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COMMENTARY

FOLATE METABOLISM, THE ENTEROHEPATIC CIRCULATION AND ALCOHOL

DONALD G. WEIR*, PETER G. McGING and JOHN M. SCOTT
Departments of Clinical Medicine and Biochemistry, Trinity College, Dublin 2, Ireland

The association between chronic alcoholism, folate deficiency and megaloblastic anaemia has been recognised for over 40 years [1]. Initially, the connection was considered to be related to the dietary problems of the malnourished derelict alcoholic, especially when associated with alcoholic liver disease [2, 3], since alcoholics with good nutrition did not demonstrate folate deficiency [4–6]. Although reduced dietary folate is necessary for the production of megaloblastic anaemia, both acute and chronic alcohol administration can produce profound metabolic effects on folate metabolism in the intestine, liver and bone marrow. Chronic alcoholics with megaloblastic anaemia put on supplemental dietary folate (PteGlu 75 mg/day), which would normally correct megaloblastosis due to nutritional folate deficiency, were shown not to revert to normal when the subjects continued to take alcohol [7]. When volunteer chronic alcoholics were placed on a low folate diet and a constant alcohol intake, they were shown to develop megaloblastic anaemia at a rate which was two to three times faster than controls on a low folate diet alone [8]. This finding may relate to the abrupt fall in serum folate following acute alcohol intake, apparently without an associated increase in urinary folate excretion [9]. Of all the dietary vitamins, in developing countries deficiency of folate is the commonest [10, 11]; in western societies, it is predominantly associated with poverty, old age, and alcoholism [1].

As a consequence, the association between alcohol and folate metabolism has stimulated a large number of reviews, the most recent of which include Scott and Weir [12], Halsted [13], Lindenbaum [1], Bonjour [14], Chanarin [15] and Hillman and Steinberg [16].

This review will concentrate on the effects of alcohol on the bio-availability of dietary folate, folate metabolism and the enterohepatic circulation of folate.

Dietary folate

Folate is contained in yeast, green leafed vegetables and liver in the form of folate polyglutamates [17]. The folate content of individual dietary items has been recorded by Chanarin [18]. The daily dietary folate requirement which is recommended as being necessary to maintain a normal serum folate is 400 μg [*Recommended Dietary Allowances*, pp. 106–13. National Academy of Sciences, Washington DC (1980)]. Higher levels are required at times of increased demands, such as pregnancy [19] and infection precipitating megaloblastic anaemia in intensive care ward patients [20, 21]. However, this level appears to be sufficient for normal requirements as demonstrated by the low level of folate deficiency occurring in elderly patients on a dietary folate intake of approximately this level [22]. The factor most consistently associated with folate deficiency in elderly subjects, when it occurs, is alcoholism [22].

Dietary folate can be affected by the normal processes of food presentation [23]. Certain folyl-monoglutamates [24, 25] and -polyglutamates [26] normally present in food are unstable under such conditions. The bio-availability is altered by binders in food such as milk [27] and by factors affecting folate absorption [28], e.g. interluminal inhibitors of folate deconjugation [29].

Absorption

Dietary folyl-polyglutamates are absorbed by the proximal intestinal mucosa after they have been deconjugated to folyl-monoglutamates by conjugase enzymes in the bowel, lumen and intestinal mucosa [30]. Conjugase enzymes appear to be in two forms: an intracellular microsomal enzyme with a pH optimum of 4.5 [31] and a brush border membrane variety which is active at pH 7.5 [32]. Conjugase enzymes with two pH optima, 4.5 to 5.0 and 6.7 to 7.5, are also present in bile [33] and pancreatic secretion [34]. Recent evidence suggests that luminal folyl-polyglutamate conjugase deficiency causes folate malabsorption in aged rats [34], and this may explain why folyl-polyglutamates are poor sources of dietary folates in elderly subjects [35]. In chronic alcoholics with liver disease it has been suggested that, in contra-distinction to monoglutamates, folyl-polyglutamates are a poor source of folate [36].

