For most of the twentieth century, the development of medications to treat epilepsy relied on trial and error. “The drugs were taken through development and introduced on to the market before any molecular target or targets in the brain were identified,” says Michael Rogawski, a neurologist at the University of California, Davis, adding that we still don’t know the molecular target for some agents.

In the 1960s, for example, researchers in France noted that every drug they tested reduced seizures in animals. The reason, they discovered, was that they had dissolved their compounds in valproic acid, a common practice back then. It was the solvent — not the candidate drugs — that was responsible for the anticonvulsive effects. They’d accidently uncovered the potential of a drug now known as valproate. Within a year, valproate was approved and is now the most widely prescribed antiepileptic drug in the world.

Despite such successes, there is a growing realization that the old approaches are not enough. Existing medications control seizures in about 70% of people with epilepsy, but for those 30% with drug-resistant seizures, treatments remain scarce. To move forward, pharmaceutical companies and other researchers are looking to change tack. Some are shifting away from the traditional rodent model so they can ramp up their ability to screen many compounds. Others are exploring new treatments aimed at specific molecular targets.

FISH FOR SUCCESS

The traditional way of testing for antiepilepsy drugs involves the generation of epilepsy-like convulsions in rats and mice by administering electrical stimuli or chemicals such as pentylenetetrazol. A drug developer administers compounds to find ones that protect the animals from the seizures, and these then move on to human clinical trials. Nearly all of the 25 or so marketed antiepileptic drugs were identified this way, says Rogawski.

To test a wider range of targeted treatments, some researchers are turning to animals that are easier and cheaper to keep, and quicker to breed, than rodents — such as fish. Scott Baraban, a researcher at the University of California, San Francisco, has been investigating Dravet syndrome, a rare and severe form of epilepsy that affects children. It is one of the most drug-resistant types of epilepsy. Around 70–80% of patients with Dravet syndrome carry a mutation in a gene called SCN1A, which plays a fundamental role in activating neurons; the...
Some other researchers ran into trouble getting the drugs to the intended target; one drug they tested couldn’t cross the blood–brain barrier. “Eisai, from the start, had strict criteria: they wanted a potent, orally active molecule with the right properties” including reaching and binding to the receptor, says Kate Carpenter, medical affairs manager at Eisai. It took more than 12 years to move a developmental compound into an approved product. Perampanel is currently approved as an add-on treatment for patients with partial-onset seizures (seizures that affect only one hemisphere of the brain).

Researchers see the potential for other drugs aimed at receptors related to epilepsy. Studies have shown that a neurotransmitter called γ-aminobutyric acid (GABA) can inhibit neurons that tend to get overexcited during an epileptic seizure (see page S4). So it might be possible to design a drug that could produce this inhibition by raising the availability of GABA, as valproate does through unknown means. Or a drug might directly activate GABA receptors, with similar effects.

Rogawski and his colleagues are working on neuroactive steroids, which target a class of GABA receptors known as GABA<sub>α</sub> receptors. Specific mutations that make this receptor insensitive can trigger epilepsy. Conversely, a drug that turns on the GABA<sub>α</sub> receptor could potentially be used to inhibit epileptic seizures.

Researchers are also attempting to develop therapies through studying the mode of action of existing antiepileptic medications. In 1999, the Belgian pharmaceutical firm UCB, in Brussels, received approval from the FDA for a drug called levetiracetam as a treatment for epilepsy. Levetiracetam binds to a protein called synaptic vesicle glycoprotein 2A (SV2A), which is found in a wide range of neuronal vesicles — spheres that contain neurotransmitters. The drug seems to inhibit the release of neurotransmitters that contribute to uncontrolled activity of the central nervous system in epilepsy<sup>4</sup>, but it has the drawback of side effects including dizziness, drowsiness and infections such as the common cold. UCB scientists started to look for alternative compounds that bind to SV2A and found brivaracetam<sup>5</sup>, which resembles levetiracetam in structure but binds more strongly to SV2A. It is currently in phase III trials. Higher affinity for its target should allow brivaracetam to be effective at lower doses, meaning fewer side effects<sup>6</sup>.

**LIGHT AHEAD**

Despite advances in identifying molecular targets for drugs, the number of improved or new antiepilepsy medications has been slight. Consequently, many of the major pharmaceutical companies — with the notable exceptions of UCB, Eisai and Pfizer — no longer have epilepsy programmes. That leaves the bulk of the discovery and development work to academics, small biotech firms and specialty pharmaceutical companies. The result is a limited number of players in the field and some of them, such as academics, are unable to finance clinical trials, which explains the low number of trials recruiting patients to test epilepsy treatments (see ‘New treatments trickling in’).

Schmidt is optimistic that future research will lead to the development of drugs that will reach specific molecular targets and with fewer unwanted side effects. If we could understand how and why epilepsy develops in the first place, it might even be possible to prevent the condition in people at high risk, such as those who have had severe head trauma or stroke. ■

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