New hope for the treatment of epilepsy

This scientific commentary refers to ‘Targeting pharmacoresistant epilepsy and epileptogenesis with a dual-purpose antiepileptic drug’ by Doeser et al. (doi: 10.1093/brain/awu339).

Compared to many other chronic neurological diseases, epilepsy can be regarded as relatively amenable to treatment, given that about two-thirds of patients become seizure-free with available medications. However, there are two major problems with current treatment using antiepileptic drugs. First, about one-third of patients with epilepsy are resistant to the available antiepileptic drugs, and second, the treatment is purely ‘symptomatic’, i.e. when the drugs are stopped, epileptic seizures usually recur, as the underlying cause of the seizures is still present. Epileptogenesis describes the process of development of epilepsy after an initial brain insult, such as trauma or a prolonged febrile seizure (Fig. 1) (Pitkänen and Lukasiuk, 2011). However, there are no current treatments that target the process of epileptogenesis in an effort to prevent or at least modify the disease. There is only one possibility to cure epilepsy, namely epilepsy surgery, a treatment that can only be applied to selected patients in whom the epileptic focus can be surgically removed. Thus, new therapeutic approaches are urgently needed. In this issue of Brain, Doeser et al. (2014a) report that an existing AED, eslicarbazepine acetate (ESL), has unexpected effects with the potential to address both pharmacoresistance and epileptogenesis.

ESL is a derivative of the long-established drug carbamazepine (CBZ) and its first modification oxcarbazepine (OXC). Toxic epoxides are not formed from ESL, and unlike OXC, which is converted into both eslicarbazepine (S-Lic) and (R)-licarbazepine, ESL is mainly converted to S-Lic. Based on these chemical properties, ESL has been developed for clinical use mainly to improve tolerability by reducing side effects of CBZ and OXC. Only recently, it has been reported that the effects these drugs exert on sodium channels seem to differ (Hebeisen et al., 2014).

Doeser et al. (2014a) now present two major novel findings concerning S-Lic/ESL. First, S-Lic has additional efficacy over CBZ in vitro in hippocampal brain slices from (i) pharmacoresistant patients with mesial temporal lobe epilepsy (TLE) who underwent epilepsy surgery with resection of the hippocampus; and (ii) a rat model of mesial TLE. Second, they observed an anti-epileptogenic, disease-modifying effect of ESL when the drug was administered early in the course of development of epilepsy in a mouse model. The authors describe an additional, previously unknown, mechanism of action of S-Lic that may explain this anti-epileptogenic activity.

More than 10 years ago, the group of Heinz Beck first described a correlation between the clinical response to CBZ in patients and the in vitro effect of CBZ on hippocampal brain slices obtained from the same patients. They were able to reproduce this finding in the rat pilocarpine model of mesial TLE (Remy et al., 2003). Interestingly, the difference in the effect of CBZ in pharmacoresistant and (partially) pharmacoresponsive cases was restricted to a single property of voltage-gated sodium channels—the target of CBZ, OXC and S-Lic—namely, the recovery from fast inactivation. In another study, the same group found evidence that the sodium channel β1-subunit, a smaller subunit which has modifying effects on the main α-subunits, modifies CBZ-sensitivity of persistent sodium currents, but this could not explain altered effects of CBZ on the recovery from fast inactivation (Uebachs et al., 2010). They also showed later on that the drug effect of S-Lic is not influenced by loss of the β1-subunit (Doeser et al., 2014b).

