EJN fens European Journal of Neuroscience

European Journal of Neuroscience, Vol. 34, pp. 235–236, 2011 doi:10.1111/j.1460-9568.2011.07792.x

NEUROSYSTEMS

$GABA_A$ receptor mutations in epilepsy (Commentary on Lachance-Touchette *et al.*)

Christopher A. Reid[1,2] and Dimitri M. Kullmann[1]
[1]UCL Institute of Neurology, University College London, London, UK
[2]Florey Neuroscience Institutes, University of Melbourne, Melbourne, Australia

Although idiopathic epilepsy has long been known to have high heritability, the first gene was not identified until 1995 (Steinlein *et al.*, 1995), a breakthrough that started to unravel the genetic architecture of this disease. Whereas some evidence exists for a genetic component of the focal epilepsies, a more complete understanding is emerging for generalized syndromes. Indeed, a re-classification of idiopathic generalized epilepsy (IGE) to genetic generalized epilepsy has been recently proposed, highlighting the importance of genetic mechanisms in this disease (Berg *et al.*, 2010). Strikingly, the overwhelming majority of genes identified have encoded ion channels, both voltage-gated and ligand-gated. In this issue of the *European Journal of Neuroscience*, Lachance-Touchette *et al.* (2011) add to our understanding of the role of genetic variability of $GABA_A$ receptors in IGE by describing three novel mutations. Although many puzzles remain, these 'epileptic channelopathies' provide the most compelling insights into the causation of a serious neurological disorder.

Lachance-Touchette *et al.* (2011) screened three French Canadian families with IGE for mutations in *GABRA1* and *GABRG2*, which encode the $\alpha 1$ and $\gamma 2$ subunits of the $GABA_A$ receptor, respectively. These subunits co-assemble together with β subunits to make up an abundant receptor subtype expressed in the forebrain. The authors report two previously unreported mutations in *GABRA1*, and the results of functional analysis are consistent with a reduction in cell surface expression of the mature protein in both cases. Only two previous *GABRA1* mutations have been reported, one a familial mutation associated with juvenile myoclonic epilepsy (Cossette *et al.*, 2002), and another in a sporadic case of childhood absence seizures (Maljevic *et al.*, 2006). Interestingly, the seizure phenotypes of the families harbouring the newly reported mutations are different, and include febrile seizures, generalized tonic–clonic seizures and photosensitive seizures. This broad seizure spectrum occurs despite a common mutation-mediated loss of protein function. Clinical heterogeneity is a common feature of the 'monogenic' causes of epilepsy, and strongly suggests that other genetic factors are critical in defining seizure outcome (Reid *et al.*, 2009).

Lachance-Touchette *et al.* (2011) also describe a novel *GABRG2* mutation in a large family with febrile seizures and IGE. The mutation is found in all nine affected individuals, so it comes as some surprise that they are unable to identify a functional deficit. This is particularly true given the proximity of the mutation to a well-validated *GABRG2* variant in a family with a similar spectrum of seizures (Wallace *et al.*, 2001). Lachance-Touchette *et al.* (2011) confirm that the receptors are insensitive to Zn^{2+} and are potentiated by diazepam, important controls to show that the $\gamma 2$ subunit is incorporated into $GABA_A$ receptors at the cell surface. The mutation is highly unlikely to be a rare polymorphism, because it affects a conserved residue and co-segregates with the phenotype. So how can the lack of functional effect be reconciled with a causative role in epilepsy? A possible explanation is that the experiments were performed at room temperature. Indeed, there is a precedent for a febrile seizure-associated *GABRG2* mutation only altering trafficking at higher temperatures (Kang *et al.*, 2006). Another subtlety of *GABRG2* mutations is that their functional consequences can differ with the identity of the co-expressed $GABA_A$ receptor α subunits. For example, the $GABA_A\gamma 2$ (R43Q) mutation has no impact on $\alpha 1$ expression (Tan *et al.*, 2007), whereas the same mutated protein reduces $\alpha 5$ surface expression (Eugene *et al.*, 2007), and may also alter the stoichiometry of $GABA_A$ receptors containing the $\alpha 3$ subunit (Frugier *et al.*, 2007). Because Lachance-Touchette *et al.* (2011) only examined $\alpha 1$ subunit-containing $GABA_A$ receptors, this leaves open the possibility that altered channel expression or function could be revealed by other combinations of subunits.

