Chapter 2
Taurine as the Nutritional Factor for the Longevity of the Japanese Revealed by a World-Wide Epidemiological Survey

Yukio Yamori, Longjian Liu, Mari Mori, Miki Sagara, Shigeru Murakami, Yasuo Nara, and Shunsaku Mizushima

Abstract The initial observation that taurine (T) prevented stroke in stroke-prone spontaneously hypertensive rats (SHRSP) led us to study the effects of T on cardiovascular diseases (CVD), as well as the epidemiological association of T and mortality rates, by using the data from WHO-coordinated Cardiovascular Disease and Alimentary Comparison Study, which covered 61 populations in 25 countries. In this study, 24 hour urine (24-U) samples were examined along with biomarkers of CVD risk. The mortality rate from ischemic heart disease (IHD), which was lowest among the Japanese compared to the populations of other developed countries, was positively related to total serum cholesterol (TC) and inversely related to 24-U taurine excretion (24-UT), as well as the n-3 fatty acid to total phospholipids ratio of the plasma membrane, both biomarkers of seafood intake. Analysis of 5 diet-related factors revealed that TC and BMI were positively associated with IHD mortality in both genders while Mg and T were negatively associated with IHD mortality. TC and sodium (Na) were negatively and positively associated with stroke mortality, respectively. 24-UT was negatively associated with stroke mortality. These five diet-related factors explained 61 and 49% of IHD and stroke variances in male, 63 and 36% of IHD and stroke variances in female, respectively.

Abbreviations *T*, taurine; *Na*, sodium; *Mg*, magnesium; *CVD*, cardiovascular diseases; *IHD*, ischemic heart diseases

2.1 Introduction

Taurine (T) is abundant in the seafood consumed in large quantities by the Japanese, who are presently enjoy the longest life expectancy in the world, with a life expectancy of 86 among females and 79 among males, the latter which rates

Y. Yamori (✉)
Mukogawa Women's University, Japan

second in the world. Since various experimental studies, as well as epidemiological evidence from our world-wide cooperative study on nutrition and cardiovascular disease (CVD), suggest the importance of T in reducing the risk of CVD, it is possible that T is a food factor that contributes to Japanese longevity.

2.2 Basic Studies of T Effect on CVD Risks

2.2.1 T Effect on Hypertensive Models

Basic research on hypertension and stroke has made remarkable progress since the establishment of rat models of hypertension and stroke, the spontaneously hypertensive rat (SHR) (Okamoto and Aoki 1963) and the stroke-prone SHR (SMRSP) (Okamoto et al. 1974; Yamori 1984). These animal models develop severe hypertension and die from hemorrhagic and ischemic stroke, making these useful in studying the pathogenesis, prevention and treatment of hypertension and stroke (Yamori 1981; Yamori et al. 1987).

The effect of fish protein-rich diet on stroke prevention was first demonstrated by Yamori et al. (Yamori 1981; Yamori et al. 1987). When SHRSP were fed a normal or low protein diet maintained on drinking water containing 1% salt, they quickly developed severe hypertension and all died of stroke within a short period. Without excess salt, 80% of them died of stroke. In contrast, when fed a high protein fish diet with excess salt, the incidence of stroke was markedly reduced. And in the group fed a high protein fish diet without excess salt intake, the development of severe hypertension was attenuated and no stroke was observed. Thus, it can be concluded that a high protein fish diet attenuates the development of severe hypertension and counteracts the adverse effect of salt.

Of the amino acids in fish and protein that could attenuate the development of severe hypertension and counteract the adverse effect of salt in SHR and SHRSP were the sulfur amino acids, T and methionine (Yamori 1981; Yamori et al. 1987; Nara et al. 1978). T supplementation also prevented the development of hypertension in DOCA-salt hypertensive rats (Sato et al. 1991) and suppressed the elevation in plasma epinephrine and norepinephrine levels, which is likely one of the possible mechanisms underlying the anti-hypertensive actions of T.

2.2.2 Physiological Effect and Distribution of T

Although a simple sulfur amino acid, T has been experimentally found to exert various effects (Huxtable 1992, 2000), such as an antihypertensive effect through central suppression of sympathetic tone, a hypocholesterolemic effect through activation of hepatic 7α-hydroxylase activity to accelerate cholesterol excretion into bile acids and an antiatherogenic effect possibly through the scavenging of hypochlorous acid and formation of T chloramines (Jerlich et al. 2000).

