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Nutrients in the shadow-nutrients of substance

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Abstract. While the dietary importance of proteins, essential fatty acids, vitamins and trace elements has been well recognised, the role of shadow nutrients, a class of metabolites, which are biosynthesized in the body and serve vital functions, such as lipoic acid, choline, inositol, taurine and carnitine, has not been adequately appreciated. There are reasons to believe that during infancy and in ageing, biosynthesis of these metabolites may be limited. The objective of this review is to highlight the essentiality of these nutrients and the need for their supplementation in the diets of infants and in elderly people. Provision of shadow nutrients where the necessary biosynthetic machinery might not have developed to full stature or might have slowed down, is a new concept in nutrition which needs attention.

Keywords. Shadow nutrients; lipoic acid; diabetes; choline; acetyl choline; neuronal deficiency; inositol; taurine; carnitine; infant nutrition.

Introduction

It is well recognised that certain essential amino acids, vitamins, fatty acids and trace elements are needed in the diet (Olson, 1978). It is often taken for granted that the mere provision of these essential nutrients in the diet, generates through biosynthesis all of the nutrients and intermediary metabolites necessary for normal health. Examples of these subsidiary nutrients or shadow nutrients are: nicotinic acid from tryptophan, choline from methionine and ethanolamine, vitamin B-12, and biotin endogeneously made available by intestinal microorganisms in the gut, carnitine from lysine, inositol from glucose, lipoic acid from arachidonic acid and methionine and taurine from methionine. While these 'shadow' nutrients are produced in sufficient quantities under conditions of normal health, it is known that the physiological availability or biosynthesis of some of these nutrients is diminished in infancy, during ageing or when health is impaired. This is true not only of metabolic intermediates from nutrients, but also of neurotransmitters like serotonin, dopamine, epinephrine and acetylcholine formed from precursors such as tryptophan, tyrosine and choline (Wurtman, 1981). In this review we would like to highlight the nutritional importance of some of these factors such as lipoic acid, choline, taurine, inositol and carnitine.

The diet supplied to infants should be designed to bridge the nutritional gap between total intra-uterine dependence and complete extra-uterine independence and as such

Abbreviations used: PD, Pyruvate dehydrogenase; PC, pyruvate carboxylase; CoA, coenzyme A; AcCoA, acetyl CoA; AcAcCoA, acetoacetyl CoA; Ac.ch., acetyl choline; CAT, carnitine acyltransferase.

should contain easily digestible carbohydrates (lactose) and assimilable protein (non-coagulable protein) and easily digestible fat (triglycerides containing medium chain fatty acids and arachidonic acid). Further, due to the higher extra cellular fluid content, the lower ability of an infant's renal system to produce urine of increased specific gravity, the decreased renal clearance capacity and the incomplete development of the microsomal system for detoxification, infants need milk to graduate them to adult levels of absorption, digestion, assimilation and excretion. Histidine is essential in infants whereas in adults, it could be biosynthesized (Snyderman *et al.,* 1959, Holt and Snyderman, 1961). Other shadow nutrients which may be limiting in infancy are taurine and carnitine. There is danger in considering the infant as a miniature adult in terms of nutrition and metabolism.

Similarly, during ageing the metabolic availability of shadow nutrients such as lipoic acid, choline and inositol may be decreased either due to reduced rates of synthesis or due to the reduced caloric intake and consequent reduction in the ingestion of essential ingredients (McGandy *et al.,* 1966, Exton-Smith, 1980, Zeisel *et al.,* 1980). There is considerable evidence indicating deceleration during ageing of certain metabolic capabilities, such as neuronal acetyl choline synthesis and of inositol from glucose. (Campling and Nixon, 1954; Hauser, 1963; Davies and Maloney, 1976).

Lipoic acid

Lipoic acid (figure 1) has long been recognised as a vital cofactor in the enzyme complexes that catalyse the oxidative decarboxylation of α-keto acids such as pyruvic, α-ketoglutaric and branched chain α-keto acids formed during the catabolism of branched chain amino acids. Recently the decarboxylation of glycine has been shown to require lipoic acid (Fujiwara *et al.,* 1979). A dietary requirement for lipoic acid in animals has not been established, nor has a systematic estimation of the lipoic acid content in animals during ageing been done. The coenzymic role of lipoic acid in transacylation reactions involved in the oxidation of pyruvate is presented in figure 1.

