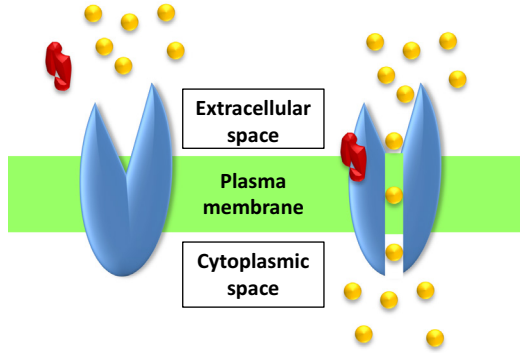

FIGURE 3.31 Ligand-gated channels are closed in the absence of a ligand (red). Binding of the ligand to channel leads to conformational changes that cause the channel to open, allowing migration of suitable ions through the channel. Removal of the ligand causes the channel to close, stopping ion flow. Ligand-gated channels can be activated by synthetic ligands or blocked with antagonists (compounds that bind to the ligand-binding site, but do not lead to channel opening). Direct blockade of the channel is also possible.

Modulation of ligand-gated channel activity can be accomplished in a number of ways. Activation of the channel can be accomplished with compounds that mimic the natural ligand. Nicotine, for example, is an agonist of nAChR, and its activity at this ligand-gated channel is at least partially responsible for activation of reward system of the brain by tobacco products.[66] The smoking-cessation medication Chantix® (Varenicline) is a partial agonist of nAChR, and provides a lower level of channel activity upon binding than nicotine.[67] It has been successfully employed to decrease the cravings and the pleasurable effects of nicotine, as it competes with nicotine for the same binding site on nAChR (Figure 3.32).[68]

Blocking activity of a ligand-gated channel is also possible. Compounds that compete for the natural ligands binding site, but do not cause the conformational changes associated with ligand binding will prevent opening of the channel, acting as functional antagonists. Similarly, compounds that bind to an allosteric site and either stabilize the closed form of the channel or cause conformational changes that prevent binding of the natural ligand also act as functional antagonists. The α-neurotoxins, for example, are a family of peptides from snake venom that are antagonists of postsynaptic nAChR located in neuromuscular synapses (Figure 3.33). These relatively small proteins (60–75 amino acid residues) tightly bind to nAChR in skeletal muscle, preventing acetylcholine-mediated neurotransmission through the opening of nAChR, causing paralysis in snake bite victims.[69] Of course, it is also possible to block the channel itself. In this case, the presence of an ligand opens the