Following deconjugation, dietary folate is composed of 5-$CH_3H_4PteGlu_1$, 5-CHO-$H_4PteGlu_1$, 10-CHO-$H_4PteGlu_1$ and, depending on circumstances, a varying degree of oxidised derivatives including $PteGlu_1$. The oxidised derivatives are reduced and methylated during the absorption process [37, 38]. Oxidised folate is malabsorbed following intestinal infections [39] and chronic alcoholism [40]. The reduced folyl-monoglutamates, especially 5-$CH_3H_4PteGlu$, are absorbed by two separate mechanisms [41, 42]: a carrier-mediated active transport [43–46] and by a pH sensitive passive diffusion pro-

* Address all correspondence to: Prof. D. G. Weir, Department of Clinical Medicine, Medical School Building, St. James' Hospital, Dublin 8, Ireland.

cess associated with the acid microclimate of small intestinal mucosal enterocytes [47, 48], a process which is enhanced by the presence of glucose [49] and inhibited by widespread use of antacids and cimetidine [48].

Binge drinking alcoholics often have associated diarrhoea, and one-third have been reported to have abnormal jejunal visceral biopsies [50]. Folate malabsorption, due to alcoholism, was first suggested by Halsted and his colleagues [40]. Subsequently, they demonstrated that administration of alcohol to normal subjects produced malabsorption of thiamin and cyanocobalamin, but not of folate [51]. Folate malabsorption occurred only in the presence of folate deficiency [52], which suggested a synergistic effect of folate deficiency and alcohol [51]. Alcohol ingestion was shown to reduce the enhanced absorption of folate seen in partially starved rats [53].

Recently, the effect of chronic alcohol ingestion on folate absorption has been studied in non-human primates whose nutritional status was maintained by a balanced diet [54]. Although alcohol ingestion had been sufficiently prolonged to produce the classical liver changes of steatosis and mega-mitochondria [55], the jejunal mucosal histology, light and electron microscopy, and both the mucosal disaccharidase and folyl-polyglutamyl conjugase content were normal. Although there was no significant difference in the faecal fat excretion, nitrogen balance or D-xylose absorption between the alcoholic and control monkeys, there was a significant decrease in folate absorption and hepatic folate content in the alcoholic monkeys. Studies on the effect of alcohol *in vitro* on the absorption of folate in rat proximal jejunum suggest that the mechanism of the malabsorption could relate to the effects of alcohol on the acid microclimate [56].

In summary, it appears that alcohol does affect folate absorption, which in turn presumably affects the enterohepatic circulation of folate, thereby enhancing the tissue folate depletion described above.

Metabolism

Alcohol has been reported to affect folate metabolism in a variety of ways:

(1) Following acute alcohol intake, there is an acute fall of serum folate level [9].

(2) Chronic alcoholism enhances folate binding by high-affinity serum binders [57].

(3) *In vitro*, alcohol reduces transport of PteGlu into, and retention by, freshly isolated hepatocytes [58].

(4) *In vitro*, alcohol increases uptake of 5-CH_3H_4PteGlu and its retention by isolated hepatocytes [58].

(5) Alcohol enhances retention of intracellular folate with impaired release [59] causing interference with the normal enterohepatic cycle of folate [60].

(6) Polyglutamate synthesis has variously been reported to be either impaired [61] or to occur at an enhanced rate to the normal pentaglutamate [62].

(7) Alcohol prevents the normal reduction in cystathione synthetase activity at times of folate depletion [63], which causes an excessive loss of methionine and an increased requirement for 5-CH_3H_4PteGlu.

(8) Alcohol inhibits formyltetrahydrofolate synthetase (EC 6.3.4.3) [64].

