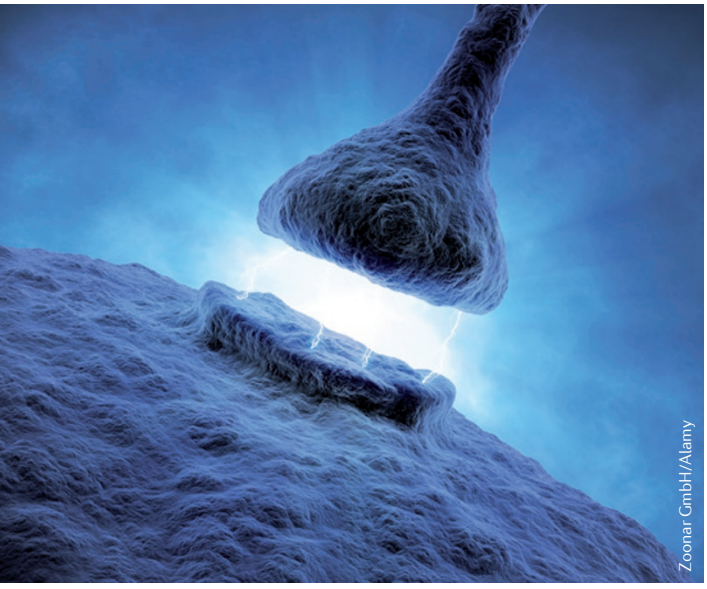
Nature Reviews Drug Discovery | AOP, published online 22 August 2014; doi:10.1038/nrd4418

EPILEPSY

Endocannabinoid metabolism offers handle to dampen down excitability

Current drugs for epilepsy mainly target voltage-gated ion channels to reduce the aberrant neuronal excitability that underlies seizures, but almost one-third of patients are refractory to treatment. Now, reporting in *Neuron*, Nephi Stella and colleagues show that targeting the serine hydrolase α/β-hydrolase domain 6 (ABHD6), which is involved in endocannabinoid (eCB) metabolism, can protect against seizures in mouse models of epilepsy.

The eCB system in the brain controls presynaptic neurotransmitter release. The two main eCBs are anandamide and 2-arachidonoylglycerol (2-AG), which are produced 'on-demand' by specific lipases in response to synaptic activity, and are inactivated by specific hydrolases. In a process called presynaptic inhibition, eCBs produced by postsynaptic neurons can act retrogradely on CB_1 receptors on presynaptic terminals, leading to a reduction of neurotransmitter release. Synthetic agonists of CB_1 receptors have been shown to protect against seizures in rodent models. However, these agents can cause motor and cognitive impairment, precluding further development.



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Based on their recent discovery that ABHD6 fine-tunes the production of 2-AG in the postsynaptic neuron, the authors investigated whether inhibitors of ABHD6 may boost presynaptic inhibition and exert anticonvulsant effects.

The small molecule WWL123 was identified in a screen for serine hydrolase inhibitors as a specific ABHD6 inhibitor, and found to be blood–brain barrier penetrant. In a mouse-model of pentylenetetrazole (PTZ)-induced seizures, pre-treatment with WWL123 by intraperitoneal injection blocked seizure-related mortality and reduced the severity and frequency of seizures. To test whether this effect was mediated via enhanced activity of 2-AG on CB_1 receptors, the experiments were repeated in CB_1-knockout mice. Surprisingly, WWL123 retained its anti-seizure effect in these mice, and also in mice that were deficient for CB_2 (the other, predominantly non-neuronal, eCB receptor) — leading the authors to investigate which other receptor might reduce seizure risk in response to 2-AG.

As recent studies had shown that 2-AG can also act as a positive allosteric modulator of $GABA_A$ (γ-aminobutyric acid, type A) receptors, which are expressed postsynaptically and mediate inhibitory neurotransmission, WWL123 was tested in combination with the $GABA_A$ receptor antagonist picrotoxin in the PTZ-induced seizure model. Picrotoxin abolished the anti-seizure effects of WWL123, indicating a role for $GABA_A$ receptors in the mechanism of action of WWL123.

WWL123 was also tested in R6/2 mice, which develop spontaneous seizures. Mice were injected daily with WWL123, which reduced the incidence of spontaneous seizures. Combination treatment with the CB_1 inhibitor SR1 did not antagonize the effect of WWL123, again demonstrating that there is no CB_1 receptor involvement in the protective effect of WWL123.

Together, these data indicate that WWL123 exerts its anti-epileptic activity by increasing the levels of 2-AG through inhibition of its negative regulator ABHD6, leading to allosteric activation of $GABA_A$ receptors and increasing inhibitory neurotransmission, thereby reducing hyperexcitability. Importantly, unlike CB_1 receptor agonists, the compound did not induce cognitive or motor impairment. Also, there was no evidence of tolerance induced by chronic treatment. This suggests that ABHD6 inhibitors may be amenable to long-term use, and have potential as a novel anti-epileptic strategy.

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ORIGINAL RESEARCH PAPER Naydenov, A. V. *et al.* ABHD6 blockade exerts antiepileptic activity in PTZ-induced seizures and in spontaneous seizures in R6/2 mice. *Neuron* **83**, 361–371 (2014)