There are species differences in T synthesis with synthesis being particularly poor in humans and cats (Huxtable 1992). In newborn humans, T is considered to be an essential amino acid, since the potential to synthesize T is limited (Huxtable 2000).

In men, T in mainly obtained from fish and seafood, which contain large amounts of T compared to meat (Tsuji and Yano 1984) and are eaten customarily by the Japanese.

2.3 Epidemiological Survey of T Effect on CVD Risks and Mortality

2.3.1 Food Culture and Lifespan in Various Populations

In order to prove whether or not dietary components, such as T, are important in preventing hypertension and atherosclerosis in humans, as well as in animal models, Yamori introduced the idea of performing a world-wide epidemiological study to WHO in 1982. The CARDIAC Study is the acronym of *Car*diovascular *Di*seases and *A*limentary *C*omparison Study and the study was designed to investigate the relation of biological markers of diet with hypertension in"Core Study"and with CVD mortalities in "Complete Study" (WHO and WHO Collaborating Centers 1986; Yamori, 1981, 1989, 2006; Yamori et al. 1990, 2006).

This epidemiological survey has been carried out over the past 20 years in 61 populations in 25 countries (Fig. 2.1). About 100 males and 100 females in ages ranging from 48 to 56 were randomly selected, with the number of participants being over 14,000 in all. Some study sites were revisited at 10 year intervals for a follow-up health survey (MONALISA study; *Mon*eo *Ali*mentationis *Sa*nae = Reminding healthy food), and we noted the populations marked with large clear dots in Fig. 2.1
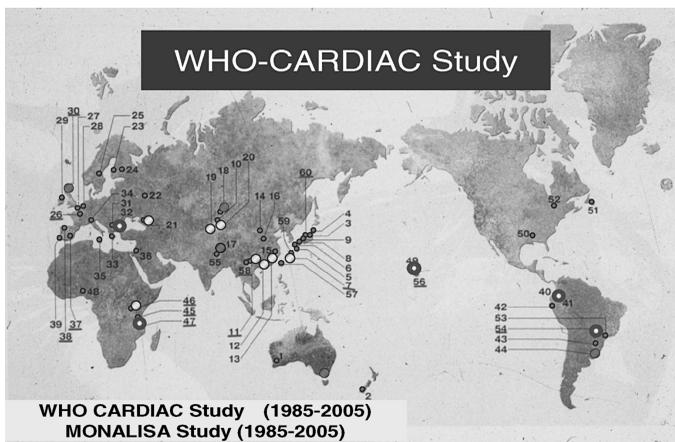

Fig. 2.1 Distribution of study sites in the world, 61 in total, for the WHO-coordinated Cardiovascular Diseases and Alimentary Comparison (WHO-CARDIAC) Study

had lesser risks of lifestyle-related diseases, as well as longer life-expectancy, such as Okinawans in the late 20th century. In contrast, the populations marked with large black dots, had higher risks and shorter life-expectancy. In some populations encircled with large black circles exhibited increased risk factors which shortened their life-expectancy due to the deterioration of their traditional food patterns, such as eating seafood.

2.3.2 Fish Intake and Urinary T Excretion

The CARDIAC study used the world-wide distribution of 24-UT excretion as an index of seafood intake (Yamori et al. 1996). T intake estimated by 24-UT (μmol/day) is high, particularly among the Japanese population (male, 1700–3300) and moderately high among the Mediterranean population (male, 1300–1700). The distribution among the Chinese population is variable, being lowest among Tibetans (male, 350) and among the Uygurs living in Oasis, but moderately high among the southern Chinese population living near the sea (Guangzhou, male, 1500).

The frequency analysis of fish consumption (x; times a week) was positively related with 24-UT excretion (y; μmol/day) [y=277.3x+302.6, r=0.723, r^2=0.522, p<0.001], indicating that T is a reliable bio-marker of fish intake. These data also indicate that Japanese and Mediterranean populations customarily eat seafood and consume considerable T. This may be associated with the epidemiological finding that both Japanese and Mediterranean foods are cardioprotective.

2.3.3 Low CVD Risks in Fish Eaters

Our CARDIAC Study populations can be classified into 2 groups, fish eaters and non-fish eaters according to the cut off level of 24-U taurine value of 1000 μmoles in males and 800 μmoles in females. We noted fish eaters had a lower prevalence of obesity, hypertension and hypercholesterolemia in comparison with that of non-eaters (data are not shown).

