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Valproate and carbamazepine increase prefrontal dopamine release by 5-HT_{1A} receptor activation

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Abstract

The anticonvulsant mood stabilizers valproic acid (250, 500 but not 50 mg/kg) and carbamazepine (6, 12.5 but not 3 mg/kg) were found to increase extracellular dopamine levels in rat medial prefrontal cortex, but not nucleus accumbens. Increased prefrontal dopamine was completely abolished by the selective 5-HT_{1A} receptor antagonist *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-cyclohexanecarboxamide (WAY100635, 0.05 mg/kg). Anticonvulsants and clozapine may share a common mood stabilizing mechanism since clozapine is reported to have mood stabilizing effects and increase prefrontal dopamine by 5-HT_{1A} receptor activation.

Keywords: Anticonvulsant mood stabilizer; Dopamine; 5-HT_{1A} receptor

Anticonvulsants such as valproic acid and carbamazepine are extensively used as mood stabilizers in patients with bipolar affective disorder and schizophrenia. However, little is known about the mechanisms underlying the mood stabilizing effects of these anticonvulsants. Interestingly, clozapine, an atypical antipsychotic drug, has also been reported to be an effective mood stabilizer in that it reduces both the number of affective episodes and rehospitalizations in patients with severe refractory bipolar illness or schizoaffective mania (Zarate et al., 1995; Calabrese et al., 1996), who respond little or none to lithium, carbamazepine or valproic acid. Thus, the possibility that clozapine and the anticonvulsant mood stabilizers share a common mechanism of action requires investigation. Clozapine preferentially increases dopamine release in the medial prefrontal cortex compared to the nucleus accumbens (Kuroki et al., 1999). This increase is mediated, in part, by 5-HT_{1A} receptor activation (Rollema et al., 1997). Various antidepressants, e.g., fluoxetine and imipramine, have also been reported to preferentially increase dopamine release in the medial prefrontal cortex (Tanda et al., 1994). There is no data on whether mood stabilizers also increase dopamine release in the medial prefrontal cortex. We have tested this hypothesis in microdialysis experiments, and report the first in vivo evidence that valproic acid and carbamazepine preferentially increase extracellular dopamine levels in the medial prefrontal cortex, also by a 5-HT_{1A} receptor-mediated mechanism.

We used Sprague–Dawley albino rats (Zivic-Miller, PA), weighing 250–350 g throughout the experiments. Details of the method have already been reported (Kuroki et al., 1999). In brief, 3–5 days after cannulation surgery, rats were received dual probe implantation for the medial prefrontal cortex and nucleus accumbens (coordinates: A +3.2, L +0.8, V −5.5 and A +2.0, L −1.5, V −7.5 mm, respectively, relative to bregma). After overnight perfusion of the probe (0.4 μl/min), dialysate samples were collected every 30 min and analyzed for dopamine with high performance liquid chromatography (HPLC). Valproic acid and carbamazepine were dissolved in 45% 2-hydroxypropyl-β-cyclodextrin, and *N*-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinyl-cyclohexanecarboxamide (WAY100635), selective 5-HT_{1A} receptor antagonist, was dissolved in deionized water. Vehicle or drugs were administered subcutaneously (s.c.). All drugs were purchased from RBI (Natick, MA). The location of the dialysis probe was verified at the end of each experi-

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ment by brain dissection. Repeated measure analysis of variance (ANOVA) followed by Fisher's protected least significant difference post hoc pairwise comparison procedure and one-way ANOVA were used to determine group differences (StatView® 4.02 for the Macintosh). The procedures applied in these experiments were approved by the Institutional Animal Care and Use Committee of Vanderbilt University in Nashville, TN.

Valproic acid (250, 500 but not 50 mg/kg) and carbamazepine (6, 12.5 but not 3 mg/kg) dose-dependently increased extracellular dopamine levels in the medial prefrontal cortex but had no effect in the nucleus accumbens (Fig. 1B and D). The increases in the medial prefrontal cortex were completely abolished by pretreatment with the selective 5-HT_{1A} receptor antagonist WAY100635 (0.05 mg/kg) (Fig. 1A and C).

