The effects of dietary choline

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Abstract: Food intake can influence neuronal functions through different modulators expressed in the brain. The present review is a report through relevant experimental findings on the effects of choline, a nutritional component found in the diet, to identify a safe and effective dietary solution that can offer some protection against neurotoxicity and neurological disorders and that can be implemented in animals and humans in a very short period of time.

Keywords: choline; neurotoxicity; neuroprotection

1 Introduction

Neuroscience research includes attempts to improve the quality of life by discovering nutritional solutions for physiological and clinical problems from infancy to old age. One of the major concerns is the exposure of soldiers to neurotoxic agents during conflict. Neurotoxicity may arise from exposure to weapons of mass destruction, such as weaponized anticholinesterases, to prophylactic compounds such as pyridostigmine, to insecticides, pesticides, combustion products and even pharmaceuticals. A highly desirable solution consists of a safe neuroprotective treatment that military personnel could implement before exposure to these agents, without impairing physical and mental performance. Studies on the effects of choline, an organic dietary micronutrient and precursor of acetylcholine (ACh),

on neuroplasticity in animals have revealed that dietary supplementation with choline is neuroprotective, while deficiency of choline promotes neurotoxicity^[1–17].

2 Choline and diet

Choline was discovered by Adolph Strecker in 1864 and experimentally synthesized in 1866. It is found in supplementary forms, including ACh, phosphatidylcholine (PC), choline chloride, choline bitartrate, choline inositol, choline succinate^[13] and choline alfoscerate^[18]. Also called vitamin J, choline is classified as a member of the vitamin B complex. In 1998, the Food and Nutrition Board of the Institute of Medicine (USA) considered choline an essential water-soluble nutrient in the animal and the human diet^[19]. Although choline can be produced by the liver, it must be consumed through the diet to maintain health of humans and animals^[20–22]. In the US Department of Agriculture (USDA) Nutrients Databases (available at: <http://www.ars.usda.gov/nutrientdata>. 2008), examples of foods particularly high in choline are listed, including vegetables (spinach, potato, cauliflower, tomato, banana, orange, lentil, bean, pea, almond, nut, peanut, and amaranth), cere-

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als (brown rice, soybean products, bean curd, oats, corn, sesame seed, barley, flax seed, wheat germ, and quinoa), and meat (liver, muscle meats, fish, chicken, milk, and egg yolk)^[23]. The minimum daily requirement for choline has not been determined yet, but the Food and Nutrition Board of the National Institute of Medicine (USA) in 1998 recommended approximately 500 mg/day for adult humans (550 mg/day for men and 425 mg/day for women)^[24]. Choline demand differs depending on age, sex, weight and state of health (in mg/day): pregnant women, 450; infants < 6 months, 125; infants 7–12 months, 150; children 1–3 years, 200; children 4–8 years, 250; children 9–13 years, 375^[24]. A recent study by Zeisel and colleagues found that postmenopausal women with low estrogen levels deprived of a minimum dose of choline developed liver or muscle damage^[25]. Choline is safe for adults when used appropriately. However, consumers of high choline may have side effects like sweating, increased salivation, gastrointestinal pain, diarrhea, nausea, vomiting, feeling faint or dizzy, low blood pressure, depression, and a fishy body odor. A high intake of choline may also be responsible for colon adenomas and breast cancer in women^[26] but not for colorectal cancer in men^[27]. To avoid any risk, daily consumption of choline should not exceed the tolerable upper intake level for choline^[24].

3 Choline functions

After ingestion, choline enters different metabolic pathways: it is converted to PC or oxidized to betaine in the liver or transformed into ACh in the brain. In conditions of deficiency, choline is redistributed from the kidney, lung and intestine to the brain and liver^[28,29]. Choline has a wide spectrum of actions. As a constituent of PC, it is critical for the synthesis of membrane phospholipids and is important for cell formation as well as tissue growth and repair^[30,31]. Food and Nutrition Board of the Institute of Medicine (USA) found that choline is absorbed into the circulation and transported across the blood-brain barrier at a rate proportional to its serum concentration^[24]. In addition, as a basic component of the neurotransmitter ACh, choline is essential for many brain and nerve

functions. Studies in epilepsy, Parkinson's disease, and Alzheimer's disease have shown that choline improves memory deficit problems, attention deficit, hyperactivity disorders, neuromuscular disorders, and general manic disorders^[19,32-34].

The neurochemical mechanisms underlying the action of choline remain elusive. In Alzheimer's disease, choline acts on cerebral blood flow through vasodilatation, activating the $\alpha 7$ nicotinic receptor on sympathetic nerves^[35]. Responses in spatial memory tasks induced by choline supplementation are associated with anatomical^[36,37], biochemical^[38], and physiological^[39-41] changes of neurons in the hippocampus and the basal forebrain regions involved in learning and memory. In pregnant rats, choline supplementation increases basal and metabotropic glutamate receptor-stimulated phospholipase D activity in the hippocampus of the offspring^[42]. The effects of choline supplementation on memory of the offspring are related to increased brain choline and ACh release. Morphological changes in cellular structures during early brain development have long-term effects on neuronal excitability: choline reduces the threshold for long-term potentiation (LTP)^[43-45], increasing the sensitivity of CA1 hippocampal neurons to LTP stimulation^[46]. Choline, in the forms of PC and sphingomyelin, is responsible for maintenance of the structural and the functional integrity of cells. Altered PC content, accumulation of ceramide and diacylglycerol, and caspase activation are typical markers of choline deficiency-induced apoptosis^[36,37]. Choline-derived betaine resynthesizes *L*-methionine from homocysteine, maintaining low levels of homocysteine, which may be beneficial in cardiovascular and neurological disorders.

The neurotoxicity caused by N-methyl-*D*-aspartate (NMDA) antagonists has been demonstrated^[47-49]. Prenatal choline supplementation makes offspring resistant to MK-801 exposure, with enhanced learning and memory capacities, although the underlying mechanism remains still unknown^[1]. The interaction between NMDA antagonists and the cholinergic system may be important for blocking the neurotoxicity due to convulsants, because drugs with mixed anticholinergic and NMDA antagonistic actions

may hold special promise for use against nerve agent-induced seizures.

Studies have also demonstrated the role of choline in the morphogenesis and development of the central nervous system (CNS), as in neural tube closure and hippocampal development, which facilitates neuroplasticity and improves cognitive functions such as learning and memory in the offspring of choline-fed mothers^[50-56]. The mechanisms for these effects may involve DNA methylation, altered gene expression, and changes in stem cell proliferation and differentiation^[41,57-64].

4 How do cells respond to rapid application of choline in the diet?

Dietary choline exerts its actions via nicotinic $\alpha 7$ receptors in the brain^[65]. Through $\alpha 7$ receptors, choline increases calcium levels in human and mouse neurons^[66-69], resulting in a cascade of metabotropic effects. In 1997, Alkondon *et al.* reported that low levels of choline desensitize $\alpha 7$ receptors. They showed that $\alpha 7$ receptors mediate fast synaptic transmission in rat hippocampal interneurons and that through this effect, they cause phasic firing of interneurons, which excites or inhibits CA1 pyramidal neurons^[70-74]. Since 1997, the protective role of $\alpha 7$ nicotinic receptors has been revealed in extreme conditions such as excitotoxicity, ethanol exposure, withdrawal of nerve growth factor, hypoxia, and aging disorders^[75-83]. The proposed mechanism is the inhibition of calcium influx after desensitization of these receptors by an $\alpha 7$ agonist^[84].

