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Hebbian and homeostatic synaptic plasticity of AMPA receptors in epileptogenesis

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AMPA receptors' synaptic plasticity is involved in epileptogenesis. In this issue, Eiro et al.[1] demonstrate that Hebbian plasticity is responsible for increased AMPAR in focal seizures, while homeostatic plasticity induces the reduction of AMPAR in generalized onset seizures.

The healthy brain is a dynamic system based on the intrinsic capability of the synapses to adapt their strength in response to experience. Hebbian synaptic plasticity represents the most widely studied form of long-lasting activity-dependent changes in synaptic strength based on positive feedback mechanisms.[2] Long-term potentiation (LTP) and long-term depression (LTD) are examples of the Hebbian form of synaptic plasticity and use positive feedback mechanisms to reinforce the more active synapses or weaken those that are less active. Potentiated synapses are more excitable and may drive the system to a state prone to hyperexcitability if not kept under control. To prevent the destabilizing effect of the Hebbian plasticity, neurons are able to sense their own excitability and trigger homeostatic synaptic plasticity, which uses negative feedback mechanisms to maintain the overall neuronal output as close as possible to a prefixed set point, restraining neuronal networks from becoming either silent or hyper-excitable.[3] Homeostatic compensations are often presented as relatively slow processes developing in response to prolonged perturbations of the neuronal activity. Hebbian and homeostatic synaptic mechanisms could interfere with each other in the same subset of synapses. While several studies pointed out the role of homeostatic plasticity in several neurological disorders,[4] including epilepsy,[5] the role that Hebbian plasticity may have in epileptogenesis is less investigated.[6]

Epilepsy is a neurological disorder characterized by the occurrence of unprovoked seizures defined as transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.[7] Different molecular and cellular mechanisms leading to a hyper-excitable neuronal network have been demonstrated. Considering the synaptic plasticity as a possible mechanism of epileptogenesis, it has been suggested that epilepsy can be considered a failure of homeostatic plasticity that is not able to counteract aberrant network activity. One possible explanation for this failure, plausible for acquired epilepsies, is that a gradual weakening of the homeostatic response may be due to the neuronal degeneration occurring during epileptogenesis. In genetic epilepsies, the homeostatic processes occurring during epileptogenesis (e.g., the compensation of a mutated gene function) may not be able to constantly compensate for the chronic loss of proteins fundamental to maintain the brain within physiological boundaries.[8]

Chemical synapses are connections between two neurons, and in excitatory synapses, the communication between pre- and post-synaptic entities is mostly mediated by glutamate interacting with receptors embedded in the post-synaptic membrane. AMPA receptors (AMPARs) are transmembrane proteins sustaining a cationic conductance mediating fast excitatory chemical synapses. AMPARs are involved in epileptogenesis: investigations involving human epileptic specimens reveal a general increment in the mRNA and protein levels of AMPARs. Controversial results were reported about several AMPAR subtypes in epileptic human and animal models.[9] The limitations of many of these studies relies, however, on the fact that most often (1) only mRNA or protein levels are investigated, (2) results are obtained from *in vitro* or *ex vivo* studies where connectivity is not preserved, and (3) control groups include non-epileptic autopsy cases (e.g., tumors, vascular abnormality).

Positron emission tomography (PET) is a technique that can be performed on living subjects. In individuals with epilepsy, PET allows a precise presurgical study of the epileptogenic foci; however, PET represents a valuable tool also for the investigation of cellular mechanisms underlying epileptogenesis, allowing a reliable control group (healthy living subjects) and the preservation of the *in vivo* connectivity and its properties. Takahashi's group recently developed a PET tracer for AMPARs, [11C]K-2; it has been previously used and validated in healthy humans and in an exploratory clinical study including individuals with temporal lobe epilepsy.[10] [11C]K-2 tracer provides information about the functional AMPARs, being a valuable tool to selectively quantify AMPARs expressed on the cell membrane surface, which represent that portion of AMPARs that are functional and contribute to the synaptic transmission. In this issue, Eiro and colleagues[1] used the [11C]K-2 tracer in individuals with focal onset seizures, with focal to bilateral tonic-clonic seizures (FBTCS), and with generalized onset seizures.

