EPILEPSY CURRENTS

Current Literature
In Basic Science

Cognitive and Behavioral Comorbidities in Epilepsy: The Treacherous Nature of Animal Models

Different Emotional Disturbances in Two Experimental Models of Temporal Lobe Epilepsy in Rats.

Inostroza M, Cid E, Menendez de la Prida L, Sandi C. *PLoS ONE* 2012;7:e38959.

Affective symptoms such as anxiety and depression are frequently observed in patients with epilepsy. The mechanisms of comorbidity of epilepsy and affective disorders, however, remain unclear. Diverse models are traditionally used in epilepsy research, including the status epilepticus (SE) model in rats, which are aimed at generating chronic epileptic animals; however, the implications of different SE models and rat strains in emotional behaviors has not been reported. To address this issue, we examined the emotional sequelae of two SE models of temporal lobe epilepsy (TLE)—the lithium-pilocarpine (LIP) model and the kainic acid (KA) model—in two different rat strains (Wistar and Sprague-Dawley), which differ significantly in the pattern and extent of TLE-associated brain lesions. We found differences between LIP- and KA-treated animals in tests for depression-like and anxiety-like behaviors, as well as differences in plasma corticosterone levels. Whereas only LIP-treated rats displayed increased motivation to consume saccharin, both SE models led to reduced motivation for social contact, with LIP-treated animals being particularly affected. Evaluation of behavior in the open field test indicated very low levels of anxiety in LIP-treated rats and a mild decrease in KA-treated rats compared to controls. After exposure to a battery of behavioral tests, plasma corticosterone levels were increased only in LIP-treated animals. This hyperactivity in the hypothalamus-pituitary-adrenocortical (HPA) axis was highly correlated with performance in the open field test and the social interaction test, suggesting that comorbidity of epilepsy and emotional behaviors might also be related to other factors such as HPA axis function. Our results indicate that altered emotional behaviors are not inherent to the epileptic condition in experimental TLE; instead, they likely reflect alterations in anxiety levels related to model-dependent dysregulation of the HPA axis.

Commentary

In their quest to understand and treat epilepsy and its comorbidities, researchers often have to rely on animal models. However, because the origin of a number of syndromes is poorly understood—as is the case of temporal lobe epilepsy (TLE)—choosing a model that encompasses the most relevant aspects of the disease can be challenging.

For decades, the pilocarpine (PILO) (1) and kainic acid (KA) (2) models of prolonged status epilepticus have been widely used to investigate temporal lobe epilepsy (TLE). Apart from the ease of induction, this success comes from the replication of several characteristics of the patient's condition, such as the progression of the syndrome (initial insult, latent period followed by chronic epilepsy), pathological findings (hippocampal sclerosis, cell loss, and sprouting), or semiology (seizure types, progression, and interictal abnormalities). Because of the similarities, these models were also used to investigate the mechanisms and properties of behavioral and cognitive comorbidities in TLE. However, the severity and range of impairments vary greatly among laboratories, depending on the convulsant used, rat strain (3), age (4), or the induction protocol. In parallel, the anatomical findings in these studies also vary extensively, suggesting that both these aspects may be linked. Such variability also led to debate regarding which of these models is the most appropriate.

Inostroza and colleagues designed a series of experiments (5) comparing cognitive and behavioral performance as well as anatomical findings between PILO and KA models either in Wistar or Sprague Dawley rat strains. In 2011 (5), they demonstrated that performance in traditional spatial cognition (Morris water maze) and anxiety (elevated plus-maze) tasks were strongly correlated with the extent of brain damage in PILO and KA models in both strains. Hippocampal injury was less severe in their KA rats, and lesions in PILO animals also affected neighboring structures such as perirhinal cortex and amygdala, likely explaining their poor performance in a cued version of the water maze and increased anxiety in the elevated plus-maze. Finally, Wistar rats were remarkably preserved after KA treatment, both in terms of brain lesions and cognitive performance. Importantly, during the chronic epileptic phase, there was no difference in the severity and frequency of seizures between groups. Therefore, in their hands, KA treated rats that developed spontaneous seizures

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and thereby constituted a valid model of TLE showed mild to no spatial performance impairment.