A recent literature suggests that nicotinic agonists may be neuroprotective, but the mechanisms have not been elucidated. In 1986, Morley and Garner showed that dietary choline increases the concentration of α -bungarotoxin binding sites in 60-day-old rats^[85]. They subsequently showed that this increase in nicotinic receptors is dose-dependent and attributable to choline supplementation^[86]. This work was extended by Coutcher *et al.*^[87] who showed that dietary choline increases nicotinic binding sites without altering muscimol or flunitrazepam binding, suggesting that this change is selective for nicotinic receptors.

Furthermore, choline and its metabolites are impor-

tant for the structural integrity of cell membranes during neurogenesis and synaptogenesis, which could persist for the lifespan. Alteration of cellular structures during early brain development can have long-term effects on neuronal excitability^[88-90].

Zeisel reported^[91] and reviewed^[21] the beneficial effects of choline on liver functions: lipoprotein transport, hepatic metabolism, water balance, regulation of apoptotic signaling in liver cells, suppression of hepatic inflammation^[92], and carcinogenesis^[93-95]. Choline is also recognized as a methyl donor for methionine formation and in the synthesis of essential compounds like folic acid and vitamin B12^[96]. It prevents gallstones^[97]. Besides, its role in the transformation of homocysteine in the blood helps to prevent cardiovascular problems^[98-102] and osteoporosis^[103]. In addition, choline assists in health-threatening pathologies like type II diabetes, anemia, respiratory distress^[104], viral infections^[105,106], and traumatic injury^[11]. Finally, choline has a considerable role in animal and human reproduction^[107,108].

5 Choline restriction effects

Not all people have an adequate intake of choline^[19,109]. Very few people have diet devoid of choline, but since its major sources are eggs and beef liver^[24], people who avoid eggs and liver to control their lipid profile may be somewhat choline-deficient. Choline deficiency may also have a higher incidence in athletes, vegetarians, over-consumers of hard drugs and alcohol, those allergic to choline, third world populations^[110], and to a greater extent, in the vulnerable people such as patients having by-pass surgery, cirrhosis, or anti-convulsants therapy.

Dietary choline deficiency may cause health problems such as liver dysfunction^[111,112], compromised memory and other brain functions^[16,17,113], as well as altered osteogenesis and hematopoiesis^[114]. Choline deficiency is also linked to high risks of cardiovascular and circulatory problems^[115], hypertension, respiratory distress, and infertility. Dessau and Oleson reported that choline deficiency causes renal injury which provokes vascular syndrome through the autonomic nervous system^[116]. In addition, convincing data show that dietary choline changes alter cerebrospinal fluid choline

levels^[117,118]. Three weeks of choline deficiency diet treatment reduces plasma choline levels in humans^[19]. An interesting finding by Klein *et al.* is that prolonged choline deficiency produces problems in re-establishing choline plasma levels, even if choline is restored by a mechanism of brain choline uptake-release^[119]. However, choline deficiency is indicated a high level of liver alanine aminotransferase.

Expression of different genes in humans with low-choline diet has been investigated. Single-nucleotide polymorphisms of genes involved in choline metabolism may increase the probability of developing pathologies. When choline is low, the development of dysfunctions is influenced by expression changes in the genes involved in folate and choline metabolism. Genetic polymorphisms could explain the influence of gender on the dietary requirement for choline. This finding opens a new field of research, that is, characterizing other gene-nutrient interactions to better understand the role of diet and neuronal activity in normal brain development, to prevent pathological disorders^[15,120-125].

However, mechanisms re-establishing choline levels may be neuroprotective in specific brain areas in choline deficiency conditions. Mellott *et al.* have reported a compensatory mechanism of ACh synthesis even in low prenatal choline conditions. This involves increases in the mRNA levels of the high-affinity choline transporter in specific brain areas^[126]. Besides, Raubenheimer *et al.* have found increases in the mRNA levels of PC and of enzymes involved in free fatty acid esterification in the liver in mice under choline-deprivation conditions^[127].

6 Why investigate this chemical as a neuro-protectant?

The neuroprotective effect of dietary choline has been explored in rat models. A considerable amount of literatures have shown the correlation between prenatal and perinatal choline intake and mental performance. Dietary choline supplementation in pregnant rats enhances learning capacity in the offspring, including facilitated neuroplasticity. Studies conducted at the Veterans Affairs Medical Center (Durham, NC, USA) confirmed that manipulation of dietary choline in pregnant rats during gestational days 11–

17 has profound effects on CNS function in the offspring. These effects include modulation of learning and memory in spatial and temporal tasks, regulation of synaptic potentiation, and protection against neurotoxins^[1,14,128-130]. Behavioral changes in rats prenatally exposed to choline may be attributed to choline-dependent changes in hippocampus^[10]. Using Golgi staining, Meck *et al.* found increases in dendritic branching and spine density in the granule cells of the dentate gyrus and in CA1 and CA3 pyramidal cells in rats prenatally supplemented with choline^[131]. Furthermore, hypertrophy of cortical neurons in the prefrontal cortex has been reported in rats prenatally supplemented with choline^[90]. All these findings imply that prenatal choline supplementation is valuable for brain function. Moreover, the prenatal protection against MK-801 neurotoxicity afforded by dietary choline continues beyond the juvenile period into adulthood^[2]. Meck and Williams found that early choline dietary supplementation has long-lasting effects on memory capacity and attentional processes throughout the lifespan^[12]. Choline exposure during the prenatal and the perinatal periods influences cholinergic organization during brain development, modifying the distribution and size of cells in the basal forebrain^[132-134]. Glenn *et al.* have provided evidence that prenatal choline supplementation preserves hippocampal plasticity which still occurs even at 2 years of age^[135]. Furthermore, it has been suggested that early dietary intervention may reduce the severity of fetal alcohol effects^[5-9].

The molecular effects of prenatal choline intake have been revealed as changes in the expression levels of genes encoding signaling proteins in some regions important for cognitive functions, such as the hippocampus and the cortex of adult rats. A supplemented diet increases calcium/calmodulin (CaM)-dependent protein kinase (CaMK) I in the cortex and the transcription factor Zif268/EGR1 in the cortex and the hippocampus, while deficiency increases CaMKII β , protein kinase C β 2, and GABA(B) receptor 1 levels in the hippocampus^[126]. In 2008, some studies identified choline's modulation of growth factor content as a likely crucial aspect of its neuroprotective effects. Between postnatal days 18 and 80, higher levels of insulin-like

growth factor II (IGF2) and IGF2 receptor (IGF2R) are measured in the frontal cortex and the hippocampus of the offspring after prenatal choline supplementation, stimulating endogenous ACh release and enhancing cholinergic neurotransmission^[136]. Another study demonstrated that prenatal choline supplementation increases object exploration in young females, accompanied by increased levels of vascular endothelial growth factor and neurotrophin-3 in the hippocampus^[135]. Furthermore, it can improve motor performance in a mouse model of Rett syndrome through striatal nerve growth factor^[137], and protect against kainic acid neurotoxicity, enhancing cognitive functions through brain-derived nerve growth factor^[3].

