

REVIEW

Stress control and human nutrition

Eiji Takeda, Junji Terao, Yutaka Nakaya, Ken-ichi Miyamoto, Yoshinobu Baba, Hiroshi Chuman, Ryuji Kaji, Tetsuro Ohmori, and Kazuhito Rokutan

Project team of the 21st century COE program "Human Nutritional Science on Stress Control", Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan

Abstract : Stress is a pervasive factor in everyday life that critically affects development and functioning. Severe and prolonged stress exposure impairs homeostatic mechanisms, particularly associated with the onset of depressive illness. Brain food is aimed at preventing as well as treating a growing number of stress-related mental disorders. Some topics on the association of stress and nutrition is reviewed. (1) An increased activity of serotonergic neurons in the brain is an established consequence of stress. An increase in brain tryptophan levels on the order of that produced by eating a carbohydrate-rich/protein-poor meal causes parallel increases in the amounts of serotonin released into synapses. (2) Eating is thought to be suppressed during stress, due to anorectic effects of corticotrophin releasing hormone, and increased during recovery from stress, due to appetite stimulating effects of residual cortisol. (3) A strong inverse association between coffee intake and risk of suicide. (4) Night eating syndrome has been found to occur during periods of stress and is associated with poor results at attempts to lose weight and disturbances in the hypothalamic-pituitary-adrenal axis. (5) Dietary antioxidants present in fruits and vegetables may improve cognitive function. Therefore, it is concluded that the establishment of functional foods that correctly regulate stress response must be firmly based upon scientific knowledge and legal regulation. *J. Med. Invest.* 51 : 139-145, August, 2004

Keywords : stress, nutrition, functional food, serotonin, antioxidant

INTRODUCTION

Stressful life events may contribute to the onset and course of mood deterioration and affective disorders such as depression (1, 2). Stress is a pervasive factor in everyday life that critically affects development and functioning. It has been hypothesized that stress exposure has important adaptive consequences by enhancing neurobehavioral ontogeny for virtually all animal species (3). However, severe and prolonged

stress exposure impairs homeostatic mechanisms that can adversely affect functioning of multiple organ systems. Stress appears to play a major role in the pathophysiology of nearly all psychiatric disorders particularly depressive illness (4-9).

The goals of the 21st century COE program "Human Nutritional Science on Stress Control" in The University of Tokushima Graduate School are to develop a novel scientific field for human nutrition in stress research and to employ these strategies to examine the functions of foods on human mind. In this manuscript, the association of stress/mind/cognition and eating/food/nutrient is reviewed.

Received for publication May 10, 2004 ; accepted May 25, 2004.

Address correspondence and reprint requests to Eiji Takeda, M.D., Ph.D., Department of Clinical Nutrition, Institute of Health Biosciences, The University of Tokushima Graduate School, Kuramoto-cho, Tokushima 770-8503, Japan and Fax : +81-88-633-7094

STRESS CONTROL AND FUNCTIONAL FOOD

The proportion of senior citizens and children in relation to the general population is rapidly increasing and continuously decreasing, respectively, in Japan. Today the percentage of people over 65 in Japan is approximately 17%. With the development of an unbalanced and senior society, human activities and lifestyles generate numerous forms of environmental stress. This outstanding level of stress is certainly reflected by the number of Japanese people (more than 30,000) who commit suicide, and mental and physical disorders caused by stress are serious social and economic problems. Food environment, such as eating styles or nutrients, greatly affects mental health especially in children and teenager. The need for medical treatment is expected to increase, but in many cases it may not improve the quality of life. Therefore, the goal of functional foods is to improve or maintain quality of life in mental health before medical treatment is required.

It is proposed that foods have three functions. The primary function is a nutritional function, which is essential to human survival. The secondary function is a sensory functions involving both flavor and texture to satisfy sensory needs. The tertiary function is physiological functions such as regulation of biorhythms, control of aging, the immune system, and body defense. The project defined a functional food as a food having some tertiary function. We will establish novel functional foods, so called "brain foods", which can modify genetic and psychological aspects of human life, and preventing as well as treating a growing number of stress-related mental disorders.