Doeser et al. (2014a) have now examined the effects of S-Lic (applied to brain slices) and ESL (administered to mice) in human and rodent mesial TLE. The authors’ experiments were guided by clinical studies that showed evidence for additional beneficial effects of ESL, also in CBZ-resistant patients (Elger et al., 2009). Those results were surprising and went unexplained at the time, since the same mechanism of action was initially presumed for both drugs. When Doeser and colleagues (2014a) applied S-Lic in addition to CBZ to hippocampal brain slices of CBZ-resistant patients or rats, they observed that S-Lic was able to overcome the CBZ-resistance on recovery from fast inactivation, as S-Lic potently slowed the recovery process. Interestingly, this add-on effect of S-Lic to CBZ was restricted to recovery from fast inactivation; S-Lic did not add to the effects of CBZ on other properties of sodium currents. S-Lic alone also had clear effects on various properties of sodium currents, but these did not differ between epileptic animals and non-epileptic controls. When added to CBZ, S-Lic also produced an additional reduction in repetitive neuronal firing in human brain slices. For unknown reasons, this latter add-on effect of S-Lic to CBZ could not be reproduced in the pilocarpine model.

Doeser et al. (2014a) further discovered that S-Lic has an additional mechanism of action on another ion channel, the T-type calcium channel CaV3.2. This channel plays an important role in epileptogenesis, because this process is largely inhibited in CaV3.2 knock-out mice (Becker et al., 2008). These observations triggered another series of experiments in which Doeser and colleagues examined whether ESL exhibits anti-epileptogenic effects in the mouse pilocarpine model of mesial TLE. After inducing status epilepticus with pilocarpine, they applied ESL or vehicle for 6 weeks in two dosages adapted from pharmacokinetic data.
obtained in man. Chronic seizures were then recorded following an established protocol. ESL reduced the number of seizures significantly, indicating that it does indeed have an anti-epileptogenic effect. Further indirect effects of anti-epileptogenesis by ESL were observed on known histological characteristics of mesial TLE in mice. ESL-treated animals showed reduced mossy fibre sprouting and significantly less neuronal cell loss in the CA1 and CA3 regions of the hippocampus, again consistent with anti-epileptogenic effects.

The work by Doeser and colleagues (2014a) has several clinical implications. Concerning pharmacoresistance, this publication offers an explanation as to why some patients with resistance to CBZ did respond to ESL (Elger et al., 2009), even though the latter is a derivative of the former and both were thought to have similar or the same mechanisms of action. Furthermore, the authors nicely show that mechanism of action does matter in the combination of different AEDs (Brodie et al., 2011), as S-Lic was able to overcome CBZ resistance of an in vitro effect that correlates with clinical CBZ pharmacoresistance in epilepsy (Remy et al., 2003). The exact mechanism by which S-Lic leads to a slowing of recovery from fast inactivation in CBZ-resistant cases remains to be elucidated, since this cannot easily be explained by the additional mechanisms that have been described for S-Lic, i.e. enhancement of sodium channel slow inactivation (Hebeisen et al., 2014) and blockade of Cav3.2 channels (Doeser et al., 2014a). The different effects of CBZ and S-Lic on persistent sodium currents in the absence of the β1-subunit (Uebachs et al., 2010; Doeser et al., 2014b) cannot explain this either, as the lack of the β1-subunit did not influence recovery from fast inactivation (Uebachs et al., 2010), and the persistent current was modified equally by CBZ and S-Lic in the pilocarpine model (Doeser et al., 2014a).

Despite the discovery of several anti-epileptogenic effects in animal models of epilepsy (Pitkänen and Lukasiuk, 2011), there are as yet no clinically approved drugs with such properties. Anti-epileptogenic effects of other AEDs have been suggested, but it is unclear if these AEDs truly modify epileptogenesis in mesial TLE, or if alleviation of the induced status epilepticus led to a reduction in chronic seizures (Pitkänen and Lukasiuk, 2011). Doeser et al. (2014a) now present evidence that ESL may serve a true anti-epileptogenic purpose, as the development of chronic seizures and histological alterations associated with chronic epilepsy was reduced by transient ESL application in the pilocarpine mouse model after the induced status epilepticus. Clinical studies to prevent or modify the course of epilepsy could be performed with ESL as an approved AED on the basis of the presented data. To design such clinical trials is a challenge, since preventive treatment may come too late in most cases, when epilepsy is already established. Furthermore, most events—such as prolonged febrile seizures, trauma or stroke—lead to epilepsy in only a small percentage of patients and sometimes after long periods, even up to decades. Long-term treatment with anti-epileptogenic drugs with potential side effects would be difficult to justify in these cases. On the other hand, it seems to be sufficient to apply anti-epileptogenic treatment during a limited time period after the initial insult, as shown here by Doeser et al. (2014a) for ESL. Moreover, clinical conditions that lead to severe chronic epilepsy in a high percentage of patients and that would be suitable for testing anti-epileptogenic treatment in clinical trials could be identified. Limbic encephalitis, which often leads

