of inflammatory and neuropathic pain. Moreover, gain-of-function mutations of $Na_V1.7$ have been found in patients suffering from inherited pain disorders, whereas loss-of-function mutations result in congenital insensitivity to pain. This thereby tightly link $Na_V1.7$ function to capability of experiencing pain. Likewise, gain-of-function mutation in $Na_V1.8$ and $Na_V1.9$ lead to small-fiber neuropathy and congenital insensitivity to pain, respectively. From a therapeutic point of view, these α-subunits are therefore of particular interest, since compounds capable of selectively blocking $Na_V1.7$–$Na_V1.9$ channels could have great potential as analgesics.

13.4.3 Pharmacology of Voltage-Gated Sodium Channels

A large number of natural products (peptides and alkaloids) have been found to bind Na_Vs with high affinity. Radioligand binding, photoaffinity labeling, and mutagenesis techniques have been used to identify the regions of the α-subunit to which these substances bind. Six binding sites for these toxins are therefore used to provide the conceptual framework for understanding the pharmacology of Na_Vs (Table 13.3; Figure 13.9b). Given the high degree of homology between the Na_V1 subunits, very few examples of subunit-selective toxins are known. The substances mentioned in Table 13.3 thus bind to nearly all Na_V1 subunits. Most toxins act as gating modifiers, and only tetrodotoxin and saxitoxin binding to site 1 are pore blockers. The crystal structure of a homologous bacterial Na_V channel demonstrated how the binding sites create a drug site that when occupied blocks the pore. Access to this site by hydrophilic or larger molecules requires opening of the intracellular gate. This helps to explain how use-dependent block by anesthetics and other drugs arise, because they would bind more when the channel is opened frequently. The structure also revealed fenestrations in the sides of the pore penetrated by fatty acyl chains that extend into the central which could function as portals for the entry of small, hydrophobic resting state pore-blocking drugs.

In addition to toxins, a number of clinically used drug molecules are known to exert their pharmacological action through inhibition of Na_V function. Consistent with the physiological roles of Na_Vs, these drugs include antiepileptic compounds (carbamazepine, lamotrigine, phenytoin), local anesthetic and analgetic compounds (lidocaine), and drugs used to treat cardiac arrhythmia (class I anti-arrhythmics including quinidine, lidocaine, mexiletine, and flecainide). Recently, a lot of effort has been placed on finding subtype-selective Na_V blockers, especially targeting $Na_V1.7$ for treatment of pain, with several compounds demonstrating different levels of subtype selectivity and with several compounds having entered clinical trials. For now, the latest marketed drug is lacosamide which was approved in 2008 for the treatment of diabetic neuropathic pain and partial onset seizures.

TABLE 13.3
Toxin Binding Sites on Na_V Channels

Site No.	Site Location	Toxins Binding to Site	Mechanism of Action
1	Selectivity filter of pore	Tetrodotoxin, saxitoxin	Pore block
2	Interface between the S6 segments of domains I and IV	Plant alkaloid toxins: grayanotoxin, batrachotoxin, and veratridine	Inhibition of inactivation and channel opening at resting potential
3	Outer pore loop regions of domains I and IV	Sea anemone peptide toxins and α-scorpion toxins	Slow inactivation
4	Extracellular S3–S4 loop close to the voltage sensor	Large β-scorpion peptide	Enhance opening at negative membrane potential
5	Interface between the IS6 and IVS5 segments	Plant alkaloids ciguatoxins and brevetoxins	Enhance activation and inhibit inactivation
6	Unknown	δ-Conotoxins	Slow inactivation