ELSEVIER

RESPONSE

Response☆

Dr. Carroll has assumed that the readership of this journal is considerably less sophisticated than we do. Although not explicitly stated in our introduction, it is self-evident that we hypothesized that valproate may produce net inhibition of CRFergic neurotransmission, via effects on gene expression, peptide synthesis and/or CRF receptor regulation. Indeed, we found that 1-week valproate treatment in rats produced modest decreases in CRF mRNA expression in the paraventricular nucleus and central nucleus of the amygdala, larger decreases in CRF peptide concentration in the median eminence and raphe nucleus, and a very small increase in the frontal cortex. There were no effects of chronic drug treatment on the bed nucleus of the stria terminalis gene expression, or on peptide concentration in three other brain regions. Acute (90 min) treatment with valproate did not alter CRF peptide concentration in any region examined.

In conducting these studies, we encountered difficulties with non-linear pharmacokinetics and toxicity at high valproate concentrations, which we felt were findings sufficiently important to alert other investigators in the field. We agree with Dr. Carroll that the rat may not be an ideal species for pharmacologic studies of valproate. Nevertheless, the same problems could potentially occur in other species and our studies represent a detailed attempt at utilizing a clinically relevant dosing paradigm to study valproate pharmacology in laboratory animals. Furthermore, our study was certainly not "invalidated" by these difficulties. First, the fact that mean serum valproate was 38 μg/ml after chronic treatment rather than the therapeutic range in humans of 50–100 μg/ml suggests only that larger effects or effects in other brain regions potentially escaped detection due to suboptimal dosing. Moreover, as Dr. Carroll is surely aware, this therapeutic plasma range has hardly been established for the treatment of bipolar disorder. Second, there was no drug toxicity observed at the dose studied; the animals which exhibited fatal toxicity in our pilot study had much higher serum valproate concentrations (approximately 600 μg/ml). Third, although the rats treated for one week with valproate did exhibit elevated corticosterone concentrations, ACTH concentrations were not significantly different between the two groups and PVN CRF mRNA expression was decreased, not elevated in the valproate group. The latter two measures are not consistent with a chronic stress effect in the valproate-treated rats. We do not have a straightforward explanation for the discrepancy between ACTH and corticosterone measurements, though such a mismatch has been reported in a variety of pathological situations. We did include in our discussion the possibility of a direct adrenal effect of valproate, with the understanding that this is one putative mechanism that needs to be explored. Indeed, all animals were killed in the morning during nadir HPA axis activity; because of space considerations, we neglected to state this in the Methods section.

Dr. Carroll is mistaken in suggesting that we expressed corticosterone concentrations incorrectly. All corticosterone values are expressed in ng/ml rather than the archaic and unintuitive 'μg/dL' or μg%. Dr. Carroll doubts the control animals in the acute valproate study exhibited corticosterone concentrations of 10–20 ng/ml, 90 min (not 20–90 min as mistakenly suggested by Dr. Carroll) following s.c. saline injection. In our experience, this is a very minor stressor in handled rats. Although we do not know the time course of the HPA axis response to s.c. saline injection, it is revealing that rats exposed to a more severe stress, 5-min ether exposure, were shown to have nearly basal corticosterone concentrations, well below 100–200 ng/ml, after 60

☆Refers to PII S0893-133X(00)00243-8

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Received September 25, 2001; accepted September 26, 2001.

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

0893-133X/02/$–see front matter
PII S0893-133X(01)00381-5

min (Kovács and Sawchenko 1996). We are unsure of Dr. Carroll's underlying thoughts for 'support for his conclusion' when he references a human study completely unrelated to these studies as support for our making a mistake in the units of concentration for corticosterone.

We recognize that the potential relevance of our findings "for mood disorders or for the clinical use of valproate" remains to be established. However, the validity of the study cannot be dismissed on the basis of stress, drug toxicity, or any error in the corticosterone assay.

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