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Letter to the Editor

Valproic Acid Induces Manifestations of Simultaneous Dopamine Enhancement and Reduction in Schizophrenia

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Sir

Our article discussing valproic acid (VPA) augmentation of atypical antipsychotics in schizophrenia (Casey *et al*, 2003) re-stated our position that pharmacological doses of VPA affect GABA, and subsequently dopamine (Wassef *et al*, 1999, 2003). Dr Winterer's letter (Winterer, 2003) disagreed. Herein, we present two cases that support that VPA works through dopaminergic mechanisms.

Two African-American female in-patients with paranoid schizophrenia aged 44 and 21 had been receiving, without adverse drug reactions (ADRs), haloperidol 15 mg, benztropine 4 mg, and VPA (1750 and 1500 mg/day—VPA concentrations = 111 and 98 μg/ml). Both discontinued VPA but continued haloperidol and benztropine unaltered. A rater unaware of the patients' medicines rated the patients on the Positive and Negative Symptoms Scale (PANSS).

At 3 days post VPA discontinuation, the first patient had 'heavy tongue' and slurred speech. Additional benztropine partially ameliorated the slurred speech, only to re-emerge 2 days later, along with neck spasticity and pain. Auditory hallucinations and paranoid delusions re-emerged. PANSS score deteriorated from 62 to 84. She reduced haloperidol to 5 mg/day. Extrapyramidal symptoms resolved but psychosis deteriorated further. VPA was reinstated at 1750 mg/day (VPA serum concentration = 118 μg/ml), increasing her cooperation. Gradual haloperidol titration to 15 mg/day and benztropine reduction to 4 mg/day over the following 11 days produced no extrapyramidal symptoms and improved PANSS to 63.

VPA discontinuation in the second patient produced marked galactorrhea, forcing her to change shirts several times a day. Additionally, PANSS deteriorated from 101 to 114. Upon resuming VPA at 1000 mg/day (VPA concentration = 113 μg/ml), PANSS score improved to 74 after 10 days. Galactorrhea declined upon reinstating VPA and ceased by day 14.

DISCUSSION

Withdrawal and reinitiation of pharmacologic VPA doses produced reversible *concomitant* classic manifestations of dopamine enhancement and reduction in different brain areas. A differential GABA effect occurred in cortical and subcortical dopamine (reviewed by Wassef *et al*, 2003). GABA modulation of dopamine depends on GABAergic stimulation intensity and pre-existing dopaminergic activity. VPA withdrawal eliminated the facilitatory GABA effect on dopamine in the quiescent nigrostriatal circuits and tuberoinfundibular-pituitary axis. It also *increased* dopamine release in the highly activated mesolimbic system in schizophrenia, exacerbating psychosis. Thus, GABA acted as a physiologic dopamine regulator, a thermostat of sorts. The cases suggest that GABA may play a more central role in dopamine regulation and schizophrenia. We thank Dr Winterer for his intriguing remarks.

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