Eiro et al.[1] performed a very interesting investigation on the dynamics of AMPARs and correlated it with the dynamic of the electrical activity measured by electroencephalogram. In individuals with focal

onset seizures, a positive correlation was found between AMPAR density and amplitude of both gamma and theta activities. In individuals with FBTCS, abnormal gamma and theta activities were detected in different electrodes; in particular, a positive correlation between AMPAR density and the amplitude of gamma activity was observed in the areas where the positive correlation was identified in individuals with focal onset seizures without generalization. On the contrary, a negative correlation between AMPAR density and amplitude of theta activity was found in areas complementary to those exhibiting the positive AMPAR-gamma activity coupling. These results suggest that the disappearance of positive AMPAR-theta activity coupling and the spread of negative AMPAR-theta activity coupling underlie the transition from focal to generalized seizures. Interestingly, in individuals with generalized onset seizures, a negative correlation was found between AMPARs and amplitude of gamma activity, while no correlation was found between AMPARs and theta activity.

Compared with healthy subjects, the authors[1] found a general decreased AMPAR density in large cortical areas of individuals with epilepsy. Cell surface AMPARs were reduced compared with healthy subjects in brain areas that did not produce AMPAR-mediated epileptic activity. Indeed, limited areas with decreased AMPAR density overlapped with those exhibiting positive AMPAR-gamma activity coupling or positive AMPAR-theta activity in individuals with focal onset non-generalizing seizures. In individuals with FBTCS, brain areas with decreased AMPAR density minimally overlapped to those with positive AMPAR-gamma activity coupling or negative AMPAR-theta activity coupling, areas shown to be involved in epileptogenic activity or in the transition from focal to spreading seizures. Interestingly, in individuals with generalized onset seizures, decreased AMPAR density was observed in areas overlapping with the negative AMPAR-gamma activity coupling regions.

In conclusion, the study by Eiro et al.[1] provides evidence to hypothesize that both Hebbian and homeostatic plasticity of AMPARs play crucial roles in epileptogenesis, demonstrating that the increased AMPAR density mediating epileptic activity in focal seizures could result from Hebbian synaptic plasticity, while a homeostatic compensatory downregulation of AMPARs due to epileptic long-term neuronal firing occurs in individuals with generalized onset seizures for whom epileptic discharge can be induced by other causes that are AMPAR independent.

DECLARATION OF INTERESTS

The author declares no competing interests.

REFERENCES

1. Eiro, T., Miyazaki, T., Hatano, M., Nakajima, W., Arisawa, T., Takada, Y., Kimura, K., Sano, A., Nakano, K., Mihara, T., et al. (2023). Dynamics of AMPA receptors regulate epileptogenesis in patients with epilepsy. Cell Rep. Med. *4*, 101020.
2. Hebb, D.O. (1949). The Organization of Behavior; A Neuropsychological Theory (Wiley).
3. Pozo, K., and Goda, Y. (2010). Unraveling mechanisms of homeostatic synaptic plasticity. Neuron *66*, 337–351.
4. Letellier, M., and Cingolani, L.A. (2021). Editorial: Homeostatic synaptic plasticity: from synaptic circuit assembly to neurological disorders. Front. Cell. Neurosci. *15*, 695313.
5. Issa, N.P., Nunn, K.C., Wu, S., Haider, H.A., and Tao, J.X. (2023). Putative roles for homeostatic plasticity in epileptogenesis. Epilepsia *64*, 539–552.
6. Galanis, C., and Vlachos, A. (2020). Hebbian and homeostatic synaptic plasticity-Do alterations of one reflect enhancement of the other? Front. Cell. Neurosci. *14*, 50.
7. Fisher, R.S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J.H., Elger, C.E., Engel, J., Jr., Forsgren, L., French, J.A., Glynn, M., et al. (2014). ILAE official report: A practical clinical definition of epilepsy. Epilepsia *55*, 475–482.
8. Lignani, G., Baldelli, P., and Marra, V. (2020). Homeostatic plasticity in epilepsy. Front. Cell. Neurosci. *14*, 197.
9. Ren, E., and Curia, G. (2021). Synaptic reshaping and neuronal outcomes in the temporal lobe epilepsy. Int. J. Mol. Sci. *22*, 3860.
10. Miyazaki, T., Nakajima, W., Hatano, M., Shibata, Y., Kuroki, Y., Arisawa, T., Serizawa, A., Sano, A., Kogami, S., Yamanoue, T., et al. (2020). Visualization of AMPA receptors in living human brain with positron emission tomography. Nat. Med. *26*, 281–288.