EBioMedicine 8 (2016) 5–6

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Gap Junctions and Epileptogenesis: No Laughing Matter

Elisabetta Gazzerro [a,*], Pasquale Striano [a,b]

[a] Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, "G. Gaslini" Institute, Genova, Italy
[b] Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, G. Gaslini Institute, Genova, Italy

ARTICLE INFO

Article history:
Received 18 May 2016
Accepted 18 May 2016
Available online 24 May 2016

Hypothalamic hamartoma (HH) is a rare (about 1:100,000) developmental, non-neoplastic malformation involving the small hypothalamic area located between the infundibular stalk and the mammillary bodies (Maixner, 2006). HH can be associated with a range of neurological and/or endocrinogical manifestations (Striano et al., 2005; Munari et al., 1995). However, HH typical clinical hallmarks are compulsive bursts of laughter of epileptic nature with no sense of mirth, called gelastic seizures, and first described by Trousseau in 1877 (Berkovic et al., 1998). These attacks usually start during infancy or childhood and were demonstrated to originate directly from the HH (Striano et al., 2009). Moreover, in most patients, other seizure types may occur in association with a severe encephalopathy that can eventually lead to intellectual disability within few years (Berkovic et al., 1998; Striano et al., 2009). Antiseizure drugs are inexorably ineffective and cannot avoid the cognitive dysfunction whereas the catastrophic evolution can be interrupted up to completely reverted by HH surgical ablation (Striano et al., 2009). Hence, this potentially reversible encephalopathy is an amazing in vivo model to investigate the process of human epileptogenesis and to find new therapeutic options in patients with drug-resistant epilepsy. The intrinsic epileptogenicity of HH is explained by the peculiar anatomo-functional organization and, in particular, by the electrophysiological properties of small acid gamma-aminobutyric (GABA)-ergic neurons that make this structure highly epileptogenic and refractory to antiseizure drugs, regardless their mechanism of action. Li and colleagues (Li et al., 2011) previously demonstrated, by means of patch-clamp recordings, the functional rundown of GABA-A receptors in neurons from surgically resected HH tissue, in line with the view that a dysfunction of GABAergic transmission plays a crucial role in epileptogenesis in these patients. Nonetheless, it is unlikely that GABA rundowns are the only functional changes occurring in HH tissue.

Gap junctions are cell-to-cell channel-forming structures formed by specialized proteins (connexins [Cx]) which allow direct electrical coupling and chemical communication between adjacent neurons in central nervous system (CNS) (Cruikshank et al., 2005). Cx36 is the main neuronal connexin, although others have been variably detected in mature neurons. In most CNS regions, including the cortex and hypothalamus, the incidence of neuronal gap-junctions physiologically increases during the first two postnatal weeks and then decrease by the end of the third–fourth week. Cx36 and gap-junctions expression are transiently stimulated following a wide range of neuronal injuries, such as ischemia, spinal cord injury, epilepsy and inflammation (Belousov & Fontes, 2013).

Gap junctions likely contribute to the pathogenesis of epilepsy, particularly with respect to enhancing synchronous GABA activity of neuronal subgroups within epileptic networks (Cruikshank et al., 2005; Traub et al., 2004). However, although the pharmacological blockade of gap junctions significantly reduces seizure occurrence (Traub et al., 2004), the potential for gap-junction blockers for treatment of human epilepsy remains still largely unexplored.

In this issue of *EBioMedicine*, Wu and colleagues demonstrated that, in human HH, neuronal gap junctions between small GABAergic HH neurons participate in the genesis of epileptic-like discharges (Wu et al., 2016). The authors studied surgically resected HH tissue obtained from 27 patients all affected by treatment-resistant epilepsy and a history of gelastic seizures. Intellectual disability or developmental retardation was present in 13 (48%) patients and prior history of central precocious puberty was present in nine (33%) subjects. Wu and colleagues showed that HH tissue displayed a marked up-regulation of Cx43 and Cx36 protein levels when compared to normal hypothalamic control tissue. The increase of both connexins may relate to immature properties of HH tissue and immunohistochemistry confirmed that Cx36 was mainly expressed within neuron clusters while Cx43 was detected outside of neuronal networks. Biocytin injection into single recorded small HH neurons showed labeling of adjacent neurons, which was not observed in the presence of the neuronal gap-junction blocker, mefloquine. Finally, microelectrode field recordings from freshly resected HH slices demonstrated spontaneous ictal/interictal-like discharges which were significantly reduced by the application of gap-junction blockers without alterations of the action-potential firing of small GABA neurons observed with patch-clamp whole-cell recordings.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2016.04.026.
* Corresponding author at: Unit of Paediatric Neurology, G. Gaslini Institute, Italy.
E-mail address: elisabettagazzerro@ospedale-gaslini.ge.it (E. Gazzerro).

