channels—presumably the ones responsible for a given disorder—will be inhibited, while less frequently activated channels are spared, thereby reducing the risk of adverse effects.

13.3.3.2 Ca_V2 Family (N-, P/Q-, and R-Type Current)

Within this family, the $Ca_V2.2$ subunit (N-type current) has attracted the most attention as potential drug target. The most efficient inhibitors of N-type currents are peptide toxins isolated from the venom of fish-eating marine snails that use these toxins to paralyze their prey. The category includes the 25–30 amino acid residue peptides ω-conotoxin GVIA and ω-conotoxin MVIIA (Figure 13.8) which bind to $Ca_V2.2$ with very high affinity and selectivity. Binding of ω-conotoxin GVIA mainly occurs to residues located in the pore loop region of domain III, suggesting that this toxin acts as a pore blocker of the $Ca_V2.2$ subunit.

The reason for the pharmacological interest in $Ca_V2.2$ is that these channels are responsible for neurotransmitter release in neural pathways relaying pain signals to the brain. Although ω-conotoxins are poorly suited for use as drugs because of their lack of biomembrane permeability, ω-conotoxin MVIIA (Ziconotide/Prialt®) was recently approved for use in humans. Since the drug has to be given through an intrathecal catheter to circumvent the blood–brain barrier, the clinical use of ω-conotoxin MVIIA is limited to severe chronic pain in particular patients such as those suffering from terminal cancer or AIDS. A search for selective, nonpeptide $Ca_V2.2$ blockers that can be administered orally is still ongoing.

$Ca_V2.1$ channels (P/Q-type current) are generally involved in neurotransmitter release in most synapses throughout the brain. $Ca_V2.1$ can be blocked by peptide toxins from either *Conus* snails (ω-conotoxin MVIIC) or from spider venom (ω-agatoxin IVA) (Table 13.2). From a drug discovery point of view their widespread role in neurotransmitter release represents a major safety liability.

The function(s) and pharmacology of $Ca_V2.3$ channels (R-type current) are not well understood. As is the case for $Ca_V2.1$ no selective inhibitor of $Ca_V2.3$ has been declared. A peptide toxin, SNX-482, isolated from tarantula venom was initially thought to be a selective blocker of $Ca_V2.3$ channels, but was later found to block other Ca_V, Na_V, and for K_V channels even at lower concentrations.

13.3.3.3 Ca_V3 Family (T-Type Current)

Certain small-molecule compounds appear to act as moderately selective blockers of Ca_V3. The vasodilating compound mibefradil (Figure 13.8) which has been used widely for treatment of hypertension and angina pectoris, inhibits $Ca_V3.1$–$Ca_V3.3$ channels in a use-dependent way with ~10-fold selectivity over $Ca_V1.2$ channels. Moreover, certain novel dihydropyridine compounds (e.g., (*R*)-efonidipine, Figure 13.8) inhibit Ca_V3 channels up to ~100-fold more potently compared to Ca_V1 channels. It is not yet known exactly how these compounds interact with Ca_V3, but this family of ion channels could have the potential as drug targets for treatment of cardiovascular disease. Certain classical antiepileptic compounds, such as ethosuximide, phenytoin, and zonisamide exert their antiepileptic action at least partly via inhibition of Ca_V3 channels. Substances such as nickel ions (Ni^{2+}), *n*-octanol, and the diuretic amiloride display moderate selectivity for Ca_V3 channels over the other Ca_V channel types. Kurtoxin is a scorpion venom toxin which produces potent blockade of Ca_Vs containing $Ca_V3.1$ and $Ca_V3.2$ but not $Ca_V3.3$ subunits.

13.3.3.4 Auxiliary Subunits

The drugs gabapentin and the more recently developed pregabalin are used clinically for the treatment of epilepsy and neuropathic pain. Their mechanism of action was not understood before the discovery that gabapentin binds with extremely high affinity to the $\alpha_2\delta$ subunit of Ca_Vs. This impairs the trafficking function of $\alpha_2\delta$ subunit which normally increases Ca_V channel cell surface expression. Thereby, gabapentin decreases the amplitude of calcium currents partially without producing the complete blockade seen with Ca_V inhibitors targeting the α_1 subunit. Both $Ca_V2.1$ and $Ca_V2.2$ are involved in mediating the effects of gabapentin/pregabalin. Both drugs are nontoxic which may be related to their partial blocking effect.