It has been widely demonstrated that MK-801 exposure causes specific neurodegenerative responses in piriform cortex (Pir), amygdala, dentate gyrus (DG), entorhinal cortex, and the most affected retrosplenial cortex (RSC) in a dose-dependent manner^[138–141]. A more recent study^[142] has investigated the extent to which choline protects against MK-801 neurotoxicity, in which male and female rats received 30 or 60 d of dietary choline supplementation at 4 increasing doses, followed by one injection of MK-801 or saline. The results revealed that females were more vulnerable to neurotoxicity than males, and neurodegeneration in the RSC occurred. Although postnatal choline supplementation is not completely effective in preventing neurotoxicity, especially in females, neurotoxicity in the Pir of immature females treated for 60 d is suppressed by low levels of dietary choline. Although the mechanism involved is elusive, this finding suggests that the effects of choline-deficient diet might mimic the molecular and cellular effects of dietary restriction on neurodegeneration^[143–145]. Furthermore, no signs of neurodegeneration in the male Pir or in corticolimbic areas such as the amygdala and DG of either gender were detected. That study was designed with animals at a vulnerable age (adolescent and post-adolescent), a high dose of MK-801 (3.0 mg/kg), postnatal choline administration without pre-exposure, and a specific subtype of choline as choline bitartrate, without any other type of supplementary choline.

One conclusion from this study is that it is critical to

ensure an adequate level of choline in the diet. The optimal period for dietary choline supplementation is not known yet, but longer exposure which more closely resembles the normal dietary pattern is more effective postnatally, especially for deficient diet. The animal studies that tried this all showed protection by postnatal supplementation with choline. In a study by Holmes *et al.*^[146], choline supplementation before or after kainic acid-induced status epilepticus protected rats from memory deficits induced by the seizures.

There is reasonable justification for using choline supplementation in postnatal conditions. In adult animals, a low dietary intake of choline results in loss of memory functions, while choline-supplemented diet diminishes the memory impairment^[147,148]. Different studies have demonstrated that postnatal administration of choline in adult rats increases ACh synthesis^[149,150]. Alterations/decline of memory may be inhibited by preservation of synaptic structures in choline-supplemented postnatal 90-day-old mice^[150,151]. The effects of short-term choline administration on memory in normal humans have also been investigated. In normal college students, PC (25 g) causes a significant improvement in memory^[152]. Modest improvements in a memory test have been reported in Alzheimer patients treated with 25 g/day PC for 6 months^[153]. This effect may depend on when choline is made available, before or after neurological disorders or insults. It has been found that choline ameliorates the physical and the mental performance of athletes^[154–158]. Choline is used to synthesize the neurotransmitter ACh, which is needed to keep muscles active. Daily intake of choline is associated with positive effects like vigor and less fatigue before and after athletic performance in students^[159]. In one study, 2 grams of choline before exercise prevented the low levels of choline associated with prolonged physical activity.

7 Choline as a therapy

Because of the critical role of choline in the brain, dietary supplementation has been modestly attempted as a therapy for a number of diseases. An intriguing study by Wecker *et al.*^[160] showed that dietary or parenteral cho-

line supplementation in rats prevented the lethality from seizures in response to nicotine, the anticholinesterase paraoxon, and other convulsants. Moreover, alcoholics benefit from choline^[161]. A potential neuroprotective drug, citicoline, is transformed into citidine and choline when absorbed and has been widely studied in a variety of models with success^[162-165]. One attraction of this drug is that it has virtually no side-effects. The mechanisms of action are not known, but it acts as a choline donor in the metabolic pathways for the biosynthesis of ACh and neuronal membrane phospholipids, and part of its action is presumed to be from the availability of choline^[166].

8 Choline-estrogen relation

Clinical studies have suggested that estrogens act as a growth and protective factors against disorders aggravated by choline deficiency in the adult brain^[167-169]. Choline synthesis seems to depend on the presence of a specific hepatic gene activated by estrogen. Bioinformatics systems have shown that estrogens influence phosphatidylethanolamine N-methyltransferase (PEMT) gene expression, increasing the level and the activity of this enzyme. PEMT promoters in humans and rodents contain similar regions with 3 estrogen regulatory factors recognized as estrogen response elements^[170-173].

Cholinergic activity in the forebrain of adult and ovariectomized rats was determined after treatment with estrogen and/or progesterone: an increase of ACh activity was evident after 2 weeks of repeated administration but the effects did not persist after prolonged exposure^[174,175]. The interactions between androgens and cholinergic neurons have also been investigated in areas particularly involved in cognition and memory in adult male rats. Results demonstrate that the presence or absence of testosterone for 4 weeks influences the cholinergic population in specific regions^[176].

9 Conclusion

The aim of this review was to describe a natural, inexpensive, and readily available nutrient which improves mental and physical health, without side-effects. Preven-

tive measures for neurotoxicity treatment are of value. It has been realized that choline supplementation can relatively, but not completely, prevent neurotoxicity. At this point, it is necessary to determine the mechanisms through which choline exerts its actions. However, so far, little is known about the relationship between the right dose of postnatal choline supplementation and the responses in different models of neurotoxicity. Future research should be extended to postnatal choline treatment of cases particularly sensitive to choline consumption. An interesting proposal is to explore the extent to which choline is neuroprotective in adult animals and the underlying mechanisms. In addition, since choline affects many cellular processes through $\alpha 7$ receptors, it is necessary to carry out pilot electrophysiological experiments to test if and how dietary choline modifies nicotinic $\alpha 7$ receptor functions and elucidate the mechanism by which it regulates neurotoxicity. It is important to investigate the intrinsic electrophysiological characteristics of principal cells and interneurons and the synaptic inputs of these cells, and to test their sensitivity to choline.

To assess the effects of postnatal choline supplementation or choline deficiency on the development of dendritic processes and the soma of cortical pyramidal neurons, comparative studies of the morphology of cortical pyramidal neurons are required.

Although protection against neurotoxicity is valuable for any veteran suffering from disorders producing neuronal death, protecting military personnel on the battlefield from the life-long consequences of exposure to neurotoxin agents such as nerve agents, insecticides and other drugs could be helpful. It would be very beneficial if personnel receive safe neuroprotective treatment prior to exposure to potentially toxic agents. However, if research confirms the value of choline in the adult diet, there will be a strong impetus for further research in this area to develop pharmaceuticals that may be far more efficacious. In the meantime, almost any protection for those exposed in an attack would be helpful in reducing morbidity.

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References:

- [1] Guo-Ross SX, Clark S, Montoya DAC, Jones KH, Obernier J, Shetty AK, *et al.* Prenatal choline supplementation protects against postnatal neurotoxicity. *J Neurosci* 2002, 21(195): 1–6.
- [2] Guo-Ross SX, Jones KH, Shetty AK, Wilson WA, Swartzwelder HS. Prenatal dietary choline availability alters postnatal neurotoxic vulnerability in the adult rat. *Neurosci Lett* 2003, 341: 161–163.
- [3] Wong-Goodrich SJ, Mellott TJ, Glenn MJ, Blusztajn JK, Williams CL. Prenatal choline supplementation attenuates neuropathological response to status epilepticus in the adult rat hippocampus. *Neurobiol Dis* 2008, 30: 255–269.
- [4] Wong-Goodrich SJ, Glenn MJ, Mellott TJ, Liu YB, Blusztajn JK, Williams CL. Water maze experience and prenatal choline supplementation differentially promote long-term hippocampal recovery from seizures in adulthood. *Hippocampus* 2011, 21(6): 584–608.
- [5] Thomas JD, La Fiette MH, Quinn VR, Riley EP. Neonatal choline supplementation ameliorates the effects of prenatal alcohol exposure on a discrimination learning task in rats. *Neurotoxicol Teratol* 2000, 22: 703–711.
- [6] Thomas JD, Garrison M, O'Neill TM. Perinatal choline supplementation attenuates behavioral alterations associated with neonatal alcohol exposure in rats. *Neurotoxicol Teratol* 2004, 26: 35–45.
- [7] Thomas JD, Biane JS, O'Bryan KA, O'Neill TM, Dominguez HD. Choline supplementation following third-trimester-equivalent alcohol exposure attenuates behavioral alterations in rats. *Behav Neurosci* 2007, 121: 120–130.
- [8] Ryan SH, Williams JK, Thomas JD. Choline supplementation attenuates learning deficits associated with neonatal alcohol exposure in the rat: Effects of varying the timing of choline administration. *Brain Res* 2008, 1237: 91–100.
- [9] Thomas JD, Abou JE, Dominguez HD. Prenatal choline supplementation mitigates the adverse effects of prenatal alcohol exposure on development in rats. *Neurotoxicol Teratol* 2009, 31: 303–311.
- [10] Moon J, Chen M, Gandhi SU, Strawderman M, Levitsky DA, Maclean KN, *et al.* Perinatal choline supplementation improves cognitive functioning and emotion regulation in the Ts65Dn mouse model of Down syndrome. *Behav Neurosci* 2010, 124(3): 346–361.
- [11] Guseva MV, Hopkins DM, Scheff SW, Pauly JR. Dietary choline supplementation improves behavioral, histological, and neurochemical outcomes in a rat model of traumatic brain injury. *Neurotrauma* 2008, 25(8): 975–983.
- [12] Meck WH, Williams CL. Metabolic imprinting of choline by its availability during gestation: implications for memory and attentional processing across the lifespan. *Neurosci Biobehav Rev* 2003, 27: 385–399.
- [13] Pomytkin NA, Storozheva ZI, Semenova NA, Proshin AT, Sherstnev VV, Varfolomeev SD, *et al.* Neuroprotective effect of choline succinate in rats with experimental chronic cerebral ischemia evaluated by cognitive ability tests. *Izv Akad Nauk Ser Biol* 2007, 2: 183–187.
- [14] Zeisel SH, Niculescu MD. Perinatal choline influences brain structure and function. *Nutr Rev* 2006, 64(4): 197–203.
- [15] Zeisel SH. Nutritional genomics: defining the dietary requirement and effects of choline. *J Nutr* 2011, 141(3): 531–534.
- [16] Mehendint MG, Craciunescu CN, Zeisel SH. Maternal dietary choline deficiency alters angiogenesis in fetal mouse hippocampus. *Proc Natl Acad Sci U S A* 2010, 107(29): 12834–12839.
- [17] Niculescu MD, Craciunescu CN, Zeisel SH. Dietary choline deficiency alters global and gene-specific DNA methylation in the developing hippocampus of mouse fetal brains. *FASEB J* 2006, 20(1): 43–49.
- [18] Tomassoni D, Avola R, Mignini F, Parnetti L, Amenta F. Effect of treatment with choline alfoscerate on hippocampus microanatomy and glial reaction in spontaneously hypertensive rats. *Brain Res* 2006, 1120(1): 183–190.
- [19] Zeisel SH, da Costa KA. Choline: an essential nutrient for public health. *Nutr Rev* 2009, 67(11): 615–623.
- [20] Zeisel SH. Choline: an essential nutrient for humans. *Nutrition* 2000, 16: 669–671.
- [21] Zeisel SH. Choline: critical role during fetal development and dietary requirements in adults. *Annu Rev Nutr* 2006, 26: 229–250.
- [22] Buchman AL. The addition of choline to parenteral nutrition. *Gastroenterology* 2009, 137(5 Suppl): S119–128.
- [23] Zeisel SH, Mar MH, Howe JC, Holden JM. Concentrations of choline-containing compounds and betaine in common foods. *J Nutr* 2003, 133(5): 1302–1307.
- [24] A Report of the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes and its Panel on Folate, Other B Vitamins, and Choline and Subcommittee on Upper Reference Levels of Nutrients, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B-6, Vitamin B-12, Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academy Press, 1998: 390–422.
- [25] Fischer L, da Costa K, Kwock L, Stewart P, Lu T, Stabler S, *et al.* Sex and menopausal status influence human dietary requirements for the nutrient choline. *Am J Clin Nutr* 2007, 85(5): 1275–1285.
- [26] Xu X, Gammon MD, Zeisel SH, Lee YL, Wetmur JG, Teitelbaum SL, *et al.* Choline metabolism and risk of breast cancer in a population-based study. *FASEB J* 2008, 22(6): 2045–2052.
- [27] Lee JE, Giovannucci E, Fuchs CS, Willett WC, Zeisel SH, Cho E. Choline and betaine intake and the risk of colorectal cancer in men. *Cancer Epidemiol Biomarkers Prev* 2010, 19(3): 884–887.