Furthermore, the indices of obesity, body mass index (BMI) (24.3 ± 0.1 in male (m), 24.4 ± 0.1 in female (f)), the grades of hypertension (systolic blood pressure (SBP) 124.3 ± 0.8 mmHg in m, 120.5 ± 0.8 mmHg in f, as well as hypercholesterolemia (total cholesterol (TC); 175.4 ± 1.5 mg/dl in m, 184.3 ± 1.5 mg/dl in f) were significantly lower in fish eaters than in non-fish eaters (BMI; 26.1 ± 0.1 in m, 26.7 ± 0.1 in f, SBP; 128.9 ± 0.6 in m, 128.7 ± 0.7 in f. TC; 201.3 ± 1.3 in m, 200.8 ± 1.5 in f).

2.3.4 T Effect on BP in Non-Fish Eaters

Since Tibetans were consuming too much salt and eating virtually no fish because of their strict religious discipline, the prevalence of hypertension was high, with

40% of the people aged 48 to 56 being hypertensive, which is nearly twice the world average of 20%. Moreover, the grades of hypertension were severe, many over 200 mmHg.

We, therefore, carried out an intervention study for Tibetans living in Namche Bazaar, which is located at the foot of Mt. Everest. After completing the WHO-CARDIAC health survey, volunteers with relatively high blood pressure were administered 3 g of T a day, 1 g of T per meal added to the tea. Their systolic and diastolic BP was significantly reduced in 2 months (Yamori et al. 1996).

2.3.5 Low Fish Intake and CVD Risks in Japanese Brazilians

Among the 61 populations examined were Okinawans living in Okinawa, Hawaii and Brazil in the 1990s. CVD risks were the lowest in Okinawans living in Okinawa, whose life expectancy was the longest in Japan and thus in the world (Yamori 2006). However, CVD mortality was higher and the life span was shorter in Japanese immigrants living in Brazil, indicating the importance of environmental factors in longevity (Mizushima et al. 1992). The most common Brazilian food is meat; Brazilians eat roasted meat seasoned with a lot of salt, with over 500 g of meat in one meal. Consequently, the prevalence of hypertension, hypercholesterolemia and obesity among Japanese immigrants living in Brazil were significantly higher than those living in Okinawa (Mizushima et al. 1992).

Among the Japanese immigrants living in Brazil, particularly in Campo Grande far from the sea coast, the frequency of fish intake was the lowest. They ate fish only once every 2 weeks and their life span was 17 years shorter than the Japanese living in Japan, an effect related to the very high IHD mortality rate. Low fish consumption and reduced T intake appeared to increase IHD.

2.4 T Effect on Hypercholesterolemia and Atherosclerosis

2.4.1 Experiments in SHRSP

The effects of T on hyperlipidemia and atherosclerosis were investigated experimentally in various animal models, particularly in SHRSP developing hypercholesterolemia and arterial fat deposits in response to high-fat cholesterol diet feeding (Yamori et al. 1975). Taurine supplementation attenuated the elevation of TC in SHRSP fed a high-fat-cholesterol diet (Murakami et al. 1996a) and decreased fat deposits in the mesenteric artery which were visible within a few weeks after high cholesterol feeding (Murakami et al. 1996b). Thus, the cholesterol-lowering and anti-atheroscle-rotic effects of T were confirmed in the hypertensive rat models.

2.4.2 Mechanisms of Hypocholesterolemic Effect

The mechanisms by which T lowers liver and serum TC levels appears to be linked in part to the acceleration in bile acid production and cholesterol 7α-hydroxylase activity, the rate-limiting enzyme of bile acid synthesis (Yokogoshi et al. 1999). Indeed, an inverse correlation exists between mRNA levels of the cholesterol 7α-hydroxylase (CYP7A1) gene and serum TC levels, indicating that T-mediated enhancement of cholesterol 7α-hydroxylase gene expression stimulates bile acid synthesis from cholesterol and lowers cholesterol levels (Yokogoshi et al. 1999).

The effect of T on serum TC levels and liver LDL receptors was studied in hamsters, because of the similarities between hamsters and humans relative to serum TC levels and cholesterol metabolism (Murakami et al. 2002a). T supplementation attenuated the rise of serum atherogenic LDL and VLDL cholesterol induced by the ingestion of a high-fat diet.

The effect of T on hepatic LDL receptor activity was evaluated by monitoring the disappearance of radio-labeled LDL from the blood. Although no difference was noted in non-receptor-mediated uptake of methylated LDL by liver cells, receptor-mediated LDL uptake was accelerated in T-treated hamsters (Murakami et al. 2002a).

Therefore, it is concluded that T stimulates bile acid synthesis from cholesterol through the enhancement of cholesterol 7α-hydroxylase activity, leading to depletion of the hepatic free cholesterol pool and resulting in enhanced LDL clearance.

