LETTERS

Behavioral and neuroendocrine assays for studying epilepsy-associated depression

To the Editors:

In their review, Brooks-Kayal et al. (2013) provided guidelines for using certain assays to study epilepsy-associated depression in the laboratory. These guidelines should be further refined so as to improve construct validity of models in question, throughput of preclinical trials, and the reliability of the findings.

1 The authors propose the Porsolt test to study the inability of animals to cope with a stressful situation. The Porsolt test, which has been proposed for the use in inherently normal animals, consists of two steps. Step 1 is a 15-min swimming session purposed to induce depression; step 2 is the test proper, where animal's immobility is measured during the 5-min swimming trial. Models of major depression that involve animals with an inherently depressive phenotype, do not utilize the Porsolt test. Indeed, if the animal is already depressed, the first (i.e., depressogenic) swimming session is no longer required. Instead, a single 5-min trial is used, whereby depressed animals exhibit-prolonged immobility vis-à-vis normal counterparts (Overstreet & Wegener, 2013). Epileptic rats show consistently increased immobility in the single-session test, that is they are depressed by the virtue of having epilepsy (Mazarati et al., 2008). Hence, the Porsolt test becomes unnecessary. The single-session test can be successfully applied for screening of effective therapies (Pineda et al., 2012). Not only would replacement of the Porsolt test with the single-session test reduce time, labor, and animals stress, but it may also improve the search for effective medications. Indeed, since psychostimulants reduce immobility in the Porsolt test, the specificity of the latter for selecting antidepressant drugs has been questioned (Petit-Demouliere et al., 2005).

2 Given the strong subjective component associated with the interpretation of behavioral tests, having an additional, preferably objective, assay would be useful. The combined dexamethasone/corticotropin-releasing hormone (DEX/CRH) test can reveal the dysregulation of the stress hormone axis in depression (Watson et al., 2006). Indeed, in animals with chronic epilepsy, DEX/CRH test is consistently positive (Mazarati et al., 2009). The test is objective, inexpensive, and quick. In addition, the positive DEX/CRH test may serve as an independent disease biomarker, thereby addressing another important issue discussed by Brooks-Kayal et al. (2013).

DISCLOSURE

The author declares no conflicts of interest. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Authors response to letter by A. Mazarati

To the Editors:

We have read and appreciate Dr. Mazarati's comments related to our recent review on issues related to preclinical studies of epilepsy comorbidities (Brooks-Kayal et al. Issues related to symptomatic and disease modifying treatments affecting cognitive and neuropsychiatric comorbidities of epilepsy. *Epilepsia* 2013;54(Suppl. 4):44–60). Dr. Mazarati points out that the tests for depressive-like behavior are not as well validated as those for anxiety-like behavior, particularly in the context of epilepsy models.

We agree with his comments that if you are looking for a true depression phenotype, there may not be a need to elicit depressive-like behavior with a forced swim session before the forced swim test. However, we would like to note that this approach is useful because it provides an opportunity to collect data from two forced swim sessions, which can be valuable. It may give greater insight into the behavioral phenotype. It would then be important for investigator(s) to carefully consider all of the data and report whether there were effects that could be interpreted as a basal change in behavior or a difference (from controls) only during the task. Our overall impression is that several types of analysis for any given behavioral test can often be very helpful and provide in depth information that can be analyzed and reported. Another example of such an analysis would be analyzing and comparing both the first 3 min as well as the first 5 min in Object Recognition and Object Placement testing.

We further agree that Dr. Mazarati's suggestion to include the dexamethasone/corticotropin-releasing hormone test (DEX/CRH) test is valuable and appropriate. Because all behavioral tests have their limitations, utilizing more than one test to demonstrate a consistent phenotype is the optimal approach.

Disclosure

Dr. Berg has received speaker honoraria and travel support from BIAL and MUSC, and serves on advisory boards for CURE and Eisai. Dr. Galanopoulou has received speaker honorarium from Novartis. Dr. Kanner has served as member of a data safety board for Vertex. Dr. O'Brien has received research grant support from the NHMRC (Australia), the Royal Melbourne Hospital Neuroscience Foundation, Sanofi-Aventis, UCB, SciGen, GlaxoSmithKline, Novartis, and Janssen-Cilag, and speaker honorarium from Sanofi-Aventis, UCB, SciGen, GlaxoSmithKline, and Janssen-Cilag. None of the other authors have any conflicts of interest to report related to this manuscript. The authors confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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ANNOUNCEMENTS

2013 American Epilepsy Society Annual Meeting

6–10 December 2013 in Washington, DC, U.S.A. http://www.aesnet.org/meetings-and-events/annual-meeting

2014 Congresses

4th Course on Epilepsy Surgery (EPODES)

13–17 January, 2014 Brno, Czech Republic. Registration deadline 1 November, 2013. http://www.ta-service.cz/epodes2014/

5th SEEG Course on Seizures of the Motor System

4–8 February, 2014; Venice, Italy. More information from seeg@ant-congres.com or +33 (0) 4 67 10 92 23