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ELEVATED CHOLINE CONCENTRATION IN NEONATAL PLASMA

Steven H. Zeisel,[1] Michael F. Epstein,[2] and Richard J. Wurtman[1]

[1]Laboratory of Neuroendocrine Regulation
Department of Nutrition and Food Science
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

[2]Joint Program in Neonatology
Boston Hospital for Women
Boston, Massachusetts 02115

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Summary

Plasma choline concentrations were measured in humans, rats, and rabbits within the first few hours of life, before any food was ingested. Neonatal animals and humans had markedly elevated plasma choline levels compared to adult animals or humans. Possible mechanisms responsible for this elevation are discussed and possible consequences for brain function, lung function, and growth are presented.

Plasma choline constitutes an important source of choline both for neuronal acetylcholine synthesis (1-3), and for producing the lecithin (4) present in surfactant and all membranes. In normal adult humans (5,6) and rats (2,7), plasma choline concentrations vary from 5 μM to 18 μM, tending toward the lower limit after fasting. Administration of exogenous free choline or of lecithin [the usual dietary source of choline (8)] can ameliorate the manifestations of the movement disorder tardive dyskinesia (6,9) and may also be useful in treating other neurologic diseases characterized by inadequate release of acetylcholine [e.g., Huntington's disease, Freidrich's ataxia, and the memory deficits associated with aging and Alzheimer's disease] (6,10-12). Therapeutically effective doses elevate plasma choline concentrations to 20-40 μM; similar elevations caused by administering choline or lecithin to rats are associated with significant increases in brain acetylcholine levels (2,5).

We now observe that plasma choline concentrations in normal human infants are substantially higher than those in adults and are comparable to, or higher than, those in patients responding therapeutically to exogenous choline or lecithin (Fig. 1). Similarly high plasma choline concentrations are found in neonatal rats and fetal rabbits.

Blood samples were obtained from human neonates, from the radial artery, umbilical artery, umbilical vein, or via heel stick. Blood was collected from neonatal Sprague-Dawley rats and New

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Zealand Albino rabbits by decapitation. Samples from fasting adult humans (ages 13-40 years) were drawn by venepuncture. Arterial blood was drawn from rat dams and rabbit does at the time of delivery. All samples were collected in heparinized tubes, placed on ice, and centrifuged at 3000 rpm for 5 min. Plasmas were aspirated and frozen (-80°C) until assay.

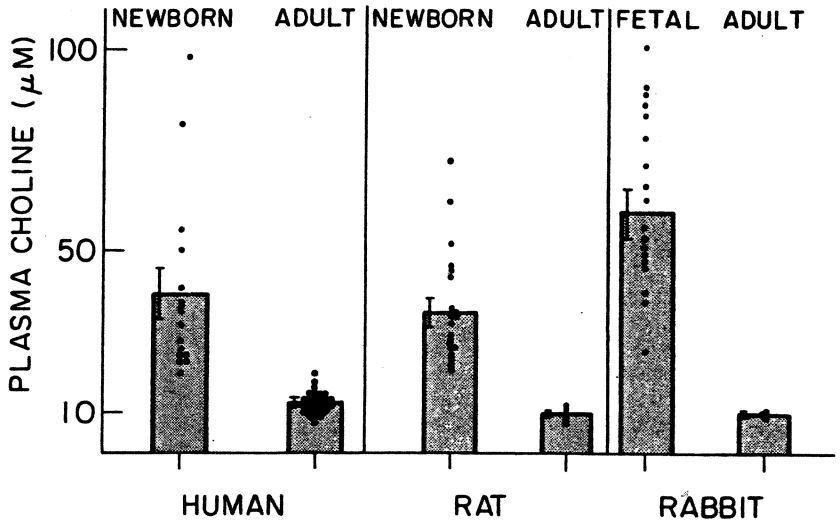

FIGURE 1

Plasma choline concentrations in neonatal humans, rats, and rabbits. Newborn humans (n = 16), newborn rats (n = 21), and fetal rabbits (n = 18) have elevated plasma choline concentrations compared with those of adult humans (n = 125), adult rat dams (n = 5), and adult rabbit does (n = 3). Means and standard errors of the mean are indicated.

