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Review Article
Brain Aging and Nutrition

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Abstract

In the "Brain Aging and Nutrition" symposium at the 2010 10th Scientific Meeting of the Japanese Society of Anti-Aging Medicine, three experts were invited to report recent findings on maintenance of brain health. Speaking on "The association of postural instability with brain atrophy/cognitive impairment", Dr. Michiya Igase (Department of Geriatric Medicine & Neurology, Ehime University Graduate School of Medicine) described the importance of Anti-Aging examination for early discovery and early treatment of decreased cognitive function according to an Anti-Aging examination, particularly stressing on the importance of preventing frailty in the elderly. Dr. Toru Mizoguchi (Shinjuku Mizoguchi Clinic), speaking on "Improved brain function and nutrition", discussed how low intake of glucose, amino acids, vitamins, and minerals leads to metabolic abnormalities in the brain and low production of neurotransmitters, which can cause depression and many other psychiatric illnesses not only in the elderly, but in middle age too. In "The brain prefers ketones to carbohydrates as an energy source", Dr. Yoichi Ogushi (Department of Medical Informatics, Tokai University School of Medicine) presented data showing that a ketotic diet, also known as a low-carbohydrate diet (Atkins' or Bernstein's diet), is safe, and, moreover, that ketones are used as an energy source by the brain. This work suggested that advanced glycosylation end product is a risk factor for Alzheimer's and Perkinson's disease, and that glucose is only utilized after keton bodies by the brain. This notion in turn raises the possibility that a ketotic diet may prevent or slow the progression of Alzheimer's disease.

Anti-Aging measures above mentioned may play crucial roles in preventing brain atrophy, cognitive impairment, and depression which are closely related to the aging process. Stable energy supply and adequate nutritional distribution to neurons in the brain are keys to maintain brain function through neuronal survival and biosynthesis of neurotransmitters.

KEY WORDS: Cognitive impairment, postural instability, depression, very low-saccharide diet, ketones

Introduction

Anti-Aging Medicine has expanded rapidly, with physically-oriented measures achieving great success. However, Anti-Aging therapies for maintaining cognitive function have not yet been established. Metabolic syndrome is a primary cause of cerebral arteriosclerosis and has been suggested as a risk factor for Alzheimer's disease (AD), but some data also suggest that malnutrition of the brain is related to depression and dementia among the elderly.

We feel certain that the most recent findings on maintenance of brain health, as reported by three experts in this symposium, are significant for Anti-Aging research on the brain.

1. The association of postural instability with brain atrophy/cognitive impairment

In the aging society Japan now faces, the focus has turned to healthy life expectancy, defined as living in "a condition where daily living is independent without need for nursing care." While Japan today has the world's greatest healthy life expectancy among both males and females, it is considered a problem that males require an average of 6 years of nursing care, and females 7.6 years. According to data from the 2007 (FY2007) "Comprehensive Survey of Living Conditions" conducted by the Japanese Ministry of Health, Labour and Welfare, the most frequent cause of a need for nursing care is cerebrovascular disease, followed in order by dementia, debilitation (including ambulatory debilitation), and falls and fractures (***Figure 1***). Among these, dementia is associated with what are termed cognitive impairment and brain atrophy, and debilitation and falls/fractures are associated directly or indirectly with body balance.

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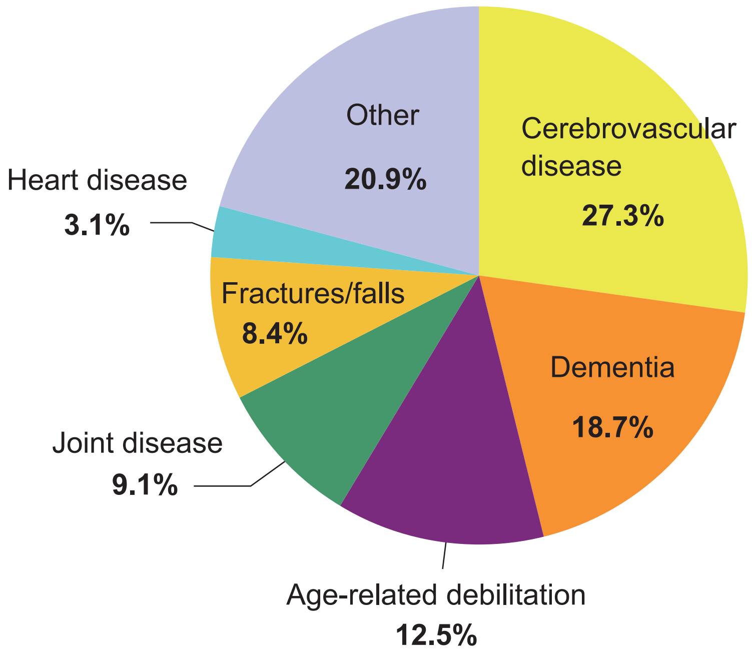