Pyruvate is at the centre of metabolic disposition of substrates from the utilisation of proteins and carbohydrates and pyruvic dehydrogenase (PD) (EC 1.2.4.1) is crucial for the complete oxidation of glucose and for lipid biosynthesis from glucose (Jungas, 1970,1971; Halperin, 1970). PD exists in a catalytically active (dephosphorylated) and an inactive (phosphorylated) form. Though the content of PD is the same in normal and diabetic livers, a larger proportion of the enzyme is in its inactive state in streptozotocin induced diabetes in rats (Weinberg and Utter, 1980). Similar reductions in active PD has been, reported in perfused rat heart in alloxan diabetes (Kerbey *et al.,* 1976). Administration of insulin restored the PD activity to normal levels (Hughes *et al.,* 1980). We have found that administration of lipoic acid, like insulin treatment increases PD activity in the livers of both normal and diabetic rats (table 1). From table 2 it can be seen that blood pyruvate levels in alloxan diabetic rats are about 60% higher than normal and administration of lipoic acid reduces the elevated blood pyruvate in diabetic rats to near normal values in 60 min. We have previously shown that biochemical abnormalities such as hypoglycemia, ketonemia, reduction in liver glycogen and impaired incorporation of 2- [^{14}C] -acetate into fatty acids in alloxan

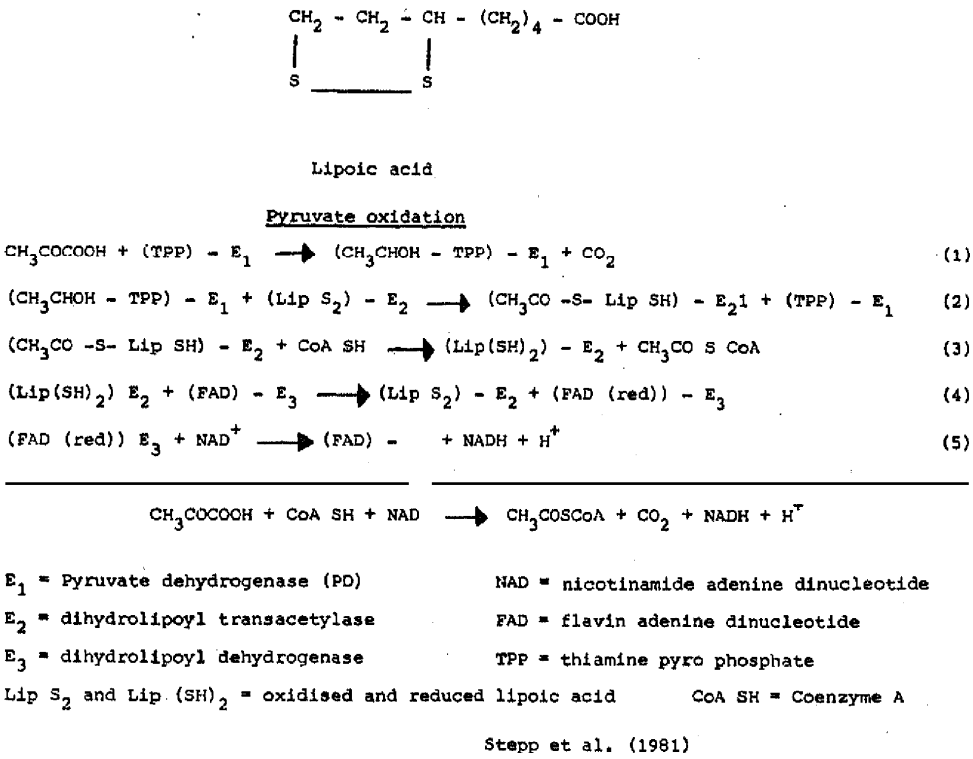

Figure 1. Lipoic acid

Table 1. PD activity in normal and diabetic rat livers.

Rats	PD activity n mol/min/mg protein
Normal	2·7 ± 0·28
Normal + lipoic acid	4·3 ± 0·19[a]
Normal + insulin	4·7 ± 0·42[a]
Diabetic	1·26 ± 0·29[a]
Diabetic + lipoic acid	2·40 ± 0·30[b]
Diabetic + insulin	2·66 ± 0.10[c]

All the determinations are means of 6 animals ± S.E.
[a] Significantly different from normal at $P < 0.01$
[b] Significantly different from diabetic at $P < 0{\cdot}05$
[c] Significantly different from diabetic at $P < 0{\cdot}01$

diabetic rats were brought to near normal levels by the oral or intraperitoneal administration of lipoic or dihydrolipoic acid (Natraj *et al.,* 1984). Lipoic acid content in diabetic livers is markedly reduced as compared to its amount in normal liver (Natraj *et al.,* 1984).

