Reviewer's report

Title: Significance of MDR1 and Multiple Drug Resistance in Refractory Human Epileptic Brain

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Reviewer: Michael Rogawski

Reviewer's report:

This study provides various new results on MDR1 in human cortical tissue resected at the time of epilepsy surgery. In addition, the report raises a very interesting hypothesis that MDR1 may enhance the viability of neurons or glia, at least in regard to toxicity from xenobiotics such as phenytoin. The study is of considerable potential interest given the possibility that MDR1 is responsible for antiepileptic drug pharmacoresistance. However, the report does not clearly state the purpose of the experiments and the conclusions are vague. In particular, it is not apparent whether the study intends to demonstrate that MDR1 is overexpressed in human epileptic tissue or whether the authors believe that this has already been well demonstrated in previous studies, in which case the main purpose of the study would be to demonstrate alterations in glial or neuronal vulnerability resulting from the overexpression. In fact, if the authors intend to conclude from their immunocytochemistry experiments that MDR1 is overexpressed in epileptic tissue, the results presented are not adequate since no control data are presented. While it is clear that a high proportion of glia and neurons express MDR1 (Fig. 1), one wonders whether glia and neurons from non-epileptic human brain would similarly show high MDR1 expression as detected using the present methods. There are also concerns with adequate controls in other parts of paper. While the functional data on astrocyte uptake is presented with a control, it is not clear that the cryopreserved astrocytes which were used are appropriate. Perhaps these cells have lost MDR1 activity as a result of processing and storage. A more convincing control would have been astrocytes prepared in an identical fashion to those obtained from the epilepsy patients, but from non-epileptic subjects undergoing other types of brain surgeries (e.g., resection of brain tumors). Finally, the data on phenytoin toxicity, while interesting, are also not presented with a control. In the end, we are left with an interesting set of results from which it is difficult to draw any specific conclusions. The authors could add the appropriate control data and demonstrate significant differences (when analyzed by a blind observer to avoid bias). In this case, the article would potentially be of exceptional interest warranting publication in a high visibility journal. Alternatively, the authors may simply wish to present a study characterizing MDR1 expression, glial MDR1 activity, and the cytoprotective role of MDR1 in cells from human brain without concluding that their results show anything special about epileptic tissue. These results characterizing MDR1 in human brain tissue would potentially be appropriate for publication in a subject-specific journal.

Which journal?: Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:
I am a personal friend of one of the authors (AV); I have neither met any of the other authors nor do I know them from the literature. Otherwise, I do not have any competing interests.

Please note that I am raising a question to the editors as to whether the stated author's contributions of AV is appropriate for authorship ("provided drugs used in pharmacological experiments"). Perhaps AV actually made a larger contribution and this ought to be acknowledged.