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Editorial

Antiepileptic drugs, folate and one carbon metabolism revisited

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When training in neurology at the National Hospital, London in the mid-1960s, my first research interest was on the effects of antiepileptic drugs (AEDs) on folate and vitamin B12 metabolism and their implications. At that time, my colleagues and I found that the front-line drugs, phenobarbitone, primidone, and phenytoin, caused a reduction in serum, red cell, and cerebrospinal fluid (CSF) folate in a high proportion of patients with epilepsy [1,2]. Treatment with folic acid for one to three years appeared to improve the mental state, mainly alertness, motivation, mood, and sociability, in many patients and exacerbate the epilepsy in a few [3]. Experimental studies by several groups confirmed that folate derivatives were convulsant, especially if the highly efficient blood–brain barrier mechanism for the transport form of methylfolate into the brain is bypassed [4–6]. I therefore proposed that not only folate deficiency may contribute to some cognitive, mood, and other psychiatric complications of epilepsy but also the antiepileptic action of the drugs may be related to their antifolate action [2,3].

At that time, almost nothing was known about the role of folate in the nervous system except that it was harmful if administered inappropriately for patients with pernicious anemia or vitamin 12 deficiency [7]. Since then, I have developed a career-long interest in folate and vitamin B12 metabolism in the fields of neurology and psychiatry apart from epilepsy [8,9]. It is now recognized that there is a considerable overlap between the neuropsychiatric complications of folate and vitamin B12 deficiency, with or without megaloblastic anemia. These include cognitive impairment, depression, and less commonly spinal cord and peripheral nerve involvement [9]. Over the last 50 years, there has also been increasing recognition of the overlapping developmental and neurological manifestations of inborn errors of folate and vitamin B12 metabolism, most recently cerebral folate deficiency [9,10]. Finally, over the last 30 years, it has been established that periconceptual folic acid will reduce the risk of neural tube defects (NTDs) and other congenital malformations, so much so that over 80 countries have introduced mandatory fortification of grains and cereals [11].

For all these reasons, it is clear that folate and vitamin B12 are fundamental to nervous system function at all ages. There is interest in the role of these vitamins not only in the prevention of developmental disorders in the fetus, infant, and child but also in the prevention of cognitive and mood disorders in the elderly [9]. Folic acid is an unnatural synthetic form of folate which, as illustrated in the figure, must first be reduced before entering the complex folate/one carbon cycle, where the reduced tetrahydrofolate picks up a single carbon unit from serine, which is further reduced to methyltetrahydrofolate which participates with vitamin B12 in the synthesis of methionine from homocysteine. Ultimately, the methyl group is passed on via S-adenosylmethionine (SAM) in numerous crucial methylation reactions involving deoxyribonucleic acid (DNA), ribonucleic acid (RNA), neurotransmitters, and many other pathways requiring methyl group transfers. At the same time, the folate cycle is required for the synthesis of purine and thymidine nucleotides. Thus, disruption of the folate cycle has potentially wide ranging effects including impairment of DNA transcription, methylation, including epigenetic modification, all of which can affect tissue growth, differentiation, and repair, as well as excitatory and inhibitory mechanisms [12,13].

However, interest in the relationship between antifolate and antiepileptic mechanisms waned for several reasons. Treatment with folic acid for relatively short periods did not appear to exacerbate epilepsy in most patients [7]. In the 1970s, two new AEDs with very different chemical structures, i.e., carbamazepine and sodium valproate (VPA), were marketed. Both drugs did exhibit mild lowering of blood folate levels in patients with epilepsy [14,15]. However, the marketing of lamotrigine by 1990 was said to have undermined any relationship between antifolate and antiepileptic mechanisms. Interestingly, the development of lamotrigine was based on the antifolate–antiepileptic hypothesis [16]. Wellcome Laboratories already had the following two antifolate drugs in their portfolio: 1) pyrimethamine, a potent inhibitor of mammalian dihydrofolate reductase (DHFR) utilized as an antimalarial, which Miller and colleagues [5] now confirmed experimentally, was a potent AED; and 2) a related pyrimidine, trimethoprin, which was a weaker DHFR inhibitor and weaker AED. At the same time, they confirmed experimentally that folates including folinic acid were convulsant [5]. By manipulating the structure of pyrimethamine, Wellcome reported that the resulting lamotrigine retained the antiepileptic potency of the former but was now a weaker DHFR inhibitor. Lamotrigine was therefore marketed as a novel and successful AED with little or no antifolate activity [16].

