787–799, 1967.
8. Docter, R. F. and R. B. Perkins. The effects of ethyl alcohol on autonomic and muscular responses in humans. I. Dosage of 0.5 milliliter per kilogram. *Q. Jl Stud. Alcohol* **22:** 374–386, 1961.
9. Donald, P. R., C. J. Abnash, T. D. Joseph and N. Y. Albany. Acute hemodynamic effects of ethanol on normal human volunteers. *Am. Heart J.* **78:** 592–597, 1969.
10. Eade, N. R. Mechanism of sympathomimetic action of aldehydes. *J. Pharmac. exp. Ther.* **127:** 29–34, 1959.
11. Eriksson, C. J. P. Ethanol and acetaldehyde metabolism in rat strains genetically selected for their ethanol preference. *Biochem. Pharmac.* **22:** 2283–2292, 1973.
12. Eriksson, C. J. P. Hepatic acetaldehyde metabolism during ethanol oxidation. In: *Alcohol and Aldehyde Metabolizing Systems,* Vol. III, edited by R. G. Thurman, J. R. Williamson, H. R. Drott and B. Chance. New York/San Francisco/London: Academic Press, 1977, pp. 285–294.
13. von Euler, U. S. and I. Floding. A fluorometric micromethod for differential estimation of adrenaline and noradrenaline. *Acta physiol. scand.* **33:** 45–62, 1955.
14. Ewing, J. A., B. A. Rouse and E. D. Pellizzari. Alcohol sensitivity and ethnic background. *Am. J. Psychiat.* **131:** 206–210, 1974.
15. Feingold, A. Effects of adrenal ligation and adrenergic blockade in pressor responses to acetaldehyde in dogs. *Proc. Soc. exp. Biol. Med.* **80:** 667–668, 1952.
16. Fewings, J. D., M. J. D. Hanna, J. A. Walsh and R. F. Whelan. The effects of ethyl alcohol on the blood vessels of the hand and forearm in man. *Br. J. Pharmac. Chemother.* **27:** 93–106, 1966.
17. Garlind, T., L. Goldberg, K. Graf, E. S. Perman, T. Strandell and G. Ström. Effect of ethanol on circulatory, metabolic, and neurohormonal function during muscular work in men. *Acta Pharmac. Toxicol.* **17:** 106–114, 1960.
18. Gillespie, J. A. Vasodilator properties of alcohol. *Br. Med. J.* **2:** 274–277, 1967.
19. Graf, K. and G. Ström. Effect of ethanol ingestion on arm blood flow in healthy young men at rest and during leg work. *Acta Pharmac. Toxicol.* **17:** 115–120, 1960.
20. Grollman, A. The influence of alcohol on the circulation. *Q. Jl Stud. Alcohol* **3:** 5–14, 1942.
21. Hald, J. and E. Jacobsen. The formation of acetaldehyde in the organism after ingestion of Antabuse (tetraethylthiuram disulfide) and alcohol. *Acta Pharmac. Toxicol.* **4:** 305–310, 1948.
22. Handovsky, H. Au sujet des propriétés biologiques et pharmacodynamiques de l'acétaldéhyde. *C.r. Séanc. Soc. Biol.* **117:** 238–241, 1934.
23. Herman, H., J. Chatonnet and J. Vial. Les propriétés pharmacodynamiques et particuliérement sympathicomimétiques de l'éthanol. *Archs int. Pharmacodyn. Thér.* **102:** 432–449, 1955.
24. Holmberg, G. and S. Martens. Electroencephalographic changes in man correlated with blood alcohol concentration and some other conditions following standardized ingestion of alcohol. *Q. Jl Stud. Alcohol* **16:** 411–424, 1955.
25. Horwitz, O., H. Montgomery, E. D. Longaker and A. Saÿen. Effects of vasodilator drugs and other procedures on digital cutaneous blood flow, cardiac output, blood pressure, pulse rate, body temperature and metabolic rate. *Am. J. Med. Sci.* **218:** 669–682, 1949.
26. Klingman, G. I. and McC. Goodall. Urinary epinephrine and levarterenol excretion during acute sublethal alcohol intoxication in dogs. *J. Pharmac. exp. Ther.* **121:** 313–318, 1957.