In diabetes, along with impairment of pyruvate oxidation (Villee and Hastings, 1949),

Table 2. Pyruvate levels in blood.

	Pyruvate levles μ mol/litre
Normal (4)	85·4 ± 16·4
Diabetic (5)	137·4 ± 3.7*
Diabetic + lipoic acid after 60 min (5)	93·1 ± 17·2**

Numbers in the parenthesis indicate the number of animals. The values are expressed as mean ± S.E.
α-Lipoic acid (sodium salt, 10 mg/100g) was injected intraperitoneally as a solution in 0·1 ml water.
* Significantly different from normal $P < 0{\cdot}05$.
** Significantly different from diabetic $P < 0{\cdot}05$.

increased gluconeogenesis also occurs (Felig *et al.,* 1970; Felig, 1975). Enhanced activities of specific gluconeogenic enzymes including cytosolic phosphoenolpyruvate carboxykinase (EC 4.1.1.32), fructose 1,6-bisphosphatase (EC 3.1.3.11), glucose 6-phosphatase (EC 3.1.3.9) and pyruvic carboxylase (EC 6.4.1.1) have been reported in experimental diabetes (Prinz and Seubert, 1964; Filsell *et al.,* 1969; Wilmhurst and Manchester, 1970; Chang and Schneider, 1971; Weiss *et al.,* 1971). Mitochondrial pyruvic carboxylase (PC) catalyses and initiates gluconeogenesis. Weinberg and Utter (1980) using immunochemical techniques, demonstrated that in the livers from streptozotocin induced diabetic rats, pyruvic carboxylase activity was twice that in normal rat livers when expressed in terms of DNA or body weight; this increase was shown to be due to significant increases in the rate of synthesis of the enzyme; whereas the rates of synthesis and degradation of PD were not affected. The flux of pyruvate carbon atoms through PD and PC and the regulation of these enzyme activities are shown in figure 2. It is interesting to note that the high production of acetyl (Ac)-coenzyme A-(CoA) and generation of aceto-acetate in diabetes appears to arise not from the oxidative decarboxylation of pyruvate but through the increased oxidation of fatty acids (Randle *et al.,* 1966).

It has been proposed that the increased oxidation of fatty acids generates excess AcCoA and acetoacetyl CoA (AcAcCoA) which acylate the lipoic acid residues of PD. Acylated lipoic acid has been shown to activate PD kinase and thus bring about inhibition of PD (Cate and Roche, 1979). The respective metabolic roles of PD and PC in various organs are illustrated in table 3. It will be seen from the table that PC is crucial for gluconeogenesis, whereas PD is essential for energy production. In diabetes, the energy production occurs through the oxidation of fatty acids, and it is well recognised that the respiratory quotient is low due to abnormal fatty acid oxidation (Randle, 1976). In gluconeogenic organs such as the kidney, PC > PD, but in energy consuming organs like the heart PD > PC. Whereas in the normal liver PD and PC are finely balanced, in the diabetic liver PC > PD due to the increased demand for glucose (Randle *et al.,* 1977).

A decreased glucose tolerance is common in a majority of people during ageing. The diminution in the levels of lipoic acid in the liver of diabetic rats and the effectiveness of

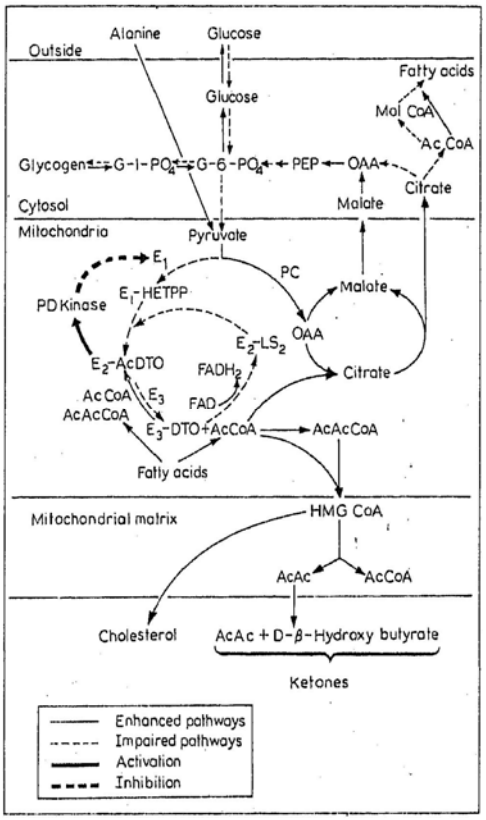

Figure 2. Metabolic map in diabetes.

Table 3. Regulation of PD and PC in various organs.

