THE RELATIONSHIP BETWEEN CHOLINE AND FOLATE METABOLISM

Choline is needed for synthesis of the phospholipids in cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signaling, lipid-cholesterol transport and metabolism (1) (Fig. 1). Cells require choline (2) and die by apoptosis when deprived of this nutrient (3–6). When fed a choline deficient diet, humans and many species of animals deplete choline stores and develop liver dysfunction (7–11). Animals fed a choline-deficient diet may also develop growth retardation, renal dysfunction and hemorrhage, or bone abnormalities (10,12,13). The human diet must contain choline because the only endogenous pathway for synthesis of this nutrient [via the sequential methylation of phosphatidylethanolamine (14)] cannot meet the entire requirement for choline (15,16). This pathway that forms choline moiety de novo from S-adenosylmethionine and the pathway in which the choline metabolite betaine donates a methyl group in the remethylation of homocysteine form the interfaces between choline metabolism and one-carbon metabolism (methylfolate and methionine metabolism). Because of this metabolic interrelationship, it is especially appropriate to consider the effects of choline on brain development whenever we think about the mechanisms that might underlie the effects of dietary folate on brain and neural tube development.

CHOLINE AND PREGNANCY

Given the essential role of choline in cell function, nature has developed a number of mechanisms to ensure that a developing animal gets adequate amounts of choline. In mammals, the placenta transports choline to the fetus.
Fig. 1. Folate and choline metabolism are highly interrelated. Choline, via its oxidation product betaine, can donate a methyl-group to homocysteine, forming methionine. In parallel, methyltetrahydrofolate is an alternative donor of a methyl-group to homocysteine. Choline can also be formed de novo from methyl-groups (derived from S-adenosylmethionine) and phosphatidylethanolamine.

(17); human amniotic fluid choline concentration is 10-fold greater than that present in maternal blood (Zeisel, unpublished observations). This depletes maternal stores of choline (18). Because so much choline must be transported to the infant, pregnancy may be a time when dietary supplies of choline are especially limiting. Though female rats are resistant to choline deficiency, pregnant rats are as vulnerable to deficiency, as are males (19). The capacity of the brain to extract choline from blood is greatest during the neonatal period (20). There is a novel phosphatidylethanolamine-N-methyltransferase (synthesizes choline de novo) in neonatal rat brain that is extremely active (21). This special enzyme is not present in the adult brain. In the brains of newborn rats, S-adenosylmethionine concentrations are 40–50 nmol/g of tissue (22). These levels are probably sufficient to enable the neonatal form of phosphatidylethanolamine-N-methyltransferase to maintain high rates of activity. At birth, humans and other mammals have plasma choline concentrations that are much higher than those in adults (23). The supply of choline to the infant after birth is maintained, as mammary epithelial cells are capable of concentrative uptake of choline from maternal blood (24). Human and rat milk provide large amounts of choline to the neonate (25–27). Because so much choline is transferred in milk, lactating rats are more sensitive to choline deficiency than are nonlactating rats (19). These