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Genetic Factors Which Regulate Alcohol Drinking Behavior and Their Effects on Health Status

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Abstract High alcohol sensitivity common among Orientals is mainly due to genetic polymorphism in the low K_m aldehyde dehydrogenase (*ALDH2*) gene. The relation of the *ALDH2* genotype to alcohol sensitivity and drinking behavior was investigated in a Japanese occupational population. The frequency of alcohol-associated symptoms generally increased in the order of the typical homozygote, heterozygote, and atypical homozygote. Both drinking frequency and amounts of alcohol consumption were also significantly affected by the polymorphism. Polymorphism in the alcohol dehydrogenase β-subunit (*ADH2* gene) appeared to contribute to skin flushing post-alcohol exposure but not to alcohol drinking behavior. Multivariate analysis revealed that high alcohol consumption, the ALDH2*1/*1 genotype, and high daily hassles levels significantly contribute to the prevalence of those with a high problem-drinking score in an occupational population. In the study to assess the effects of the *ALDH2* polymorphism and alcohol use on the induction of chromosome alterations in peripheral lymphocytes, we found that lymphocytes from habitual drinkers with the atypical *ALDH2* genotypes had significantly higher frequencies of sister-chromatid exchange (SCE) than those from the typical *ALDH2* genotype. We also measured acetaldehyde reversibly bound to hemoglobin (HbAA). In volunteers with the *ALDH2*1/*2* genotype, the HbAA levels increased immediately after the drink and the elevated levels persisted up to 48 h. Among male workers, HbAA levels were significantly correlated with the recent alcohol consumption levels in both the *ALDH2*1/*1* and *ALDH2*1/*2* genotypes. However, the slope was much steeper in the *ALDH2*1/*2* than in the *ALDH2*1/*1*. SCE and HbAA may be utilized as a good biomarker for health problems in the atypical ALDH2 genotype. Further extensive studies are required for evaluation of the interactive effects of genetic and environmental factors on alcohol-related health problems.

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Allylnitrile-Induced Behavioral Abnormalities and Findings Relating to the Mechanism Underlying Behavioral Abnormalities

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Abstract Nitriles are widely used in industry as plastics, solvents, and synthetic intermediates. It has been shown that the thermal degradation of acrylonitrile-based plastics leads to the emission of a great variety of nitriles. Exposure of humans and experimental animals to some nitriles has been shown to lead to disorders of the central nervous, hepatic, cardiovascular, renal, and gastrointestinal systems. Iminodipropionitrile has long been known to induce in experimental animals behavioral syndromes that other nitriles have not been reported to induce. Recently, we have found that a single administration of allylnitrile, an analog of acrylonitrile, induces in rodents behavioral abnormalities including head twitching, head weaving, random circling, increased locomotor activity, backward pedaling, pivoting, and somersaulting. The induced abnormalities were persistent. Crotononitrile and 2-pentenenitrile also are able to produce behavioral abnormalities. Thus, the nitriles appear as a new class of neurotoxic compounds with potential relevance to the human health. The mechanism by which allylnitrile induces and maintains the behavioral abnormalities is summarised below.

1. Allylnitrile activates the serotonin (5-HT) system in the central nervous system, and as a consequence activation of 5-HT-2 receptors due to increased 5-HT may lead to induction of head twitching.

2. Although the data available indicate that the dopamine (DA) system may be involved in allylnitrile-induced behavioral abnormalities, it remains unknown how the DA system relates to the abnormalities.

3. Allylnitrile decreases the noradrenaline level in the central nervous system, which is thought to be secondary to the 5-HT system activation mentioned above. The allylnitrile-induced head twitching ,however,may occur in consequence to both enhanced β-adrenoceptor stimulation and to the removal of tonic inhibitory control by α-2-adrenoceptors.

4. The neuropathological data indicate an important role of the medial habenular and raphe nuclei in allylnitrile-

induced behavioral abnormalities. Onset of the behavioral abnormalities appears to be associated with the impairment in the medial habenulo-raphe relay owing to activation of apoptotic cascade in neurons.

5. On the basis of the findings with iminodipropionitrile and crotononitrile, allylnitrile might produce pathological changes in the vestibular sensory hair cells.

Further studies are needed to explore the mechanism underlying the allylnitrile-induced syndromes.

