Abstractions

FIRST AUTHOR

Geologists have long believed that a collision between the world's largest and thickest oceanic plateau, the Ontong Java Plateau (OJP), and the Australian plate may have triggered a reorganization of tectonic plates in the South Pacific. But how or when the collision occurred has been unclear — in part because the evidence is deep beneath the ocean. Earth scientist Kurt Knesel and his colleagues at the University of Queensland, Australia, sought more accessible land-based evidence in Australia's volcanoes. On page 754, they provide evidence of a previously unknown short-lived period of slowed plate motion. Knesel tells *Nature* that these results help to resolve several ongoing debates.

Little is known about the OJP. Why?

It is buried under kilometres of sediment, making it difficult to sample. It is the size of Greenland, but we aren't certain when it formed or how long this took.

How did you study plate tectonics on land?

We used argon isotopes to chronicle the age of the lava flows in more than 100 eastern Australian volcanoes to track their migration over time. Hotspots of volcanic activity — driven by plumes of deep upwelling mantle — often occur at plate boundaries, which drift, allowing us to use the geometry and age distribution of volcanic chains as a forensic tool. We found that southward migration of land-based volcanoes slowed drastically 26–23 million years ago, which suggests slowing plate motion.

Do your findings correlate with oceanic clues?

We looked for volcanic remains on the seafloor that corresponded in time and space to our estimate of the OJP's arrival. My co-author Ben Cohen noticed bends in two chains of volcanoes off eastern Australia. The chains had been offset at the same time that volcano migration slowed on land, lending further weight to the idea that the OJP arrived at that time and caused the westward plate motion. We think the OJP's arrival blocked the Australian plate's northerly movement, rapidly altering the pattern of volcanic activity.

What does your work tell us about the collision's impact?

Our results show how the OJP's immense size contributed to plate reorganization. They also inform a separate ongoing debate about whether hotspots themselves can drift. To determine that, we have to be able to separate the plate's motion from the hotspot's motion. ■

MAKING THE PAPER

David Colquhoun & Lucia Sivilotti

Flipping the switch on ion channel 'partial' activation.

David Colquoun (left) and Lucia Sivilotti.

Many drugs work by binding to specific cell receptors and stimulating the receptors' activity, triggering a cascade of events in the cell. Such drugs, and naturally occurring chemicals with the same modus operandi, are called agonists. Some elicit a powerful response, whereas others generate a smaller response, even when they are at high enough levels to occupy all the available receptors. The latter are known as partial agonists. They can make good therapeutics, with low toxicity and few side-effects, but exactly how they work has been unclear.

In the case of ligand-gated ion channels, agonist binding opens the channel and allows ions — and so current — to cross the cell membrane. Since their discovery in the 1950s, it has generally been assumed that partial agonists produce a weaker response because they are less efficient at keeping ion channels in their open state. Now two pharmacologists at University College London, David Colquhoun and Lucia Sivilotti, and postdoc Remigijus Lape have found a mechanism that explains how receptors respond to partial agonists.

"Up until 2004, everyone supposed that ion channels existed in only two states: shut or open," says Colquhoun. "But both we and others wondered whether there might be intermediate shut states." At the end of that year, he, Sivilotti and their colleagues proposed a new explanation of agonist binding in the *Journal of Neuroscience*. According to this theory, an agonist-bound receptor can exist in one of three states: resting (shut), partially activated (in which its shape has changed, or 'flipped', from resting but it is still shut) and open. Now they show the role of flipping in the responses of acetylcholine and glycine receptors to full and partial agonists (see page 722). They find that partial agonists can open receptors just as well as agonists — where they falter is in producing the flip.

Earlier work on a mutant glycine receptor that causes a neurological disorder known as 'startle disease' pointed the researchers in the right direction to verify the three-state explanation experimentally. Once they had done this, they came to the question of what makes a partial agonist partial. "The conventional models didn't fit very well," says Colquhoun.

Acetylcholine and glycine are natural neurotransmitters and powerful agonists, keeping their respective receptors open almost continuously (94–98% of the time). By contrast, taurine, a partial agonist of the glycine receptor, holds receptors open only about 54% of the time, and, similarly, tetramethylammonium keeps the acetylcholine receptor open just 78% of the time. The authors measured the effects of these compounds on the opening of individual ion channels from humans and rats.

> **"I think it is one of the best things I've been associated with."**
> — David Colquhoun

Along the way, they encountered several hurdles. Purity, says Sivilotti, was a big problem. During manufacture, the group's taurine was contaminated with glycine — only tiny amounts, but sufficient to ruin the work. Discovering the contamination and rectifying it took well over a year. "It was a major step finding someone to purify it because, as electrophysiologists, we couldn't have done it easily ourselves," says Sivilotti.

Detecting the 'flipped' change in receptor shape was also difficult. The channels stay in the partially activated state for only a very brief period — about 8 microseconds. The researchers turned to statistician Alan Hawkes at Swansea University in Wales, who had developed computer programs to analyse single-channel recordings. "These involve sophisticated mathematics," says Colquhoun, "and were crucial to the analysis." The analysis revealed that when a channel is bound by glycine, it flips quickly. But when taurine binds, it takes almost 30 times longer to flip. Once the channel has reached the flipped state — regardless of which chemical has bound — it opens very quickly.

Lape, who did the experiments and the bulk of the analysis, says that a lot of their early data on mutant glycine receptors seemed odd and were difficult to interpret. The new three-step mechanism could explain those puzzling results.

Both Colquhoun and Sivilotti say that Lape's patience and persistence was central to the project's success. "He was unwilling to publish half-baked work," says Colquhoun. The work is also a bit of a swansong for Colquhoun, who has been studying ion channels for more than three decades. "I think it is one of the best things I've been associated with, so I'm quite excited about it, and I don't think I'll improve on it now," he says. "It's not going to be my last paper, but in terms of mechanisms, this is the one I'm most pleased with." ■

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