Fig. 1. Underlying diseases among Japanese individuals requiring nursing care
Ministry of Health, Labour and Welfare: Derived from summary of 2007 "Comprehensive Survey of Living Conditions"

One concept now proposed is that these factors are linked in a complex fashion, leading to frailty, a condition linked to death or a need for nursing care. To evaluate body function among elderly individuals and determine the association between brain atrophy and cognitive impairment, we quantitatively evaluated postural instability, an index of body balance function, by gravicorder and single-leg stance time with eyes open [1]. We describe primarily these results.

The subjects were 390 individuals undergoing an Anti-Aging examination, and those with a prior history of distinct cerebrovascular disease were excluded. Postural instability was measured through two different tests.

1. Center of gravity sway testing: Subjects stood with both feet on the triangular platform of a gravicorder (GS5500, Anima), directed their gaze to a red mark located 2 m forward at the height of their line of sight, and maintained a standing position for 60 seconds during measurement. Data with eyes open were used.

2. Single-leg stance time with eyes open: Subjects selected the standing leg, and measurement of stance time ended either at an upper limit of 60 seconds, or when a hand touched an object or the lifted leg touched the floor. Two measurements were made, and the highest value was used.

3. Brain atrophy index: The temporal horn of the lateral ventricle area (THA) [2], an index of medial temporal lobe atrophy, was used as an index of brain atrophy. Center of gravity displacement and area, the indices of postural instability studied in our research, were significantly correlated with THA even after adjustment for age.

4. Mild cognitive impairment (MCI): The "demented level check test" [3], the Japanese language version of the MCI screening test [4] developed in the US by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD), was used for evaluation. MCI was evaluated in 5 tasks, including immediate repetition and delayed repetition, and cross-validity was determined even for testing on Japanese subjects.

5. AD was diagnosed clinically by the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). There were 21 AD patients with a mean age of 79 years, and 6 patients were males.

The results were as follows. The mean age of examined individuals was 67 years, and 151 were males. Hypertension was present in 59%, and type 2 diabetes in 9%, equivalent to the prevalence among the general community residents in Japan. Hypertension was under treatment in 30% of the hypertensive subjects, and diabetes under treatment in 90% of the diabetic subjects. Center of gravity displacement and area, indices of postural instability, both showed a significant, positive correlation to THA, and only THA was correlated with postural instability even in age-adjusted studies. Based on many reports of correlation between silent cerebrovascular diseases and brain atrophy, we investigated associations between THA and silent lacunar infarction (SLI), cerebral microbleed (CMB), and periventricular hyperintensity (PVH). The results showed that, among the three conditions, THA was significantly enlarged in the presence of PVH of Grade 1 (*i.e.* slight PVH) or higher grades.

Subjects were next divided into 4 groups representing 20-second increments of single-leg stance time with eyes open, and investigation of the association between stance time and THA showed that THA was significantly enlarged in those able to stand for less than 40 seconds versus those able to stand for 60 seconds (***Figure 2***). To evaluate further the association between postural instability and brain atrophy, multiple regression performed on THA showed that increased center of gravity displacement and one-leg standing time with eyes open <40 seconds were independent risk factors for enlarged THA, even when adjusted for age, height, antihypertensive administration, and PVH status. Given that increased instability in standing position was significantly correlated with organic brain damage, we investigated the association between single-leg stance time and decreased cognitive

