Neuropsychopharmacology (2004) 29, 1218–1220

www.neuropsychopharmacology.org

Reply to Lopez *et al*

Reply: Valproate Treatment in Schizophrenia: Interaction of GABA with Dopamine?

Georg Winterer*[,1], Ulrich Schmitt[1] and Lutz G Schmidt[1]

[1]*Department of Psychiatry, Johannes Gutenberg-University Hospital, Mainz, Germany*

Neuropsychopharmacology (2004) **29,** 1218–1220. doi:10.1038/sj.npp.1300462

Sir

Presenting two clinical cases of schizophrenic patients, Cassey *et al* seek to back up their previously presented argument that the therapeutic action of valproic acid (VPA) could result from a modulation of dopamine (DA) signaling via GABAergic mechanisms (Casey *et al*, 2003; Wassef *et al*, 2003). The authors now describe that they obtained evidence from treating two patients concomitantly with VPA and neuroleptic drugs that VPA withdrawal is dampening postsynaptic DA signaling in the nigrostriatal circuit and tuberoinfundibular–pituitary axis (ie extrapyramidal symptoms and galactorrhea emerged) while increasing DA transmission in the mesolimbic system (ie psychotic symptoms increased). In the opinion of the authors, these effects of VPA would further strengthen the view that VPA impacts DA transmission via an increase of brain GABA concentrations, although in a differential way, depending on the target system. The notion, however, that VPA affects DA signaling via GABAergic mechanisms was recently put into question by us in pointing out that electrophysiological animal experiments did not find any effect of VPA administration on GABA-receptor-mediated neuronal activity at doses that are considered to be in the 'therapeutic' range (Winterer and Herrmann, 2000; Winterer, 2003).

The VPA effects on DA signaling that were suggested on the basis of the two clinical cases certainly cannot prove that GABAergic mechanisms account for the observed clinical changes that are generally related to DA transmission. VPA is a 'dirty' drug and affects many neurotransmission systems as reviewed elsewhere (Winterer and Herrmann, 2000). It is therefore conceivable that any effect of VPA on DA signaling is indirectly mediated by mechanisms that are independent of GABA. Also, it is uncertain as to whether the emergence of extrapyramidal symptoms or galactorrhea on discontinuation of VPA treatment during neuroleptic treatment can be generalized to larger patient populations. Likewise, it is currently not really clear as to whether VPA is possessing 'antipsychotic' treatment effects or whether it is rather 'antiaggressive', which may confound psychopathological assessments of psychotic symptoms (Winterer and Herrmann, 2000). In other words, it still remains to be shown whether VPA has any impact on GABAergic transmission and indirectly on DA signaling and whether these effects are the relevant mechanisms of VPA with regard to the treatment of schizophrenic patients. Nevertheless, the notion that VPA affects DA signaling via GABAergic mechanisms remains an attractive idea – simply because VPA increases GABA brain levels (Goden *et al*, 1969; Sawaya *et al*, 1975) and because VPA is effective in augmenting antipsychotic treatment of schizophrenic patients.

Under the assumption that VPA affects DA signaling through GABAergic mechanisms in schizophrenia illness, it appears to be pertinent for the illustration of the complexity of the problem to summarize briefly our current knowledge on the interaction of the two neurotransmission systems. During the past few years, it has become increasingly apparent that altered GABAergic function may critically contribute to schizophrenia pathophysiology. In particular, fast-spiking parvalbumin immunoreactive interneurons, that is, Chandelier cells, which seemingly play a central role in cortical recurrent inhibition and signal-to-noise ratio during information processing (Volk *et al*, 2002), have been implicated. For instance, several *post-mortem* studies of schizophrenic patients have consistently found decreased mRNA expression of glutamic acid decarboxylase GAD67, which is responsible for presynaptic GABA synthesis (Akbarian *et al*, 1995; Volk *et al*, 2000; Heckers *et al*, 2002) and these molecular changes do not appear to result from antipsychotic drug treatment (Lipska *et al*, 2003). Consequently, the question came up whether diminished GABAergic function interacts with impaired DA signaling in schizophrenia, since DA is considered another key player in schizophrenia illness (Kapur and Lecrubier, 2003).

