Reversal of hyperhomocyst(e)inaemia in chronic renal failure—is folic or folinic acid the answer?

Ziad A. Massy

Division of Nephrology, C.H. Beauvais, and INSERM U 507, Necker Hospital, Paris, France

Introduction

Moderate elevation of plasma total homocyst(e)ine (Hcy) concentration is present in the early stage of chronic renal failure (CRF), increases in parallel with the degree of reduction in renal function, and persists after starting dialysis [1,2]. In view of the potential athero-thrombogenic role of hyperhomocyst(e)inaemia, attempts have been made to lower plasma tHcy concentrations in CRF patients. Routine minimal folic acid supplementation of 1 mg daily, in contrast to what has been generally observed in the population at large, does not have an effect on plasma total Hcy concentration, despite a supernormal plasma folate level reached in CRF patients [3]. Even worse, the oral supplementation with high doses of folic acid (up to 15 mg daily), which leads to a 20- to 50-fold increase of plasma folate concentrations, is only partially effective in reducing plasma total Hcy, and only few CRF patients entirely normalize their Hcy concentrations [4–6]. These data suggest the presence of resistance to folic acid action in CRF patients.

On the other hand, the oral treatment using the reduced form of folate, i.e. methyltetrahydrofolate (MTHF), has led to a significant decrease (70%) in plasma total Hcy levels in 14 HD patients, with five patients achieving normal total Hcy concentrations [7]. Recently, we found that once weekly i.v. administration of 50 mg folinic acid, i.e. of the immediate precursor of MTHF, when associated with pyridoxine administration, is even more effective in correcting the hyperhomocyst(e)inaemia of haemodialysis patients, as attested by normalization of plasma total Hcy concentrations in 78% of patients [8]. Such efficacy was seen, even though the concentrations of plasma folate were lower than usually observed with folic acid treatment [8]. Moreover, no apparent toxicity was noted with this regimen [8]. Although these data need confirmation by a prospective, controlled, and randomized study, they suggest that reduced forms of folate, i.e. MTHF or folinic acid, are more efficient than folic acid in normalizing plasma total Hcy concentrations in CRF patients. In this editorial, we shall briefly outline folate metabolism in normal subjects and CRF patients as background information which makes it easier to understand the potential causes of such increased efficacy.

Folate metabolism in normal subjects

Folates are water-soluble vitamins which are synthesized by plants and micro-organisms. These substances are not endogenously synthesized in the body and therefore are derived solely from food. Oral folates are generally available in two supplemental forms, folic and folinic acid [9,10].

Folic acid is a complex mixture of polyglutamate conjugate compounds with variable numbers of glutamate molecules covalently linked to the folate moiety. Folic acid is initially deconjugated in the cells of the intestinal wall to monoglutamate forms by γ-glutamylcarboxypeptidase or conjugase (Figure 1) [9,10]. The monoglutamate forms are rapidly absorbed and taken-up into the portal circulation. The intestinal absorption occurs mainly through an active transport system...
which is saturable, specific and mediated by a membrane protein, the folic acid-binding protein (FABP) [9]. In the liver, these compounds are reduced to dihydrofolate and subsequently to tetrahydrofolate (THF) via folate and dihydrofolate reductase (Figure 1) [9,10]. Both enzymes require NADPH (niacin dependent) as a cofactor. The next step is the conversion of THF to 5,10-methyltetrahydrofolate (5,10-METHF) using serine as a major carbon source, and pyridoxal phosphate (B6) dependent serine hydroxymethyltransferase as an enzyme (Figure 1). A portion of 5,10-METHF thus produced undergoes irreversible enzymatic reduction to 5-MTHF by methylene tetrahydrofolate reductase (MTHFR) (Figure 1) [9,10]. The other portions of 5,10-METHF are required for the synthesis of thymidylate, and 10-formyltetrahydrofolate (used in purine synthesis) (Figure 1) [9,10]. After 5-MTHF has been synthesized in the liver, this metabolically active compound is secreted into the small intestine with bile, where it is reabsorbed and distributed to tissues throughout the body (Figure 1) [9,10]. The cellular uptake of 5-MTHF is in part carried out by an active transport system, probably mediated by membrane folate receptors presenting the same characteristics as serum FABP [9]. The 5-methyl group of 5-MTHF can only be used metabolically for transfer to Hcy via methionine synthase, which results in the regeneration of methionine and THF (Figure 1) [9,10]. Unless THF is used for the synthesis of thymidylate or 10-formyltetrahydrofolate, it is rapidly transformed to THF polyglutamates by polyglutamate synthetase (Figure 1) [9]. THF polyglutamates are used as a source of folates during periods of deprivation, since they are hydrolysed to monoglutamates by folylpolyglutamyl hydrolase (Figure 1) [9].