PD and PC are mitochondrial enzymes
PD is required for energy production
PC is required for gluconeogenesis
PD + PC is required for fatty acid biosynthesis
In heart PD > PC (energy consuming organ)
In kidney PC > PD (gluconeogenic organ)
In adipose tissue PD = PC (fatty acid biosynthetic)
In liver PD = PC (all the above three)
In diabetic liver PC > PD (gluconeogenic)

From Randle *et al.* (1977).

dietary lipoic acid in restoring most of the biochemical abnormalities in diabetes led us to consider whether the biosynthesis of lipoic acid is impaired during ageing/diabetes. Though lipoic acid is a ubiquitous component in all aerobic organisms and animals, most tissues and microorganisms contain only minute quantities of this material. Lipoic acid is biosynthesized in *Escherichia coli* from octanoic acid, hydroxy octanoic acid and more efficiently from thiooctanoic acid (White, 1980a,b; 1981). Carreau *et al.*

Table 4. Incorporation of 1-[^{14}C]-labelled compounds into liver fat and lipoic acid.

Labelled precursor	Rats	Amount perfused in liver cpm ($\times 10^6$)	Radioactivity incorporated in fat cpm ($\times 10^6$)	per cent	Radioactivity recovered in TLC fraction cpm ($\times 10^3$)	per cent	Radioactivity recovered in HPLC-lipoic acid cpm (10^3)	per cent
Arachidonic acid	N	1·9	1·06	55·6	16·6	0·87	2400	0·125
	D	1·7	0·690	40·3	6·84	0·398	560	0·032
Octanoic acid	N	3·2	NE	NE	23·56	0·73	3520	0·109
	D	4·3	0·34	7·9	8·05	0·185	508	0·012
Linoleic acid	N	8·18	2·59	31·7	48·20	0·59	6650	0·081
	D	4·8	0·89	18·4	0·59	0·012	ND	ND
Palmitic acid	N	8·0	0·15	1·94	0·10	0·001	ND	ND

Livers were perfused with the labelled precursor for 1 h and incubated for 3 h at room temperature. Lipoic acid was isolated by extraction followed by TLC. The TLC fraction was further purified by HPLC.
NE—not estimated. ND—not detectable.

(1977) have shown that linoleic acid and to a smaller extent oleic acid, act as precursors for lipoic acid biosynthesis in the rat. Further, the subcellular location of lipoic acid biosynthesis has been shown to be the microsomal fraction in rat liver (Spoto *et al.,* 1982). However, as shown in table 4, in animal tissues arachidonic acid appears to be the most immediate precursor followed by linoleic acid, though octanoic acid incorporated into lipoic acid is unlikely to be of physiological significance in view of the unlikely occurrence of free octanoic acid in body metabolism. The scheme of biosynthesis of lipoic acid from arachidonic acid is given in figure 3.

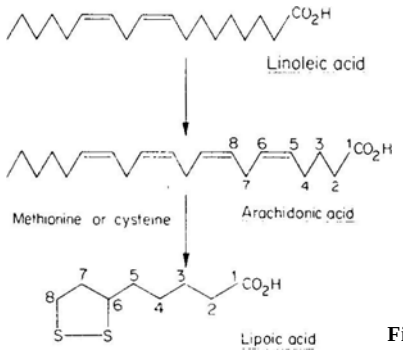

Figure 3. Biosynthesis of lipoic acid.

Further, methionine and cysteine have been shown to be equally effective as sulphur donors in the biosynthesis of lipoic acid (Dupre *et al.,* 1980). We have confirmed this finding in experiments with diabetic rats. We have further demonstrated that the biosynthesis of lipoic acid from linoleic acid is impaired in diabetes and administration of insulin enhances this conversion (table 5).

Table 5. Incorporation of l-[^{14}C]-linoleic acid into lipoic acid in presence of insulin.

Rats	Radioactivity (cpm)				Per cent incorporation	
	Amount perfused ($\times 10^6$)	Fat ($\times 10^6$)	Lipoic (TLC)	Lipoic (HPLC)	Fat	Lipoic (HPLC)
Normal	5·27	1·72	27,000	3,800	32·6	0·072
Diabetic	3·63	0·54	6,100	N.D.	14·4	N.D
Diabetic + insulin	2·24	0·8	3,500	810	35·7	0·036

N.D.—not detectable

Livers were perfused with the labelled precursor for 1 h and incubated for 3 h at room temperature. In experiments with insulin, 0·25 i.u./ml of insulin was used in the perfusion medium. Lipoic acid was isolated and purified as described in table 4.