STRESS AND SEROTONIN LEVEL IN THE BRAIN

An increased activity of serotonergic neurons in the

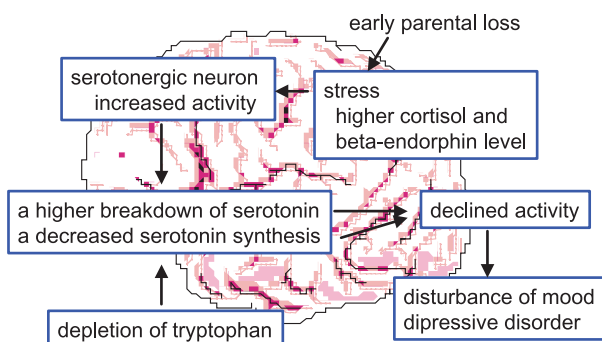


Figure 1. Stress and serotonin level

brain is an established consequence of stress, and a declined activity of these serotonergic neurons has been demonstrated in disturbances of mood and depressive disorders (10-13). Hence, a rise in the activity of the central serotonergic system is regarded as a biological condition to cope with stress and to prevent stress-induced depression (14-16). As the higher serotonergic activity during stress leads to a higher breakdown of serotonin, continuing stress may lead to a functional shortage of the supply of this neurotransmitter, its expenditure exceeding its synthesis. Consequently, coping, mood and accuracy of performance deteriorate. Depletion of the precursor of serotonin synthesis, tryptophan, has been found to increased depressive mood in healthy subjects and subjects with a prior history of depressions (17-19) (Fig.1).

The findings that depressed and schizophrenic patients have increased neurobiological responses to stress is in agreement with the clinical data that environmental stress is associated with the onset of these disorders and exacerbates their course of illness. Among subjects with early parental loss histories, those who develop psychopathology have higher resting plasma cortisol and beta-endorphin levels in comparison to subjects with no histories of adult psychopathology. In addition, the severity of the loss was a powerful predictor of adult psychopathology. It is also suggesting that the subjects who had poorer adjustments to loss in childhood had increased resting hypothalamic-pituitary-adrenal axis activation in adulthood.

SEROTONIN AND CARBOHYDRATE RICH FOOD

An increase in brain tryptophan levels, on the order of that produced by eating a carbohydrate-rich, protein-poor (CR/PP) meal, causes parallel increases in the amounts of serotonin released into synapses (20). This change of a neurochemical signal provides the brain with on-line information about the nutritional state and about the macronutrient composition of the last meal or snack. The brain can then use this information in deciding what should be eaten next.

Dietary carbohydrate enhances the uptake of circulating tryptophan into the brain mediated by modifying the plasma amino acid pattern. Insulin has little or no effect on plasma tryptophan levels, but it markedly lowers the plasma levels of the large neutral amino acids (LNAA), which compete with tryptophan for passage across the blood-brain barrier. This decrease allows more tryptophan to enter the brain and resolves

the paradox of why dietary carbohydrates, which lack tryptophan, should increase brain levels of this amino acid while protein-rich foods fail to do so. Dietary proteins raise plasma tryptophan levels. However, since tryptophan tends to be the least abundant of the 22 amino acids in proteins, this rise is small relative to the increases in such other, more abundant LNAA as leucine, isoleucine, and valine. The CR/PP diet caused a significant 42% increase in plasma tryptophan / Σ LNAA (sum of LNAA) compared with the protein rich, carbohydrate poor (PR/CP) diet (21).

Under conditions of acute stress, increases in brain serotonin may improve stress adaptation and thus may contribute to the initiation as well as termination of a cortisol response by way of different serotonergic pathways in the brain (14-16) (Fig. 2). If an increased serotonin level constitute a biological condition to improve stress adaptation in stress-prone subjects, serotonin activity might be continuously increased after chronic stress experiences. Ultimately, this may lead to a functional shortage in serotonin, causing a subsequent deficiency of brain serotonin activity (21, 22).

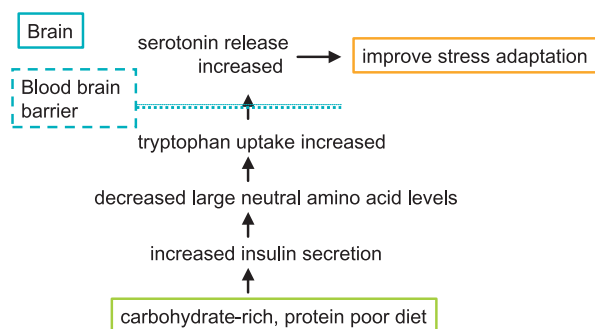


Figure 2. Serotonin and carbohydrate rich food

STRESS, CORTISOL AND APPETITE

Eating is thought to be suppressed during stress due to anorectic effects of corticotrophin releasing hormone, and increased during recovery from stress due to appetite stimulating effects of residual cortisol (23). Cortisol clearly plays an important role in energy regulation, increasing available energy through gluconeogenesis and lipolysis. Glucocorticoids lead to hyperphagia and weight gain, and are necessary for the expression of their obesity (24).