- [28] Machlin LJ. Hand Book of Vitamins: Nutritional, Biochemical, and Clinical Aspects. New York: Marcel Dekker, 1984: 556.
- [29] Li Z, Vance DE. Phosphatidylcholine and choline homeostasis. *J Lipid Res* 2008, 49(6): 1187–1194.
- [30] Zeisel SH. Choline and phosphatidylcholine. In: Shils M, Olson JA, Shike M, Ross AC (eds). *Modern Nutrition in Health and Disease*, 9th ed. Baltimore: Williams & Wilkins, 1999: 513–523.
- [31] Hollenbeck CB. The importance of being choline. *J Am Diet Assoc* 2010, 110(8): 1162–1165.
- [32] Bjelland I, Tell GS, Vollset SE, Konstantinova S, Ueland PM. Choline in anxiety and depression: the Hordaland Health Study. *Am J Clin Nutr* 2009, 90(4): 1056–1060.
- [33] Chan KC, So KF, Wu EX. Proton magnetic resonance spectroscopy revealed choline reduction in the visual cortex in an experimental model of chronic glaucoma. *Exp Eye Res* 2009, 88(1): 65–70.
- [34] Mizumori SJY, Patterson TA, Sternberg H, Rosenzweig MR, Bennett EL, Timiras PS. Effects of dietary choline on memory and brain chemistry in aged mice. *Neurobiol Aging* 1985, 6(1): 51–56.
- [35] Arenda HEA Van Beek, Jurgen AHR Claassen. The cerebrovascular role of the cholinergic neural system in Alzheimer's disease. *Behav Brain Res* 2011, 221(2): 537–542.
- [36] Holmes-McNary MQ, Loy R, Mar MH, Albright CD, Zeisel SH. Apoptosis is induced by choline deficiency in fetal brain and in PC12 cells. *Devel Brain Res* 1997, 101: 9–16.
- [37] Yen CL, Mar MH, Zeisel SH. Choline deficiency-induced apoptosis in PC12 cells is associated with diminished membrane phosphatidylcholine and sphingomyelin, accumulation of ceramide and diacylglycerol, and activation of a caspase. *FASEB J* 1999, 13: 135–142.
- [38] Fisher MC, Zeisel SH, Mar MH, Sadler TW. Inhibitors of choline uptake and metabolism cause developmental abnormalities in neuroregulating mouse embryos. *Teratology* 2001, 64: 114–122.
- [39] Tees RC. The influences of sex, rearing environment, and neonatal choline dietary supplementation on spatial and nonspatial learning and memory in adult rats. *Dev Psychobio* 1999, 135: 328–342.
- [40] Tees RC, Mohammadi E, Adam TJ. Altering the impact of early rearing on the rat's spatial memory with pre- and postnatal choline supplementation. *Soc Neurosci Abstr* 1999, 17: 1401.
- [41] Albright CD, Friedrich CB, Brown EC, Mar MH, Zeisel SH. Maternal dietary choline availability alters mitosis, apoptosis and the localization of TOAD-64 protein in the developing fetal rat septum. *Brain Res Dev Brain Res* 1999, 115: 123–129.
- [42] Holler T, Cermak J M, Blusztajn JK. Dietary choline supplementation in pregnant rats increases hippocampal phospholipase D activity of the offspring. *FASEB J* 1996, 10: 1653–1659.
- [43] Meck W, Williams C. Simultaneous temporal processing is sensitive to prenatal choline availability in mature and aged rats. *Neuroreport* 1997, 8: 3045–3051.
- [44] Meck W, Williams C. Characterization of the facilitative effects of perinatal choline supplementation on timing and temporal memory. *Neuroreport* 1997, 8: 2831–2835.
- [45] Meck W, Williams C. Perinatal choline supplementation increases the threshold for chunking in spatial memory. *Neuroreport* 1997, 8: 3053–3059.
- [46] Ricceri L, Berger-Sweeney J. Postnatal choline supplementation in preweanling mice: sexually dimorphic behavioral and neurochemical effects. *Behav Neurosci* 1998, 112: 1387–1392.
- [47] Sveinbjornsdottir S, Sander JWAS, Upton D, Thompson PJ, Patsalos PN, Hirt D, *et al.* The excitatory amino acid antagonist D-CPP-ene (SDZ EAA-494) in patients with epilepsy. *Epilepsy Res* 1993, 16: 165–174.
- [48] Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, *et al.* Subanesthetic effects of the non competitive NMDA antagonist, ketamine, in humans. *Arch Gen Psychiatry* 1994, 51: 199–214.
- [49] Jentsch JD, Roth RH. The neuropsychopharmacology of phenylcyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 1999, 20: 201–225.
- [50] Zeisel SH. Choline: needed for normal development of memory. *J Am Coll Nutr* 2000, 19(5 Suppl): S528–531.
- [51] Zeisel SH. Nutritional importance of choline for brain development. *J Am Coll Nutr* 2004, 23(6 Suppl): S621–626.
- [52] Shaw GM, Carmichael SL, Yang W, Selvin S, Schaffer DM. Periconceptional dietary intake of choline and betaine and neural tube defects in offspring. *Am J Epidemiol* 2004, 160: 102–109.
- [53] Zeisel SH. The fetal origins of memory: the role of dietary choline in optimal brain development. *J Pediatr* 2006, 149(5 Suppl): S131–136.
- [54] Sanders LM, Zeisel SH. Choline: dietary requirements and role in brain development. *Nutr Today* 2007, 42(4): 181–186.
- [55] Signore C, Ueland PM, Troendle J, Mills JL. Choline concentrations in human maternal and cord blood and intelligence at 5 y of age. *Am J Clin Nutr* 2008, 87(4): 896–902.
- [56] Shaw GM, Finnell RH, Blom HJ, Carmichael SL, Vollset SE, Yang W, *et al.* Choline and risk of neural tube defects in a folate-fortified population. *Epidemiology* 2009, 20(5): 714–719.
- [57] van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 1999, 2: 266–270.
- [58] Markakis EA, Gage FH. Adult-generated neurons in the dentate gyrus send axonal projections to field CA3 and are surrounded by synaptic vesicles. *J Comp Neurol* 1999, 406: 449–460.
- [59] Fisher MC, Zeisel SH, Mar MH, Sadler TW. Perturbations in choline metabolism cause neural tube defects in mouse embryos *in vitro*. *FASEB J* 2002, 16: 619–621.

- [60] Alonso-Aperte E, Varela-Moreiras G. Brain folates and DNA methylation in rats fed a choline deficient diet or treated with low doses of methotrexate. *Int J Vitam Nutr Res* 1996, 66: 232–236.
- [61] Paulsen M, Ferguson-Smith AC. DNA methylation in genomic imprinting, development, and disease. *J Pathol* 2001, 195: 97–110.
- [62] Reinhart B, Eljanne M, Chaillet JR. Shared role for differentially methylated domains of imprinted genes. *Mol Cell Biol* 2002, 22: 2089–2098.
- [63] Albright CD, Tsai AY, Friedrich CB, Mar MH, Zeisel SH. Choline availability alters embryonic development of the hippocampus and septum in the rat. *Brain Res Dev Brain Res* 1999, 113: 13–20.
- [64] Albright CD, Mar MH, Friedrich CB, Brown EC, Zeisel SH. Maternal choline availability alters the localization of p15Ink4B and p27Kip1 cyclin-dependent kinase inhibitors in the developing fetal rat brain hippocampus. *Dev Neurosci* 2001, 23: 100–106.
- [65] Guseva MV, Hopkins DM, Pauly JR. An autoradiographic analysis of rat brain nicotinic receptor plasticity following dietary choline modification. *Pharmacol Biochem Behav* 2006, 84(1): 26–34.
- [66] Tsuneki H, Klink R, Lena C, Korn H, Changeux JP. Calcium mobilization elicited by two types of nicotinic acetylcholine receptors in mouse substantia nigra pars compacta. *Eur J Neurosci* 2000, 12(7): 2475–2485.
- [67] Patterson D, Nordberg A. Neuronal nicotinic receptors in the human brain. *Prog Neurobiol* 2000, 61(1): 75–111.
- [68] Albuquerque EX, Pereira EF, Mike A, Eisenberg HM, Maelicke A, Alkondon M. Neuronal nicotinic receptors in synaptic functions in humans and rats: physiological and clinical relevance. *Behav Brain Res* 2000, 113(1–2): 131–141.
- [69] Papke RL, Porter Papke JK. Comparative pharmacology of rat and human $\alpha 7$ nAChR conducted with net charge analysis. *Br J Pharmacol* 2002, 137: 49–61.
- [70] Alkondon M, Pereira EF, Cortes WS, Maelicke A, Albuquerque EX. Choline is a selective agonist of $\alpha 7$ nicotinic acetylcholine receptors in the rat brain neurons. *Eur J Neurosci* 1997, 9: 2734–2742.
- [71] Albuquerque EX, Alkondon M, Pereira EF, Castro NG, Schratzenholz A, Barbosa CT, *et al.* Properties of neuronal nicotinic acetylcholine receptors: pharmacological characterization and modulation of synaptic function. *J Pharmacol Exp Ther* 1997, 280(3): 1117–1136.
- [72] Alkondon M, Braga MF, Pereira EF, Maelicke A, Albuquerque EX. $\alpha 7$ nicotinic acetylcholine receptors and modulation of gabaergic synaptic transmission in the hippocampus. *Eur J Pharmacol* 2000, 393(1–3): 59–67.
- [73] Mike A, Castro NG, Albuquerque EX. Choline and acetylcholine have similar kinetic properties of activation and desensitization on the $\alpha 7$ nicotinic receptors in rat hippocampal neurons. *Brain Res* 2000, 882(1–2): 155–168.
- [74] Alkondon M, Pereira EF, Eisenberg HM, Albuquerque EX. Nicotinic receptor activation in human cerebral cortical interneurons: a mechanism for inhibition and disinhibition of neuronal networks. *J Neurosci* 2000b, 20(1): 66–75.
- [75] Kihara T, Shimohama S, Sawada H, Kimura J, Kume T, Kochiyama H, *et al.* Nicotinic receptor stimulation protects neurons against beta-amyloid toxicity. *Ann Neurol* 1997, 42(2): 159–163.
- [76] Meyer EM, Tay ET, Zoltewicz JA, Meyers C, King MA, Papke RL, *et al.* Neuroprotective and memory-related actions of novel $\alpha 7$ nicotinic agents with different mixed agonist/antagonist properties. *J Pharmacol Exp Ther* 1998, 284: 1026–1032.
- [77] Strahlendorf JC, Acosta S, Miles R, Strahlendorf HK. Choline blocks AMPA-induced dark cell degeneration of Purkinje neurons: potential role of the $\alpha 7$ nicotinic receptor. *Brain Res* 2001, 901(1–2): 71–78.
- [78] Li Y, Meyer EM, Walker DW, Millard WJ, He YJ, King MA. $\alpha 7$ nicotinic receptor activation inhibits ethanol-induced mitochondrial dysfunction, cytochrome c release and neurotoxicity in primary rat hippocampal neuronal cultures. *J Neurochem* 2002b, 81: 853–858.
- [79] Jonnala RR, Buccafusco JJ. Relationship between the increased cell surface $\alpha 7$ nicotinic receptor expression and neuroprotection induced by several nicotinic receptor agonists. *J Neurosci Res* 2002, 66(4): 565–572.
- [80] Utsugisawa K, Nagane Y, Obara D, Tohgi H. Overexpression of $\alpha 7$ nicotinic acetylcholine receptor prevents G1-arrest and DNA fragmentation in PC12 cells after hypoxia. *J Neurochem* 2002, 81: 497–505.
- [81] Zanardi A, Leo G, Bigini G, Zoli M. Nicotine and neurodegeneration in ageing. *Toxicol Lett* 2002, 127: 207–215.
- [82] Mudo G, Belluardo N, Fuxe K. Nicotinic receptor agonists as neuroprotective/neurotrophic drugs. Progress in molecular mechanisms. *J Neural Transm* 2007, 114(1): 135–147.
- [83] Toyohara J, Hashimoto K. $\alpha 7$ Nicotinic receptor agonists: potential therapeutic drugs for treatment of cognitive impairments in Schizophrenia and Alzheimer's disease. *Open Med Chem J* 2010, 4: 37–56.
- [84] Ferchmin PA, Perez D, Eterovic VA, de Vellis J. Nicotinic receptors differentially regulate N-methyl-D-aspartate damage in acute hippocampal slices. *J Pharmacol Exp Ther* 2003, 305: 1071–1078.
- [85] Morley BJ, Garner LL. Increases in the concentration of brain α -bungarotoxin binding sites induced by dietary choline are age-dependent. *Brain Res* 1986, 378(2): 315–319.
- [86] Morley BJ, Fleck DL. A time course and dose-response study of the regulation of brain nicotinic receptors by dietary choline. *Brain Res* 1987, 421(1–2): 21–29.
- [87] Couthner JB, Cawley G, Wecker L. Dietary choline supplementation increases the density of nicotine binding sites in rat brain. *J*

