Sodium ion unlocks understanding of channel blockade

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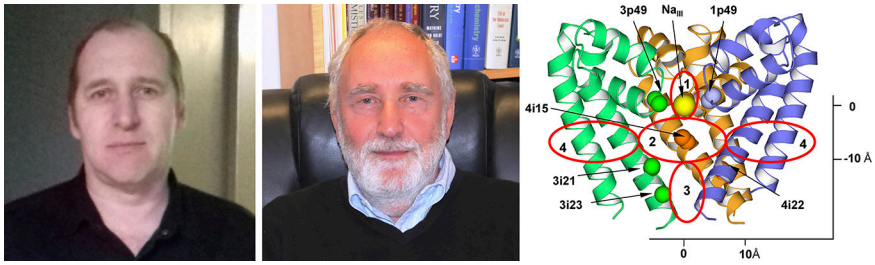
New simulations explain how several types of drugs block sodium channels.



Simulations performed by co-authors Denis Tikhonov (left) and Boris Zhorov (right) demonstrate how sodium channel blockers that bind near the Nav1.4 selectivity filter (circled region 1) achieve current blockade in the presence and absence of a sodium ion (yellow). PHOTOS COURTESY OF THE AUTHORS.

Sodium channel blockers have applications in many medically important settings (1). In their paper published this month in JGP, Denis Tikhonov and Boris Zhorov show how local anesthetics, antiarrhythmics, and anticonvulsants achieve sodium channel blockade (2).

A survey of the structural features of these drugs gives little hint of how they might work; they don't seem to have much in common. Local anesthetics like lidocaine are small molecules, with a positively charged ammonium group at one end linked to a polar moiety and an aromatic ring. Anticonvulsants such as carbamazepine also have an aromatic ring at one end, but they're capped with a polar group at the other and are electroneutral. Meanwhile, cocaine resembles neither of these with its bulky and stiff structure. And yet, mutational studies have shown that all these compounds bind at the same site within the sodium channel's pore near the protein's ion selectivity filter.

"It's a paradox, and I love paradoxes," says Zhorov, Professor Emeritus at McMaster University in Canada. Many efforts have been made to investigate the positioning of sodium channel blockers within the channel pore, and various binding modes have been proposed for such drugs. But according to Zhorov, most of these models were missing something.

"Our basic idea was that many drugs work in ion channels…in complex with permeant metal ions—in this case, with sodium," recalls Zhorov. Experimental support for this idea is lacking because the drugs have low affinity for sodium in solution, but Zhorov proposes that such interactions might be altered when they occur in the close confines of an ion channel's pore. In fact, prior studies from Zhorov's group have pointed to interactions between the sodium channel toxin batrachotoxin and permeating sodium ions (3) and shown that electroneutral drugs bind potassium to block potassium channels (4).

However, it wasn't known whether—or where—sodium ions might be available to interact with channel-blocking drugs until the publication of an x-ray crystallographic structure of the bacterial sodium channel NavMs. The structure showed the channel in a presumably open conformation, with a sodium ion caught in the act of passing through the channel and perched near the site where the various sodium channel blockers bind (5). There is also a NavMs structure showing a local anesthetic in the pore (6). Spurred by these discoveries, Tikhonov and Zhorov used the bacterial channel structure to develop a model of the eukaryotic sodium channel Nav1.4 and then used Monte Carlo energy minimization simulations to explore possible binding configurations for lidocaine and carbamazepine within the channel pore.

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Consistent with the structural data and other studies, the simulations suggested lidocaine's positively charged ammonium group may evict the sodium ion from its perch, while other portions of the drug contact amino acid residues lining the channel's pore. Ensconced in this orientation, lidocaine's ammonium group would repel permeating ions from the pore. Cocaine, with its bulky ammonium group, jams its way into the sodium ion's roost in an analogous manner. In contrast, the polar group on electroneutral carbamazepine binds the sodium ion, immobilizing it where it can repel additional incoming ions.

The researchers then found that other local anesthetics and anticonvulsants readily followed these patterns of binding. Even structurally dissimilar compounds, such as the pollutant bisphenol A and the anticonvulsant lamotrigine, incorporated interactions with the sodium ion to block the pore. "Only when we couldn't falsify our hypothesis did we start believing it," says Zhorov.

These explanations for how drugs bind at this region of the sodium channel should prove useful to computational chemists seeking to identify novel sodium channel blockers, who can now model drug–channel interactions in the presence and absence of the sodium ion to obtain more candidates for high-throughput screens. For his part, Zhorov wants to solve other paradoxes in drug–ion channel interactions.

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