EFFECT OF CHRONIC VALPROATE TREATMENT ON FOLATE-DEPENDENT METHYL BIOSYNTHESIS IN THE RAT

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Folate deficiency has been associated with chronic anticonvulsant therapy. Characterization of the effects of individual anticonvulsants has been undertaken. Chronic treatment of rats with sodium valproate caused a decrease in liver folate concentration with concomitant increases in brain and plasma folate concentrations. After several weeks, these trends were reversed and folate concentrations tended to normalize. Chronic valproate treatment affected the activities of folate-dependent one-carbon enzymes: Serine hydroxymethyltransferase activity in liver was increased; methylenetetrahydrofolate reductase activity in both brain and liver was decreased; and methyltetrahydrofolate: homocysteine methyltransferase activity in both brain and liver decreased initially but returned toward normal with continued treatment. Methionine adenosyltransferase activity in brain declined after several weeks of treatment but the concentration of S-adenosylmethionine in liver increased with chronic valproate treatment. These data are consistent with the hypothesis that the effects of anticonvulsants on folates are a consequence of the mechanism of action of the anticonvulsant.

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Abbreviations: SHMT, serine hydroxymethyltransferase; MAT, methionine adenosyltransferase; MHMT, methylenetetrahydrofolate:homocysteine methyltransferase; MTR, methylenetetrahydrofolate reductase; and AdoMet, S-adenosylmethionine.
INTRODUCTION

It has been known for some time that chronic pharmacotherapy with anticonvulsants can lead to folate deficiency and in some cases to frank megaloblastic anemia. However, more insidious effects have recently been associated with less severe folate deficiency. For example, psychiatric (1-3), neurological (4-7) and intellectual (8) deficits have been attributed to folate depletion. Whether anticonvulsant induced folate deficiencies lead to these abnormalities has not been established. Phenytoin is the anticonvulsant most often linked to folate deficiency (9) but phenobarbital (9, 10), primidone (9), carbamazepine (10, 11) and valproate (11) have also been implicated. Phenytoin, phenobarbital, primidone and carbamazepine are nitrogenous ring structures but valproate is an organic acid having little in common chemically with the other four anticonvulsants.

Animal models have been developed for studying the chronic effects of phenytoin (12), phenobarbital (13), primidone (14) and valproate (15). In the rat oral doses of phenytoin, phenobarbital and primidone can be administered such that continuous, non-toxic protection from induced seizures is attained. Using these models, we have demonstrated that each of these three anticonvulsants initiates a decrease in folate concentrations (12-14) and that each significantly affects the activities of folate-dependent one-carbon enzymes (12-14). Valproate, on the other hand, does not lend itself to the creation of a continuously protective, non-toxic model in the rat with specifically defined, timed doses (15). However, valproate, like phenytoin, phenobarbital and primidone, has been shown to affect a folate-dependent one-carbon enzyme. The glycine cleavage system is inhibited by valproate and consequently glycine concentrations increase both in animals (16) and patients (17, 18) treated with valproate.

The mechanism by which anticonvulsants induce folate deficiency is unknown but it has been suggested that the interaction of anticonvulsants with folates might be an essential component of the mechanism of action of the anticonvulsants (19). The epileptogenic action of folates (20, 21) has been sited as support for this suggestion. However, controlled studies of folate supplementation in anticonvulsant-treated epileptics have failed to show a negative effect of supplementation on the efficacy of the drugs (22-26). It should be noted here that while folate supplementation has been shown to increase serum folate levels in patients (22-26), no investigations have attempted to determine if folate supplementation reverses the effects of anticonvulsants on folate-dependent one-carbon metabolism. However, the timing of significant effects of anticonvulsant treatment on folate-dependent one-carbon metabolism (13, 14, 27) would in-