There was only a weak correlation between cortisol and energy intake. Therefore, it is likely that cortisol reflects or modulates other stress responsive factors, such as leptin, neuropeptide Y or cytokines that more directly affect appetite rather than having direct effects

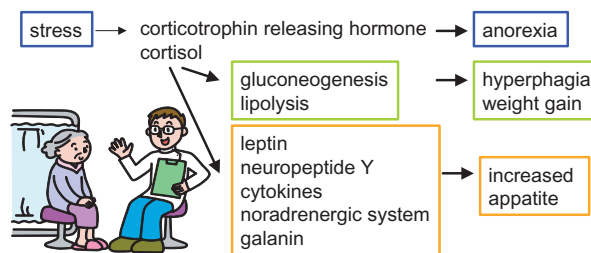


Figure 3. Stress, cortisol and appetite

itself. Stress affects every bodily system, and thus there are multiple and complex pathways through which stress can affect eating. Exposure to stress increases neuropeptide Y, which can increase appetite (25, 26). Further, the stress-sensitive adrenal steroids, specifically, modulate neurotransmitters that affect appetite, such as noradrenergic systems, neuropeptide Y and galanin (27) (Fig. 3). Cortisol may also blunt taste threshold sensitivity (28, 29).

Several studies have shown that people under chronic stress tend to gain weight over time, which may be due to both stress-related endocrine changes, as well as coping behaviors (30). It was hypothesized that high cortisol reactivity in response to stress may lead to eating after stress, given the relations between cortisol with both psychological stress and mechanisms affecting hunger. High cortisol reactors consumed more energy on the stress day compared to low reactors, high reactors ate significantly more sweet food across days. Increases in negative mood in response to the stressors were also significantly related to greater food consumption. Thus, psychophysiological response to stress influences subsequent eating behavior. The current results mirror those of a similar study of college undergraduate women (31). During a control day, dieting was related to eating less, whereas on a stress day, cortisol reactivity predicted eating more. Multiple comparisons of food type consumed by reactivity group revealed further differences; of the sweet food consumed after stress, the high reactors consumed significantly more high fat food.

COFFEE INTAKE AND SUICIDE REDUCTION

A strong inverse association has been reported between daily coffee intake and risk of suicide in a prospective 8-year follow-up study of 128, 934 persons (32). Of the numerous chemicals that have been identified in coffee, the main ingredient with central nervous system effects is caffeine, which acts principally as a stimulant (33). Caffeine acts principally as a central

nervous system stimulant. A close of two cups of coffee improves psychomotor performance and increases vigilance, while reducing fatigue (34). Long-term caffeine users also have been reported to experience a host of subjective effects following coffee consumption, including improved mood and well-being (35-37).

The effects of caffeine on mood depend on dose and habituation. Habitual coffee drinkers report pleasant effects of decreased irritability and improvement in mood following coffee consumption, whereas nondrinkers are more likely to report dysphoria even after a single dose (35, 36). Administration of small doses of caffeine (100mg per day) has been shown to produce increased subjective feelings of well-being, social disposition, self-confidence, energy, and motivation for work, compared with placebo (37). In the psychiatric setting, reports suggest that patients experience improved mood after coffee drinking and decreased irritability following the administration of up to 1000 mg of caffeine (38, 39). A cross-sectional study of Japanese medical students found that high intake of caffeine was associated with fewer depressive symptoms among female college students but not male college students (40). Thus, the data suggest a strong inverse association between coffee intake and risk of suicide (Fig. 4).

