Dysfunction of the brain calcium channel $\text{Ca}_{V}2.1$ in absence epilepsy and episodic ataxia—authors’ response

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Sir,

We thank Professor Strupp and colleagues for the pertinent points they raise in relation to our recent publication in Brain (Imbrici et al., 2004). They highlight important issues in relation to treatment options in episodic ataxia type 2 (EA2) and absence epilepsy. Furthermore, their recent findings in combination with ours highlight the possible role of $\text{Ca}_{V}2.1$ dysfunction in human absence epilepsy (Jouvenceau et al., 2001; Imbrici et al., 2004; Strupp et al., 2004).

In our experience, most patients with uncomplicated ‘pure’ EA2 harbouring a mutation in the $\text{CACNA1A}$ gene do respond well to acetazolamide therapy, although a proportion of such cases do not. This is also the experience in a series recently published by Jen et al. (2004). The precise mechanism underlying this acetazolamide response remains uncertain. Furthermore, the treatment of acetazolamide-resistant cases is problematic. The recent finding of Strupp et al. (2004) that episodes of ataxia in a genetically proven case of EA2 were resistant to acetazolamide but responded convincingly to 4-diaminopyridine (4-AP) is therefore potentially important.

It is now recognized that certain patients with EA2 also exhibit an epilepsy phenotype (Jouvenceau et al., 2001; Imbrici et al., 2004; Jen et al., 2004; Strupp et al., 2004).

In our experience, this is usually a primary generalized form with a 3 Hz spike–wave EEG. It is perhaps not unexpected that humans with $\text{CACNA1A}$ mutations might exhibit an epilepsy phenotype, when one considers the spontaneously occurring $\text{CACNA1A}$ mouse mutants. These mice frequently exhibit a spike–wave epilepsy phenotype (Steinlein et al., 2000). The first human EA2 epilepsy case we described in 2001 exhibited a severe phenotype manifesting frequent episodes of ataxia and poorly controlled absence seizures, and generalized tonic–clonic seizures (Jouvenceau et al., 2001). The episodes of ataxia were unresponsive to acetazolamide, and a variety of different anticonvulsants did not fully control the seizures. This case harboured a truncation mutation in exon 36 (C5733T) of the $\text{CACNA1A}$ gene—the same mutation having now been identified in an unrelated case by Strupp et al. (2004). Both cases are similar in that the episodes of ataxia responded poorly to acetazolamide; however, our case is notable for a more severe epilepsy phenotype. Furthermore, in our case, the ataxia had been ascribed to anticonvulsant medication toxicity despite the absence of toxic levels. This apparent particular sensitivity to anticonvulsants was a notable feature in the recent family we described in Brain (Imbrici et al., 2004).

Taken together, these observations raise a number of points requiring further study.

First, it remains possible that other cases of epilepsy with a primary generalized EEG disturbance who develop ataxia might have this wrongly ascribed to anticonvulsant toxicity, when in fact they may harbour a mutation in $\text{CACNA1A}$. We are currently analysing the entire coding region of $\text{CACNA1A}$ in a cohort of cases with clinically definite EA2 accompanied by a 3 Hz spike–wave EEG manifesting as absence epilepsy and/or generalized tonic–clonic seizures, in order to address this question.

Secondly, the role of $\text{CACNA1A}$ in common forms of absence epilepsy (3 Hz EEG) remains unresolved despite studies addressing this question (Chioza et al., 2002; Sander et al., 2002).

Thirdly, the findings of Strupp et al. (2004) that their case with EA2 harbouring the C5733T mutation (and with a resolved 7 year history of absence epilepsy) had only a transient response to acetazolamide, but a convincing response to the potassium channel blocker 4-AP, may be important. We note with interest that 4-AP was reported to ‘completely prevent attacks of ataxia’ in the tottering mouse mutant (which harbours a $\text{CACNA1A}$ mutation). It is interesting that blocking potassium channel conductance with 4-AP improves episodic ataxia in EA2, whilst EA1 is caused by a loss of potassium channel function (Kv1.1). However, it is possible that the concentrations of 4-AP achieved are in...
the range which block ‘transient’ I(A)-type K channels rather than shaker-type Kv1 channels. It is likely that these observations underline the fundamental differences in the pathophysiological mechanisms causing these two important forms of episodic ataxia.

We agree that further trials of 4-AP in acetazolamide-resistant EA2 need to be undertaken. Indeed, it may be that a head to head trial of acetazolamide versus 4-AP should be considered. Clearly, multicentre international treatment trial collaboration will be one way to achieve this and is now being established for a number of neurological channelopathies including EA2 (R. G. Griggs Rochester NY personal communication; J. Jen UCLA, personal communication). The issue is more complicated in EA2 cases with epilepsy because of the potentially pro-convulsant effect of potassium channel blockade. It would be of considerable interest to establish if the tottering mouse seizure phenotype or frequency altered with the use of 4-AP.

References