In fact, there is currently emerging evidence—mainly from basic animal experiments—that an interaction

*Correspondence: Dr G Winterer, Department of Psychiatry, Johannes Gutenberg-University Hospital Mainz, Untere Zahlbacher Str. 8, Mainz 55131, Germany, Tel: +49-06131-17-2488, Fax: +49-06131-17-6690, E-mail: interer@psychiatrie.klinik.uni-mainz.de
Received 16 March 2004; accepted 18 March 2004
Online publication: 18 March 2004 at http://www.acnp.org/citations/Npp03240404125/default.pdf

between GABA and DA exists in both directions and at least on three levels, that is, (1) on the synaptic level, (2) on the level of neuronal microcircuits, and (3) on the level of neuronal macrocircuits. On the synaptic level, a crosstalk between DA D5 and GABA-A receptors resulting from direct protein–protein coupling has been recently reported (Liu *et al*, 2000). It was found that agonist-dependent protein–protein complex formation between the C-terminal tail domain of DA D5 receptors and the intracellular domain (IL2) of GABA-A receptors γ_2 subunits permits the rapid, reciprocal modulation of GABA-A $\alpha_1\beta_2\gamma_2$ and DA D5-receptor-mediated events independent of their respective classically defined signal transduction cascades. The authors proposed that this mechanism might be potentially relevant in schizophrenia pathophysiology. On the microcircuit level, another GABA–DA interaction has been described. Using whole-cell patch-clamp recordings *in vitro*, and receptor-subtype-specific agonists and antagonists, Seamans *et al* (2001) demonstrated that DA D2-receptor agonists induce an early and brief (ie phasic) decrease in GABA release probability of cortical interneurons and a reduction of the response to a GABA-A agonist, whereas DA D1-receptor agonists cause a delayed and long-lasting (ie tonic) increase of the intrinsic excitability of interneurons. This D1-receptor-mediated action of DA appears to be specific for parvalbumin immunoreactive interneurons (Gorelova *et al*, 2002) and the relevance of these DA effects on GABAergic transmission with regard to schizophrenia pathophysiology are currently a matter of discussion (Winterer and Weinberger, 2004). Most investigations on the interaction between DA and GABA, however, have been conducted on the macrocircuit level. Thus, it is known already for some considerable time that GABA is influencing the firing of the nigrostriatal, mesolimbic, and mesocortical DA tracts. For instance, an inhibitory effect on DA neuronal firing has been demonstrated by iontophoretic application of GABA and GABA antagonists into the substantia nigra (SA) and ventral tegmental area (VTA) (Wolf *et al*, 1978; Waszczak and Walters, 1979). In addition, electrical stimulation of the targets of these tracts, that is, the nucleus caudatus and nucleus accumbens, exerts a reciprocal inhibition of the SA and VTA, which is blocked by the GABA antagonist bucculline (Yoshida and Precht, 1971; Wolf *et al*, 1978). On the other hand, there are also reports in conflict with these findings. Waszczak and Walters (1979) found that systemic application of the GABA agonist muscimol produced *increased* firing in DA neurons in pars compacta of SN, whereas non-DA neurons in the adjacent pars reticulata were inhibited. Similar findings were obtained by Grace *et al* (1980) and with regard to the DA cell firing in the VTA by Waszczak ans Walters (1979) or more recently by Cruz *et al* (2004). Therefore, the conclusion drawn by Garbutt and Van Kammen (1983), that is, that the effect of GABA on DA signaling depend on the brain region assayed, the duration of stimulation, and whether DA antagonists are administered, is probably correct.

The chain of arguments of Casey *et al*, that is, that VPA affects DA signaling via GABAergic mechanisms essentially rests on the early findings of a macrocircuit interaction of GABA and DA and the notion that VPA is increasing brain GABA concentrations via synthesis, reuptake, and metabolism. On the other hand, there is our argument that VPA does not affect GABA-mediated postsynaptic signaling in the therapeutic range in animal experiments. Given our current knowledge on the multilevel complexity of GABA–DA interactions, there are several theoretical possibilities that could reconcile this apparent contradiction. First of all, there is the very fundamental argument that animal findings cannot necessarily be generalized to humans. By extension, it also conceivable that the conditions in schizophrenic patients differ substantially from healthy humans. For instance, the above-cited evidence from *post-mortem* studies that GABAergic interneurons are functionally downregulated in schizophrenia could imply that VPA helps to restore interneuron function by increasing GABA synthesis. In other words, VPA may be functionally more relevant at pathologically low GABA baseline levels, whereas comparatively little effects are seen under normal conditions. Another question is whether VPA exerts its effects primarily on GABAergic and DA transmission on the level of macrocircuits as postulated by Casey *et al*. Thus, on the level of microcircuits, DA may have a differential impact via DA D1 and D2 receptors on interneurons depending on the – pathologically changed – GABA synthesis rate in these neurons. In principle, similar thoughts may also apply to the functional coupling of DA and GABA receptors on the synaptic level.