- Pharm Exp Ther 1992, 262(3): 1128–1132.
- [88] Mainen ZF, Sejnowski TJ. Influence of dendritic structure on firing pattern in model neocortical neurons. *Nature* 1996, 382: 363–366.
- [89] Meck WH, Smith RA, Williams CL. Organizational changes in cholinergic activity and enhanced visuospatial memory as a function of choline administered prenatally or postnatally or both. *Behav Neurosci* 1989, 109: 1234–1241.
- [90] Williams CL, Meck WH, Heyer DD, Loy R. Hypertrophy of basal forebrain neurons and enhanced visuospatial memory in perinatally choline-supplemented rats. *Brain Res* 1998, 794: 225–238.
- [91] Zeisel SH, Blusztajn JK. Choline and human nutrition. *Annu Rev Nutr* 1994, 14: 269–296.
- [92] Detopoulou P, Panagiotakos DB, Antonopoulou S, Pitsavos C, Stefanadis C. Dietary choline and betaine intakes in relation to concentrations of inflammatory markers in healthy adults: the ATTICA study. *Am J Clin Nutr* 2008, 87(2): 424–430.
- [93] Xu X, Gammon MD, Zeisel SH, Bradshaw PT, Wetmur JG, Teitelbaum SL, *et al.* High intakes of choline and betaine reduce breast cancer mortality in a population-based study. *FASEB J* 2009, 23(11): 4022–4028.
- [94] Tolvanen T, Yli-Kerttula T, Ujula T, Autio A, Lehtikainen P, Minn H, *et al.* Biodistribution and radiation dosimetry of [^{11}C]choline: a comparison between rat and human data. *Eur J Nucl Med Mol Imaging* 2010, 37(5): 874–883.
- [95] Ueland PM. Choline and betaine in health and disease. *J Inher Metab Dis* 2010, 34(1): 3–15.
- [96] Zeisel SH. Importance of methyl donors during reproduction. *Am J Clin Nutr* 2009, 89(2): S673–677.
- [97] Kritchevsky D, Klurfeld DM. Influence of vegetable protein on gallstone formation in hamsters. *Am J Clin Nutr* 1979, 32: 2174–2176.
- [98] Gerhard GT, Duell PB. Homocysteine and atherosclerosis. *Curr Opin Lipidol* 1999, 10: 417–428.
- [99] Olthof MR, Brink EJ, Katan MB, Verhoef P. Choline supplemented as phosphatidylcholine decreases fasting and postmethionine-loading plasma homocysteine concentrations in healthy men. *Am J Clin Nutr* 2005, 82(1): 111–117.
- [100] Bidulescu A, Chambless LE, Siega-Riz AM, Zeisel SH, Heiss G. Usual choline and betaine dietary intake and incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *BMC Cardiovasc Disord* 2007, 7: 20.
- [101] Chiuve S, Giovannucci E, Hankinson S, Zeisel SH, Dougherty LW, Willett WC, *et al.* The association between betaine and choline intakes and the plasma concentrations of homocysteine in women. *Am J Clin Nutr* 2007, 86: 1073–1081.
- [102] Dalmeijer GW, Olthof MR, Verhoef P, Bots ML, van der Schouw YT. Prospective study on dietary intakes of folate, betaine, and choline and cardiovascular disease risk in women. *Eur J Clin Nutr* 2008, 62: 386–394.
- [103] Van Meurs J, Dhonukshe-Rutten RA, Pluijm SM, Van der Klift M, de Jonge R, Lindemans J, *et al.* Homocysteine levels and the risk of osteoporotic fracture. *N Engl J Med* 2004, 350: 2033–2041.
- [104] Das S, Gupta K, Gupta A, Gaur SN. Comparison of the efficacy of inhaled budesonide and oral choline in patients with allergic rhinitis. *Saudi Med J* 2005, 26(3): 421–424.
- [105] DPhil T, Carr CA, Guimares AR, Worth JL, Navia BA, Gonzalez RG. Brain choline-containing compounds are elevated in HIV-positive patients before the onset of AIDS dementia complex: A proton magnetic resonance spectroscopic study. *Neurology* 1996, 46: 783–788.
- [106] Jones KD, Barkley JA, Warner JO. Perinatal nutrition and immunity to infection. *Pediatr Allergy Immunol* 2010, 21(4 Pt 1): 564–576.
- [107] Chan J, Deng L, Mikael LG, Yan J, Pickell L, Wu Q, *et al.* Low dietary choline and low dietary riboflavin during pregnancy influence reproductive outcomes and heart development in mice. *Am J Clin Nutr* 2010, 91(4): 1035–1043.
- [108] Quintans CJ, Donaldson MJ, Bertolino MN, Pasqualini RS. Birth of two babies using oocytes that were cryopreserved in a choline-based freezing medium. *Hum Reprod* 2002, 17(12): 3149–3152.
- [109] Bidulescu A, Chambless LE, Siega-Riz AM, Zeisel SH, Heiss G. Repeatability and measurement error in the assessment of choline and betaine dietary intake: the atherosclerosis risk in communities (ARIC) study. *Nutr J* 2009, 8(1): 14.
- [110] Hasler CM. The changing face of functional foods. *JACN* 2000, 19(5 Suppl): S499–506.
- [111] Buchman AL, Dubin MD, Moukartzel AA, Jenden DJ, Roch M, Rice KM, *et al.* Choline deficiency: a cause of hepatic steatosis during parenteral nutrition that can be reversed with intravenous choline supplementation. *Hepatology* 1995, 22(5): 1399–1403.
- [112] Albright CD, Liu R, Bethea TC, da Costa KA, Salganik RI, Zeisel SH. Choline deficiency induces apoptosis in SV40-immortalized CWSV-1 rat hepatocytes in culture. *FASEB J* 1996, 10(4): 510–516.
- [113] Stevens KE, Adams CE, Mellott TJ, Robbins E, Kisley MA. Perinatal choline deficiency produces abnormal sensory inhibition in Sprague-Dawley rats. *Brain Res* 2008, 1237: 84–90.
- [114] da Costa KA, Niculescu MD, Craciunescu CN, Fischer LM, Zeisel SH. Choline deficiency increases lymphocyte apoptosis and DNA damage in humans. *Am J Clin Nutr* 2006, 84(1): 88–94.
- [115] da Costa KA, Gaffney CE, Fischer LM, Zeisel SH. Choline deficiency in mice and humans is associated with increased plasma homocysteine concentration after a methionine load. *Am J Clin Nutr* 2005, 81(2): 440–444.
- [116] Dessau FI, Oleson JJ. Nature of renal changes in acute choline deficiency. *Proc Soc Exp Biol Med* 1947, 64(3): 278.
- [117] Klein J, Köppen A, Löffelholz K. Small rises in plasma choline reverse the negative arteriovenous difference of brain choline. *J*