2.4.3 Effect of T on Atherosclerotic Lesions

The effect of T on the development of atherosclerosis was further studied in genetically hyperlipidemic models, such as Watanabe heritable hyperlipidemic (WHHL) rabbits (Murakami et al. 2002b), in which T supplementation (1% in drinking water) suppresses the development of atherosclerotic lesion formation, such as lipid-rich macrophage accumulation in the aorta.

Thiobarbituric acid reactive substances (TBARS) in the serum and aorta were decreased in T-treated rabbits. Furthermore, ex-vivo experiments demonstrated that LDL isolated from T-treated rabbits was more resistant to copper-induced oxidation. Consequently, the formation of oxidized LDL was significantly suppressed in the T-treated rabbits (Murakami et al. 2002b).

The effects of T on cholesterol metabolism were different in various animal models, but the anti-atherosclerotic effects of T seemed to be universal (Kondo et al. 2001; Murakami et al. 1996a, b, 2002a, b; Yokogoshi et al. 1999), suggesting that the antioxidant actions of T might be involved in its anti-atherosclerotic effects. The important role of oxidized LDL in the pathogenesis and progression of atherosclerotic lesions has been well established (Penn and Chisoim 1994). Oxidized LDL itself is cytotoxic to endothelial cells, and accelerates the proliferation and the migration of smooth muscle cells. Moreover, excess uptake of oxidized LDL by macrophages results in the formation of lipid-laden foam cells. Oxidized

LDL also modulates the production of cytokines through the endothelial scavenger receptor, LOX-1 (Alexander 1995). Recently, T has been shown to suppress the upregulation of LOX-1 in the kidney of salt-loaded Dahl salt-sensitive rats and to normalize the salt-induced increase in 8-hydroxy-deoxy guanosine content (Chiba et al. 2002), confirming further the importance of the antioxidant effect of T against atherosclerosis.

2.5 Epidemiological Evidence for Anti-Atherosclerotic Nutrients

2.5.1 T as Putative Preventive Nutrient Against IHD

Our world-wide epidemiological study was the first to demonstrate a significant inverse relationship between 24-UT excretion and IHD in males (Fig. 2.2) and in females (Yamori 2006; Yamori et al. 1992, 1996, 2001, 2006) suggesting the importance of T found in the rich seafood diet in preventing IHD. The populations in Fig. 2.2 with the highest T excretion and the lowest IHD mortality are all Japanese populations who also enjoy the longest life expectancy. The Mediterranean populations were second to the Japanese in these parameters. From these data, the dietary goal for the prevention of IHD is the maintenance of sufficient T intake to yield a urinary T excretion rate of over 2000 μmole per day.

2.5.2 T Intake, IHD and Longevity

Japanese, particularly Japanese women enjoy the longest life span in the world, including the lowest mortality rate for IHD, all of which may be ascribed to the highest T intake in the form of seafood.
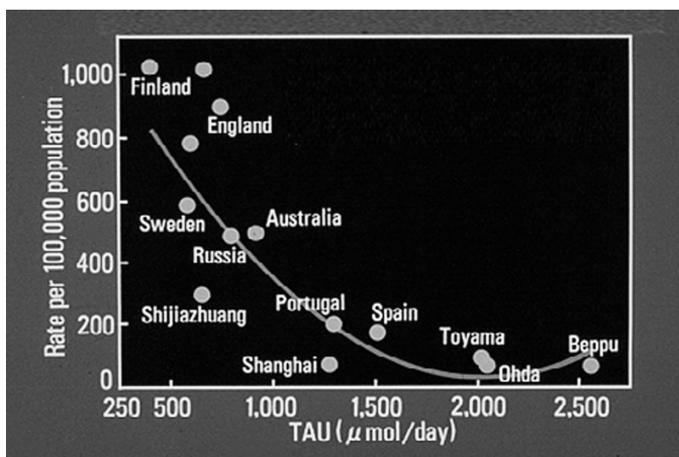

Fig. 2.2 Association between 24-hour urinary taurine (TAU) excretion (x) and age-adjusted mortality rates of IHD (y) in males ($y = 2.95 \times 10^{-4}\chi^2 - 1.21\chi + 1256$, $r = 0.759$, $p = 0.0011$)

Our CARDIAC Study indicates that the average life expectancy is inversely associated with the age-adjusted IHD mortality rate (Yamori 2006). The Japanese populations with the lowest IHD mortality rates had the longest life expectancy of the developed countries. The French population in Orlean had the second longest life expectancy and the second lowest IHD mortality rate.