Essential fatty acids have an insulin sparing effect in diabetes (Houtsmuller *et al.,* 1981). Is this effect due to an increased biosynthesis of lipoic acid from linoleic acid?

To summarise, the beneficial effects of lipoic acid administration in diabetes have been recognised for some time (Pagliaro, 1956; Pagliaro and Furitano, 1956; Greco, 1957; Brusa and Serafini, 1958; Zueva, 1970). Our observations that lipoic acid acts

primarily by enhancing the utilisation of glucose for energy and fatty acid synthesis, open up the possibility of using this shadow nutrient as an adjunct in the diet in cases where the tolerance to glucose is reduced (*e.g.* ageing and diabetes).

Choline

Choline, a quaternary ammonium base, is distributed ubiquitously in biological materials. It is present as an integral part of the membranes of all cells, as a constituent of lecithins, plasmalogens and sphingomyelins. Acetylcholine is responsible for the transmission of nerve impulses from presynaptic to postsynaptic fibres in the synapses of both the sympathetic and parasympathetic nervous systems. Choline is converted into acetylcholine by choline acetylase and is hydrolysed by acetylcholinesterase into choline and acetate.

A dietary requirement of choline was first demonstrated by Best and Huntsman (1932). Since then choline deficiency has been shown to cause haemorrhagic lesions in the kidney and fatty infiltration in the liver in rats and perosis in birds (Griffith and Wade, 1939; Jukes, 1940; Hartroft, 1955). From the voluminous literature on choline it is evident that it has a lipotropic effect in the liver and increases the formation and secretion of chylomicrons in the intestine (Tidwell, 1950; Frazer, 1978). Choline is biosynthesized in the body from precursors such as methionine and ethanolamine (figure 4) and lecithin *via* methylation of phosphatidyl ethanolamine (figure 5). Though

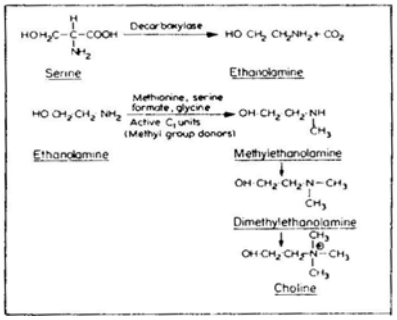

Figure 4. Biosynthesis of choline.

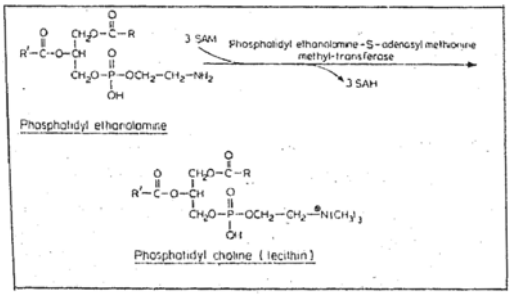

Figure 5. Biosynthesis of phosphatidyl choline.

a specific deficiency of choline has not been demonstrated in humans, in many conditions of liver dysfunction, the advantages of feeding choline or its precursors such as methionine have been well established (Kautch, 1973; Wallnofer and Hanusch, 1973).

The paradox, however, is that almost all animal cells have the biosynthetic machinery to synthesize choline from its precursors, thus rendering dietary supplementation of choline or its derivatives somewhat redundant. Further, lecithin (a phospholipid containing choline) is largely degraded in the intestine. Despite these observations, unequivocal evidence has been obtained demonstrating the beneficial effects of choline and lecithin administration in eases of tardive dyskinesia and Huntington's disease (Davis *et al.,* 1976; Tamminga *et al.,* 1977; Growdon *et al.,* 1978).

The hippocampus, a region of the brain known to be essential for the formation of new memories, has a particularly large number of cholinergic neurons. Based on the observation that muscarinic agonists such as physostigmine (inhibition of acetyl-cholinesterase) can improve memory acutely, choline and lecithin have been tried, with limited success, in patients with Alzheimer's type dementia and mild to moderate memory disorders (Etienne *et al.,* 1968; Signoret *et al.,* 1978). Further, there is recent evidence that the onset of senility is characterized by a decrease in the availability of acetyl choline (Ac.ch.) to the neuronal cells in the brain, which seems to be caused by the decreased availability of free choline (Gibson and Peterson, 1981). Since choline has been shown to diffuse across the blood brain barrier, treatments which raise serum choline such as ingesting choline rich foods would provide a way of increasing the supply to the brain.

It must be mentioned in this connection that Dysken *et al.* (1982) in a limited clinical study with patients with primary degenerative dementia failed to observe any benefit with the administration of lecithin, while earlier reports had claimed significant benefits with the administration of choline bitartarate (Fovall *et al.,* 1980; Dysken *et al.,* 1982).