(9) Folate catabolism is increased secondary to either alcohol-induced enzyme inductions which depend on folate for their synthesis [65] or by increased requirement of folate cofactors [66]. Recent evidence suggests that this is unlikely [67].

(10) Alcohol increases excretion of folate in the urine and faeces [68] as well as increasing excretion of formic acid [69].

Following the digestion and absorption of dietary folate, folate is carried in the bloodstream as 5-$CH_3H_4PteGlu_1$, 60–80% being loosely bound to serum proteins [70]. Specific high-affinity folate binders have been reported in patients with chronic granulocytic leukaemia [71]. Similar binders were reported in alcoholics with folate deficiency [57]. Subsequently, these binders were described as being of hepatic origin and associated with diseases of that organ [72].

Folate transport into hepatocytes. Transport of folate across the cell wall occurs as a result of two active transport systems, one of which is sodium dependent and the other sodium independent [58, 73]. Using an isolated perfused rat liver model, it has been confirmed that 5-$CH_3H_4PteGlu_1$ is transported by an energy-dependent carrier-mediated process in which the coenzyme is concentrated in the hepatocyte. It is concentrated to six to ten times that in the perfusion fluid and is then excreted into bile at a concentration which is fifteen to nineteen times above the level in the perfusion fluid [74].

The effect of alcohol on these transport systems remains controversial. It appears that, whereas alcohol inhibits the uptake of folic acid and methotrexate [58] and reduces the incorporation of exogenous folate [68], it specifically enhances the transport of 5-CH_3H_4THF-Glu_1 by a process which is dependent on alcohol metabolism and probably related to changes in the cytosolic NADH/NAD ratio [58]. This confirms that there is a separate mechanism for the cellular transport of 5-CH_3H_4PteGlu [75, 76]. The significance of this effect of alcohol on the transport of 5CH_3H_4THF-Glu_1 is unclear.

Folate one-carbon (C_1) intermediate metabolism. For intracellular folate to remain in the cell it must be converted back into folyl-polyglutamates which are predominantly of the pentaglutamate form in mammalian tissue [17]. Folates may also be bound by cytosolic [77] and mitochondrial [78] binders. Since 5-$CH_3H_4PteGlu_1$ is a poor substrate for folyl-polyglutamate synthetase [79, 80], it has to be demethylated by cobalamin-dependent methionine synthetase [81] to H_4PteGlu. The latter is probably the preferred substrate for folyl-polyglutamate synthetase in mammalian cells [82], although others believe that it could be 10-CHO-H_4-PteGlu [83].

The intracellular folyl-polyglutamates in the form of 5,10-$CH_2H_4PteGlu_5$ act as a substrate for thymidylate synthetase which synthesises thymidylate (DNA) and $H_2PteGlu_5$. This so-called one-carbon intermediate metabolism takes place mainly in the rapidly dividing cells of the bone marrow, intestinal mucosa or regenerating tissues [84].

It has been reported that alcohol may inhibit 10-CHO-H_4-$PteGlu_5$ synthetase activity [64]. This could

explain the enhanced excretion of formate following alcohol administration [69], since 10-CHO-H_4-Pte-Glu_5 synthetase is required for formate metabolism to CO_2.

The control of the C_I intermediate metabolism is predominantly via methylenetetrahydrofolate reductase, which, under physiological conditions, controls the one-way reaction of 5,10-$CH_2H_4PteGlu_5$ to 5-$CH_3H_4PteGlu_5$ [85]. The latter compound is required to synthesise methionine and *S*-adenosyl methionine (SAM) from homocysteine. Methionine and SAM are, in turn, required: (a) in the brain for essential methylation reactions, absence of which produces subacute combined degeneration of the central nervous system [86]; (b) in the liver to synthesise creatine for muscle metabolism; (c) in regenerating tissue to produce polyamines [87]; and (d) for other SAM-dependent reactions such as methylation of nucleic acids and methylation of proteins [88].