Taken together, it is currently still difficult to say whether VPA has an effect on DA signaling via altering GABA neurotransmission. If so, it is hard to tell on what level of neuronal processing this effect actually occurs and whether this mechanism is relevant for the VPA treatment of schizophrenia. Additional research is required to clarify these important and exciting questions.

REFERENCES

Akbarian S, Kim JJ, Potkin SG, Hagman JO, Tafazzoli A, Bunney WE *et al* (1995). Gene expression for glutamic acid decarboxylase is reduced without loss of neurons in prefrontal cortex of schizophrenics. *Arch Gen Psychiatry* **52**: 258–266.

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

Cruz HG, Ivanova T, Lunn ML, Stoffel ML, Slesinger PA, Luscher C (2004). Bi-directional effects of GABA(B) receptor agonists on the mesolimbic dopamine system. *Nat Neurosci* **7**: 153–159.

Garbutt JC, Van Kammen DP (1983). The interaction between GABA and dopamine: implications for schizophrenia. *Schizophrenia Bull* **3**: 336–353.

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

Gorelova N, Seamans JK, Yang CR (2002). Mechanisms of dopamine activation of fast-spiking interneurons that exert inhibition in rat prefrontal cortex. *J Neurophysiol* **88**: 3150–3160.

Grace A, Hommer D, Bunney CB (1980). Peripheral and striatal influences on nigral dopamine cells: mediation by reticulata neurons. *Brain Res Bull* **5**(Suppl 2): 105–109.

Heckers S, Stoue D, Walsh J, Shick J, Koul P, Benes FM (2002). Differential hippocampal expression of glutamic acid decarboxylase 65 and 67 messenger RNA in hipolar disorder and schizophrenia. *Arch Gen Psychiatry* **59**: 521–529.

Kapur S, Lecrubier Y (2003). *Dopamine in the Pathophysiology and Treatment of Schizophrenia*. Martin Dunitz: London.

Lipska BK, Lerman DN, Khaing ZZ, Weickert CS, Weinberger DR (2003). Gene expression in dopamine and GABA systems in an animal model of schizophrenia: effect of antipsychotic drugs. *Eur J Neurosci* **18**: 391–402.

Liu F, Wan Q, Pristupa ZB, Yu X-M, Wang YT, Niznik HB (2000). Direct protein–protein coupling enables cross-talk between dopamine D5 and γ-aminobutyric acid A receptors. *Nature* **403**: 274–280.

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

Seamans JK, Gorelova N, Durstewitz D, Yang CR (2001). Bidirectional dopamine modulation of GABAergic inhibition in prefrontal cortical neurons. *J Neurosci* **21**: 3628–3638.

Volk DW, Austin MC, Pierri JN, Sampson AR, Lewis DA (2000). Decreased glutamic acid decarboxylase67 messenger RNA expression in a subset of prefrontal cortical gamma-aminobutyric acid neurons in subjects with schizophrenia. *Arch Gen Psychiatry* **57**: 237–245.

Volk DW, Pierri JN, Fritschy JM, Auh S, Sampson AR, Lewis DA (2002). Reciprocal alterations in pre- and postsynaptic inhibitory markers at chandelier cell inputs to pyramidal neurons in schizophrenia. *Cereb Cortex* **12**: 1063–1070.

Wassef AA, Baker J, Kochan LD (2003). GABA and schizophrenia: a review of basic science and clinical studies. *J Clin Psychopharmacol* **23**: 601–740.

Waszczak B, Walters J (1979). Effects of GABA mimetics on substantia nigra neurons. *Adv Neurol* **23**: 727–740.

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

Winterer G (2003). Valproate and GABAergic system effects. *Neuropsychopharmacology* **28**: 2050–2051.

Winterer G, Weinberger DR (2004). Molecular mechanims of disturbed connectivity and signal-to-noise ratio in schizophrenia. *Trends Neurosci*, (submitted).

Wolf P, Olpe HR, Avrith D, Haus H (1978). GABAergic inhibition of neurons in the ventral tegmental area. *Experientia* **34**: 73–74.

Yoshida M, Precht W (1971). Monosynaptic inhibition of neurons of the substantia nigra by caudato-nigral fibres. *Brain Res* **32**: 225–228.