![Figure 1](https://example.com/figure1.png)

**Figure 1 Schematic of epileptogenesis.** After an initial insult (such as status epilepticus, trauma or stroke), chronic epilepsy develops during a latent period without seizures. This process is called epileptogenesis. It is induced and maintained by many factors, some as yet unidentified, including inflammatory and epigenetic mechanisms. The goal of anti-epileptogenic treatment is to intervene as early as possible to stop or at least attenuate the process of epileptogenesis. This is in contrast to currently available anti-epileptic drugs, which only suppress seizures ‘symptomatically’ in the phase of chronic epilepsy.
to hippocampal sclerosis in a limited period of time, in particular when associated with LGI1 antibodies (Malter et al., 2014), might be one such condition.

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doi:10.1093/brain/awu357

References

Can levodopa-induced dyskinesias go beyond the motor circuit?

This scientific commentary refers to ‘A network centred on the inferior frontal cortex is critically involved in levodopa-induced dyskinesias’ by Cerasa et al. (doi: 10.1093/brain/awu329).

Pioneers of levodopa treatment for Parkinson’s disease in the 1960s quickly realized that the dramatic motor improvement was often clouded by the occurrence of involuntary movements never previously seen in the disorder (Lees et al., 2015). Levodopa-induced dyskinesias (LIDs) have been a common problem ever since and are one of the main reasons for recommending surgical treatment in advanced cases of Parkinson’s disease. In this issue of Brain, Cerasa and colleagues test the hypothesis that LIDs arise not only from the compromised basal ganglia motor circuit at the heart of Parkinson’s disease but from disturbances in areas of frontal cortex (Cerasa et al., 2015).

LIDs comprise a range of abnormal movements that may be distinguished according to presentation and type. The most common are choreic and sometimes dystonic movements that coincide with high plasma levodopa levels and maximal anti-parkinsonian benefit; hence, these are referred to as ‘peak dose’ or ‘ON’ period dyskinesia (Fahn, 2000). Experimental models are limited to such ‘peak dose’ presentation, which is the most studied type of LID. However, the pathophysiological mechanisms that cause LIDs are still incompletely understood. Classically, it has been proposed that LIDs are related to the degree of nigrostriatal neurodegeneration and striatal changes associated with chronic levodopa therapy (Obeso et al., 2000). These interact to induce plastic synaptic abnormalities in striatal medium spiny neurons, which has the effect of altering neuronal activity in striato-pallidal circuits and leads to reduced and abnormal activity in the subthalamic nucleus (STN) and globus pallidus pars interna (Obeso et al., 2000). Observations in the monkey and in patients with Parkinson’s disease suggest strongly that most of the abnormal neuronal activity associated with LIDs occurs in sensorimotor areas of the corticobasal ganglia-thalamo-cortical loop. Thus, local administration of GABAergic drugs (e.g. bicuculline, muscimol) in the STN or in the globus pallidum pars externa provokes dyskinesias when the drugs are injected into the postero-lateral portion of these nuclei (i.e. the motor region) but not when they are delivered ventromedially (i.e. to associative and limbic regions) (Perier et al., 2002). Importantly, pallidotomy can abolish LIDs in patients when the lesion targets the motor region of the globus pallidum pars interna, but is much less effective with more rostrally placed lesions (Gross et al., 1999). Similarly, thalamotomy has a potent antidysskinetic effect when targeted at the pallidal receiving territory (Page et al., 1993).