The level of SAM controls the amount of 5-$CH_3H_4PteGlu_5$ formed by inhibiting methylene reductase [89, 90] and enhances the level of methionine synthetase [91].

During the methylation reaction, SAM is converted to *S*-adenosyl homocysteine and homocysteine. In times of excess, methionine may be degraded to formate via sarcosine and formaldehyde and by degradation of homocysteine via cystathione synthetase to cysteine and α-ketobutyrate. It has been suggested that alcohol may affect this degradation pathway by preventing the inhibition of cystathione synthetase at times of folate depletion [63]. Such a process would cause a drain of 5-$CH_3H_4PteGlu_5$ and lead ultimately to folate deficiency.

Folyl-polyglutamate synthesis and function. The significance of folate polyglutamate synthesis in C_I folate metabolism is as follows: (a) they do not cross cell membranes [92] and are thus retained within the cell; (2) they are more effective than folyl-monoglutamates as substrates for C_I metabolism; (3) they are complexed in the cell, either with protein or as multifunctional enzymes [93, 94] and channel substrates from site to site, thereby enhancing efficiency; and (4) they inhibit extraneous C_I metabolic enzymes [95, 96], thus increasing the efficiency of the relevant enzyme for the particular needs of the cell at that time.

The effect of alcohol on folyl-polyglutamate synthesis is disputed. Preliminary studies in rats suggested that alcohol inhibited folyl-polyglutamate synthesis by reducing the intracellular folate chain length from a mean of five to three [61]. Subsequent reports failed to confirm this finding and demonstrated enhanced polyglutamate formation [60]; others have found that alcohol enhanced the rate of folyl-pentaglutamate synthesis [62]. Recent work in our laboratory would support the finding of an increased rate of polyglutamate synthesis, as alcohol-treated rats show significantly higher methionine synthetase levels in the liver, but not in the brain or intestine [97]. High methionine synthetase levels could result in an increased rate of 5-$CH_3H_4PteGlu_I$ hepatic cell uptake and subsequent demethylation to $H_4PteGlu_I$, the normal substrate for polyglutamate synthesis.

Folate content of the liver. In experimental studies of prolonged dietary deficiency, the liver folate stores are sufficient to maintain serum folate levels greater than 4 ng/ml for periods in excess of 4 weeks. Two to three months of dietary deprivation are required before folate-deficient megaloblastic erythropoeisis and anaemia appear [23]. This interval is shorter in individuals previously subsisting on a marginal folate diet [8, 98].

Hillman and co-workers have, over many years, postulated that organs, such as the liver and kidney, act as tissue stores of folate which are ready to be distributed to areas of rapid cell division as and when plasma folate supplies are insufficient [16, 60, 99]. They state that "the liver and kidney can accumulate folate stores and during periods of deficiency release methyltetrahydrofolate monoglutamates for transport to other tissues. The liver in particular appears to play a central role in regulating such folate supply" [16].

This postulation is based on the following two premises.

First, during periods of folate deficiency, the liver fails to synthesise folyl-polyglutamate derivatives from whatever folate is transported into the cell. "Diminishing the synthesis of folyl-polyglutamate increases the amount of folyl-monoglutamate available for biliary release which dampens the effect of folate deprivation" [60, 100]. Two recent studies suggest that this hypothesis is wrong: (a) In mouse hepatoma cells, folate deprivation produces a *lengthening* of chain length to folyl-octaglutamates from the normal folyl-penta- and -hexaglutamate [101]; and (b) studies on Friend erythroleukaemia cells by Steinberg and colleagues have shown that 95% of the intracellular folate pool was in the form of folyl-polyglutamyl folate, even when the cells became severely deficient. They found that the most important determinant of the intracellular folate pool was the cell doubling time and that once the cell was formed the intracellular folate pool was not in equilibrium with extracellular folate [100].

Second, the liver and kidney accumulate folate stores for distribution during periods of dietary folate deficiency. When folate deficiency occurs, these stores are released for transport to other body tissues by the enterohepatic system [16].