In the 1990s, a new measure of disturbed folate and one carbon metabolism became available, i.e., plasma homocysteine. Over the last 20 years, numerous studies of children and adults with epilepsy have confirmed that phenobarbitone, phenytoin, carbamazepine, and VPA are significantly associated with the elevation of plasma homocysteine [17–19]. A more recent study found the same for levetiracetam, oxcarbazepine, and topiramate [20]. Paradoxically, lamotrigine has been least studied. Although genetic polymorphisms of folate and homocysteine, especially the C677T variant of methylenetetrahydrofolate reductase (MTHFR), may be a predisposing factor, the rise in plasma homocysteine is invariably correlated with a fall in serum folate and is reversible by treatment with folic acid, which may also improve mood [17–19,21].

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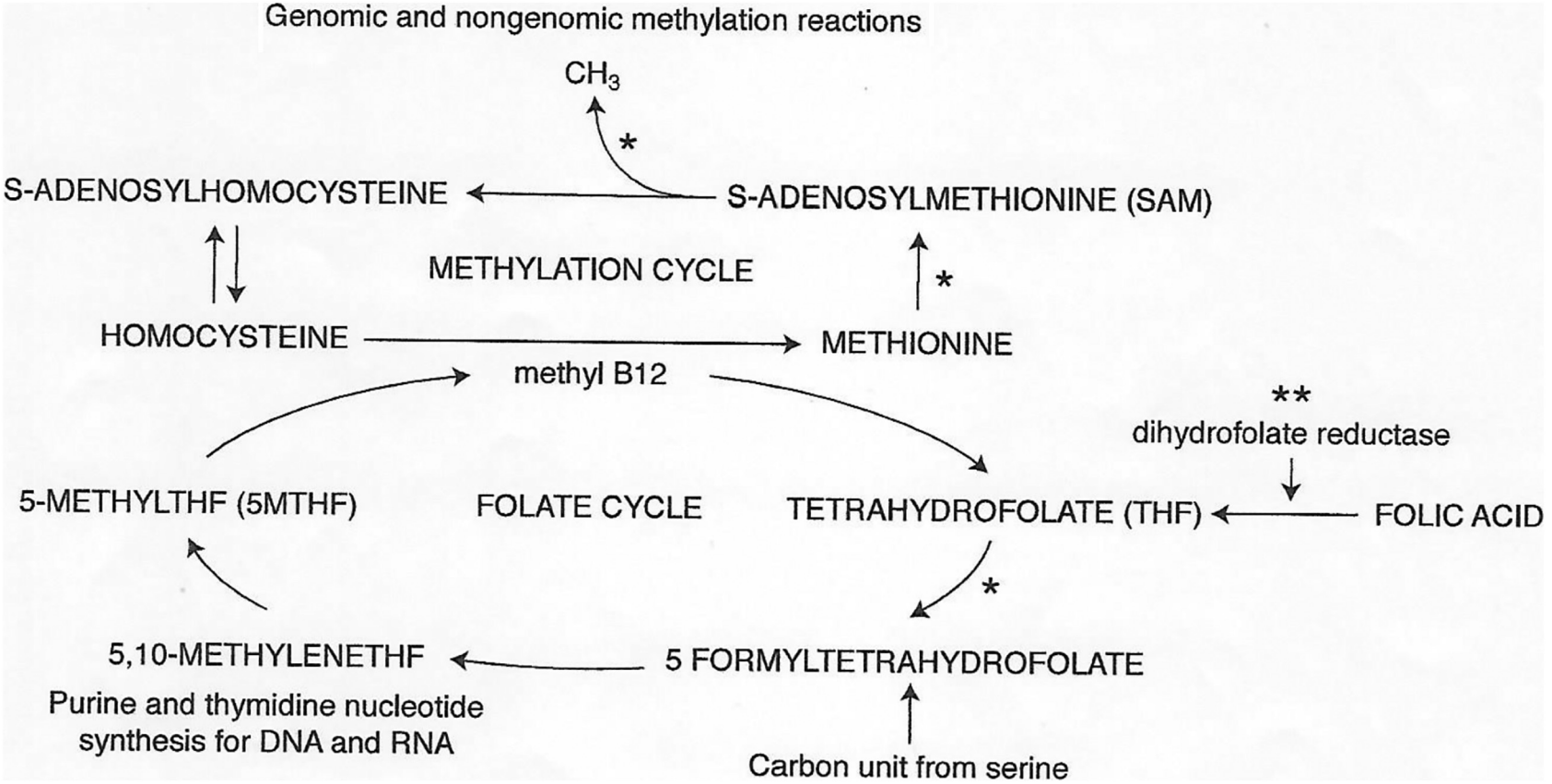