Although serum TC levels are positively associated with the IHD mortality rate (Yamori 2006; Yamori et al. 2006) a large discrepancy in the association is noted among Scottish and French people. They exhibit a large variation in the intake of vegetables and fruit containing antioxidants, as well as the intake of T from seafood, the latter which is far greater in French than in English, particularly Scottish people (Fig. 2.2). These data indicate the importance of antioxidants in the prevention of IHD.

2.5.3 Diet-Related Factors and IHD

Serum TC levels and the intake of T are positively and inversely related with IHD mortality, respectively. Consequently, we applied structural equation modeling to the male data of the CARDIAC Study populations (Fig. 2.3) (Liu and Yamori 2007). The results help clarify the effects of 5 diet-related factors, namely, TC, BMI,
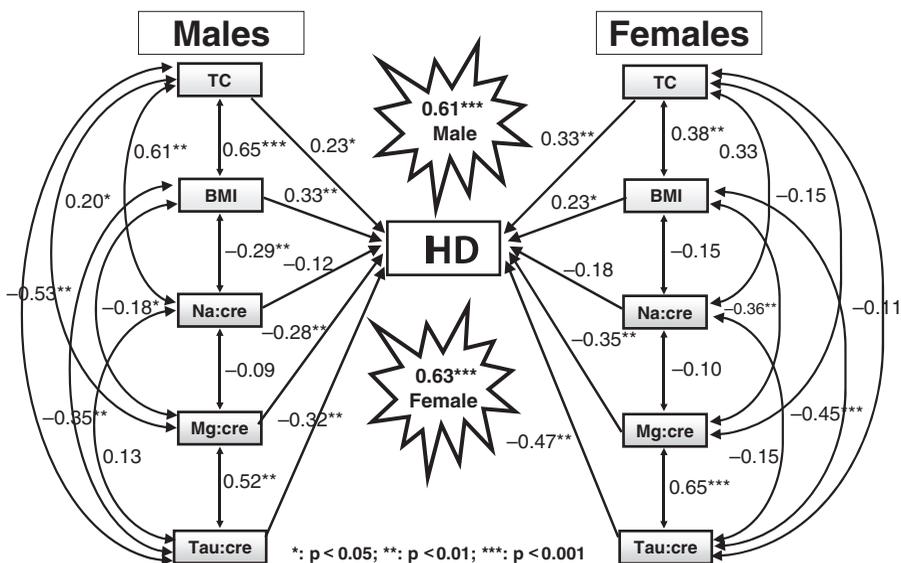

Fig. 2.3 CARDIAC Study results of structural equation modeling (SEM) of IHD. Hypothesis pathway of 5 diets related factors in relation to IHD. TC = serum total cholesterol, BMI = body mass index [weight (kg)/height (m)^2], Na:cre = 24-hour urinary sodium to creatinine ratio, Mg:cre = 24-hour urinary magnesium to creatinine ratio, Tau:cre = 24-hour urinary taurine to creatinine ratio

sodium (Na) to creatinine ratio, magnesium (Mg) to creatinine ratio and T to creatinine ratio in relation to IHD. Each regression coefficient indicates the effect of changing each factor on IHD mortality. For example, an increase in TC by one standard deviation, elevated IHD mortality by 0.33 while an increase in the T to creatinine ratio by one standard deviation reduces IHD mortality by 0.47 standard deviations in females. Thus, the T to creatinine ratio is inversely related with TC, the major risk factor of IHD and positively related with the Mg to creatinine ratio because seafood contains T, as well as Mg. Both were proven to be beneficial dietary factors against IHD. The squared multiple standard regression coefficient equals 0.61 and 0.63 for males and females respectively. It indicates that these 5 diet-related factors accountted for 61% and 63% of IHD variance in the male and female populations, respectively. Among the 5 diet-related factors T is the most potent factor in reducing IHD mortality. It's also interesting that the T to creatinine ratio is inversely related to BMI, confirming the above-mentioned finding that the populations with higher 24-UT excretion are less obese and on average showed lower BMI values.

Moreover, a recent Japanese study reported that T is produced in small-size adipocytes but its production decreases in fat-containing hypertrophic adipocytes (Tsuboyama-Kasaoka et al. 2006). Dietary T supplementation increases the mobilization of fat and basal energy expenditure. Thus, T helps prevent high fat diet-induced obesity. This experimental finding is consistent with our epidemiological data and suggests that T might attenuate obesity.