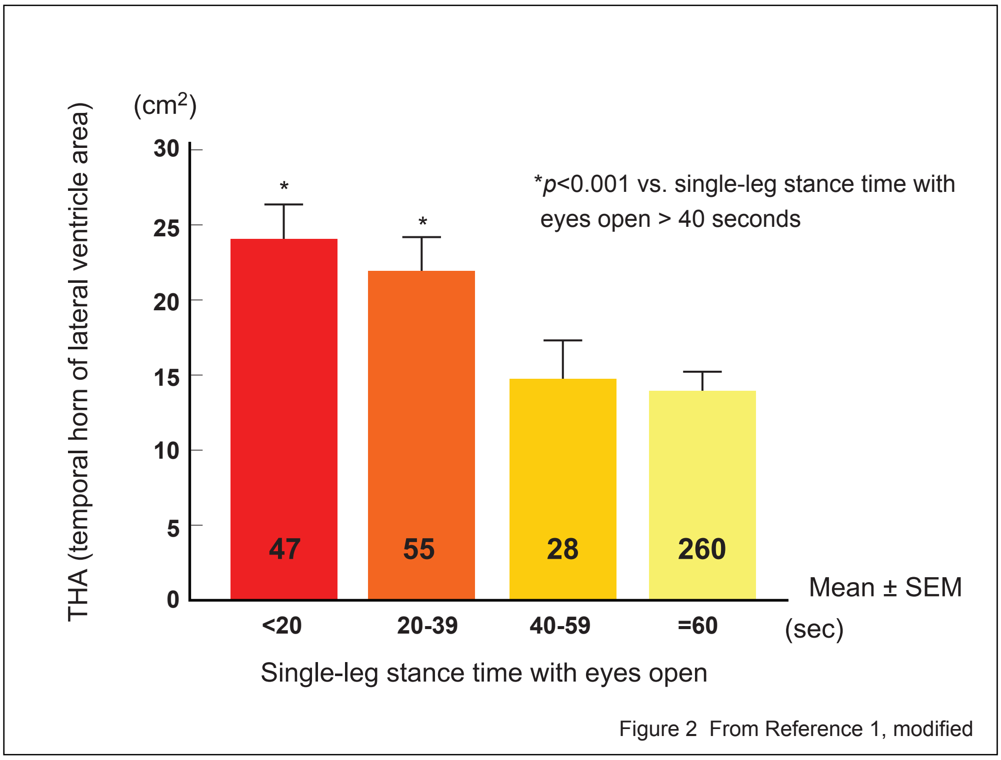

Fig. 2. Association between temporal horn of lateral ventricle area (THA) and single-leg stance time with eyes open (from Reference (2), modified)

function, the latter representing functional impairment of the brain. The results showed a significant decrease in single-leg stance time in the MCI group versus healthy controls, as well as notably shorter single-leg stance times among AD patients.

The foregoing results showed that center of gravity displacement and area, as indices of postural instability, were correlated with brain atrophy, and that THA was significantly enlarged in patients with single-leg stance times of <40 seconds. Single-leg stance times were also significantly shortened in the MCI and AD groups versus healthy controls.

As aging progresses in the elderly, various interrelated factors are believed to produce a syndrome termed "pre-frailty." Factors contributing to fall and fracture include not only the postural instability that we investigated, but also loss of bone minerals and loss of muscle mass. Meanwhile, other factors we investigated, such as the brain atrophy and cognitive impairment, are strongly associated with dementia. These elements of the pre-frailty syndrome are thought to be interrelated, lead to decreased ADL (activities of daily living), and promote a progression to frailty.

Given the association we observed between well-known elements of pre-frailty syndrome and "single-leg stance", an easily-assessed index of decreased physical function, we believe that single-leg stance time can also be used as an index of pre-frailty syndrome. However, the "60-second" method for evaluating single-leg stance time does not necessarily concur with other research reports. In the European LADIS study [5)], a large-scale investigation of cerebral white matter changes and associated disorders, single-leg stance time was measured with an upper limit of 30 seconds and a cutoff value of 15 seconds. Tinetti *et al.* [6)] made a pass-fail determination with a 5-second upper limit and reported an association with other measures such as lateral ventricle enlargement and PVH.