Human neonates sampled varied in gestational age from 25 to 43 weeks and had ingested no food at the time of initial sampling (at birth or within the first few hours of life). Samples from rabbits were obtained from fetuses at 27, 28, and 31 days gestation (full term = 31 days); rat samples were obtained at birth (21 days gestation). Choline was measured by a radioenzymatic assay using choline kinase and radioactive ATP (13). In some samples, identity of choline was determined by paper electrophoresis (14) as well as by specific extraction with tetraphenylboron-heptanone.

Plasma choline concentrations in human newborns averaged 39.8 μM ± 22.4 SD (n = 16), while those of fasting adult humans averaged 12.2 μM ± 0.3 SD (n = 125). Choline concentrations in plasmas of newborn rats were 36.6 μM ± 13.9 SD (n = 21), while those of their dams averaged 10.1 ± 1.6 SD (n = 5). In fetal rabbits from the three litters, plasma choline averaged 61.6 μM ± 26.1 SD (n = 18);

in their does, fasting plasma choline was 9.2 μM ± 1.1 SD (n = 3). (The three fetal rabbits with the highest choline concentrations were the last to be delivered; Fig. 1).

Several different blood collection techniques were used in human neonates. Choline concentrations in samples obtained simultaneously from umbilical vein and artery were identical (paired t-test; Table 1). Similarly, the method used to collect plasma samples from human newborns bore no relationship to plasma choline concentrations (one-way analysis of variance; Table 2). Choline concentrations in plasmas from adult rats collected by cardiac puncture or by decapitation also were similar (one-way analysis of variance; Table 3). Hence, the age-related differences in choline concentrations of human or rat plasma did not reflect artifacts of blood sampling.

TABLE 1
Choline Concentrations in Umbilical Artery and Vein Samples Obtained Simultaneously from Human Neonates

	Plasma Choline (μM)	
Patient	Vein	Artery
1	37.2	38.3
2	25.6	24.7
3	56.1	56.6

TABLE 2
Plasma Choline Concentrations in Samples Collected by Different Techniques in 16 Human Neonates

Collection Method	Plasma Choline (μM)
Umbilical vein	36.7, 35.9, 37.2, 25.6, 56.1, 85.0
Umbilical artery	38.3, 24.7, 56.6, 40.5, 19.3
Radial artery	28.2
Mixed cord	25.5, 100.1
Heel stick	23.8, 37.6, 32.5, 49.6, 23.9

TABLE 3
Choline Concentrations in Plasma Collected from Adult Rats by Decapitation or Cardiac Puncture

Collection Method	Plasma Choline (μM)
Cardiac puncture	11.2, 10.8, 11.2, 9.4, 7.7
Decapitation	12.1, 9.5, 7.6, 7.2, 11.1

Several mechanisms might contribute to the high plasma choline concentrations characteristic of neonates:

a) Fetal levels might be high because the placenta transports choline to the fetus against a concentration gradient (15). This would not explain the persistence of high plasma choline concentrations for at least 3 days after birth [on day 3, rat plasma choline was 36.5 μM ± 3.9 SD (n = 5)].

b) The fetal and neonatal liver might synthesize large amounts of choline in the form of lecithin, by sequentially methylating phosphatidylethanolamine, using a pathway that could be more active in newborns than in adults (16).

c) Milk in the neonates' diet contains lecithin, free choline, and sphingomyelin. These would help to prolong the elevation of plasma choline concentration postnatally, but would not account for the elevation observed at birth, before suckling.

d) Neonates might lack the intestinal bacteria that in adult humans and rats degrade choline to methylamines (17), allowing more efficient choline absorption.

e) "Sinks" for plasma choline might not be fully operative in neonates. We observe that livers from adult rats, examined *in vitro*, rapidly absorb plasma choline; perhaps this uptake mechanism is deficient in newborns, as are bilirubin metabolism, drug metabolism, and the hepatic enzyme choline oxidase, which degrades choline to betaine (18).

Our findings indicate that newborns normally have plasma choline concentrations in the range known to accelerate acetylcholine release in rat brain (2) and to alleviate signs of tardive dyskinesia in humans (6,9). High plasma choline concentrations may therefore significantly influence brain function in neonates. They may also influence choline's incorporation into lecithin in all cells, especially in lung membranes and cells producing surfactant (19,20).

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