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Letter to the Editor

Valproate and GABAergic System Effects

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Sir

During the past few years, treatment of schizophrenic patients with valproate has gained considerable interest and the first controlled clinical studies are currently being conducted. The discussion on the mechanism by which valproate exerts its therapeutic effect mostly centers on early findings that valproate elevates GABA levels in the brain. However, the opinion that GABAergic effects play an important role might be premature since basic research suggests otherwise. Rather, it appears more likely that different molecular mechanisms mediate the therapeutic effect of valproate in schizophrenic patients.

Valproate is increasingly considered a valuable off-label, add-on drug for the treatment of schizophrenic patients (Citrome *et al*, 2000; Wassef *et al*, 2000). The therapeutic potential of valproate was particularly well demonstrated in a recent double-blind, randomized multicenter study (Casey *et al*, 2003). Essentially following the elaborations of Wassef *et al* (1999) and comparable views on the effect of valproate in bipolar disorders (Emrich *et al*, 1980; Swann *et al*, 1999), the authors suggested that the beneficial effect of valproate could be mediated through GABAergic mechanisms. In particular, Casey *et al* pointed out that valproate may enhance GABAergic transmission across synapses via inhibition of dopaminergic activity in the mesolimbic system and stimulation of dopaminergic activity in the mesoprefrontocortical tract. In fact, this notion is intriguing when taking into account the growing body of literature on the role of GABA in the pathophysiology of schizophrenia (Lewis, 2000; Benes and Beretta, 2001).

The idea that the effect of valproate in schizophrenic patients might be the result of GABAergic mechanisms is based on early observations that valproate increases GABA brain levels (Goden *et al*, 1969; Sawaya *et al*, 1975). However, the inference that was drawn from these investigations, that is, that valproate in therapeutic doses exerts physiological effects, is currently not convincing as we have previously outlined in a review on the effects of valproate in schizophrenia spectrum disorders (Winterer and Herrmann, 2000). For instance, Preisendörfer *et al* (1987) reported an increase of GABA inhibitory potentials in CA3 pyramidal and dentate granule neurons in guinea-pig hippocampal slices only at supratherapeutic doses (>5 mM), whereas valproate at therapeutic doses (2 mM) was without any effect on the inhibitory potentials in CA1 cells of rat hippocampus (Perreault *et al*, 1989). Moreover, it was reported that valproate suppresses the frequency of spontaneous neuronal discharges in the presence of blockade of GABAergic inhibition with biculline (Albus and Williamson, 1998). Also, it appears as if a GABA increase in the brain is only observed at supratherapuetic doses (Sawaya *et al*, 1975; Löscher, 1981; Ko *et al*, 1985). Accordingly, it seems currently not very likely that GABAergic transmission is involved in the psychotropic action of valproate, which may also explain the low sedative effect of valproate in the therapeutic range. Rather, different molecular mechanisms of valproate might be more promising avenues that lead us to an understanding of its action in schizophrenia illness. Its involvement in serotonergic and glutamatergic transmission, energy metabolism, and neuronal membrane lipid synthesis appears to be of particular interest (for a review see Winterer and Herrmann, 2000).

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REFERENCES

Albus H, Williamson R (1998). Electrophysiologic analysis of the actions of valproate on pyramidal neurons in the rat hippocampal slice. *Epilepsia* **39**: 124–139.

Benes FM, Beretta S (2001). GABAergic interneurons: implications for understanding schizophrenia and bipolar disorder. *Neuropsychopharmacology* **25**: 1–27.

Casey DE, Daniel DG, Wassef AA, Tracy AA, Wozniak P, Sommerville KW (2003). Effect of divalproex combined with olanzepine or risperidone in patients with an acute exacerbation of schizophrenia. *Neuropsychopharmacology* **28**: 182–192.

Citrome L, Levine J, Allingham B (2000). Changes in use of valproate and other mood stabilizers for patients with schizophrenia from 1994 to 1998. *Psychiatr Serv* **51**: 634–638.

Emrich HM, von Zerssen D, Kissling W, Möller HJ, Windorfer A (1980). Effect of sodium valproate on mania. The GABA-

hypothesis of affective disorders. *Arch Psychiatr Nerven* **229**: 1–16.

Goden Y, Heiner L, Mark J, Mandel P (1969). Effects of di-*n*-propylacetate, an anticonvulsant compound, on GABA metabolism. *J Neurochem* **16**: 69–73.

Ko GN, Korpi ER, Freed WJ, Zalcman SJ, Bigelow LB (1985). Effects of valproic acid on behavior and plasma concentration in chronic schizophrenic patients. *Biol Psychiatry* **20**: 209–215.

Lewis DA (2000). GABAergic local circuit neurons and prefrontal cortical dysfunction in schizophrenia. *Brain Res Brain Res Rev* **31**: 270–276.

Löscher W (1981). Effect of inhibitors of GABA aminotransferase on the metabolism of GABA in brain tissue and synaptosomal fractions. *J Neurochem Res* **36**: 1521–1527.

Perreault P, Tancredi V, Avoli M (1989). Failure of the antiepileptic drug valproic acid to modify synaptic and non-synaptic responses of CA1 hippocampal pyramidal cells maintained '*in vitro*'. *Epilepsy Res* **3**: 227–231.

Preisendörfer U, Zeise ML, Klee MR (1987). Valproate enhances inhibitory postsynaptic potentials in hippocampal neurons *in vitro*. *Brain Res* **435**: 213–219.

Sawaya MCB, Horton RW, Meldrun BS (1975). Effects of anticonvulsant drugs on the cerebral enzymes metabolizing GABA. *Epilepsia* **16**: 649–655.

Swann AC, Petty F, Bowden CL, Dilsaver SC, Calabrese JR, Morris D (1999). Mania: gender, transmitter function, and response to treatment. *Psychiatr Res* **88**: 55–61.

Wassef AA, Dott SG, Harris A, Brown A, O'Boyle M, Meyer III WJ (1999). Critical review of GABAergic drugs on the treatment of schizophrenia. *J Clin Psychopharmacol* **19**: 222–232.

Wassef AA, Dott SG, Harris A, Brown A, O'Boyle M, Meyer III WJ (2000). Randomized, placebo-controlled pilot study of divalproex sodium in the treatment of acute exacerbations of chronic schizophrenia. *J Clin Psychopharmacol* **20**: 357–361.

Winterer G, Herrmann WM (2000). Valproate and the symptomatic treatment of schizophrenia spectrum patients. *Pharmacopsychiatry* **33**: 182–188.