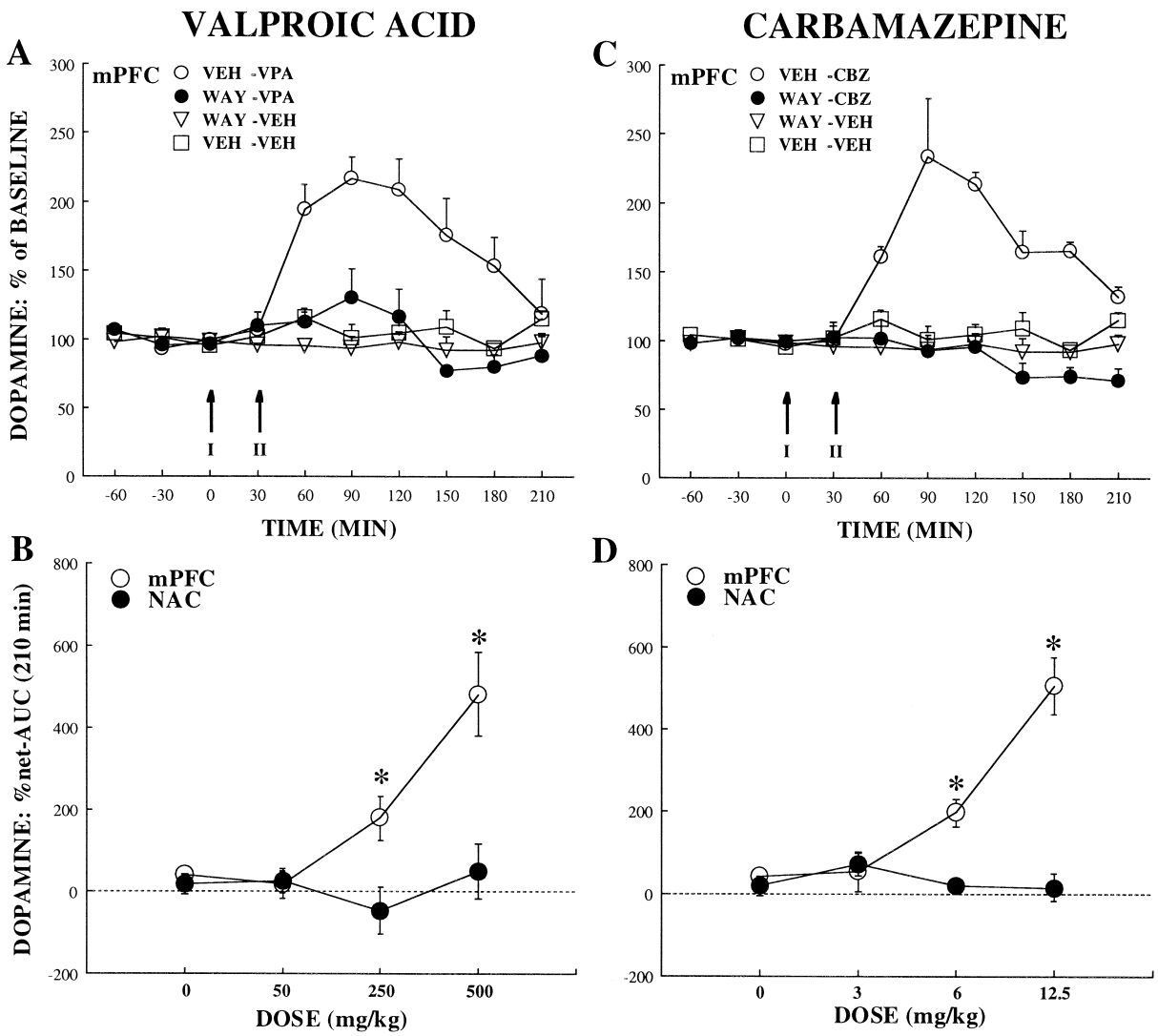

Fig. 1. Anticonvulsant mood stabilizers valproic acid (A) (VPA, 500 mg/kg, s.c., open circles) and (C) carbamazepine (CBZ, 12.5 mg/kg, s.c., open circles) significantly increased extracellular dopamine levels in the medial prefrontal cortex (mPFC) ($F(1,10) = 20.3$, $P = 0.001$; $F(1,12) = 37.5$, $P < 0.001$, respectively), compared to the vehicle controls (VEH, open squares). Pretreatment with the selective 5-HT_{1A} receptor antagonist WAY100635 (0.05 mg/kg, s.c., closed circles) completely abolished the ability of VPA and CBZ to increase extracellular dopamine levels in the mPFC ($F(1,9) = 18.4$, $P = 0.002$; $F(1,12) = 52.6$, $P < 0.001$, respectively), compared to correspondent dose effect of VPA and CBZ alone (open circles). WAY100635 (0.05 mg/kg, s.c., open triangles) alone had no significant effect on extracellular dopamine levels in the mPFC, compared to the VEH. Each data point represents the group mean ± S.E.M. (bars) of dialysate dopamine levels, as expressed as a percentage of each pre-drug baseline dopamine values (time −60, time −30 and time 0) ($N = 6–7$). The arrows indicate drug injection times (I and II). Analysis of %net AUC (area under the curve) demonstrated that VPA (B) (250, 500 but not 50 mg/kg, s.c.) and CBZ (D) (6, 12.5 but not 3 mg/kg, s.c.) dose-dependently increased extracellular dopamine levels in the mPFC (open circles) but had no effect in the nucleus accumbens (NAC) (closed circles), compared to the VEH ($N = 5–7$). Each data point represents the group mean ± S.E.M. of the %net AUC of seven samples of dialysate dopamine levels during 210 min following drug injections ($N = 5–7$). Asterisks (*) indicate significant differences from the VEH (DOSE 0) ($p < 0.01$). The net AUC (area under the curve) was calculated from the absolute net increase for a 210-min period (seven samples) after subtracting each pre-drug baseline value. The %net AUC is the net AUC value expressed as a percentage of each baseline AUC value.

