Stretch-Activated Channel Blockers

for muscle, sensory & CNS disorders

Stretch-activated cation channels (SACs) are wide-spread in the body and trigger cellular responses to mechanical stresses. SACs mediate the senses of touch and hearing and help to regulate organ functions. GsMTx4, a tarantula venom peptide, and its mirror-image enantiomer selectively block SACs. By blocking the channels, GsMTx4 and its enantiomer offer a potentially powerful therapy for arrhythmia, congestive heart failure, incontinence, muscular dystrophy, CNS disorders and other possibilities.
OVERVIEW

Stretch-activated cation channels (SACs) convert mechanical stress to cellular signals by opening when the membrane around them is stretched. When open, SACs allow cations including Na⁺, K⁺, and Ca²⁺ to flow into the cell and trigger a response. SACs are involved in hearing, touch, muscle coordination, blood pressure and regulating hollow organ filling such as the bladder and lungs. At the cellular level, they control cell volume and calcium levels. Many cell signaling events depend on calcium levels such as programmed cell death.

When overly active, SACs are involved in many pathologies including congestive heart failure, arrhythmia, incontinence, CNS disorders and muscular dystrophy.

Until this invention, there were no specific inhibitors for SAC channels, making it difficult to study their function or to treat the conditions in which they are involved.

INVENTION

A specific inhibitor for SAC channels, GsMTx4, has been isolated from the Chilean Rose tarantula. GsMTx4 inhibits SACs from a variety of cell types including chicken heart, rat astrocytes and skeletal muscles and human smooth muscle cells.

GsMTx4 is specific to SACs and does not interfere with other channels or transporters. For instance, it will not depolarize neurons which allows the neurons to function properly.

Tarantula venom is a complex mix considered non-toxic to humans. The venom mix is designed to paralyze, keep alive (temporarily) and digest the spider’s prey. GsMTx4 appears to be non-toxic both to spider prey and to mice.

The structure of GsMTx4 gives it several important features. The peptide structure is shown in figure 1. It consists of 34 amino acids with a molecular weight of about 4 kD. The low molecular weight simplifies drug administration and manufacture. It also has 3 disulfide bonds which increase its stability. Its amphilic nature allows it to be water soluble while still interacting with lipid membranes. In fact, it has a high affinity for SACs in the range of 500 nM.
Central Nervous System Disorders
Astrocytes undergo regulated volume decreases (RVD) during brain edema. As part of the process, SACs are involved with the calcium influx and membrane depolarization.

Advantages
Specific Activity
High Affinity
Stable
Wide Applicability
Digestion Resistant
Low Molecular Weight

Applications and Markets
Muscular Dystrophy
Cardiac Arrhythmias
Congestive Heart Failure
Incontinence
Ventilator Induced Lung Injury
Tumor Growth
CNS disorders

Applications
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PATENT STATUS
GsMTx4 is covered by patent US 7,125,847.
GxMTx4 enantiomer is covered by US 7,259,145.

Figure 3. The inward current (cation flow) was measured on rat astrocyte membranes. Pressure was applied to the membrane causing an inward cation flow in the control membrane. This flow was blocked by both GsMTx4 and its enantiomer, enGsMTx4.

Figure 4. Isolated rabbit hearts at various pressures were treated to induce fibrillation (hollow circles). The chance of causing fibrillation was drastically reduced when treated with GsMTx4 (solid circles). The effect is reversible when the GsMTx4 is removed. Further details can be found in Bode, et al., 2001.

Figure 5. Recovery of force following contractions of mdx muscles. Mdx mice are an animal model for muscular dystrophy.

Dr. Sachs and friend. Rosie, a Chilean Rose Tarantula, is a lab pet.
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