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Building Aging Level Indices Based on Ability to Perform Personal Care and Household Management Activities

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Abstract Defining aging as deterioration of the ability required for the activities of daily living with increasing age, we developed a formula for estimating the age of aging. In 1994 and 1995, a questionnaire survey was conducted for 11,592 individuals (4,885 men, mean age 61.6, standard deviation 14.6; and 6,677 women, mean age 63.2, standard deviation 14.8) who were members of 7 cohorts (5 community-based cohorts and 2 cohorts of examiners at a health-promotion center). The questionnaire included three groups of questions related to medical treatment, aging-related symptoms, and personal care (ADL; Activities of Daily Living) and household management (IADL: Instrumental ADL). Multiple regression analysis was made by sex and age group (over 65 years old, under 65 years old) using age as a dependent variable and the three question categories as explanatory variables. Using multiple regression analysis by question category, five items were abstracted from each of the three groups, so that a total of 15 items were abstracted from all questions. Five items were then abstracted from the 15 by multiple regression analysis, and the predicted aging age for an individual is estimated using this statistical model from the results of the questionnaire survey. The predicted aging age is significantly associated with age ($r = 0.40 - 0.49$, $p = 0.0001$). The difference between the predicted aging age and age is greater among the older or younger people. The expected predicted aging age is estimated using regression analysis of the predicted aging age on age. Aging level indices by sex and age groups were determined by the difference between the expected predicted aging age and age.

We are planning to carry out an epidemiological study on the risk factor for aging using the aging level indices in seven cohorts.

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Serum Leptin Level among Non-obese Students : Relationship to Body Fat, Blood Pressure, Serum Lipids, Physical Activity, and Eating Habits.

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Abstract An experimental study was performed on orchiopathy (testis disorder) by using cadmium (Cd) and on the prevention of orchiopathy by the administration of selenium (Se). By a single administration of Cd 1.4 mg/kg (12.4 μ mol/kg) or a second administration of Cd 1.4 mg/kg 24 hr after the administration of Cd 1.0 mg/kg (8.9 μ mol/kg), the testis of a mouse showed ex-tensive necrosis, and an extreme decrease of glutathione (GSH) concentration accompanied by an increase of thiobarbituric acid reactive substances (TBARS). When Se 1.4 mg/kg (17.7 μ mol/kg)was given at the same time as Cd 1.0 mg/kg, the disorder was completely prevented and their serum Cd and Se concentrations were 1165 $\pm$ 268 ng/ml and 534 $\pm$ 128 ng/ml, respectively. However,when Se was given, separately from the Cd administration, either 24 hr or 72 hr before Cd administration, no effect to prevent testis disorder was found. On the other hand, when Se 1.4mg/kg and Cd 1.0 mg/kg were given simultaneously and then Cd 1.4mg/kg was administered 24 hr and 72 hr after the simultaneous injection,respectively, there was no sign of disorder caused by the second administration of Cd. When Cd was given after administration of Cd and Se, Cd concentration in the testis (0.88 $\pm$ 0.078 μ g/g and 0.77 $\pm$ 0.03 μ g/g) was about twice as much as the concentration inthe case of no administration of Se (0.30 $\pm$ 0.04 μ g/g). The tes-ticular dysfunction could not be explained by the increased Cd concentration in the testis. The groups with high Cd concent-ration in the testis were accompanied by an increase in metallo-thionein(92.8 $\pm$ 18.6 μ g/g and 92.5 $\pm$ 7.3 μ g/g), but these did notexceed the level of the control group (94.5 $\pm$ 8.4 μ g/g) which hadneither Cd nor Se injections. In the groups with testicular necrosis, concentrations of zinc (Zn) and magnesium (Mg) were decreased while an increase in concentrations of calcium (Ca) andiron (Fe) was observed. These results suggest that Se concent-ration must be maintained to prevent the testicular disorder caused by Cd.

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Preventive Effect of Selenium against the Testicular Injury by Cadmium.

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Abstract The differences of the diagnosis from December 1975 to April 1981 and from May 1981 to July 1992 of the Committee on Certification of Minamata Disease based on the medical records of 3,870 applicants who had been examined from December 1975 to April 1981 by the Committee were compared and analyzed from a statistical point of view.

Three hundred forty inhabitants from December 1975 to April 1981 and two hundred ninety eight inhabitants from May 1981 to July 1992, in total six hundred and thirty eight inhabitants, were certified to have Minamata disease by the Committee on Certification of Minamata Disease.

One hundred and eleven inhabitants who were judged likely to have Minamata disease by application of the present criteria presented by the Japanese Environmental Agency in 1977 were certified by the committee from May 1981 to July 1992, and one hundred and thirty three inhabitants who were judged not likely to have Minamata disease by application of the present criteria were certified from May 1981 to July 1992.

The author concluded that certification of the patients of Minamata disease by the Committee was inconsistent with the results of applying the present criteria to the data and that the prevalence of the symptoms of the inhabitants certified from December 1975 to April 1981 was inconsistent with that from May 1981 to July 1992.

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An Appraisal of the Judgements of the Kumamoto Minamata Disease Certification Commission from May 1981 to July 1992 for Applicants from December 1975 to April 1981

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Abstract The differences of the diagnosis from December 1975 to April 1981 and from May 1981 to July 1992 of the Committee on Certification of Minamata Disease based on the medical records of 3,870 applicants who had been examined from December 1975 to April 1981 by the Committee were compared and analyzed from a statistical point of view.

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