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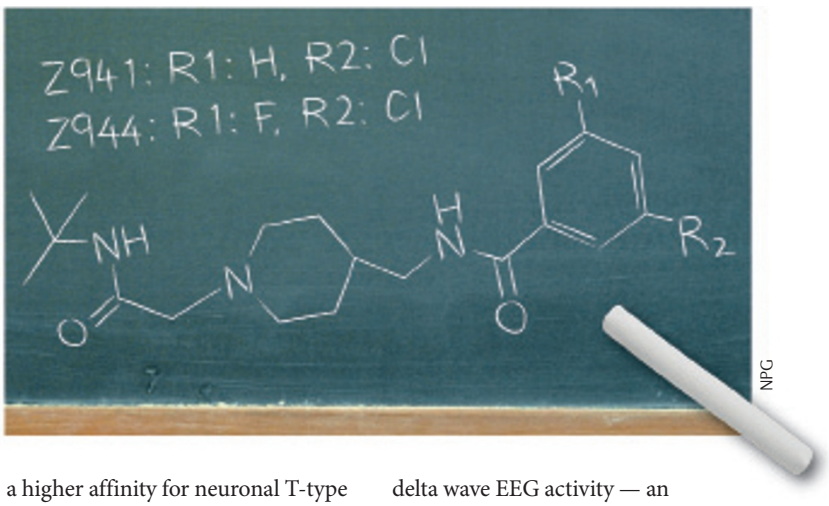
NEUROLOGICAL DISORDERS

A class of its own

Absence seizures — which are a common type of seizure in children with genetic generalized epilepsy — could now be treated by a potential new class of drugs with enhanced selectivity and efficacy over the drugs that are currently used in the clinic.

The molecular mechanisms underlying absence seizures are unclear; nevertheless, current literature indicates that the low-voltage-activated Cav3.1 and Cav3.2 T-type calcium channels have a crucial role. T-type calcium channels are also thought to be the site of action of the first-line drug ethosuximide; however, as it is nonspecific, ethosuximide causes side effects such as drowsiness, and not all patients respond to treatment. Therefore, the authors sought to identify a more specific and potent T-type calcium channel blocker.

A rational drug design approach produced two candidates — Z941 and Z944 — that had suitable properties for further development. They both had nanomolar affinities for Cav3.2 channels and significantly improved potencies compared to ethosuximide and valproate (another drug used for treating absence seizures). Importantly, Z944 has a higher affinity for the inactivated state of T-type channels (the state that is predominant during seizure activity) than for the closed state, and



NPG

a higher affinity for neuronal T-type channels than for the cardiovascular-related channels.

In a rat model of absence epilepsy (GAERS model), Z941 and Z944 significantly reduced the time spent in seizure activity and the number of seizures per hour. Interestingly, Z941 and Z944 were also able to reduce the individual duration of seizures, an effect not previously seen with other antiepileptic drugs investigated so far in the GAERS model. By comparing electroencephalogram (EEG) traces, it was shown that these two compounds reduced the cycle frequency of spike-and-wave discharges (distinct patterns observed in patients experiencing absence seizures) compared with ethosuximide. Moreover, Z944 did not affect delta wave EEG activity — an indication that it does not induce drowsiness. The two investigational compounds were also well tolerated and minimal neurotoxic effects were observed.

Together, these results suggest that Z941 and Z944 constitute a potential new class of drugs for treating absence seizures. Indeed, Z944 has been selected for progression into Phase I studies.

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ORIGINAL RESEARCH PAPER Tringham, E. *et al.* T-type calcium channel blockers that attenuate thalamic burst firing and suppress absence seizures. *Sci. Transl. Med.* **4**, 121ra19 (2012)
FURTHER READING Bialer, M. & White, H. S. Key factors in the discovery and development of new antiepileptic drugs. *Nature Rev. Drug Discov.* **9**, 68–82 (2010)