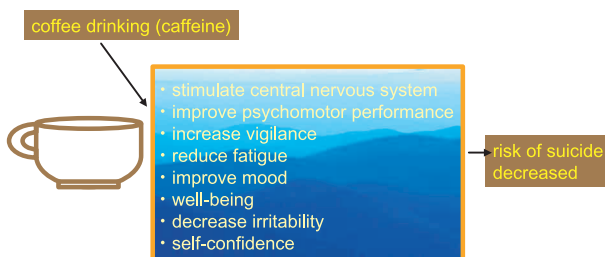


Figure 4. Coffee and suicide reduction

NIGHT EATING SYNDROME AND STRESS

Night eating syndrome (NES), as first described by Stunkard *et al.*, is characterized by the following three criteria: no appetite for breakfast, 50% or more of daily food intake after 6.00p.m., and trouble getting to and/or staying asleep (41). It is estimated to affect 1.5% of the general population, and 8.9% of patients in weight reduction programs (42, 43). A recent study compared overweight and obese adults with and without NES on both behavioral and neuroendocrine characteristics (44). Compared to the non-NES subjects, the NES group had significantly lower mood scores throughout the day, the mood scores of the NES group fell while those of the controls remained unchanged. The NES group had significantly higher levels of cortisol, a glu-

cocorticoid released by the body during times of stress, throughout the majority of the day and an attenuation of the nocturnal rise of melatonin, which is suppressed by corticotropin releasing factor, whose levels are increased by stress (44). This syndrome has been found to occur during periods of stress, and is associated with poor results at attempts to lose weight and disturbances in the hypothalamic-pituitary-adrenal axis (41, 45, 46).

ANTIOXIDANTS AND COGNITIVE FUNCTION

Decline of cognitive function with age is another factor that hinders independence and activity in the elderly. Current evidence indicates that both increased oxidative stress and antioxidant status imbalance contribute to the decline of cognitive function with age. Several studies have found associations between the decline of memory performance with age and lower status of dietary antioxidants (47, 48). The effect of dietary antioxidants on the prevention of vascular dementia, stroke, and atherosclerosis are other mechanisms by which dietary antioxidants may reduce the risk of dementia associated with vascular dysfunction and probably Alzheimer's disease. Elderly over the age of 60 years were tested for their cognitive function in relation to plasma antioxidant status. The study reported that vitamins C, E, A, carotenoids, and selenium levels were correlated with memory function (48). The odds ratios for poor memory performance consistently were high with low levels of plasma vitamin E. Furthermore, supplementation with vitamin E was reported to delay progression of Alzheimer's disease (49). Therefore, it appears that dietary antioxidants present in fruits and vegetables may improve cognitive function (50, 51) (Fig. 5).

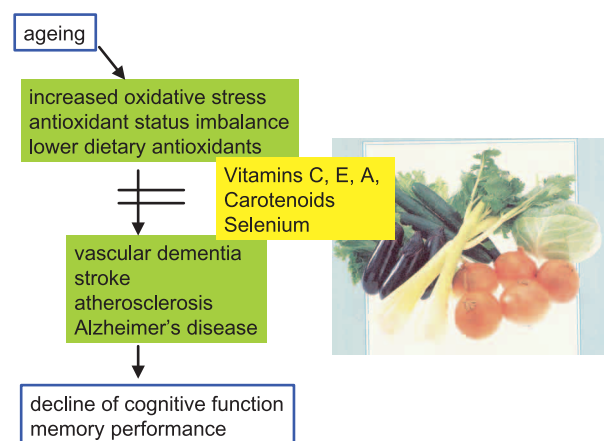


Figure 5. Antioxidants and cognitive function

CONCLUSION

The establishment of functional foods that correctly regulate stress response must be firmly based upon scientific knowledge and legal regulation. Therefore, efficient biomarkers related to pathological stress responses must be found. Furthermore, it is essential to analyze possible diet or nutrient interactions as well as it is indispensable to conduct valid studies on humans.

ACKNOWLEDGEMENT

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture, Japan, and the 21st Century COE Program, Human Nutritional Science on Stress Control, Tokushima, Japan.