Recently, the same group used identical protocols (PILO vs. KA; Wistar vs. Sprague Dawley) to investigate emotional and social impairment, also common in TLE. Inostroza and colleagues performed three tests: saccharin consumption (an anhedonia assay of depression), open field (an anxiety test), and social interaction tests. They correlated their findings with pre- and post-behavioral plasma levels of corticosterone that had been previously correlated with depression state in animal models of TLE (6). Overall, their results were similar to what was found in the cognitive comorbidities study: PILO rats showed the most significant alterations in all tests while KA animals were less affected. In addition, performance scores were strongly correlated with post-behavioral cortisol levels, confirming previous reports that alterations of the HPA axis were strong predictors of emotional comorbidities in TLE.

Nevertheless, the Inostroza papers show that for the same protocol induction types, PILO does extensive damage to the brain and causes more severe cognitive and behavioral impairments compared to KA. Therefore, if KA treatment can induce chronic epilepsy with minimal lesion, some may consider this model as the "good" one and reject PILO as a dirty model. Before throwing decades of research into oblivion, it is important to consider that the use of a model depends on what aspect one wants to reproduce. In patients, TLE is often associated with brain lesions, some of them being extensive. Hippocampal sclerosis can be visible or absent, and lesions can be restricted to the hippocampus or involve other structures such as the amygdala or adjacent cortices. Similarly, the extent of cognitive or behavioral impairments varies drastically from patient to patient. Therefore, PILO may be a good model for TLE with extensive lesion and cognitive impairment, while KA would be more relevant to milder epileptic syndromes. Further, based on the results from this series of papers, investigators interested in cognitive–behavioral comorbidities should probably avoid KA treatment in Wistar rats since they show little to no impairment. However, it is also possible that these rats do have subtle impairments that were not investigated here. Therefore, further investigations in this model may be beneficial to understand the relative contribution of seizures in these comorbidities.

A surprising feature of this last paper is that anxiety and depression results in PILO rats are opposite to what would be expected from anxious and depressed rats. In the open field test, anxious rats tended to avoid visiting the center of the apparatus, being more exposed. Here, PILO rats explored this region more, as though they were less anxious. Similarly, in the 2011 paper and other reports (7), PILO rats spent more time in the open arm of the elevated plus-maze instead of spending most of their time in the closed arms, as an anxious rat would do (8). The saccharin consumption test is often used as a test of anhedonia, the inability to experience pleasure from normally enjoyable stimuli such as sweet drinking water. As for rat models of depression, PILO rats were previously reported to fail to consume more saccharin solution (9). In the current paper, however, Inostroza showed the opposite behavior: The rats consumed more saccharin, as though they were "hedonic" instead of anhedonic. Again, this discrepancy between reports points to the large variability in these models, not only among treatments and strains but also among laboratories and induction protocols. For instance, unlike the present report, significant water maze impairments have been documented in an intrahippocampal KA model, expected to be milder than the IP version (10). In general, these results warrant more investigation of the mechanisms responsible for treatment and strain susceptibility to anatomical, inflammatory, and behavioral alterations.

Overall, these results show that KA and PILO rats did not differ in terms of severity and frequency of seizures but that cognitive and emotional outcomes instead strongly correlated with the extent of anatomical lesions and cortisol levels. Therefore, the findings support the notion that the epileptic condition (i.e., the fact of having seizures) is not the only contributor to cognitive and emotional outcomes and that treatments focusing only on seizures may not be sufficient to improve these comorbidities. Strategies aimed at preserving and restoring the integrity of the underlying substrate may also critically improve patients' quality of life.

by Pierre-Pascal Lenck-Santini, PhD

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