2.5.4 T and Heart Rate

Further analysis of the epidemiological data demonstrate that fish eaters, whose 24-UT excretions were over 1000 μmoles in males and 800 μmoles in females, had significantly lower BP and also significantly slower heart rates (68.1 ± 0.4 in m, 71.4 ± 0.4 in f) than non-fish eaters (70.0 ± 0.4 in m, 74.1 ± 0.4 in f). Population studies in the US (Dyer et al. 1980; Palatini and Julius 1997), as well as an extensive cohort study in Japan (Okamura et al. 2004) showed that heart rates are inversely related with life expectancy in the elderly. Therefore, more T intake may contribute to longevity by slowing down heart rate.

2.5.5 Five Diet-related Factors and Stroke

We first noted the beneficial effect of T against stroke in SHRSP (Yamori 1981, 1984; Yamori et al. 1987). The results of our structural equation modeling for males and females relating to stroke among CARDIAC populations demonstrated the clear adverse effect of Na on stroke (Fig. 2.4). As Na goes up one standard deviation, it is estimated that stroke mortality goes up 0.49 and 0.35 standard deviations in males and females, respectively. In contrast to Na, when the T to creatinine ratio
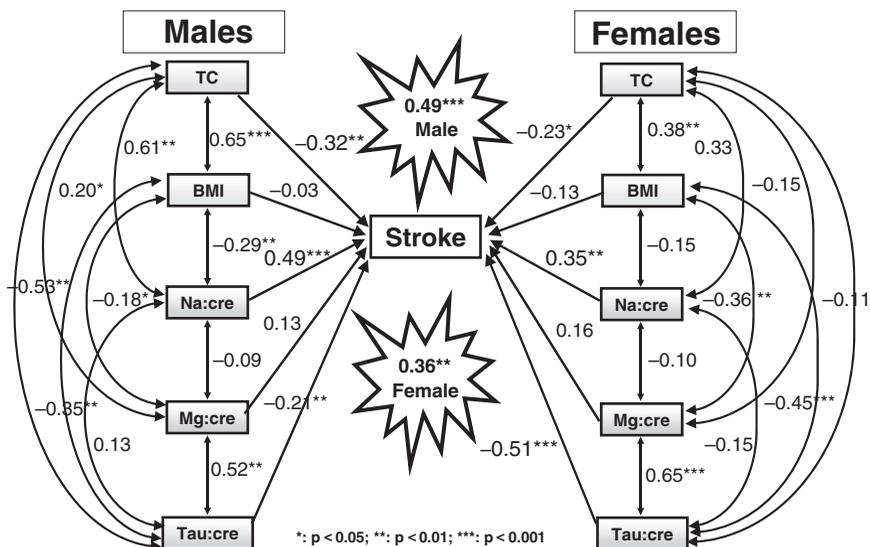
Fig. 2.4 CARDIAC Study results of the structural equation modeling (SEM) for stroke. Hypothesis pathway of 5 diet-related factors in relation to stroke. Abbreviations are explained in the legend for Fig 2.3

goes up one standard deviation, it is estimated that stroke mortality goes down 0.21 and 0.51 standard deviations in males and females, respectively. These five diet-related factors explain 49 and 36% of the variability in stroke among males and females, respectively. These data allow us to speculate that T is protective against both IHD and stroke, the mortality rates of which are inversely related to average life expectancy. Therefore, we conclude that T is a food factor that contributes to longevity.

The role of T in the prevention of stroke may be ascribed to its anti-inflammatory action (Schuller-Levis and Park 2004). Recent epidemiological studies indicate that C-reactive protein (CRP), the marker of inflammation, is closely related not only to IHD but also to stroke. Moreover, since there is early involvement of macrophages in the development of cerebrovascular lesions in SHRSP and humans (Tagami et al. 1993), CRP may be regarded as a predictive marker for stroke (Ballantyne 2005). T may be beneficial by producing T chloramines and attenuating oxidative stress arising from the inflammatory process.

2.6 Conclusion

T has various physiological and pharmacological effects on lifestyle-related diseases (Jacobsen and Smith 1968). Such beneficial effects can be attributed to its basic physiological actions, including osmoregulation, antioxidant/membrane

stabilization and calcium regulation, for which there has been abundant research done internationally.

Our data based on experimental and epidemiological studies support the hypothesis that T intake beneficially affects IHD and stroke, the major outcome of life style-related diseases, through physiological effects on cell viability and function.

Therefore, an adequate level of T inside the body may be important for reducing the risk of IHD and stroke and for the prevention of lifestyle-related diseases.