- Neurochem 1990, 55(4): 1231–1236.
- [118] Klein J, Gonzalez A, Köppen A, Löffelholz K. Free choline and choline metabolites in rat brain and body fluids: sensitive determination and implications for choline supply to the brain. *Neurochem Int* 1993, 22(3): 293–300.
- [119] Klein J, Köppen A, Löffelholz K. Regulation of free choline in rat brain: dietary and pharmacological manipulations. *Neurochem Int* 1998, 32(5–6): 479–485.
- [120] da Costa KA, Kozyreva OG, Song J, Galanko JA, Fischer LM, Zeisel SH. Common genetic polymorphisms affect the human requirement for the nutrient choline. *FASEB J* 2006, 20(9): 1336–1344.
- [121] Zeisel SH. Gene response elements, genetic polymorphisms and epigenetics influence the human dietary requirement for choline. *IUBMB Life* 2007, 59(6): 380–387.
- [122] Zeisel SH. Genetic polymorphisms in methyl-group metabolism and epigenetics: lessons from humans and mouse models. *Brain Res* 2008, 1237: 5–11.
- [123] Zeisel SH. Epigenetic mechanisms for nutrition determinants of later health outcomes. *Am J Clin Nutr* 2009, 89(5): S1488–1493.
- [124] Zeisel SH. Choline: clinical nutrigenetic/nutrigenomic approaches for identification of functions and dietary requirements. *World Rev Nutr Diet* 2010, 101: 73–83.
- [125] Niculescu MD, Wu R, Guo Z, da Costa KA, Zeisel SH. Diethanolamine alters proliferation and choline metabolism in mouse neural precursor cells. *Toxicol Sci* 2007, 96: 321–326.
- [126] Mellott TJ, Kowall NW, Lopez-Coviella I, Blusztajn JK. Prenatal choline deficiency increases choline transporter expression in the septum and hippocampus during postnatal development and in adulthood in rats. *Brain Res* 2007b, 1151: 1–11.
- [127] Raubenheimer PJ, Nyirenda MJ, Walker BR. A choline-deficient diet exacerbates fatty liver but attenuates insulin resistance and glucose intolerance in mice fed a high-fat diet. *Diabetes* 2006, 55: 2015–2020.
- [128] McCann JC, Hudes M, Ames BN. An overview of evidence for a causal relationship between dietary availability of choline during development and cognitive function in offspring. *Neurosci Biobehav Rev* 2006, 30(5): 696–712.
- [129] Cheng RK, Meck WH. Prenatal choline supplementation increases sensitivity to time by reducing non-scalar sources of variance in adult temporal processing. *Brain Res* 2007, 1186: 242–254.
- [130] Zeisel SH. Is maternal diet supplementation beneficial? Optimal development of infant depends on mother's diet. *Am J Clin Nutr* 2009, 89(2): S685–687.
- [131] Meck WH, Williams CL, Cermak JM, Blusztajn JK. Developmental periods of choline sensitivity provide an ontogenetic mechanism for regulating memory capacity and age-related dementia. *Front Integr Neurosci* 2007, 1: 7.
- [132] Brady RJ, Phelps PE, Vaughn JE. Neurogenesis of basal forebrain cholinergic neurons in rat. *Dev Brain Res* 1989, 47: 81–92.
- [133] Semba K, Fibiger HC. Organization of central cholinergic systems. *Prog Brain Res* 1989, 79: 37–63.
- [134] Loy R, Heyer D, Williams CL, Meck WH. Choline-induced spatial memory facilitation correlates with altered distribution and morphology of septal neurons. *Adv Exp Med Biol* 1991, 295: 373–382.
- [135] Glenn MJ, Kirby ED, Gibson EM, Wong-Goodrich SJ, Mellott TJ, Blusztajn JK, *et al.* Age-related declines in exploratory behavior and markers of hippocampal plasticity are attenuated by prenatal choline supplementation in rats. *Brain Res* 2008, 1237: 110–123.
- [136] Napoli I, Blusztajn JK, Mellott TJ. Prenatal choline supplementation in rats increases the expression of IGF2 and its receptor IGF2R and enhances IGF2-induced acetylcholine release in hippocampus and frontal cortex. *Brain Res* 2008, 1237: 124–135.
- [137] Nag N, Mellott TJ, Berger-Sweeney JE. Effects of postnatal dietary choline supplementation on motor regional brain volume and growth factor expression in a mouse model of Rett syndrome. *Brain Res* 2008, 1237: 101–109.
- [138] Olney JW, Labruyere J, Wang G, Wozniak DF, Price MT, Sesma MA, *et al.* NMDA antagonist neurotoxicity: mechanism and prevention. *Science* 1991, 254: 1515–1518.
- [139] Fix AS, Wozniak DF, Trex LL, McEwan M, Miller JP, Olney JW. Quantitative analyses of factors influencing neuronal necrosis induced by MK-801 in the rat posterior cingulate/retrosplenial cortex. *Brain Res* 1995, 696: 194–204.
- [140] Horvath ZC, Czopf J, Buzsaki G. Research report MK-801-induced neuronal damage in rats. *Brain Res* 1997, 753: 181–195.
- [141] Noguchi KK, Nemmers B, Farber NB. Age has a similar influence on the susceptibility to NMDA antagonist-induced neurodegeneration in most brain regions. *Brain Res Dev Brain Res* 2005, 158: 82–91.
- [142] Biasi E. Effects of postnatal dietary choline manipulation against MK-801 neurotoxicity in pre and postadolescent rats. *Brain Res* 2010, 1362: 117–132.
- [143] Pinto LSNM, Gualberto FAS, Pereira SRC, Barros PA, Franco GC, Ribeiro AM. Dietary restriction protects against chronic-ethanol-induced changes in exploratory behavior in Wistar rats. *Brain Res* 2006, 1078: 171–181.
- [144] Lee J, Duan W, Mattson MP. Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *J Neurochem* 2002, 82: 1367–1375.
- [145] Lee J, Seroogy KB, Mattson MP. Dietary restriction enhances neurotrophin expression and neurogenesis in the hippocampus of adult mice. *J Neurochem* 2002c, 80(3): 539–547.
- [146] Holmes GL, Yang Y, Liu Z, Cermak JM, Sarkisian MR, Stafstrom CE, *et al.* Seizure-induced memory impairment is reduced by choline supplementation before or after status epilepticus. *Epilepsy*