Folinic acid (5-formyl tetrahydrofolate) is an immediate precursor of 5,10-METHF. It is directly converted to 5,10-methenyl tetrahydrofolate by an ATP dependent enzyme, 5,10-methenyl tetrahydrofolate synthetase (Figure 1). 5,10-Methenyl, 5,10-METHF, and 10-formyl tetrahydrofolate are interconvertible [9]. Oral administration of folinic acid bypasses the deconjugation and reduction steps required for the synthesis of folic acid, and the major proportion of folinic acid is metabolized to 5-MTHF directly during absorption in the intestine. Folinic acid is also available for
intravenous administration. Most commercially available folic acid preparations are racemic mixtures of L- and D-isomers, but only natural L-isomers are pharmacologically active [11]. Whether unnatural D-isomers are inert in vivo or whether they modify specific aspects of folate metabolism is still unclear [11].

**Folate metabolism in chronic renal failure**

The metabolism of folic acid has not been well evaluated in CRF. However, some of the available data are consistent with abnormal metabolism of folic acid in CRF. Livant et al. found that plasma folate conjugase activities are reduced in haemodialysis patients by the presence of plasmatic inhibitors [12]. Such inhibition of plasma folate conjugase activities might impair the cleavage of polyglutamate forms of folate into monoglutamate. Limited data in uraemic rats [13] and uraemic patients [14] also suggest that the intestinal absorption of MTHF is impaired in CRF. Finally, inhibition of trans-membrane folate transport has been reported in CRF and this is presumably mediated by anions which cumulate in uraemia [15].

Taken together, these data suggest that the resistance to folic acid action observed in CRF patients is caused by abnormalities of (i) deconjugation, (ii) reduction, and (iii) membrane folate receptors (or FABP) leading to insufficient intracellular concentrations of functionally active MTHF (Figure 1). The fact that, in normalizing plasma total Hcy concentrations in CRF patients, oral MTHF and i.v. folic acid are more efficient than the parent compound folic acid is an indirect argument in favour of this hypothesis. Direct determination of circulating and cellular MTHF is required to prove the exactitude of this hypothesis [11,16]. It should be noted that the determination of circulating MTHF cannot be performed solely with currently available commercial assays, since these assays measure all folate derivatives, including MTHF [7,8,17].

**Conclusion**

Preliminary data suggest that the reduced forms of folate, i.e. MTHF and folic acid, are metabolically more active than native folic acid. They are also capable of normalizing plasma total Hcy concentrations in CRF patients where the effect of the parent compound is limited. The reason for their higher efficiency may be related to abnormalities of folate metabolism in CRF. The efficacy, optimal treatment modality, and safety of administration of reduced forms of folate must be confirmed in prospective studies. Until such data are available, we think it is reasonable to wait before the routine use of reduced forms of folate in CRF patients is proposed. Nevertheless, the above data offer new insights into the potential role of abnormalities of folate metabolism, particularly of MTHF, as determinants of abnormal plasma total Hcy concentrations in CRF patients.

**References**

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