REFERENCES

1. Brawn GW, Bifulco A, Harris TO : Life events, vulnerability and on-set of depression : some refinements. *Br J Psychiatry* 150 : 30-42, 1987
2. Cooke DJ, Hole DJ : The etiological importance of stressful life events. *Br J Psychiatry* 143 : 397-400, 1983
3. Selye H : The stress concept today. In : Dutash IL, Schlesinger LB (eds), *Handbook of Stress and Anxiety*. Jossey-Bass Inc., London, 1980, pp127-143
4. Paykel ES, Myers JK, Dienelt MN, Klerman GL, Lindenthal JJ, Pepper MP: Life events and depression : A controlled study. *Arch Gen Psychiatry* 21 : 753-760, 1969
5. Leff MJ, Roatch JF, Bunney WE : Environmental factors preceding the onset of severe depression. *Psychiatry* 33 : 298-311, 1970
6. Thompson K, Hendric H : Environmental stress in primary depressive illness. *Arch Gen Psychiatry* 26 : 130-132, 1972
7. Brown GW, Harris TO, Peto J : Life events and psychiatric disorders. II. Nature of causal links. *Psychol Med* 3 : 159-176, 1973
8. Goodwin FK, Bunney WE : Psychobiological aspects of stress and affective illness. In : Scott JP, Senay EC(eds), *Separation and Aggression : Clinical and Research Aspects*. AAAS, Washington, DC, 1973
9. Lloyd C: Life events and depressive disorder reviewed. I. Events as predisposing factors. *Arch Gen Psychiatry* 37 : 529-535, 1980
10. Joseph MH, Kennett GA : Stress-induced release of 5-HT in the hippocampus and its dependence on an increased tryptophan availability : an *in vivo* electrochemical study. *Brain Res* 270:251-257, 1983
11. Stanford SC : Monoamines in response and adaptation to stress. In : Stamford SC, Salmon P, editors, *Stress, from Synapse to Syndrome*. Academic Press, London, 1993, pp.24-30
12. Delbeinde C, Delarue C, Lefebvre H, Tranchand-Bunel D, Szafarczyk A, Mocaer E., Kamoun A, Jegou S, Vaudry H : Glucocorticoids, tractsminers and stress. *Br J Psychiatry* 160(suppl.15) : 24-34, 1992
13. Praag van MM : Depression. *Lancet* 2 : 1259, 1984
14. Anisman H, Zacharko RM:Depression as a consequence of inadequate neurochemical adaption in response to stressors. *Br J Psychiatry* 160 (suppl. 15) : 36-43, 1992
15. Deakin JWF : Depression and 5-HT. *Int Glin Psychopharmacol* 3 : 23-28, 1991
16. Deakin JWF, Graeff FG : 5-HT and mechanisms of defense. *J Psychopharmacol* 5:305-315, 1991
17. Smith SE, Pihl RO, Young SN, Ervin F : A test of possible cognitive and environmental influences on the mood lowering effect of tryptophan depletion in normal males. *Psychopharmacology* 91 : 451-457, 1987
18. Young SN, Smith SE, Pihl RO, Ervin FR : Tryptophan depletion causes a rapid lowering of mood in normal males. *Psychopharmacology* 87:173-177, 1985
19. Heninger GR, Delgado PL, Charney DS : The revised monoamine theory of depression : a modulatory role for monoamines, based on new findings from monoamine depletion experiments in humans. *Pharmacopsychiatry* 29 : 2-11, 1996
20. Schaechter JD, Wurtman RJ : Serotonin release varies with brain tryptophan levels. *Brain Res* 532 : 203-210, 1990
21. Markus CR, Panhuysen C, Tuiten A, Koppeschaar H, Fekkes D, Peters M : Does carbohydrate-rich, protein-poor food prevent a deterioration of mood and cognitive performance of stress-prone subjects when subjected to a stressful task? *Appetite* 31 : 49-65, 1998
22. Lieberman HR, Wurtman JJ, Chow B : Changes in mood after carbohydrate consumption among obese individuals. *Am J Clin Nutr* 44 : 772-778, 1986
23. Sapolsky R : Why Zebras don't get Ulcers : An

