Technology Available for Licensing
UB Dockets 5593 and 5942

stor
UB Office of Science, Technology Transfer and Economic Outreach

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.

Stretch-Activated Channel Blockers
for muscle, sensory & CNS disorders

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 Ca^{2+} 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.

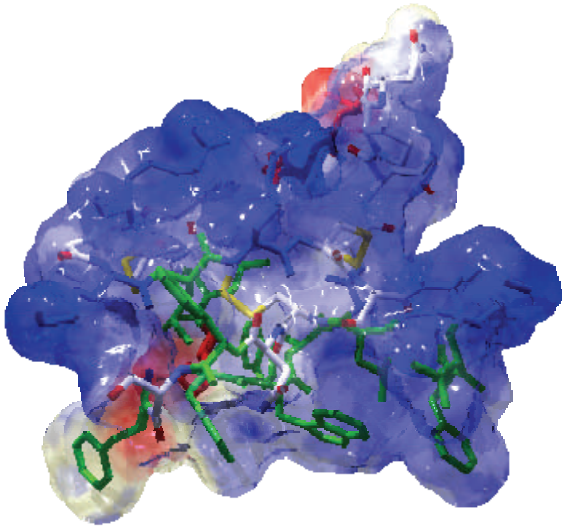

Figure 1. Rendered image of GsMTx4. GsMT4 is an amphilic molecule meaning it has a water soluble portion and a fat soluble side, much like a detergent.

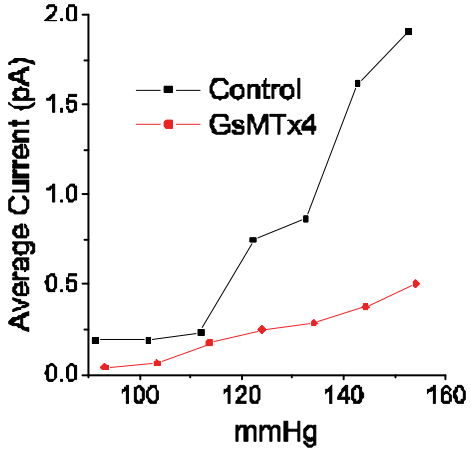

Figure 2. GsMTx4 increases the amount of pressure (x-axis) required to open the SAC and allow cations (y-axis: shown as current) to enter the cell.

In an important development, the mirror-image enantiomer of GsMTx4 is as effective as the original structure (see figure 3). "This was an awesome tool to find," according to Dr. Sachs, one of the co-inventors. "Because this peptide works in its right-handed form, and the normal left-handed digestive enzymes and left-handed antibodies don't recognize it, oral administration is a definite possibility. It may be more than a lead compound for drug development. It may work just as it is."

Intellectual Property Division, UB Technology Incubator, Suite 111, 1576 Sweet Home Road, Amherst, NY 14228
Tel: (716) 645-5500 Fax: (716) 645-3436 Web: www.stor.buffalo.edu

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.

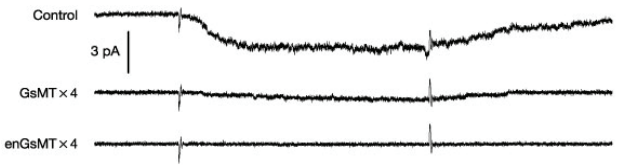

Figure 3. The inward current (cation flow) was measured on rat astrocyte membranes. Pressure was applied to the membrane causing an inward cation flow in the control membrane. This flow was blocked by both GsMTx4 and its enantiomer, enGsMTx4.

Arrhythmia

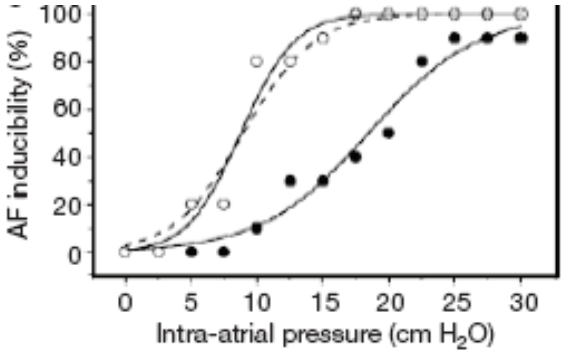

Figure 4. Isolated rabbit hearts at various pressures were treated to induce fibrillation (hollow circles). The chance of causing fibrillation was drastically reduced when treated with GsMTx4 (solid circles). The effect is reversible when the GsMTx4 is removed. Further details can be found in Bode, et.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

Muscular Dystrophy

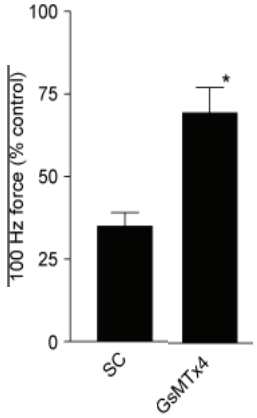

Figure 5. Recovery of force following contractions of *mdx* muscles. *Mdx* mice are an animal model for muscular dystrophy.