http://dx.doi.org/10.1016/j.ebiom.2016.05.024

Using a wide array of histological and electrophysiological experimental approaches, these data clearly support a mechanistic role of neuronal gap junctions in the intrinsic epileptogenicity of human HH and strenghten the cellular model in which HH neuron clusters of spontaneously firing interneurons paradoxically excite projection neurons in a functional network (Belousov & Fontes, 2013). Although the increase in Cx36 may be due to the developmental phenotype of HH neurons, the study suggests relevant insights on future therapeutic strategies, i.e. the use of gap-junction blockers such as carbenoxolone and tonabersat, to address the severely drug-refractory epileptic encephalopathy that affects patients.

There are open questions as yet, however. It is still possible that neither neuronal gap junctions or impaired GABAergic function are the primary mechanisms that contribute to epileptogenesis in these patients, and that they can represent a secondary or compensatory event.

Finally, much more importantly, the electrophysiological features of HH neurons do not explain per se the natural history of HH patients, i.e. the epileptic encephalopathy that occurs in most cases with deterioration in seizure type and development of neocortical onset of seizures (secondary epileptogenesis), along with the progression of cognitive impairment and psychiatric features (Berkovic et al., 1998; Striano et al., 2009) with consequent reduction in autonomy.

Is there a contribution of neuronal gap-junctions to the propagation of pro-damage molecules between the coupled neurons (Belousov & Fontes, 2013)? Clarification of the transcriptional/biochemical events that underlie Cx36-dependent neuronal developmental alterations and analysis of their role in HH and in the entire epileptogenic network are areas of great interest and hold potential translational value for the development of novel therapeutic targets. In the meantime, increased awareness of the syndrome, timely diagnosis, and appropriate treatment are needed to minimize long-term cognitive impairment and behavioral disturbances and to avoid a catastrophic evolution for the patients.

Disclosures

E. Gazzerro is funded by G. Gaslini Foundation; P. Striano received honoraria from FB Health, Kolfarma s.r.l., UCB pharma, Eisai Inc., and research support from the Italian Ministry of Health (GR-2011-02346749), and the Telethon Foundation (GGP13034).

References

Belousov, A.B., Fontes, J.D., 2013. Neuronal gap junctions: making and breaking connections during development and injury. Trends Neurosci. 36, 227–236.

Berkovic, S.F., Andermann, F., Melanson, D., Ethier, R.E., Feindel, W., Gloor, P., 1998. Hypotalamic hamartomas and ictal laughter: evolution of a characteristic epileptic syndrome and diagnostic value of magnetic resonance imaging. Ann. Neurol. 23, 429–438.

Cruikshank, S.J., Landisman, C.E., Mancilla, J.G., Connors, B.W., 2005. Connexon connexions in the thalamocortical system. Prog. Brain Res. 149, 41–57.

Li, G., Yang, K., Zheng, C., Liu, Q., Chang, Y., Kerrigan, J.F., Wu, J., 2011. Functional rundown of gamma-aminobutyric acid(A) receptors in human hypothalamic hamartomas. Ann. Neurol. 69, 664–672.

Maixner, W., 2006. Hypothalamic hamartoma: clinical, neuropathological and surgical aspects. Childs Nerv. Syst. 22, 867–873.

Munari, C., Kahane, P., Francione, S., Hoffmann, D., Tassi, L., Cusmai, R., Vigevano, F., Pasquier, B., Betti, O., 1995. Role of the hypothalamic hamartoma in the genesis of gelastic fits (a video-stereo-EEG study). Electroencephalogr. Clin. Neurophysiol. 95, 154–160.

Striano, S., Striano, P., Coppola, A., Romanelli, P., 2009. The syndrome gelastic seizures-hypothalamic hamartoma: severe, potentially reversible encephalopathy. Epilepsia 50, 62–65.

Striano, S., Striano, P., Sarappa, C., Boccella, P., 2005. The clinical spectrum and natural history of gelastic epilepsy-hypothalamic hamartoma syndrome. Seizure 14, 232–239.

Traub, R.D., Michelson-Law, H., Bibbig, A.E., Buhl, E.H., Whittington, M.A., 2004. Gap junctions, fast oscillations and the initiation of seizures. Adv. Exp. Med. Biol. 548, 110–122.

Wu, J., Gaob, M., Riced, S.G., Tsangd, C., Beggsb, J., Turnerb, D., Lib, G., Yanga, B., Xiaa, K., Gaoc, F., Qiue, S., Liub, Q., Kerrigand, J.F., 2016. Gap junctions contribute to ictal/interictal genesis in human hypothalamic hamartomas. EBioMedicine 8, 96–102.