In previous evaluations of pre-frailty syndrome based on center of gravity sway, we reported that quadriceps sarcopenia and visceral fat are risk factors for postural instability in the elderly [7)], single-leg stance time is associated with bone mass [8)], and quadriceps sarcopenia is associated with arteriosclerosis (arterial stiffness) [9)]. We also plan follow-up investigation and longitudinal research assessments based on these cross-sectional studies.

In conclusion, reduced postural instability in elderly individuals was correlated with cognitive impairment mediated by brain atrophy. We also believe that single-leg stance time with eyes open may be a simple index for evaluating brain atrophy and cognitive impairment.

2. *Improved brain function and nutrition*

Maintenance of brain function is known to require a massive energy substrate. Given that glucose is the major energy substrate for the brain, carbohydrate intake is considered requisite for maintaining brain function. More recently however, the concept of metabolic syndrome marked chiefly by insulin resistance has been proposed, and there are now many reports of an association between metabolic syndrome and mental illnesses, such as depression [10,11)]. Outside of Japan, as described in "Dysglycemia–The Common Factor in Mental Disorders" [12)], attention has been drawn to the fact that dysglycemia is profoundly associated with mental illness. But in Japan, mental illness is diagnosed mainly on the basis of patient complaints, and assessment and diagnosis of psychiatric symptoms based on medical causes such as dysglycemia, other endocrine causes, or malnutrition are seldom performed.

The Mizoguchi Clinic (Shinjuku-ku, Tokyo) has performed 5-hour, 75 g oral glucose tolerance testing (OGTT) on approximately 2000 patients presenting nonspecific complaints including psychiatric symptoms. The results showed that the pattern of change in blood sugar after glucose intake varied considerably more than is generally thought.

Figure 3 shows results for 5-hour glucose tolerance testing conducted on a 36-year-old female patient. For several years the patient had been treated by drug therapy for a diagnosis of depression at another psychiatric facility. The principal symptoms at presentation to our clinic included depression, major fatigue, and poor appetite control with abrupt episodes of hunger.

As the figure shows, no substantial elevation of blood sugar occurred after glucose intake. After 120 minutes, blood sugar had declined to 54 mg/dl, a value 27% lower than fasting blood sugar. A strong association between these fluctuations in blood sugar and symptoms such as major fatigue and abrupt hunger was subsequently confirmed by a generalized approach including dietary modification. Treatment including appropriate dietary intervention also improved symptoms and allowed cessation of the antidepressant the patient had taken for several years.

Decreased efficacy of serotonin, noradrenaline, and other neurotransmitters is regarded as the cause of depressive symptoms as well as other psychological symptoms, and a number of antidepressants have been designed to have a pharmacological effect through metabolic regulation of such neurotransmitters. Conversely, the approach of orthomolecular medicine is to use nutrients to achieve optimal concentrations of substances in the brain [13]. In this approach, substrates serving as materials are supplied to facilitate the various neurotransmitter biosynthesis and reactions shown in ***Figure 4***, and vitamins and minerals serving as coenzymes or cofactors are supplemented to obtain enzymatic activity.

What we would draw attention to is that iron (Fe) is needed as a cofactor for enzymes related to reactions located upstream. These irons are “tissue irons”, and their deficiency or excess cannot be assessed by indices such as hemoglobin concentration, nor by ordinary peripheral blood testing.

For outpatients presenting nonspecific complaints including psychiatric symptoms, our clinic is working to devise blood tests allowing evaluation of even tissue iron deficiency in all cases [11]. Our experience in very many cases is that, among patients with iron deficiency implicated by this type of detailed blood testing, many complaints are improved by appropriate iron supplementation.

If Anti-Aging of the brain is conceived as maintenance or improvement of brain function, a stable supply of energy allowing the brain to function, and adequate biosynthesis of various neurotransmitters within neurons should be requisite conditions. And because this in turn requires a stable supply of glucose serving as an energy substrate, intake of foods that elevate blood sugar rapidly must be avoided. There is widespread misunderstanding that a diet rich in fats and proteins does not increase blood sugar and thus causes problems. For physicians and other healthcare providers, it is very important to communicate to patients that blood sugar does not decline even in the absence of carbohydrate intake.