Although lecithin has been recommended and even tried in clinical trials, the practicability of including upto 70–100 g/day of lecithin in the diet poses problems.

This raises the question as to what should be the preferred dietary additive for enhancing choline availability to the brain for the synthesis of acetylcholine? There is considerable evidence indicating a lack of equilibration between choline and lecithin in the body. (1) Choline deficiency and its attendant symptoms such as impaired growth, haemorrhagic kidneys and fatty liver occur in the face of apparently normal levels of lecithin in the liver and the whole organism (Menon and Lucas, 1961). Only the administration of choline helps to overcome these problems. (2) Phospholipase D (figure 6) is responsible for the hydrolysis of lecithin to free choline. Although an enzyme with phospholipase D like activity has been isolated and purified from rat brain, the contribution of this enzyme *in vivo* for the release of free choline from lecithin is yet to be established (Taki and Kaufer, 1981). (3) Phospholipase C releases phosphoryl choline from lecithin and sphingomyelin and is present in most animal tissues. The phosphoryl choline can be cleaved by alkaline phosphatase with the release of free choline. However, this method of free choline production would require very high levels of lecithin in the tissue (brain) which may be difficult to attain. (4) Lecithin in animals is biosynthesized *via* methylation of phosphatidyl ethanolamine (cephalin) rather than from phosphatidic acid and choline, and (5) Lecithin synthesis through phosphoryl choline (PC) and α, β diglyceride requires PC synthesis from free choline.

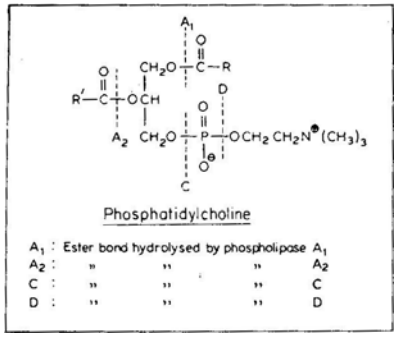

Figure 6. Phospholipases.

Thus PC is more involved in the synthesis of lecithin rather than being the source of bioavailable choline (Kornberg and Pricer, 1952; Kennedy and Weiss, 1956).

Further, there is no evidence indicating that the intake of egg yolk containing 0·9 % lecithin in humans in anyway protects them against neuropathology or dementing illnesses such as Alzheimer's disease or memory disorders associated with old age. However, both positive and negative clinical response to high doses of lecithin in Alzheimer disease and primary degenerative dementia have been reported (Etienne *et al.,* 1979). It may be stressed that here we are considering the beneficial effects on health of supplementing with small amounts, those cofactors which may be lacking in the diet and not the therapeutic treatment with choline or its derivatives (Dysken *et al.,* 1982; Karczmar, 1979).

From these considerations it would appear that in order to increase blood levels of choline one has to administer free choline or choline esters. Since free choline or even phosphoryl choline has a fishy odour and is not acceptable organoleptically for incorporation into foods, it is suggested that linoleate or palmitate esters of choline be used for this purpose.

Inositol

Like choline, inositol (figure 7) is also well recognised as a vitamin for a number of organisms. In fact, the effectiveness of hexachlorocyclohexane in killing cockroaches is due to its inhibitory effect on inositol which is an essential nutrient for insects (Slade, 1945). It must be emphasized that there is a commonality in the requirements of vitamins amongst a broad phylum of organisms including bacteria, yeast, insects and mammals, and therefore even though a specific inositol deficiency state has not been reported in humans, there is no doubt about the need for inositol in human metabolism.

Phosphatidyl inositol, one of the major anionic phospholipids of mammalian cell membranes, undergoes stepwise phosphorylation to diphosphoinositide in synaptosomal fractions in the brain and to triphosphoinositide in erythrocytes and myelin membranes (Hawthorne and White, 1975). Hormones such as vasopressin cause rapid breakdown of polyphosphoinositides and may exert a primary role in generating messenger signals responsible for intracellular Ca^{2+} mobilization (Thomas *et al.,* 1983). Recent evidence suggests that polyphosphoinositides breakdown to phosphatidylinositol in a number of systems, including muscarinic stimulation of smooth muscle, nerve