Recent work from this laboratory makes this latter theory untenable [21, 102]. In this study, the intracellular folate of rats was prelabelled with [^{3}H]Pte-Glu producing intracellular 5-CH_3[^{3}H]$PteGlu_5$. The rats were then separated into groups whose diets were either folate replete or deficient, or else into groups which did or did not receive nitrous oxide, a gas which is known to prevent hepatic cell incorporation of folate [103]. The serum and total hepatic folate concentrations fell in the rats which were either taking a folate-deficient diet or inhaling nitrous oxide. However, the radiolabelled folate which was incorporated into the intracellular folate before the change in the extracellular folate environment fell at a rate which exactly mirrored that of the radiolabelled folate in the folate-replete animals. In other words, the liver cell did *not* excrete folate via the enterohepatic cycle for distribution to other tissues at an accelerated rate.

This may explain why it is that, while a normal man on a folate-deficient diet will develop megaloblastic anaemia after 119 days [23], patients in intensive care situations can become acutely folate-deficient and progress to megaloblastic anaemia in a matter of days [104–106]. The concentration of folate in the bile, far from increasing, decreases in times of dietary restriction [60,*]. Biliary folate may be sufficient to maintain essential divisions in normal man with relatively low folate requirements when he is on a folate-deficient diet for over 100 days, while being insufficient for an acutely ill patient with excessive folate demands [21]. In other words, there is no such thing as "metabolically available folate tissue stores". Folate is secreted into the bile and the plasma from the liver cells at a rate which relates to the rate of cell turnover, a rate which is independent of the requirements of any other organ in the body.

The effect of alcohol on the total folate content of the liver varies according to the experimental conditions and the species observed. In rats, the effect of acute ingestion of alcohol on folate incorporation into the liver has been reported as being increased [60], minimally changed [62, 107,*] or reduced [108]. Furthermore, in rats treated with prolonged alcohol intake, there was no change in liver folate as compared to controls [108]. Nevertheless, the rate of synthesis of folyl-pentaglutamate is increased, which could explain in part the acute fall in serum folate following alcohol ingestion [9]. Alcohol has no apparent effect on the rate of reduction or methylation of [^{3}H]PteGlu$_1$ [58, 60].

In monkeys maintained in a good state of nutrition plus a high ethanol intake for 2 years and given a tracer dose of [^{3}H]PteGlu, normal reduction, metabolism and folyl-polyglutamate synthesis were confirmed [109]. However, there was significant reduction in hepatic uptake of a tracer dose of [^{3}H]-PteGlu due to increased urinary and faecal folate excretion [68]. These findings contradict those quoted above using rats and do not support the assertion that alcohol diverts serum folate to tissue stores.

In summary, the reported effects of alcohol on one-carbon folate intermediary metabolism are diffuse and require confirmation. Similarly, the effect of alcohol on folyl-polyglutamate synthesis remains undecided.

Enterohepatic circulation of folate (EHCF). Folate is secreted from the blood stream into the bile against a concentration gradient [110] by six to ten times in the liver and fifteen to nineteen times in the bile [74], using a carrier-mediated process similar to the one regulating folate entry into the cell [74]. The predominant form of biliary folate is 5-CH_3H_4PteGlu$_1$ [38], the absence of polyglutamate being most likely due to the presence of biliary conjugase [111, 112], which is probably derived from dead hepatocytes. This process sets up an EHCF whose interruption may lead to an acute fall in serum folate levels of 40% of the normal level [113].