- Res 2002, 48: 3–13.
- [147] Bartus RT, Dean RL, Goas JA, Lippa AS. Age-related changes in passive avoidance retention: modulation with dietary choline. *Science* 1980, 209: 301.
- [148] Hung MC, Shibasaki K, Yoshida R, Sato M, Imaizumi K. Learning behaviour and cerebral protein kinase C, antioxidant status, lipid composition in senescence-accelerated mouse: influence of a phosphatidylcholine-vitamin B12 diet. *Br J Nutr*. 2001, 86(2): 163–171.
- [149] Chung SY, Moriyama T, Uezu E, Uezu K, Hirata R, Yohena N, *et al*. Administration of phosphatidylcholine increases brain acetylcholine concentration and improves memory in mice with dementia. *J Nutr* 1995, 125(6): 1484–1489.
- [150] Mervis RF. Chronic dietary choline represses age-related loss of dendritic spines in mouse neocortical pyramidal cells. *J Neuropathol Exp Neurol* 1982, 41: 363.
- [151] Ladd SL, Sommer SA, LaBerge S, Toscano W. Effect of phosphatidylcholine on explicit memory. *Clin Neuropharm* 1993, 16: 540–549.
- [152] Levy R. Lecithin in Alzheimer's disease. *Lancet* 1982, 2: 671–672.
- [153] Little A, Levy R, Chuaqui-Kidd P, Hand D. A double-blind, placebo controlled trial of high-dose lecithin in Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1985, 48: 736–742.
- [154] Buchman AL, Jenden D, Roch M. Plasma free, phospholipid-bound and urinary free choline all decrease during a marathon run and may be associated with impaired performance. *J Am Coll Nutr* 1999, 18(6): 598–601.
- [155] Buchman AL, Awal M, Jenden D, Roch M, Kang SH. The effect of lecithin supplementation on plasma choline concentrations during a marathon. *J Am Coll Nutr* 2000, 19(6): 768–770.
- [156] Conlay LA, Wurtman RJ, Blusztajn JK, Coviellia IJ, Maher TJ, Evoniuk GE. Decreased plasma choline concentrations in marathon runners. *N Engl J Med* 1986, 175: 892.
- [157] Sandage BW, Sabounjian LA, White R, Wurtman RJ. Choline citrate may enhance athletic performance. *Physiologist* 1992, 35: 236.
- [158] Von Allworden HN, Horn S, Kahl J, Feldheim W. The influence of lecithin on plasma choline concentrations in triathletes and adolescent runners during exercise. *Eur J Appl Physiol* 1983, 67: 87–91.
- [159] Kumar R, Divekar HM, Gupta V, Srivastava KK. Antistress and adaptogenic activity of lecithin supplementation. *J Altern Complement Med* 2002, 8(4): 487–492.
- [160] Wecker L, Flynn CJ, Stouse MR, Trommer BA. Choline availability: effects on the toxicity of centrally active drugs. *Drug Nutr Interact* 1982, 1(2): 125–130.
- [161] Klatskin G, Krehl WA. The effect of alcohol on the choline requirement. II. Incidence of renal necrosis in weanling rats following short term ingestion of alcohol. *J Exp Med* 1954, 100(6): 615–627.
- [162] Adibhatla RM, Hatcher JF, Dempsey RJ. Citicoline: neuroprotective mechanisms in cerebral ischemia. *J Neurochem* 2002, 80(1): 12–23.
- [163] Fioravanti M, Buckley AE. Citicoline (Cognizin) in the treatment of cognitive impairment. *Clin Interv Aging* 2006, 1(3): 247–251.
- [164] Parisi V, Coppola G, Centofanti M, Oddone F, Angrisani AM, Ziccardi L, *et al*. Evidence of the neuroprotective role of citicoline in glaucoma patients. *Prog Brain Res* 2008, 173: 541–554.
- [165] Hurtado O, Lizasoain I, Moro MÁ. Neuroprotection and recovery: recent data at the bench on citicoline. *Stroke* 2011, 42(1 Suppl): S33–35.
- [166] Secades JJ, Lorenzo JL. Citicoline: pharmacological and clinical review, 2006 update. *Methods Find Exp Clin Pharmacol* 2006, 28(Suppl B): 1–56.
- [167] Green PS, Simpkins JW. Neuroprotective effects of estrogens: potential mechanisms of action. *Int J Develop Neurosci* 2000, 18(4–5): 347–358.
- [168] Gibbs RB. Estrogen therapy and cognition: A review of the cholinergic hypothesis. *Endocr Rev* 2010, 31(2): 224–253.
- [169] Stiliani A, Bittigau P, Felderhoff-Mueser U, Manthey D, Siffringer M, Pesditschek S, *et al*. Protection with estradiol in developmental models of apoptotic neurodegeneration. *Ann Neurol* 2005, 58(2): 266–276.
- [170] Granholm AC, Ford KA, Hyde LA, Bimonte HA, Hunter CL, Nelson M, *et al*. Estrogen restores cognition and cholinergic phenotype in an animal model of Down syndrome. *Physiol Behav* 2002, 77(2–3): 371–385.
- [171] Resseguie M, Song J, Niculescu MD, da Costa KA, Randall TA, Zeisel SH. Phosphatidylethanolamine N-methyltransferase (PEMT) gene expression is induced by estrogen in human and mouse primary hepatocytes. *FASEB J* 2007, 21(10): 2622–2632.
- [172] Fischer LM, da Costa KA, Kwock L, Galanko J, Zeisel SH. Dietary choline requirements of women: effects of estrogen and genetic variation. *Am J Clin Nutr* 2010, 92(5): 1113–1119.
- [173] Resseguie ME, da Costa KA, Galanko JA, Patel M, Davis IJ, Zeisel SH. Aberrant estrogen regulation of PEMT results in choline deficiency-associated liver dysfunction. *J Biol Chem* 2011, 286(2): 1649–1658.
- [174] Gibbs RB. Effects of gonadal hormone replacement on measures of basal forebrain cholinergic function. *Neuroscience* 2000, 101(4): 931–938.
- [175] Gibbs RB. Effects of estrogen on basal forebrain cholinergic neurons vary as a function of dose and duration of treatment. *Brain Res* 1997, 757(1): 10–16.
- [176] Nakamura N, Fujita H, Kawata M. Effects of gonadectomy on immunoreactivity for choline acetyltransferase in the cortex, hippocampus, and basal forebrain of adult male rats. *Neuroscience* 2002, 109: 473–485.

含胆碱饮食的重要性

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摘要: 日常摄取的食物能通过各种脑内表达的调节因子来影响神经功能。胆碱是常存在于食物中的一种具有多种功能的营养成分。本文对关于胆碱功能的相关实验结果进行综述, 以制定一个安全有效并能在较短的时间内得以实施的饮食方案来对抗神经毒性和神经系统疾病。

关键词: 胆碱; 神经毒性; 神经保护