lead to puzzling and even paradoxical results. Most of these still remain to be investigated from a quantum computing perspective. It is possible that one of these might result in an algorithm that could solve NP-complete problems. Such a solution would greatly increase the interest in building a quantum computer.

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PERSPECTIVES: DEVELOPMENTAL NEUROSCIENCE

Choline, a Vital Amine

Jan Krzysztof Blusztajn

In April of this year choline was classified as an essential nutrient for humans by the Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences. For the first time, recommendations were issued for the adequate intake of this small molecule (*1*). This official recognition of the importance of choline in the human diet likely foreshadows new public health initiatives on choline nutrition.

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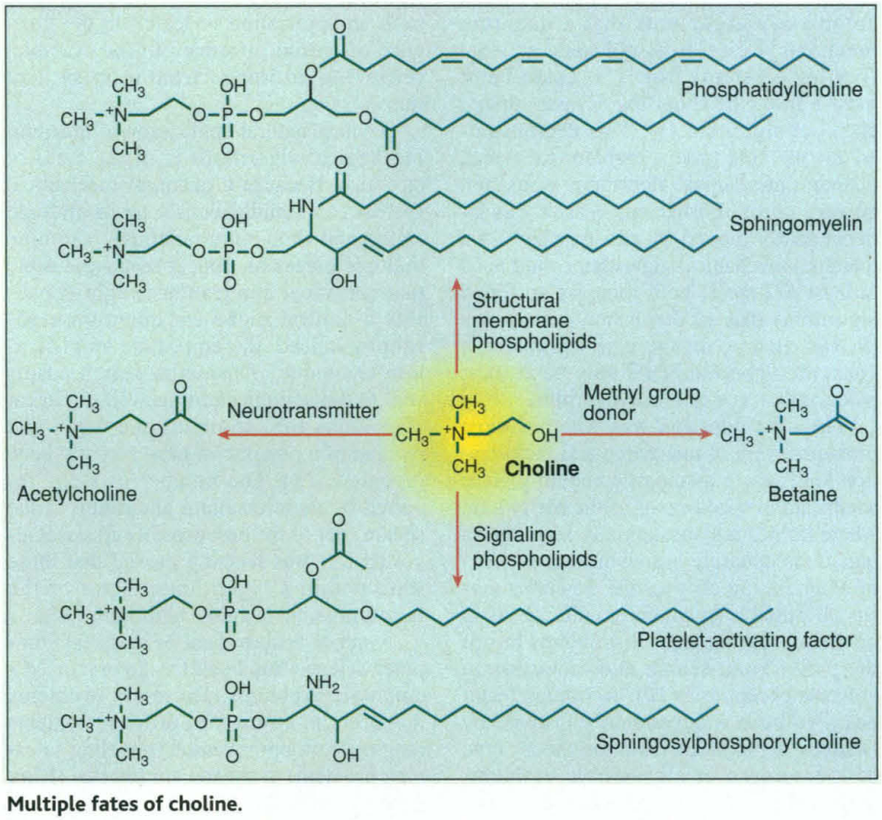
In 1912 Casimir Funk coined the term "vital amine" to describe organic compounds that are required in small amounts in the diet for the maintenance of normal health. The term later evolved into the more familiar word, vitamin. Choline fits the original definition: It is an amine and for normal health must be consumed in the diet, even though humans can biosynthesize small amounts. Choline is present in most foods (*2*) but is found in particularly high amounts in eggs, liver, peanuts, and a variety of meats and vegetables.

In the body, choline subserves several biological functions (*2*) (see figure, right). It is the precursor of phosphatidylcholine and sphingomyelin, two phospholipids that serve as components of biological membranes and as precursors for intracellular messengers such as diacylglycerol or ceramide. Choline is also the precursor of two signaling lipids, platelet-activating factor and sphingosylphosphorylcholine, and of a neurotransmitter, acetylcholine (*3*). Furthermore, choline can be enzymatically oxidized to betaine and the methyl groups of betaine then used to resynthesize methionine from homocysteine, thereby providing methionine for protein synthesis and transmethylation reactions. This last pathway is also an alternative to one that uses the cofactor methyltetrahydrofolate, and thus spares methyltetrahydrofolate for its role in the synthesis of nucleic acids.

The importance of choline for maintaining health in adults has been recognized for some time (*4*), but recent work points to its critical role in brain development. Meck, Williams, and their colleagues have tested the relation between choline availability during fetal development and brain function, initially using behavioral measurements (*5–7*). Various amounts of choline were included in the diets of pregnant rats during embryonic days 11 (E11) to E17 (a period of high cell division and programmed cell death in fetal brain). Pregnant rats ingested either no choline, control amounts of choline, or approximately three times control amounts of choline. For the remainder of their lives both mothers and offspring ate a normal diet. These alterations in choline availability during the second half of gestation resulted in life-long behavioral changes. As adults, offspring of mothers that had received choline supplements were more adept at tasks that measured spatial and temporal memory and attention (*5–7*). If the mother had received no choline, the



Multiple fates of choline.