These results indicate that valproic acid and carbamazepine, like clozapine, increase extracellular dopamine levels in the medial prefrontal cortex, and that the effects are most likely mediated by activation of 5-HT_{1A} receptors. However, there is no evidence for appreciable affinity of valproic acid and carbamazepine for 5-HT_{1A} receptors or other monoamine receptor subtypes, suggesting an indirect effect to stimulate 5-HT_{1A} receptors. Low dose (25 mg/kg) and high dose carbamazepine (100 mg/kg) have been reported to increase and decrease extracellular levels of dopamine and 5-HT in the hippocampus, respectively (Okada et al., 1997, 1998). Similarly, valproic acid (25 mg/kg) has been reported to increase extracellular levels of dopamine and 5-HT in the hippocampus (Kaneko et al., 1994). Thus, increased release of 5-HT could stimulate 5-HT_{1A} receptors, leading to an increase in extracellular dopamine levels in the medial prefrontal cortex because 5-HT_{1A} receptor activation by the 5-HT_{1A} receptor agonist 8-hydroxy-di-propyl-aminotetralin (8-OH-DPAT) has been reported to increase dopamine release in the medial prefrontal cortex (Ichikawa and Meltzer, submitted). WAY100635 has been reported to attenuate clozapine-induced dopamine release in the medial prefrontal cortex (Rollema et al., 1997; Ichikawa and Meltzer, unpublished data). Overall, it is proposed that 5-HT_{1A} receptor activation and/or resultant preferential increase in extracellular dopamine levels in the medial prefrontal cortex may contribute, at least in part, to the mood stabilizing effect of valproic acid, carbamazepine and clozapine. Thus, it is also of interest to propose that other 5-HT_{1A} receptor agonists, e.g., buspirone, which is clinically available, also increases dopamine release in the medial prefrontal cortex (Tanda et al., 1994) and might have mood stabilizing effects.

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