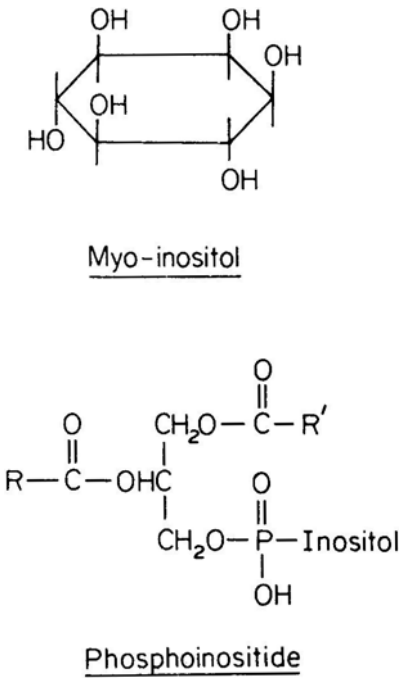

Figure 7. Inositol.

endings and parotid gland and thrombin addition to human platlets (Abdel-Latif *et al.,* 1977; Fischer and Argranoff, 1981; Weiss *et al.,* 1982; Agranoff *et al.,* 1983).

Phosphoinositides form 70 % of the phospholipids of the myelin sheath which is a major insulating material in the human nervous system and caters to the brain's conflicting needs for compact size, complex circuitry, rapid signalling and modest use of energy. The brain is especially rich in inositol phosphatides (Herken *et al.,* 1958). There is evidence to suggest that the biosynthesis of inositol from glucose is decreased as animals grow older (Hauser, 1963). Even as lecithin does not contribute to the pool of free choline in the body, inositol from phytin does not seem to be available as free inositol for the maintenance of body functions.

Inositol has been shown to be a necessary vitamin for growth of mammalian cells (Eagle, 1956); stimulation of intestinal peristalsis, in plasma membrane shape regulation (Quist and Reece, 1980); and transport of cations across membranes especially for the triggering of nerves (Martin *et al.,* 1941; Hawthorne and White, 1975). Older nutrition literature has given a significant status to inositol in reducing cholesterol esters in the liver (MacFarland and McHenry, 1945, 1948) and it is likely that inositol might also promote reduction of blood cholesterol (Rajalakshmi *et al.,* 1960). Foods containing high amounts of inositol are yeast and tea.

Taurine

Taurine (figure 8) is one of the major constituents of the free amino acid pool in all mammalian central nervous system tissues. In a mature brain it is usually exceeded in

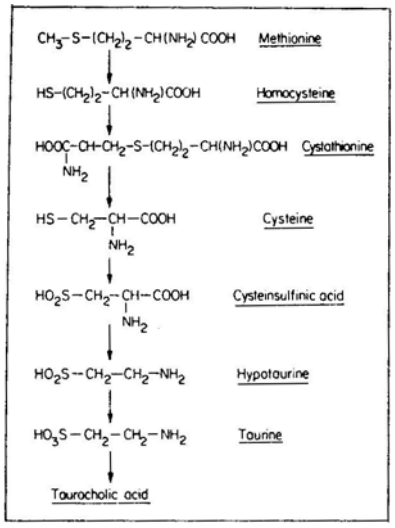

Figure 8. Biosynthesis of taurine.

concentration only by glutamic acid and in the developing brain, it is the free amino acid present in the greatest concentration. The diversity and magnitude of the functions accomplished or influenced by such a chemically simple and inert compound has only been emphasized in recent years (Jacobsen, 1980). The major physiological functions of taurine are (i) participation in bile conjugation, (ii) osmoregulation, (iii) neurotransmission and neuroregulation and (iv) membrane stabilization.

Taurine is a constituent of taurocholic acid excreted in the bile of carnivorous animals and man. Though taurine is ubiquitously present in most tissues of the body, recent evidence has surfaced on the role of taurine in moderating neurotransmission, in stimulating retinal metabolism (Mandel *et al.,* 1976; Schmidt *et al.,* 1976), and most importantly in preventing cardiac arrhythmia (Akera and Brody, 1976; Grosso and Bessler, 1976). Taurine has been shown to confer calcium and potassium stabilising capacity on the heart and the brain when circumstances of electrolyte depletion are present, thus ensuring cationic and membrane integrity (Akera and Brody, 1976). Taurine therapy has been efficacious in experimental models of epilepsy (Barbeau and Donaldson, 1973; Van Gelder *et al.,* 1975). There have also been reports of taurine depletion in cardiac ischaemia and the ameliorative effect of taurine treatment in such conditions (Huxtable and Bressler, 1974a,b). There is an increasing quantum of evidence that human infants fed casein-predominant synthetic formulations derived from bovine milk may become taurine depleted because the currently available products contain little or no taurine (Nayman *et al.,* 1979; Rigo and Senterre, 1977). In this context, it is interesting to note that recent studies have demonstrated that in infants fed human milk, bile acids predominantly conjugated with taurine during the first three months after birth, whereas in infants fed synthetic formulations the bile acids conjugated predominantly with glycine (Haber *et al.,* 1978; Watkins *et al.,* 1979). Because of its inhibitory neurotransmittary role in the brain and retina and because of its importance in the conjugation of bile acids with superior digestive and detergent

properties, there is some nutritional logic in introducing taurine as an additive in many vegetable products.