27. Koivula, T., M. Koivusalo and K. O. Lindros. Liver aldehyde and alcohol dehydrogenase activities in rat strains genetically selected for their ethanol preference. *Biochem. Pharmac.* **24:** 1807–1811, 1975.
28. Konuma, M. Introduction to the studies on alcohol intolerant constitution. On the status of multitude coexistence of this constitution with epileptoids. *Jap. J. Stud. Alcohol* **1:** 53–66, 1966.
29. Koppanyi, T. Acetaldehyde, a volatile anesthetic and sympathetic stimulant. *Anesthesiology* **6:** 603–611, 1945.
30. Luff, K. and G. Bohne. Die Pulsfrequenz als Indikation des alkoholbedingten Leistungsabfalls bei psychotechnischen Versuchen. *Ärztl. Wschr.* **9:** 1004–1008, 1954.

31. Maruyama, J., S. Hishida, T. Okada, S. Asakura and Y. Mizoi. Some problems on determination of acetaldehyde in blood after drinking. In: *Proceedings of the International Medical Symposium on Alcohol and Drug Dependence*, ICAA Symposium in Japan 1977, p. 140.
32. Nakanishi, S., H. Kohei, S. Asakawa and J. Akabane. Secretory response of the adrenal medulla to ethanol. Experiment with the perfused cat adrenals. *Med. J. Shinshu Univ.* **12:** 17–20, 1967.
33. Nelson, E. E. Pressor response to acetaldehyde and its potentiation by cocaine. *Proc. Soc. exp. Biol. Med.* **55:** 23–24, 1943.
34. Perman, E. S. The effect of acetaldehyde on the secretion of adrenaline and noradrenaline from the suprarenal gland of the cat. *Acta physiol. scand.* **43:** 71–76, 1958.
35. Perman, E. S. The effect of ethyl alcohol on the secretion from the adrenal medulla in man. *Acta physiol. scand.* **44:** 241–247, 1958.
36. Perman, E. S. Observations on the effect of ethanol on the urinary excretion of histamine, 5-hydroxy-indolacetic acid, catecholamines and 17-hydroxycorticosteroids in man. *Acta physiol. scand.* **51:** 62–67, 1961.
37. Reed, T. E., H. Kalant, R. J. Gibbins, B. M. Kapur and J. G. Rankin. Alcohol and acetaldehyde metabolism in Caucasians, Chinese and Amerinds. *Can. Med. Ass. J.* **115:** 851–855, 1976.
38. Stein, S. W., W. H. Abelmann, C. S. Lieber, C. M. Leevy and G. R. Cherrick. Hepatic and systemic blood flow in man during intravenous infusion of ethanol. *J. Clin. Invest.* **39:** 1032, 1960.
39. Teague, R. S. and C. Wingard. Sympathomimetic activity of certain aldehydes. *Fedn Proc.* **12:** 372, 1953.
40. Walsh, M. J. and E. B. Truitt, Jr. Release of 7-H^3-norepinephrine in plasma and urine by acetaldehyde and ethanol in cats and rabbits. *Fedn Proc.* **27:** 601, 1968.
41. von Wartburg, J. P., W. Berli and H. Aebi. Der Einfluss langdauernder Äthylalkoholbelastung auf die Katecholaminausscheidung im Harn der Ratte. *Helv. Med. Acta* **28:** 89–98, 1961.
42. von Wartburg, J. P. Sensitivity to alcohol, a pharmacogenetic problem? In: *Proceedings of the International Medical Symposium on Alcohol and Drug Dependence*, ICAA Symposium in Japan, 1977, p. 4.
43. Widmark, E. M. P. *Die Theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung*. Berlin: Urban and Schwarzenberg, 1933.
44. Wolff, P. H. Ethnic differences in alcohol sensitivity. *Science* **175:** 449–450, 1972.
45. Zeiner, A. R., A. Paredes and L. Cowden. Physiologic responses to ethanol among the Tarahumara Indians. *Ann. N.Y. Acad. Sci.* **273:** 151–158, 1976.