

SINGLE-GENE MUTATION LEADS TO LOCALIZED DISRUPTION OF CORTICAL INTERNEURON DEVELOPMENT AND INCREASED SEIZURE SUSCEPTIBILITY

Genetic Disruption of Cortical Interneuron Development Causes Region- and GABA Cell Type-Specific Deficits, Epilepsy, and Behavioral Dysfunction

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The generation of properly functioning circuits during brain development requires precise timing of cell migration and differentiation. Disruptions in the developmental plan may lead to neurologic and psychiatric disorders. Neocortical circuits rely on inhibitory γ -aminobutyric acid (GABA)ergic interneurons, the majority of which migrate from subcortical sources. We have shown that the pleiotropic molecule hepatocyte growth factor scatter factor (HGF/SF) mediates interneuron migration. Mice with a targeted mutation of the gene encoding urokinase plasminogen activator receptor (uPAR), a key component in HGF/SF activation and function, have decreased levels of HGF/SF and a 50% reduction in neocortical GABAergic interneurons at embryonic and perinatal ages. Disruption of interneuron development leads to early lethality in most models. Thus, the long-term consequences of such perturbations are unknown. Mice of the *uPAR*^{-/-} strain survive until adulthood, and behavior testing demonstrates that they have an increased anxiety state. The *uPAR*^{-/-} strain also exhibits spontaneous seizure activity and higher susceptibility to pharmacologically induced convulsions. The neocortex of the adult *uPAR*^{-/-} mouse exhibits a dramatic region- and subtype-specific decrease in GABA-immunoreactive interneurons. Anterior cingulate and parietal cortical areas contain 50% fewer GABAergic interneurons compared with those of the wild-type littermates. However, interneuron numbers in piriform and visual cortical areas do not differ from those of normal mice. Charac-

terization of interneuron subpopulations reveals a near complete loss of the parvalbumin subtype, with other subclasses remaining intact. These data demonstrate that a single gene mutation can selectively alter the development of cortical interneurons in a region- and cell subtype-specific manner, with deficits leading to long-lasting changes in circuit organization and behavior.

COMMENTARY

The hypothesis that loss of γ -aminobutyric acid (GABA)ergic interneurons underlies one or more of the many different forms of epilepsy has been debated for decades. The article by Powell et al. describes a mouse with a targeted mutation of the gene that encodes the urokinase plasminogen activator receptor (uPAR; see abstract), which alters the development of a fraction of the GABAergic interneurons in some areas of neocortex. The net result of the mutation is increased anxiety and seizure susceptibility. This research has several implications for epileptologists.

First, as the authors point out, most mutations that appear to involve the GABAergic system are lethal. The results of Powell et al., however, emphasize how a single gene mutation can have a relatively small effect that still clearly alters behavior and seizure susceptibility, apparently by affecting the migration of one type of interneuron in one general region of the neocortex (i.e., ~50% reduction in parvalbumin-containing interneurons in anterior cingulate and parietal cortex). Thus, developmental lesions arising from single gene mutations can alter seizure susceptibility in a manner that could easily go unrecognized without an adequate histopathologic analysis. This type of mutation in a human could thus conceivably lead to examples of a genetic form of epilepsy that would otherwise have no apparent biologic basis unless appropriate histopathologic studies (e.g., semiquantitative immunohistochemistry) were undertaken on the tissue.

Second, the developmental alterations associated with this mutation could create a cortical environment that might be more susceptible to a “second hit.” An injury during adulthood,



for example, might well be more likely to induce subsequent epileptogenesis and become an area where seizures might normally be initiated. Thus, the genetic abnormality could create a cortical region that is essentially an epileptogenic zone within a larger area that has undergone some form of injury but might not otherwise cause posttraumatic epilepsy. This is now merely a hypothesis, but it could be tested, and that might provide insight into why some head injuries lead to epilepsy and others do not.

The mice with the uPar mutation may be particularly useful for addressing issues like those raised earlier, or they could be one of hundreds whereby single gene mutations with relatively detailed cellular lesions in specific regions of the brain lead to a phenotype that is either epileptic or seizure prone.

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