Despite the fact that 'monogenic' causes of epilepsy in large families are rare, the epilepsy syndromes that they exhibit are common. This has provided a 'fast-track' to begin our understanding of the genetic architecture of epilepsy. The work of Lachance-Touchette *et al.* (2011) substantially expands our understanding of the causation of IGE, and will help in our quest to unravel the cellular and circuit mechanisms underlying this common disease.

References

Berg, A.T., Berkovic, S.F., Brodie, M.J., Buchhalter, J., Cross, J.H., van Emde Boas, W., Engel, J., French, J., Glauser, T.A., Mathern, G.W., Moshe, S.L., Nordli, D., Plouin, P. & Scheffer, I.E. (2010) Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia*, **51**, 676–685.

Cossette, P., Liu, L., Brisebois, K., Dong, H., Lortie, A., Vanasse, M., Saint-Hilaire, J.M., Carmant, L., Verner, A., Lu, W.Y., Wang, Y.T. & Rouleau, G.A. (2002) Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. *Nat. Genet.*, **31**, 184–189.

Eugene, E., Depienne, C., Baulac, S., Baulac, M., Fritschy, J.M., Le Guern, E., Miles, R. & Poncer, J.C. (2007) GABA(A) receptor gamma 2 subunit mutations linked to human epileptic syndromes differentially affect phasic and tonic inhibition. *J. Neurosci.*, **27**, 14108–14116.

Frugier, G., Coussen, F., Giraud, M.F., Odessa, M.F., Emerit, M.B., Boue-Grabot, E. & Garret, M. (2007) A gamma 2(R43Q) mutation, linked to epilepsy in humans, alters GABAA receptor assembly and modifies subunit composition on the cell surface. *J. Biol. Chem.*, **282**, 3819–3828.

© 2011 The Authors. European Journal of Neuroscience © 2011 Federation of European Neuroscience Societies and Blackwell Publishing Ltd

Kang, J.Q., Shen, W. & Macdonald, R.L. (2006) Why does fever trigger febrile seizures? GABAA receptor gamma2 subunit mutations associated with idiopathic generalized epilepsies have temperature-dependent trafficking deficiencies *J. Neurosci.*, **26**, 2590–2597.

Lachance-Touchette, P., Brown, P., Meloche, C., Kinirons, P., Lapointe, L., Lacasse, H., Lortie, A., Carmant, L., Bedford, F., Bowie, D. & Cossette, P. (2011) Novel $\alpha 1$ and $\gamma 2$ $GABA_A$ receptor subunit mutations in families with idiopathic generalized epilepsy. *Eur. J. Neurosci.*, **34**, 237–249.

Maljevic, S., Krampfl, K., Cobilanschi, J., Tilgen, N., Beyer, S., Weber, Y.G., Schlesinger, F., Ursu, D., Melzer, W., Cossette, P., Bufler, J., Lerche, H. & Heils, A. (2006) A mutation in the GABA(A) receptor alpha(1)-subunit is associated with absence epilepsy. *Ann. Neurol.*, **59**, 983–987.

Reid, C.A., Berkovic, S.F. & Petrou, S. (2009) Mechanisms of human inherited epilepsies. *Prog. Neurobiol.*, **87**, 41–57.

Steinlein, O.K., Mulley, J.C., Propping, P., Wallace, R.H., Phillips, H.A., Sutherland, G.R., Scheffer, I.E. & Berkovic, S.F. (1995) A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. *Nat. Genet.*, **11**, 201–203.

Tan, H.O., Reid, C.A., Single, F.N., Davies, P.J., Chiu, C., Murphy, S., Clarke, A.L., Dibbens, L., Krestel, H., Mulley, J.C., Jones, M.V., Seeburg, P.H., Sakmann, B., Berkovic, S.F., Sprengel, R. & Petrou, S. (2007) Reduced cortical inhibition in a mouse model of familial childhood absence epilepsy. *Proc. Natl Acad. Sci. USA*, **104**, 17536–17541.

Wallace, R.H., Marini, C., Petrou, S., Harkin, L.A., Bowser, D.N., Panchal, R.G., Williams, D.A., Sutherland, G.R., Mulley, J.C., Scheffer, I.E. & Berkovic, S.F. (2001) Mutant GABA(A) receptor gamma2-subunit in childhood absence epilepsy and febrile seizures. *Nat. Genet.*, **28**, 49–52.

© 2011 The Authors. European Journal of Neuroscience © 2011 Federation of European Neuroscience Societies and Blackwell Publishing Ltd