Fig. 1. Relationships between the folate cycle, vitamin B12, and the methylation cycle to one-carbon metabolism. *Reported inhibition by VPA. Valproate also inhibits folate receptor one (FOLRI) and possibly other folate receptors. **Reported inhibition by lamotrigine.

A review and meta-analysis of 8 studies confirmed that VPA monotherapy is invariably associated with an increase in plasma homocysteine in adults and children with epilepsy [22]. Most of the studies also reported a fall in serum folate. Vitamin B12 levels were unaffected. In a further study of VPA and lamotrigine monotherapy, only VPA was associated with a rise in homocysteine; but both drugs were associated with reduced levels of folate, which also correlated with the methylation status of peripheral blood MTHFR amplicons [23]. The authors suggest that both drugs may induce specific regions of DNA hypomethylation. Earlier, Smith et al. [24] reported decreased methylation scores across CpG islands in 50 neonates exposed in utero to various AEDs, including VPA, but mostly lamotrigine, particularly in those with the longest exposure. There is also experimental evidence that acute VPA exposure may inhibit glutamate formyl transferase, the enzyme mediating the formation of formyltetrahydrofolate (folinic acid) [25], and also methionine adenosyltransferase, the enzyme mediating the formation of SAM [26] (see Fig. 1). It has also been proposed recently that VPA is a histone decarboxylase inhibitor with antagonistic actions to SAM as an epigenetic modulator [27].

Perfusion of normal full-term human placentas with VPA for 180 min led to a reduction of placental folate by 25–35% and altered messenger RNA (mRNA) levels of major carriers for folate, choline, and glucose. The authors concluded that VPA targets the folate receptor FOLR1 and possibly other folate receptors leading to a direct inhibition of placental folate uptake [28]. Utilizing cell culture modeling, it was also suggested that VPA is a noncompetitive inhibitor of high-affinity folate receptors [29]. Forty years ago, before anything was known of folate receptors, Smith and Racusen reported that experimentally in the rat, both phenobarbitone and VPA lowered brain folate levels and partially blocked the reuptake of formyltetrahydrofolate (folinic acid). Phenytoin also lowered brain folate, perhaps by a different mechanism, but carbamazepine had little effect [30].

In conclusion, it is surely remarkable 1) that so many first-line AEDs of different chemical structures, i.e., phenobarbitone, primidone, phenytoin, carbamazepine, VPA, lamotrigine, and perhaps also levetiracetam, oxcarbazepine, and topiramate all interfere with folate, methylation, and one-carbon metabolism in varying ways; and 2) biological folate derivatives have convulsant and excitatory properties. The mechanisms of the AED effects on these pathways have never been clarified, perhaps because the complexity of the folate cycle, including receptor and transport processes, and their relevance were not previously understood. As illustrated in the figure VPA, probably the most studied AED, perhaps because it is the most teratogenic, may interfere with one-carbon metabolism at more than one site, including folate receptors and the transport of methylfolate into brain and placenta [31]. Likewise, the mechanisms of the excitatory properties of folate have been little investigated or understood. Are they related to the glutamate moieties of folate? Nearly 50 years ago, folate and folinate were reported to have excitatory effects on single neurons of the cat cerebral cortex, perhaps by blocking or reversing gammaaminobutyric acid (GABA) mediated inhibition [32]. Some AEDs are widely used for the treatment of bipolar disorder, not least VPA and lamotrigine, and one-carbon metabolism is now a focus of research in this disorder [33]. It has long seemed to me to be more than a coincidence that whereas folates are convulsant, the commonest neuropsychiatric complication of severe folate deficiency is depression [7,34]. Whether or not folates are involved in seizure and AED mechanisms, the evidence that disturbed folate metabolism is implicated in some of the teratogenic, developmental, and neuropsychiatric complications of AEDs is increasingly apparent [3,31].