The significance of the EHCF as a means of distributing folate for body tissue requirements remains controversial. McGuffin and co-workers [114], using a rat model, demonstrated that in folate-deficient states the fall in serum folate mirrored that in the liver and kidney. However, following acute alcohol intake there was a precipitate and disproportionate fall in the serum as opposed to the tissue folate levels. The authors suggested that this implied a direct effect of alcohol on the EHCF. However, they failed to give any values for urinary or faecal folate excretion. Subsequently, the same group [59] investigated the effect of alcohol on folate metabolism in normal, folate-deficient, and alcoholic human volunteers. They found no evidence of increased urinary loss and concluded that alcohol was inhibiting the release of 5-CH_3H_4PteGlu from tissues to plasma. Nevertheless, they did find that, following a flushing dose of PteGlu, a significantly increased amount of folate was excreted in the urine of the volunteers treated with alcohol. Hillman and colleagues [60] went on to report studies using a rat model which suggested that alcohol caused a marked decrease in biliary folate and an increased formation of folyl-polyglutamates which they believed indicated an alcohol-induced block in the biliary excretion of folate. This, they concluded, demonstrated that alcohol causes a block in the EHCF [115]. In further studies, they compared normal, folate-deficient, and alcoholic rats. Once again, they found that alcohol caused enhanced uptake of folate by the liver and "prevented the normal response of folate deprivation, that is, a shift of the polyglutamate ratio towards the monoglutamate form", which is then more amenable to biliary excretion [116]. However, as explained above [100, 101], this statement is untenable.

Recently Steinberg and colleagues [117] have developed an animal model using subcutaneous fibrosarcoma implants to study *in vivo* folate kinetics. Once again [99], they found that significantly more labelled folate was converted to folyl-polyglutamate in the subcutaneous implants in the ethanol-treated animals than in the normals, which in turn was greater than in the folate-deficient group. The authors conclude that the effect of alcohol contrasts with that of folate deficiency, in which intrahepatic folates are mobilised as the serum folate level falls [114]. It is again suggested that, as previously stated [60, 116], alcohol is inhibiting the EHFC. The peripheral supply of folate to the fibrosarcoma implants is compromised by alcohol interrupting the EHFC. Both this study, and the previous ones, cited from Hillman's laboratory, suffer from the following difficulties:

(1) In all of the animal studies, only three groups of animals were assessed, namely, normal, folate-deficient, and alcohol-treated, folate-deficient groups. In none of these studies has the further control group been added, namely, an alcohol, folate-replete group. This would give four groups, as follows: (a) normal; (b) folate-deficient; (c) alcohol-treated, normal folate; and (d) alcohol-treated, folate-deficient. Recent work by McGing and co-workers,* using the four groups as above, but otherwise following the techniques and methodology of Hillman's group, has demonstrated that alcohol had a marginal effect on hepatic folate uptake, but had *no* effect on the biliary excretion of folate. The sole

* P. G. McGing, D. G. Weir and J. M. Scott, manuscript in preparation.

factor regulating the excretion of folate into bile is the degree of serum and hepatic folate deficiency. This occurs regardless of whether or not the animal is taking alcohol. In summary, therefore, it is unlikely that alcohol induces a block of the EHFC.

(2) In the majority of the studies described, little or no attention has been paid to the effect of alcohol on the urinary excretion of folate. In a preliminary study [59], this aspect was assessed in human volunteers treated with alcohol. The results showed a small, but definite, increase in urinary folate, which was not considered relevant. However, recent studies would suggest that this is a major cause of the alcohol-induced serum folate deficiency [68, 69].

(3) The conclusions drawn by the authors are not always compatible with their results and those obtained by others. In the fibrosarcoma study, for instance, if alcohol inhibited the EHFC, why is the uptake of [^{3}H]PteGlu into the liver not higher in the alcohol group (1.56 ± 0.20) as compared with the normal group (1.57 ± 0.15)? Furthermore, great play is made of the increased folyl-polyglutamate synthesis in the peripheral fibrosarcoma nodule (52 ± 3.0) as compared with normal (41 ± 1.8), while no mention is made of the reverse trend in the liver (alcohol group: 44.4 ± 5.0, normals 50.7 ± 5.3). These findings are not compatible with their conclusions.