References

Alexander RW (1995) Theodore Cooper Memorial Lecture: Hypertension and the pathogenesis of atherosclerosis, oxidative stress and the mediation of arterial inflammatory response:a new perspective. Hypertension 25:155–161

Ballantyne CM, Hoogeveen RC, Bang H, Coresh J, Folsom AR, Chambless LE, Myerson M, Wu KK, Sharrett AR, Boerwinkle E (2005) Lipoprotein-associated phospholipase A^2, high-sensitivity c-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the atherosclerosis risk in communities (ARIC) study. Arch Intern Med 165: 2479–2484

Chiba Y, Ando K, Fujita T (2002) The protective effects of taurine against renal damage by salt loading in Dahl salt-sensitive rats. J Hypertens 20:2269–2274

Dyer AR, Persky V, Stamler J, Paul O, Shekelle RB, Berkson DM, Lepper M, Schoenberger JA, Lindberg HA (1980) Heart rate as a prognostic factor for coronary heart disease and mortality: findings in three Chicago epidemiologic studies. Am J Epidemiol 112:736–749

Huxtable RJ (1992) Physiological actions of taurine. Physiol Rev 72:101–163

Huxtable RJ (2000) Expanding the circle 1975–1999:Sulfur biochemistry and insights on the biological functions of taurine. Adv Exp Med Biol 483:1–25

Jacobsen JG, Smith LH (1968) Biochemistry and physiology of taurine and taurine derivatives. Physiol Rev 48:424–511

Jerlich A, Fritz G, Kharrazi H, Hammel M, Tschabuschnig S, Glatter O, Schaur RJ (2000) Comparison of HOCl traps with myeloperoxidase inhibitors in prevention of low density lipoprotein oxidation. Biochem Biophys Acta 481:109–118

Kondo Y, Toda Y, Kitajima H, Oda H, Nagate T, Kameo K, Murakami S (2001) Taurine inhibits development of atherosclerotic lesions in apolipoprotein E-deficient mice. Clin Exp Pharmacol Physiol 28:809–815

Liu L, Yamori Y (2007) Gender difference of cardiovascular diseases as a clue for healthier again: Asian food. Food Culture: Development and Education UNESCO:78–83

Mizushima S, Moriguchi EH, Nakada Y, Gonzalez B, Nara Y, Murakami K, Horie R, Moriguchi Y, Mimura G, Yamori Y (1992) The relationship of dietary factors to cardiovascular diseases among Japanese in Okinawa and Japanese immigrants, originally from Okinawa, in Brazil. Hypertens Res 15:45–55

Murakami S, Yamagishi I, Asami Y, Ohta Y, Toda Y, Nara Y, Yamori Y (1996a) Hypolipidemic effect of taurine in stroke-prone spontaneously hypertensive rats. Pharmacology 52:303–313

Murakami S, Nara Y, Yamori Y (1996b) Taurine accelerates the regression of hypercholesterolemia in stroke-prone spontaneously hypertensive rats. Life Sci 58:1643–1651

Murakami S, Kondo Y, Toda Y, Kitajima H, Kameo K, Sakono M, Fukuda N (2002a) Effect of taurine on cholesterol metabolism in hamsters: Up-regulation of low density lipoprotein (LDL) receptor by taurine. Life Sci 70:2355–2366

Murakami S, Kondo Y, Sakurai T, Kitajima H, Nagate T (2002b) Taurine suppresses development of atherosclerosis in Watanabe heritable hyperlipidemic (WHHL) rabbits. Atheroschlerosis 163:79–87

Nara Y, Yamori Y, Lovenberg W (1978) Effects of dietary taurine on blood pressure in spontaneously hypertensive rats. Biochem Pharmacol 27:2689–2692

Okamoto K, Aoki K (1963) Development of a strain of spontaneously hypertensive rats. Jpn Circ J 27:202–293

Okamoto K, Yamori Y, Nagaoka A (1974) Establishment of the stroke-prone spontaneously hypertensive rat (SHR). Circ Res 34/35:143–153

Okamura T, Hayakawa T, Kadowaki T, Kita Y, Okayama A, Elliott P, Ueshima H, NIPPON-DATA80 Research Group (2004) Resting heart rate and cause-specific death in a 16.5-year cohort study of the Japanese general population. Am Heat J 147:1024–1032

Palatini P, Julius S (1997) Heart rate and the cardiovascular risk. J Hypertens 15:3–17