"Vitamin" research has never attracted much investment at the clinical level, perhaps partly for commercial reasons, but one-carbon metabolism is fundamental to brain and mental development and health at all ages. For all the reasons summarized here, the time is appropriate for a major research investment in these pathways in seizure and AED's mechanisms and their complications.

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Declaration of competing interest

None declared.

References

[1] Reynolds EH, Chanarin I, Milner G, Matthews DM. Anticonvulsant therapy, folic acid and vitamin B12 metabolism and mental symptoms. Epilepsia. 1966;7:261–70.
[2] Reynolds EH. Anticonvulsants, folic acid and epilepsy. Lancet. 1973;1:1376–8.
[3] Reynolds EH. Mental effects of anticonvulsants, and folic acid metabolism. Brain. 1968;91:197–214.
[4] Spector RG. Folic acid and convulsions in the rat. Biochem Pharmacol. 1971;20:1730–2.
[5] Baxter MG, Miller AA, Webster RA. Some studies on the convulsant action of folic acid. Brit J Pharmacol. 1973;48:350–1.
[6] Hommes OR, Obbens EAMT, Wijffels CCB. Epileptogenic activity of sodium-folate and the blood brain barrier in the rat. J Neurol Sci. 1973;19:63–71.
[7] Reynolds EH. Neurological aspects of folate and vitamin B12 metabolism. In: Hoffbrand AV, editor. Clinics in haematology. London: Saunders; 1976. p. 661–96.
[8] Botez MI, Reynolds EH, editors. Folic acid in neurology, psychiatry and internal medicine. New York: Raven Press; 1979.
[9] Reynolds E. Vitamin B12, folic acid, and the nervous system. Lancet Neurol. 2006;5:949–60.
[10] Pope S, Artuch R, Heales S, Rahman S. Cerebral folate deficiency: analytical tests and differential diagnosis. J Inherit Metab Dis. 2019;42:655–72.
[11] Mills JL, Molloy AM, Reynolds EH. Do the benefits of folic acid fortification outweigh the risk of masking vitamin B12 deficiency? BMJ. 2018;360:k724. https://doi.org/10.1136/bmj.k724.
[12] Bailey LB, editor. Folate in health and disease. 2nd ed. Boca Raton: CRC Press; 2010.
[13] Green R, Allen LH, Bjorke-Monsen AL, Brito A, Gueant J-L, Miller JW, et al. Vitamin B12 deficiency. Nat Rev Dis Primers. 2017;3:17046.
[14] Goggin T, Gough H, Bissessar A, Crowley M, Baker M, Callaghan N. A comparative study of the relative effects of anticonvulsant drugs and dietary folate on the red cell folate status of patients with epilepsy. Q J Med. 1987;65:911–9.
[15] Turnbull DM, Rawlins MD, Weightman D, Chadwick DW. A comparison of phenytoin and valproate in previously untreated adult epileptic patients. J Neurol Neurosurg Psychiatry. 1982;45:55–9.
[16] Peck AW. Lamotrigine: historical background. Rev Contemp Pharmocother. 1994;6:95–105.
[17] Coppola G, Ingrosso D, Operto FF, Signoriello G, Lattanzio F, Barone E, et al. Role of folic acid depletion on homocysteine serum level in children and adolescents with epilepsy and different MTHFR C677T genotypes. Seizure. 2012;21:340–3.
[18] Bochynska A, Lipczynska-Lojkowska W, Gugala-Iwaniuk M, Lechowicz W, Restel M, Graban A, et al. The effect of vitamin B supplementation on homocysteine metabolism and clinical state of patients with chronic epilepsy treated with carbamazepine and valproic acid. Seizure. 2012;21:276–81.
