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 supratherapeutic 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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