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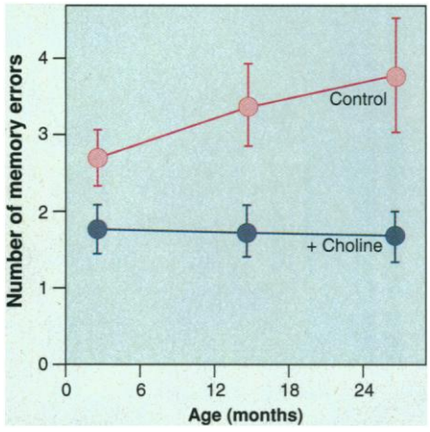
animals were impaired in attentional and certain memory tasks (*7*). These behavioral effects of choline availability in utero were remarkably long-lasting and persisted beyond the age of 2 years (*7*), an age at which a rat is developmentally old. Thus, prenatal supplementation with choline prevented the normally observed memory decline of old age (see figure, right). Together, these data suggest that choline has a permanent effect on brain organization and function.

The long-term effects of choline on the brain have also been tested with neuroanatomical (*8*), neurophysiological (*9*), and neurochemical (*10*) approaches. Hippocampal long-term potentiation (LTP), a measure of synaptic plasticity and a model for learning and memory (*11*), is facilitated by prenatal choline by a reduction in the stimulus threshold for LTP generation (*9*), whereas the threshold is increased in prenatally choline-deficient animals (*9*). Changes in synaptic function in choline-supplemented rats were also observed in studies on hippocampal acetylcholine, which is a neurotransmitter important for learning and memory (*12*). Depolarization-evoked acetylcholine release was increased in hippocampal slices obtained from rats supplemented with choline prenatally (*10*). The results of the neurophysiological and the neurochemical studies are consistent with the behavioral observations and suggest that choline availability in utero alters brain development at the cellular level. Indeed, mammalian cells in culture require choline for cell division and die without it (*13*). Hence, all cell culture media contain choline.

Choline deficiency in cell culture causes death by apoptosis (*14*), apparently as a result of decreases in membrane phosphatidylcholine content and accompanying increases in cellular concentrations of ceramide, the putative second messenger of apoptosis. Ceramide is a precursor and a metabolite of sphingomyelin, a choline-containing phospholipid, and choline deficiency would be expected to increase cellular levels of ceramide. Choline availability in utero similarly affects fetal brain development, although unlike its actions in cell culture, the in vivo effects may be indirect. Specifically, choline supplementation during E11 to E17 stimulates cell division in the embryonic brain (assessed immunohistochemically on E18 after the injection of pregnant mothers on E16 with the DNA precursor bromodeoxyuridine) (*15*), whereas choline deficiency during this period increases the rate of apoptosis (observed on E18) in hippocampus and septum (*14*, *15*), brain regions involved in memory processing.

These accumulating data point to a key role of choline in early brain development. What remains to be explained, however, is how changes in brain organization brought about by prenatal supplementation with choline can be so long-lasting as to prevent memory decline associated with aging. One possibility is that the aging process is indeed slowed. Alternatively, the rate of physiologic decline within the brain may be fundamentally unaffected but of a magnitude insufficient to manifest as deterioration in memory tests because of an increase in reserve capacity for efficient memory processing resulting from cellular and synaptic modifications occurring in early development.



DATA PROVIDED BY W. MECK AND C. WILLIAMS, DUKE UNIVERSITY

Older, but smarter. Aging in control rats is accompanied by a decline in memory (increase in the number of errors in remembering the location of food in a maze). Rats given supplemental choline before birth make fewer memory errors than do control animals and show no memory decline with age.

Choline is provided to the growing fetus and neonate in several ways. Choline in the maternal diet and in the body stores is efficiently transferred to the fetus through the placenta, and to the neonate in milk (*2*). As a result, the maternal choline pools can become diminished by pregnancy and lactation; dietary choline restores them (*16*, *17*). The maintenance of maternal choline pools can be achieved by a normal balanced diet without the use of dietary supplements. Earlier estimates of the average choline intake by breast-fed babies recently have been adjusted upward by a factor of 3 as it was found that two choline-containing compounds not previously measured, phosphocholine and glycerophosphocholine, constitute the bulk (75 to 85%) of choline in milk (*18*). Currently available infant milk formulas contain between 50 and 140% of the total choline present in breast milk, and none duplicates its composition of individual choline-containing compounds (*18*). Thus, choline intake by babies may vary depending on maternal diet and on the infant formula used. The consequences of this variation for child cognitive development are not known. Significantly, the Food and Nutrition Board report recognizes that fetal development and infancy constitute periods of increased demand for choline and issues separate guidelines for choline intake by nonpregnant, pregnant, and lactating women (425, 450, and 550 mg per day, respectively) (*1*).

Perinatal development is a period in which animals and humans are vulnerable to decreases in choline supply. Animal models show that variations in early choline nutrition result in life-long changes in cognitive functions that correlate with alterations in neuroanatomical, neurochemical, and neurophysiological measures. Additional studies are needed to elucidate the precise molecular and cellular mechanisms by which dietary choline affects brain development and aging. Moreover, it will be necessary to determine whether the profound effects of early choline nutrition on cognitive function in laboratory animals also occur in people. The hope is that, as optimal intake of folate during the periconceptual period prevents neural tube defects (*1*), so also optimal dietary choline early in life may improve human cognitive development and slow cognitive declines associated with aging.

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