Serotonin and other neurotransmitters are also synthesized within neurons by complex enzymatic reactions assisted by amino acids, vitamins, and minerals which are able to cross the blood-brain barrier. In this light, stable biosynthesis of neurotransmitters is made possible by adequate intake of proteins including the amino acids which form these ingredients, and by adequate supplementation of nutrients required in the synthesis

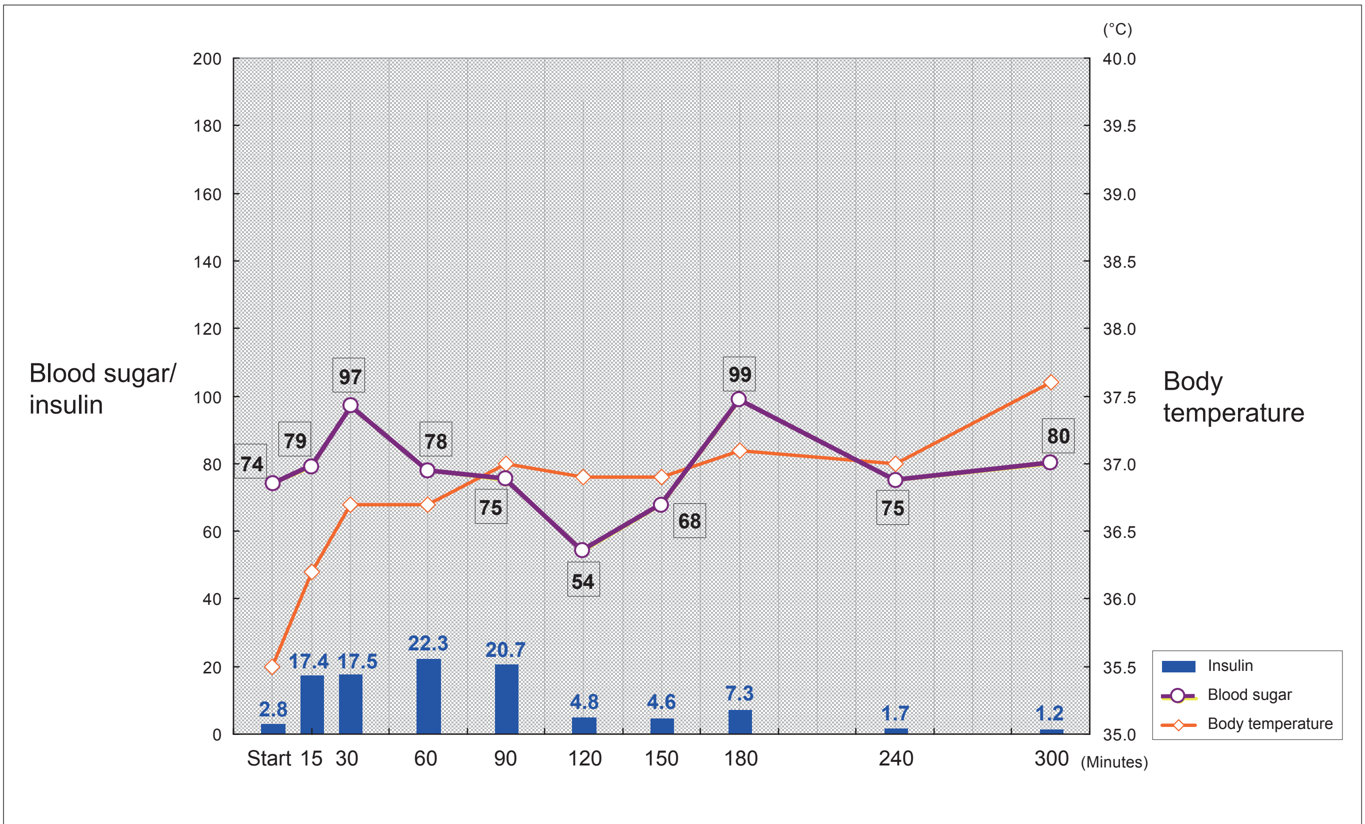

Fig. 3. 5-hour glucose tolerance testing
35-year-old female

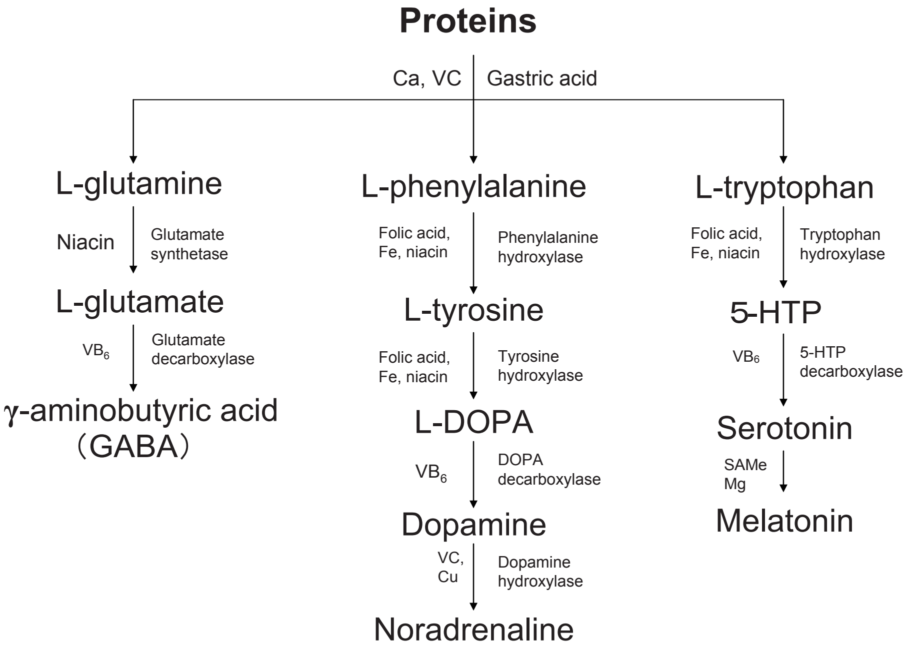

Fig. 4. GABA, noradrenaline, and serotonin synthesis pathways
Substances noted are representative enzymes, co-enzymes, and cofactors contributing to each synthesis process.

process.

Serotonin and other neurotransmitters are also synthesized within neurons by complex enzymatic reactions assisted by amino acids, vitamins, and minerals which are able to cross the blood-brain barrier. In this light, stable biosynthesis of neurotransmitters is made possible by adequate intake of proteins including the amino acids which form these ingredients, and by adequate supplementation of nutrients required in the synthesis process.

With the recent attention to "brain training" and other Anti-Aging measures for the brain, the importance of learning and stimulation has been recognized. Analogously, as we greet the super-aging society to come, we feel it important for health care providers to communicate to the general public correct information on nutrients required by the brain.

3. The brain prefers ketones to carbohydrates as an energy source

