Modulation Of Anticonvulsant Effect Of Sodium Valproate By Folic Acid: The Possible Role Of Homocysteine

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ABSTRACT

In the present work the modulation of the antiepileptic effect of Sodium Valproate (SV) by folic acid (FA) and the possible role of homocysteine (HCY) were studied. The results revealed that co-administration of SV and FA in rats significantly decreased the duration of seizures compared to the group of rats received SV alone for fourteen days. Meanwhile, no significant differences were observed in the cortical GABA and ACh concentrations between either groups. On the other hand, HCY plasma concentration significantly decreased in the group received SV and FA compared to the group received SV alone.

Accordingly, it was concluded that FA might potentiate the anticonvulsant activity of SV and this effect is not attributed to GABA or ACh concentrations in the cerebral cortex (c.c.) but it might be due to decrease in HCY plasma concentration induced by FA itself.

INTRODUCTION

Sodium Valproate (SV) has a wide spectrum of activity and has no contraindications in any type of seizures¹. Recent studies showed that children treated with antifolate drug, methotrexate, developed chronic neurological disorders including epilepsy, Alzheimer’s disease, affective disorders and cortical brain damage²,³,⁴. SV may interfere with folate metabolism⁵. The proposed mechanism may be due to interference with intestinal absorption, induction of enzymes in the liver that require and finally deplete FA or interfere with the metabolism of folic acid co-enzymes⁶. Several investigators have reported that FA deficiency induce hyperhomocysteinemia, but, oral treatment with high dose of FA correct the elevated total homocysteine⁷,⁸.

Folate is required for remethylation of HCY to methionine, so, FA deficiency may cause hyperhomocysteinemia⁹. Moreover, HCY is a convulsant and used to induce status epilepticus (S.E.) by Walton et al.¹⁰. The antiepileptic effect of SV may be attributed to elevation of GABA concentration, an important inhibitory neurotransmitter, in the c.c. and also due to decrease in ACh concentration, an excitatory neurotransmitter. GABA counteracts the excitatory effects of neurotransmitter glutamate and glycine¹¹,¹². Mudd et al.¹³ reported that high intraperitoneal dose of DL-homocysteine induced tonic-clonic grand mal seizures in rats. Walton and his colleges¹⁴ used HCY thiolactone experimentally to induce SE in rats.

In the present work a model of experimental status epilepticus was created and the antiepileptic effect of SV was detected when