Carnitine

Carnitine is a quaternary amine, β-hydroxy, γ-N-tri-methylaminobutyric acid, which is an important metabolite in mammalian tissues for the utilization of long chain fatty acids as a source of energy (Hoppel, 1982). Carnitine facilitates the transport of fatty acids from the cytosol across the mitochondrial membrane *via* the carnitine acyl-transferase (CAT) (EC 2.3.1.7) and translocase systems (figure 9) (Bremer, 1977). Carnitine is synthesized in both human liver and kidney from the essential amino acids lysine and methionine (figure 10) (Rebouche and Engel, 1980; Tanphaichitr and Broquist, 1973). Several other tissues can synthesize the immediate precursor of carnitine (γ-butyrobetaine) but lack the last biosynthetic enzyme which hydroxylates γ-butyrobetaine to form carnitine. Since cardiac and skeletal muscles cannot synthesize

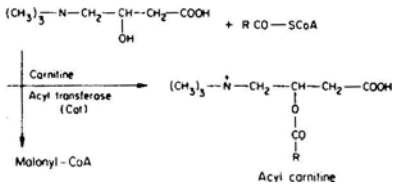

Figure 9. Fatty acid transport.

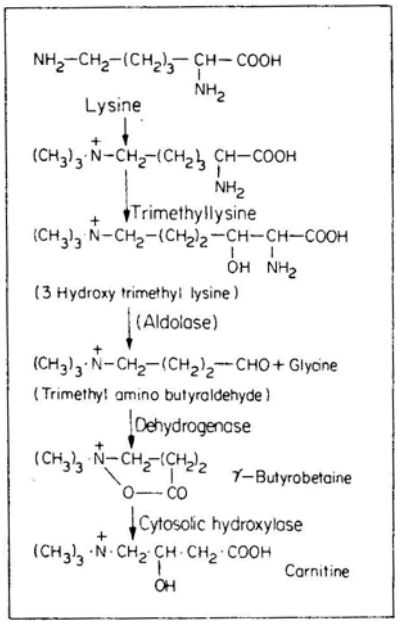

Figure 10 Biosynthesis of carnitine.

carnitine, it must be transported into these tissues from the blood stream (Borum 1981).

The ability of the rat liver to synthesize carnitine from γ-butyrobetaine increases from low values in the foetus to adult values on the eighth day after birth. The newborn's requirement for carnitine appears to be adequately met by breast milk but there is no detectable carnitine in soya protein based formulations, nor is it added to solutions used in total parenternal nutrition.

The level of malonyl-CoA determines the rate of fatty acid synthesis, whereas the activity of CAT determines the rate of fatty acid oxidation. With high dietary carbohydrate, malonyl-CoA concentration and consequently, fatty acid synthesis increase, while fatty acid oxidation is suppressed by the inhibition of CAT (figure 9). In the fasting animal and in diabetes malonyl-CoA level drops, fatty acid synthesis declines and with lower malonyl-CoA levels CAT is no longer inhibited and therefore fatty acid oxidation increases (*Nutr. Rev.,* 1980a; McGarry and Foster, 1979; McGarry *et al.,* 1978; Broquist, 1982).

Further, a role for carnitine in the metabolism of branched chain keto acids produced by the catabolism of amino acids has been suggested (*Nutr. Rev.,* 1981). Muscle weakness and pathology in humans with accompanying myoglobinuria has been shown to be due to a relative deficiency of carnitine and can be treated with high carbohydrate feeding (*Nutr. Rev.,* 1979b). Low birth weight infants with impairment in the lipid and energy utilization may have subnormal carnitine levels in the blood (*Nutr. Rev.,* 1980b). There may therefore be a nutritional advantage in incorporating carnitine or carnitine containing foods such as meat or meat extracts in infant foods.

Some of these shadow nutrients may be synthesized in the animal body in marginal quantities at certain times in the life cycle. There may be an increased need for some of these nutrients to be provided specifically in the diets of the elderly or infants. If these nutrients are not biosynthesized adequately there would be a need for supplementing these exogenously in the diet. Such nutrients may include lipoic acid, choline, taurine, inositol and carnitine.

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