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Effects of combined lamotrigine and valproate on basal and stimulated extracellular amino acids and monoamines in the hippocampus of freely moving rats.

Ahmad S[1], Fowler LJ, Whitton PS.

Author information

[1]Department of Pharmacology, School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX, UK.

Abstract

The antiepileptic drugs sodium valproate (VPA) and lamotrigine (LTG) are increasingly used in combination in patients in whom monotherapy has failed to control seizures. Although these drugs are known to interact pharmacokinetically, several authors have proposed a pharmacodynamic interaction between the two. In order to investigate this we have studied the effects of combined treatment with LTG and VPA on basal and stimulated extracellular aspartate (ASP), glutamate (GLU), taurine (TAU), gamma amino butyric acid (GABA), 5-hydroxytryptamine (5-HT) and dopamine (DA) release in the hippocampus of freely moving rats using microdialysis. Additionally, we measured the possible effect of VPA on LTG in plasma, whole brain and dialysates. Neither LTG (10 mg/kg) nor VPA (300 mg/kg) given alone significantly altered basal levels of ASP, GLU or TAU. When given together, however, the two drugs significantly reduced extracellular ASP and GLU while increasing TAU levels. In the case of GABA, LTG was without effect on basal levels of the transmitter, but these increased following VPA and this persisted with both drugs. When transmitter release was stimulated by 50 muM veratridine, marked increases in the release of all amino acids occurred and this was decreased by LTG in all cases. VPA alone only altered GABA release, increasing it by approximately the same extent as basal GABA. For all of the amino acids studied, however, VPA reversed the decreases in release seen after LTG. VPA and LTG increased and decreased respectively basal 5-HT and DA. When given together the increase in extracellular 5-HT was greatly prolonged, but no effect on DA release was seen. When 5-HT release was evoked by veratridine this was increased by VPA and no other treatment. With DA, however, neither drug alone altered evoked release, but the two combined led to a marked increase. Co-administration of VPA with LTG showed no significant effect of this combination on LTG in any of the three compartments studied indicating that in this case a significant pharmacokinetic contribution to our findings is unlikely, which suggests that there is a probable pharmacodynamic interaction of the two drugs.

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