In summary, while there is no doubt that a significant EHFC occurs, at present the evidence suggests that alcohol does not exert any significant blocking effect on hepato biliary folate excretion.

Catabolism of folate. The catabolism of intracellular folate occurs at an unknown place and time during the folate metabolic cycle. When it does occur, it is by cleavage at the C9-N10 position of the pteroyl compound, which produces pteridines and para-aminobenzoylglutamate (p-ABGlu) [118]. Since p-ABGlu is quantitatively excreted in the urine, it can be used as a measurement of folate catabolism [119].

It has been suggested that the folate deficiency associated with alcohol intake is either due to the induction of enzymes which require folate for their synthesis [65] or that microsomal enzyme induction by alcohol increases the requirement for folate cofactors [66]. Recent work, however, has demonstrated that neither acute nor chronic alcohol intake enhances the rate of folate catabolism in rats [67].

Effect of alcohol on renal excretion of folate

Studies performed on monkeys have demonstrated that folic acid is handled by a bidirectional active transport process in the kidneys [120]. It appears that there is a net folate secretion in the proximal tubule, but a saturable distal tubular reabsorption mechanism operates against a concentration gradient. The *p*-aminobenzoylglutamate portion of the folate molecule is necessary for the proximal tubular secretory mechanism, while the pteridine moiety is required for the saturable distal tubular reabsorption process [120].

Early reports in man suggested that alcohol did not have a significant effect on urinary folate loss [9, 59], although recent evidence has shown an increased excretion of folate in three human subjects who ingested alcohol [121]. Subsequent studies on the rat [69, 107] and on the monkey [68] suggest that, regardless of the route by which ethanol is administered, there is a marked increase in urinary folate excretion within 8 hr. The increase in urinary folate excretion is not a function of alcohol metabolism, as 4-methylpyrazole (4MP), a compound which inhibits alcohol dehydrogenase activity *in vivo* [122], did not affect the degree of folate excretion, even though the urinary alcohol concentration rose as expected. This suggests that the effect of alcohol on serum folate levels is enhanced renal excretion, rather than the result of interference with hepatic folate metabolism. Chronic ethanol intake in the monkey over a 2-year period also leads to a significant reduction in hepatic folate content [109]. When these animals were given a dose of [^{3}H]PteGlu, there was an early enhanced loss of the exogenous labelled folate in the urine, whereas the long-term turnover of endogenous folate remains unchanged [68]. There was also an enhanced faecal excretion of the labelled folate, which may reflect the chronic effect of alcohol in these monkeys on folate absorption following biliary excretion of the labelled folate into the intestine [54].

Ethanol also causes an increase in the urinary excretion of formate which suggests a direct effect of ethanol on the folate-dependent formate metabolic pathways. An example of this could be the reported inhibition of 10-CHO-H_4PteGlu synthetase activity [64]. This effect of ethanol on formate excretion, in contrast to its effect on urinary folate content, is inhibited by 4MP and suggests that it results from the metabolism of ethanol [69].

How ethanol effects the increased urinary folate excretion is unknown. A possible mechanism could be a direct effect of ethanol on the folate-binding protein of the brush border membrane of the kidney [123].

Conclusions

It is probable that the cause of the fall in serum folate following an acute intake of alcohol is also related to the aetiology of the folate deficiency associated with chronic alcohol intake. Analysis of the available evidence suggests that the most likely cause of the alcohol-induced folate deficiency is an increased urinary excretion of folate.

There is no doubt that there is an enterohepatic folate circulation which is influenced by body serum and hepatic folate content. The effect of alcohol on this process is disputed, but current evidence does not support claims that alcohol blocks the excretion of hepatic folate into bile to any significant extent. Any effect of alcohol on the distribution of folate to peripheral tissues is more likely to be associated with the known effect of alcohol on folate intestinal absorption and its excretion by the kidneys.

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