Advantages

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

Applications and Markets

Muscular Dystrophy
Cardiac Arrhythmias
Congestive Heart Failure
Incontinence
Ventalator Induced Lung Injury
Tumor Growth
CNS disorders

PATENT STATUS

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

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

Intellectual Property Division, UB Technology Incubator, Suite 111, 1576 Sweet Home Road, Amherst, NY 14228
Tel: (716) 645-5500 Fax: (716) 645-3436 Web: www.stor.buffalo.edu

Technology Available for Licensing
UB Dockets 5593 and 5942

stor
UB Office of Science, Technology Transfer and Economic Outreach

Stretch-Activated Channel Blockers

for muscle, sensory & CNS disorders

RELATED PUBLICATIONS

Bode F., Sachs F., Franz M. R., "Tarantula Peptide Inhibits Atrial Fibrillation". *Nature* 409:35-36 (2001).

Sachs F., "Heart Mechanoelectric Transduction", In: Jalife J, Zipes D, editors. *Cardiac Electrophysiology; From Cell to Bedside*. 4 ed. Philadelphia: Saunders (Elsevier); 2004. 96-102.

Suchyna, T. M., Tape, S. E., Koeppe, R. E., II, Andersen, O. S., Sachs, F. and Gottlieb, P. A., "Bilayer-Dependent Inhibition of Mechanosensitive Channels by Neuroactive Peptide Enantiomers", *Nature* 430: 235-240 (2004).

Chess, P. R., O'Reilly, M. A., Sachs, F. and Finkelstein, J. N., "Reactive Oxidant and p42/44 MAP Kinase Signaling is Necessary for Mechanical Strain-induced Proliferation in Pulmonary Epithelial Cells", Journal of Applied Physiology 99: 1226-1232 (2005).

Ostrow, L. W. and Sachs, F., "Mechanosensation and Endothelin in Astrocytes– Hypothetical Roles in CNS Pathophysiology", *Brain Research Reviews* 48: 488-508 (2005).

Yeung, E. W., Whitehead, N. P., Suchyna, T. M., Gottlieb, P. A., Sachs, F. and Allen, D. G., "Effects of Stretch-Activated Channel Blockers on $[Ca^{2+}]_i$ and Muscle Damage in the *mdx* Mouse", *Journal of Physiology* 562: 367-380 (2005).

Itabashi, Y., Miyoshi, S., Yuasa, S., Fujita, J., Shimizu, T., Okano, T., Fukuda, K., and Ogawa, S., "Analysis of the Electrophysiological Properties and Arrhymias in Directly Contacted Skeletal and Cardiac Muscle Cell Sheets", *Cardiovascular Research* 67:561-570 (2005).

Jacques-Fricke, B. T., Seow, Y., Gottlieb, P. A., Sachs, F. and Gomez, T. M., "Ca2+ Influx through Mechanosensitive Channels Inhibits Neurite Outgrowth in Opposition to Other Influx Pathways and Release from Intracellular Stores", *Journal of Neuroscience* 26:5656-5664 (2006).

Bowman, C. L., Gottlieb, P. A., Suchyna, T. M., Murphy, Y. K. and Sachs, F., "Mechanosensitive Ion Channels and the Peptide Inhibitor GsMTx-4: History, Properties, Mechanisms and Pharmacology", *Toxicon* 49:249-70 (2007).

CONTACT PERSON

Michael L. Fowler, Ph.D.
Commercialization Manager
UB Office of Science, Technology Transfer and Economic Outreach (STOR)
UB Technology Incubator, Suite 111
Baird Research Park
1576 Sweet Home Road
Amherst, NY 14228
Tel: (716) 645 - 8136
Email: mlfowler@buffalo.edu

PRIMARY INVENTORS

Philip Gottlieb and Tom Suchyna
Research Associate Professors
Department of Physiology and Biophysics

Frederick Sachs
Professor
Departments of Chemical and Biological Engineering,

University at Buffalo *The State University of New York*