Penn MS, Chisoim GM (1994) Oxidized lipoproteins, altered cell function and atherosclerosis. Atherosclerosis 108:21–29

Sato Y, Ogata E, Fujita T (1991) Hypotensive action of taurine in DOCA-salt rats-involve-ment of sympathoadrenal inhibition and endogenous opiate. Jpn Circ J 55:500–508

Schuller-Levis GB, Park E (2004) Taurine and its chloramine: Modulators of immunity. Neurochem Res 29:117–126

Tagami M, Tsukada T, Kubota A, Nara Y, Yamori Y (1993) Immunocytochemical study of cerebral perforating arteries in patients with cerebral infactions. Acta Histochem Cytoshem 26:109–115

Tsuboyama-Kasaoka N, Shozawa C, Sano K, Kamei Y, Kasaoka S, Hosokawa Y, Ezaki O (2006) Taurine (2-aminoethanesulfonic acid) deficiency creates a vicious circle promoting obesity. Endocrinology 147:3276–3284

Tsuji K, Yano S (1984) Taurine/cholesterol ratio of well-consumed animal foods. Sulfur Amino Acids 7:249–255

WHO and WHO Collaborating Centers (1986) CARDIAC (Cardiovascular Diseases and Alimentary Comparison) Study Protocol. Shimane, Geneva

Yamori Y (1981) Environmental influences on the development of hypertensive vascular diseases in SHR and related models, and their relation to human disease. In: Worcel M et al. (eds). New Trends in Arterial Hypertension (INSERM Symposium No. 17). Elsevier, Amsterdam: 305–320

Yamori Y (1984) The stroke-prone spontaneously hypertensive rat: Contribution to risk factor analysis and prevention of hypertensive diseases. In: de Jong W (ed). Handbook of Hypertension. Elsevier, Amsterdam:240–255

Yamori Y (1989) Hypertension and biological dietary markers in urine and blood: A progress report from the CARDIAC study group. In: Yamori Y and Strasser T (eds). New Horizons in Preventing Cardiovascular Diseases. Elsevier, Amsterdam:111–126

Yamori Y (2006) Food factors for atherosclerosis prevention. Asian perspective derived from analysis of world wide dietary biomarkers. Exp Clin Cardiol 11:94–98

Yamori Y, Hamashima Y, Horie R, Handa H, Sato M (1975) Pathogenesis of acute arterial fat deposition in spontaneously hypertensive rats. Jpn Circ J 39:601–609

Yamori Y, Horie R, Nara Y, Tagami M, Kihara M, Mano M, Ishino H (1987) Pathogenesis and dietary prevention of cerebrovascular diseases in animal models and epidemiological evidence for the applicability in man. In: Yamori Y and Lenfant C (eds). Prevention of Cardiovascular Diseases, an Approach to Active Long Life. Elsevier, Amsterdam:163–177

Yamori Y, Nara Y, Mizushima S, Mano M, Sawamura M, Kihara M, Horie R, Hatano S (1990) International cooperative study on the relationship between dietary factors and blood pressure: A report from the cardiovascular diseases and alimentary comparison study. J Cardiovas Pharmacol 16:S43–S47

Yamori Y, Nara Y, Mizushima S, Murakami S, Ikeda K, Sawamura M, Nabika T, Horie R (1992) Gene-environment interaction in hypertension, stroke and atherosclerosis in experimental models and supportive findings from a world-wide cross-sectional epidemiological survey: A WHO-CARDIAC Study. Clin Exp Pharmacol Physiol 20:43–52

Yamori Y, Nara Y, Ikeda K, Mizushima S (1996) Is taurine a preventive nutritional factor of cardiovascular diseases or just a biological marker of nutrition. Adv Exp Med Biol 403:623–629

Yamori Y, Liu L, Ikeda K, Miura A, Mizushima S, Miki T, Nara Y (2001) Distribution of twenty-four hour urinary taurine excretion and association with ischemic heart disease mortality in 24 populations of 16 countries: Results from the WHO-CARDIAC Study. Hypertens Res 24:453–457

Yamori Y, Liu L, Mizushima S, Ikeda K, Nara Y and CARDIAC Study Group (2006) Male cardiovascular mortality and dietary markers in 25 population samples of 16 countries. J Hypertens 24:1499–1505

Yokogoshi H, Mochizuki H, Nanami K, Hida Y, Miyachi F, Oda H (1999) Dietary taurine enhances cholesterol degradation and reduces serum and liver cholesterol concentrations in rats fed a high-cholesterol diet. J Nutr 129:1705–1712

.

Springer