The brain is said to require carbohydrates as an energy source. However, observations compiled by Ogushi *et al.* for adherents to a very low-saccharide diet (VLSD: meals including only 5 g saccharide or less per meal) as a therapeutic diet for diabetes have called this thinking into question. They therefore used observational data to investigate whether carbohydrates are essential as an energy source for the brain.

The subjects were 16 adherents to a VLSD (11 males, 5 females; age 62.5±10.0 years). These individuals were members of the "Very Low-Saccharide Diet Research Group" and volunteered as subjects. They initiated VLSD for reasons including type 2 diabetes, dyslipidemia, and obesity, and continue on a diet of 5 g or less saccharides per meal. The mean length of adherence to the VLSD was 43.6±35.1 months. Each subject was given a 50 g oral glucose tolerance test (OGTT) and a 35 g oral fat tolerance test (OFTT), and blood testing, urinalysis, venous blood gas measurement, and expired gas measurement were performed prior to loading and post-loading at 30, 60, 90, 120 and 180 minutes.

The results were as follows. ***Table 1*** presents mean values and standard deviations (SD) for fasting blood tests. Despite the severely carbohydrate-restricted diet, fasting blood sugar and HbA1c were maintained normally, at 91 ± 13 mg/dl and 4.7±0.3%, respectively. Respiration quotients were 0.724±0.004, ketones 1128±841 μmol/L, and free fatty acids 0.77±0.26 mEq/L, indicating a metabolic status in which fats served as the primary energy source. Venous blood pH was 7.36±0.03, indicating that acidosis did not occur. Other lipids, renal function, electrolytes, and other test results were in the same range of those of individuals on a normal diet.