- Updated Guide to Stress, Stress-related Diseases, and Coping. Freeman and Co, New York, 1998, pp 76-79
24. Bray G : Autonomic and endocrine factors in the regulation of food intake. *Brain Research Bulletin* 14, 505-510, 1985
 25. Zukowska-Grojec Z : Neuropeptide Y ; a novel sympathetic stress hormone and more. *Annals of the New York Academy of Sciences* 771 : 219-233, 1995
 26. Morley J : Neuropeptide regulation of appetite and weight. *Endocrine Review* 8 : 256-287, 1987
 27. McEwen B, Sakai R, Spencer R : Adrenal Steroid Effects on the Brain : Versatile Hormones with Good and Bad Effects. *Hormonally Induced Changes in Mind and Brain* 157-189, 1993
 28. Fehm-Wolfsdorf G, Scheible E, Zenz H, Born J, Fehm HL : Taste thresholds in man are differentially influenced by hydrocortisone and dexamethasone. *Psychoneuroendocrinol* 14 : 433-440, 1989
 29. Henkin RL : The effects of corticosteroids and ACTH on sensory systems. *Prog Brain Res* 32 : 279-294, 1970
 30. Greeno C, Wing R, Matthews K, Vitaliano P : Stress predicts overeating and weight gain outside of the laboratory : data from multiple studies. *Annals of Behavioral Medicine* 20 : S032, 1998
 31. Epel E, Lapidus R, McEwen B, Brownell K : Stress may add bite to appetite in women : a laboratory study of stress-induced cortisol and eating behavior. *Psychoneuroendocrinol* 26 : 37-49, 2001
 32. Klatsky AL, Armstrong MA, Friedman GD : Coffee, tea, and mortality. *Ann Epidemiol* 3 : 375-381, 1993
 33. Heishman SJ, Henningfield JE : Stimulus function of caffeine in humans : relation to dependence potential. *Neurosci Biobehav Rev* 16 : 273-287, 1992
 34. Chou T : Wake up and smell the coffee : caffeine, coffee, and the medical consequences. *West J Med* 1657 : 544-553, 1992
 35. Goldstein A, Kaizer S : Psychotropic effects of caffeine in man, II: alertness, psychomotor coordination, and mood. *J Pharmacol Exp Ther* 150 : 146-151, 1965
 36. Goldstein A, Kaizer S, Whitby O : Psychotropic effects of coffee in man, IV : quantitative differences associated with habituation to coffee. *Clin Pharmacol Ther* 24 : 243-252, 1978
 37. Griffiths RR, Evans SM, Heishman SJ, Preston KL, Sannerrud CA, Wolf B, Woodson PP: Low-dose caffeine discrimination in humans. *J Pharmacol Exp Ther* 2556 : 1123-1132, 1990
 38. Furlong FW : Possible psychiatric significance of excessive coffee consumption. *Can J Psychiatry* 20 : 577-583, 1975
 39. Stephenson PE : Physiologic and psychotropic effects of caffeine on man. *J Am Diet Assoc* 71: 240-247, 1977
 40. Mino Y, Yasuda N, Fujimura T, Ohara H : Caffeine consumption and anxiety and depressive symptomatology among medical students. *Jpn J Alcohol Drug Depend* 25 : 486-496, 1990
 41. Stunkard AJ, Grace WJ, Wolff HG : The night-eating syndrome : a pattern of food intake among certain obese patients. *Am J Med* 19 : 78-86, 1955
 42. Rand CS, Macgregor AM, Stunkard AJ : The night-eating syndrome in the general population and among postoperative obesity surgery patients. *Int J Eat Disord* 22 : 65-69, 1997
 43. Stunkard A, Berkowitz R, Wadden T, Tanrikut C, Reiss E, Young L : Binge eating disorder and the night-eating syndrome. *Int J Obes Relat Metab Disord* 20 : 1-6, 1996
 44. Birketvedt G, Florholmen J, Sundsfjord J, Osterud B, Dinges D, Bilker W, Stunkard A : Behavioral and neuroendocrine characteristics of the night-eating syndrome. *J Am Med Assoc* 282 : 657-663, 1999
 45. Gluck ME, Geliebter A, Satov T : Night eating syndrome is associated with depression, low self-esteem, reduced daytime hunger, and less weight loss in obese outpatients. *Obes Res* 9:264-267, 2001
 46. Birketvedt GS, Sundsfjord J, Florholmen JR : Hypothalamic-pituitary-adrenal axis in the night eating syndrome. *Am J Physiol* 282 : E366-E369, 2002
 47. Perrig WJ, Perrig P, Stavelin HB : The relation between antioxidants and memory performance in the old and very old. *J Am Geriatr Soc* 45 : 718-724, 1997
 48. Perkins A, Hendrie HC, Callahan CM, Gao S, Unverzagt FW, Xu Y, Hall KS, Hui SL : Association of antioxidants with memory in a multiethnic elderly sample using the Third National Health and Nutrition examination Survey. *Am J Epidemiol* 150 : 37-44, 1999
 49. Sano M, Ernesto MS, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, Schneider LS, Thal LJ : A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med* 336 : 1216-1222, 1997

50. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, Bickford PC : Reversals of age-related declines in neuronal signal transduction, cognitive, and motor behavioral deficits with blueberries, spinach, or strawberry dietary supplementation. J Neurosci 19 : 8114-8121, 1999
51. Joseph JA, Shukitt-Hale B, Denisova NA, Prior RL, Cao G, Martin A, Tagliamonte G, Bickford PC: Long-term dietary strawberry, spinach, or vitamin E supplementation retards the onset of age-related neuronal signal-transduction and cognitive behavioral deficits. J Neurosci 18 : 8047-8055, 1998