ELSEVIER

LETTER TO THE EDITOR

Stress Invalidates Reported Effects of Sodium Valproate on Brain CRF Systems☆

In this report the authors "hypothesized" that valproate "may act upon" corticotropin-releasing factor (CRF) systems in the brain, though no direction of effect was predicted. Moreover, the data showed that the rat is an unsuitable species in which to look for such effects. The authors encountered serious toxicity and ultra-rapid clearance of valproate in the rat. Even though they used an extremely high dose of sodium valproate (875 mg/kg/day), they could not demonstrate plasma valproate concentrations within the desired range of therapeutic human plasma valproate concentrations. The necessary condition for a valid, clinically relevant study was not confirmed. Moreover, there is clear evidence that stress associated with the extreme drug dosage also invalidated the study.

The animals that received one week of treatment with 875 mg/kg/day of valproate had a mean plasma corticosterone concentration 3.6 times that of the relevant control group, accompanied by a mean plasma ACTH concentration greater than expected for the raised corticosterone value. Parsimony requires that these animals be considered stressed. Instead, the authors suggested that "valproate produces a direct effect at the level of the adrenal cortex, or perhaps increases production of an adrenocortical-stimulating hormone other than ACTH." These two suggested factors lack any basis in experimental data, and they are inherently improbable. Neuropharmacologists know that in studies of the actions of a drug on brain CRF systems, care and skill are needed to control for the confounding effects of procedural stress on those same systems.

☆Refers to PII S0893-133X(00)00243-8

From the Pacific Behavioral Research Foundation Carmel, CA.

Address correspondence to: Dr. B. Carroll, Pacific Behavioral Research Foundation, 26386 Carmel Rancho Lane, Ste. 202, P.O. Box 223040, Carmel, CA 93922-3040, Tel.: (831) 625-4212, Fax: (831) 625-5292, E-mail: bcarroll@redshift.com

Received July 26, 2001; accepted August 24, 2001.

Re: Stout SC, Owens MJ, Lindsey KP, Knight DL, and Nemeroff CB. Effects of sodium valproate on corticotropin-releasing factor systems in rat brain. Neuropsychopharmacology 24:624-631, 2001.

The plasma corticosterone values stated for the control groups (Table 4 in the article) were about 1 μg/dL (10 ng/mL). Considering the experimental procedure, this low value suggests that the authors sampled at the circadian nadir of plasma corticosterone (they did not state the time of day at which sampling occurred). If all the data in Table 4 in the article are represented to be circadian nadir values, then the plasma corticosterone level of 6.49 μg/dL (or 64.9 ng/mL as it appears in the Table) in the rats that received one week of treatment with 875 mg/kg/day of valproate would be completely consistent with chronic stress (López et al. 1998).

There is reason to think, however, that the authors stated the units of plasma corticosterone concentrations incorrectly as ng/mL instead of μg/dL, and consequently that the treated animals manifested extreme stress. It is most unlikely that the plasma corticosterone concentrations of the control animals were only 1-2 μg/dL (∼10–20 ng/mL as shown in Table 4 in the article), considering that they received injections 20–90 min before sacrifice. The true plasma corticosterone values of the control animals more likely were 10–20 μg/dL, not 10–20 ng/mL. Support for this conclusion that the authors stated incorrect units comes from another current report of this group (Musselman et al. 2001). In this second report, confusion about units of measurement is explicit: the value 5 ng/mL is stated as a reference concentration of plasma cortisol whereas the correct value is 5 μg/dL. In all other laboratories it is understood that 5 ng/mL corresponds to only 0.5 μg/dL.

Thus, the true mean plasma corticosterone concentration of the rats that received one week of treatment with 875 mg/kg/day of valproate most likely was 64.9 μg/dL rather than 64.9 ng/mL. Psychoendocrinologists recognize that a plasma corticosterone concentration of 64.9 μg/dL signifies extreme activation of the hypothalamo-pituitary-adrenal cortical axis. The authors were silent on whether humans treated with valproate also should be monitored for drug-related hypercortisolemia, which would be a reasonable inference from

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/02/$–see front matter
PII S0893-133X(01)00382-7

their data, if indeed the data are represented to be experimentally valid and clinically relevant.

In short, interpretation of any changes described by the authors in rat brain CRF systems following one week of treatment with 875 mg/kg/day of valproate is confounded by the artifacts of stress and drug toxicity. The authors' conclusions and their speculations about the relevance of their findings for mood disorders or for the clinical use of valproate have no valid basis.

Bernard J. Carroll, M.B., B.S., Ph.D., F.R.C. Psych.
Pacific Behavioral Research Foundation
Carmel, CA

REFERENCES

López JF, Chalmers DT, Little KY, Watson SJ (1998): Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptors in rat and human hippocampus: implications for the neurobiology of depression. Biological Psychiatry 43:547–573

Musselman DL, Miller AH, Porter MR, Manatunga A, Gao F, Penna S, Pearce BD, Landry J, Glover S, McDaniel JS, Nemeroff CB (2001): Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings. American Journal of Psychiatry 158:1252–1257