[19] Semmler A, Moskau-Hartmann S, Stoffel-Wagner B, Elger C, Linnebank M. Homocysteine plasma levels in patients treated with antiepileptic drugs depend on folate and vitamin B12 serum levels, but not on genetic variants of homocysteine metabolism. Clin Chem Lab Med. 2013;51:665–9.
[20] Kim DW, Lee SY, Shon YM, Kim JH. Effects of new antiepileptic drugs on circulatory markers for vascular risk in patients with newly diagnosed epilepsy. Epilepsia. 2013;54:e146–9.
[21] Ono H, Sakamoto A, Mizoguchi N, Sakura N. The C677T mutation in the methylene tetrahydrofolate reductase gene contributes to hyperhomocysteinemia in patients taking anticonvulsants. Brain Dev. 2002;24:223–36.
[22] Ni G, Quin J, Fang Z, Chen Y, Chen Z, Zhou J, et al. Increased homocysteine levels in valproate-treated patients with epilepsy: a meta-analysis. BMJ Open. 2014;4:e004936.
[23] Ni G, Quin J, Li H, Chen Z, Zhou Y, Fang Z, et al. The effects of antiepileptic drug monotherapy on one-carbon metabolism and DNA methylation in patients with epilepsy. PLoS One. 2015;10:e0125656.
[24] Smith AK, Conneely KN, Newport DJ, Kilaru V, Schroeder J, Pennell P, et al. Prenatal antiepileptic exposure associates with neonatal DNA methylation differences. Epigenetics. 2012;7:458–63.
[25] Wegner C, Nau H. Alteration of embryonic folate metabolism by valproic acid during organogenesis: implications for mechanism of teratogenesis. Neurology. 1992;42:17–24.
[26] Ubeda N, Alonso-Aperte E, Varela-Moreiras G. Acute valproate administration impairs methionine metabolism in rats. J Nutr. 2002;132:2737–42.
[27] Ornoy A, Becker M, Weinstein-Fudim L, Ergaz Z. S-adenosine methionine (SAMe) and valproic acid (VPA) as epigenetic modulators: special emphasis on their interactions affecting nervous tissue during pregnancy. Int J Mol Sci. 2020;21:3721. https://doi.org/10.3390/ijms21103721.
[28] Rubinchik-Stern M, Shmuel M, Bar J, Kovo M, Eyal S. Adverse placental effects of valproic acid: studies in perfused human placentas. Epilepsia. 2018;59:993–1003.
[29] Fathe K, Palacios A, Finnell RH. Novel mechanism for valproate-induced teratogenicity. Birth Defects Res A Clin Mol Teratol. 2014;100:592–7.
[30] Smith DB, Carl GF. Anticonvulsant-folate interactions. In: Dam M, Gram L, Penry JK, editors. Advances in epileptology: X11th epilepsy international symposium. New York: Raven Press; 1981. p. 671–8.

[31] Reynolds EH, Green R. Valproate and folate: congenital and developmental risks. Epilepsy Behav. 2020;108:107068.
[32] Davies J, Watkins JC. Facilitatory and direct excitatory effects of folate and folinate on single neurones on cat cerebral cortex. Biochem Pharmacol. 1973;22:1667–8.
[33] Baek JH, Bernstein EE, Nierenberg AA. One-carbon metabolism and bipolar disorder. Aust NZ J Psychiatry. 2013;47:1013–8.
[34] Green R, Miller JW. Folate deficiency beyond megaloblastic anaemia; hyperhomocysteinemia and other manifestations of dysfunctional folate status. Semin Haematol. 1999;36:47–64.

Edward H. Reynolds
Department of Clinical Neurosciences, King's College, London, UK
E-mail address: reynolds@buckles.u-net.com

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