Respiration quotients indicated that the energy ratio of fats and carbohydrates consumed was 11.5:1. Assuming 1800 kcal/day, fats (ketones) provided 1656 kcal, and carbohydrates (glucose) 144 kcal. The 144 kcal carbohydrate consumption estimated from the respiration quotients of VLSD adherents coincides closely with the 36 g (137 kcal) of carbohydrates consumed by cells with the greatest preferential need for carbohydrates, such as red blood cells and white blood cells, lacking mitochondria. Though the energy required by the brain corresponded reportedly to 130 g (494 kcal) carbohydrates, almost all of this amount was provided by ketones in VLSD adherents.

In an experiment using rat brain slices, cells placed in a glucose perfusate containing increasing concentrations of beta-hydroxybutyrate showed a proportional decrease in carbon dioxide gas production derived from glucose metabolism [14]. Measurement of brain metabolism in anesthetized rats fasted for 24 hours showed that the oxygen consumption rate by ketones increased from 0.6% pre-fasting to 22% post-fasting. Additional injection of 3-hydroxybutyrate resulted in 60% oxygen consumption [15]. Based

Table 1 Fasting blood test results

Blood sugar-related

	Fasting blood sugar	HbA1c	Insulin
Mean	91	4.7	3.2
SD	13	0.3	1.6

Lipid-related

	Ketones	Triglyceride	Free fatty acids	LDL-C	HDL-C
Mean	1128	67	0.77	177	66
SD	841	22	0.26	35	12

Renal function

	Creatinine	Uric acid
Mean	0.84	7.0
SD	0.24	1.0

Electrolytes

	Na	K	Cl	Ca
Mean	139	4.5	102	9.0
SD	1.5	0.2	3.3	0.1

Respiratory/blood gas

	Respiration quotients	Venous blood pH	HCO3
Mean	0.724	7.26	25.2
SD	0.004	0.03	0.5

on these results, the central nervous system is said to use beta-hydroxybutyrate preferentially over glucose [16]. In human research, the primary energy source for brain metabolism reportedly shifted from carbohydrates to ketones in a 40-day fast [17].

Ketones produce ATP energy more efficiently than glucose and are thus regarded as a "super fuel". They are also known to protect cells from toxicity in Alzheimer's disease (AD) and Parkinson's disease [18]. Given the poor image of dietary ketosis, although it actually does not cause acidosis, Atkins suggested that dietary ketosis should be called "lipolysis." [19] Carbohydrates are one of the three major nutrients, but they are not an essential nutrient, and the amount of glucose required by cells without mitochondria can be supplied by gluconeogenesis [20].

In conclusion, we speculate that, among the VLSD adherents, ketones served as an energy source for the brain regardless of whether blood sugar was in the range of normality. Given that serum ketone concentration was 10-fold or higher than that of individuals on a normal diet, we believe that the brain uses ketones preferentially if ketones are plentiful. This fact concurs with results from animal experiments and changes observed in humans during fasting, the fact that ketones pass through the blood-brain barrier, and the supposition that human diets resembled a VLSD before agricultural societies began. In type 2 diabetes, blood sugar and HbA1c can be maintained in the range of normality on a VLSD alone, which can prevent beta cell exhaustion or other complications. VLSD are known as therapeutic diets for epilepsy and other brain diseases, but these findings suggest a potential for use as a therapeutic diet in AD and Parkinson's disease.

Conclusion

Prevention of age-related, quantitative loss or qualitative changes in brain neurons, brain atrophy, cognitive impairment, and depression are all crucial Anti-Aging measures for the brain. Postural instability testing may be a useful tool for early discovery of brain dysfunction. Insufficient intake of nutrients, including glucose, amino acids, vitamins, and minerals causes abnormal metabolism in the brain and decreased production of neurotransmitters, leading to deterioration of neuropsychiatric function. If Anti-Aging is regarded as a branch of active preventive medicine, attention should be devoted not merely to preventing deterioration of function, but also to promoting health and maintaining or improving brain function.

A stable supply of energy allowing the brain to function, and adequate biosynthesis of various neurotransmitters within neurons are seeming requisites. We hope that people will gain a better understanding of the importance of glucose metabolism, fat metabolism, and ketone synthesis within the brain, and bring these findings to actual clinical settings.

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