

*Playing with Natural Toxins to Understand Neurotransmission  
In Health and and Disease States*

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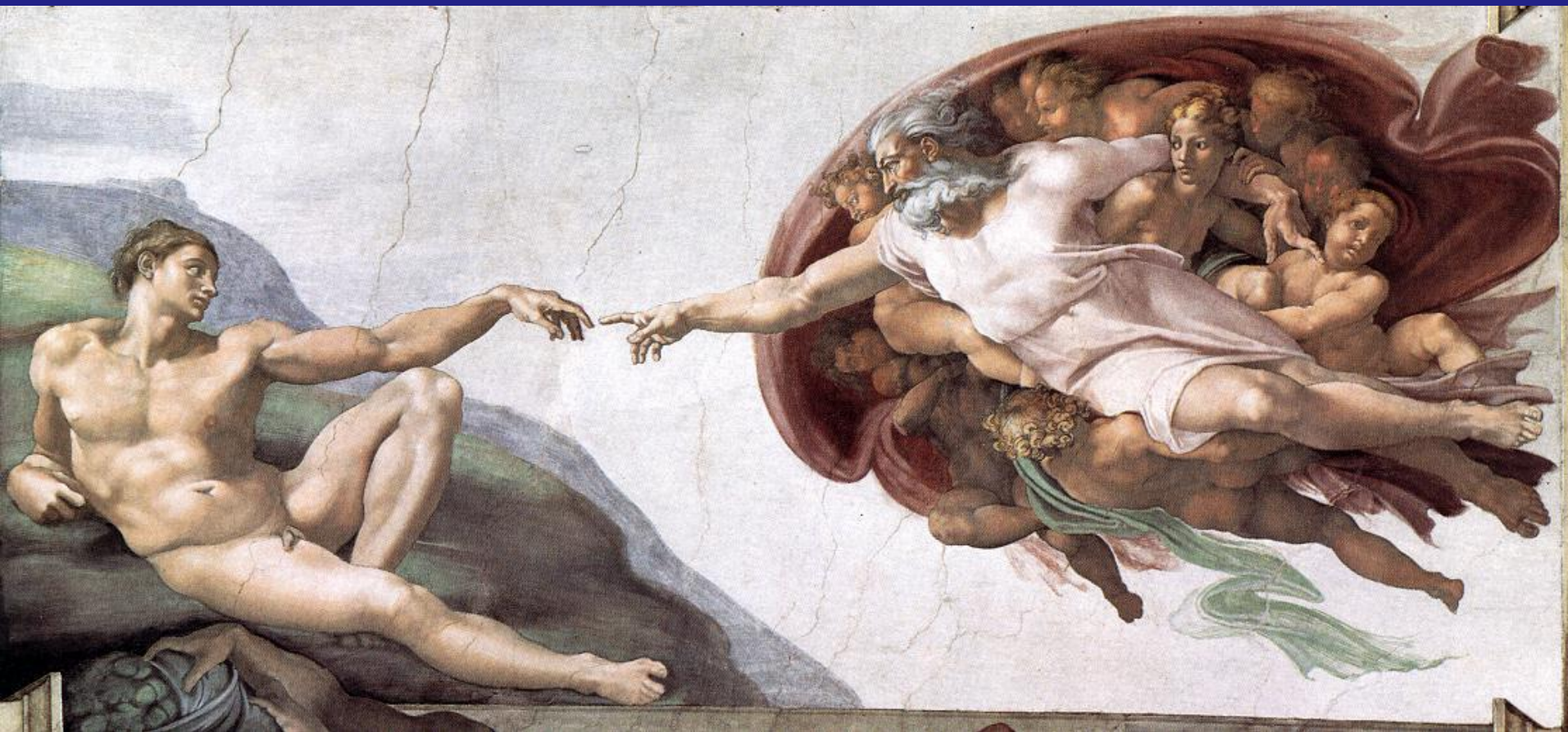
# Financial Disclosure

- I have had financial support from:  
Purdue Pharma L.P., and  
Merck Sharpe & Dohme, Corp.
- The contents of the lecture does not support or oppose any products from these companies.

# Learning Objectives

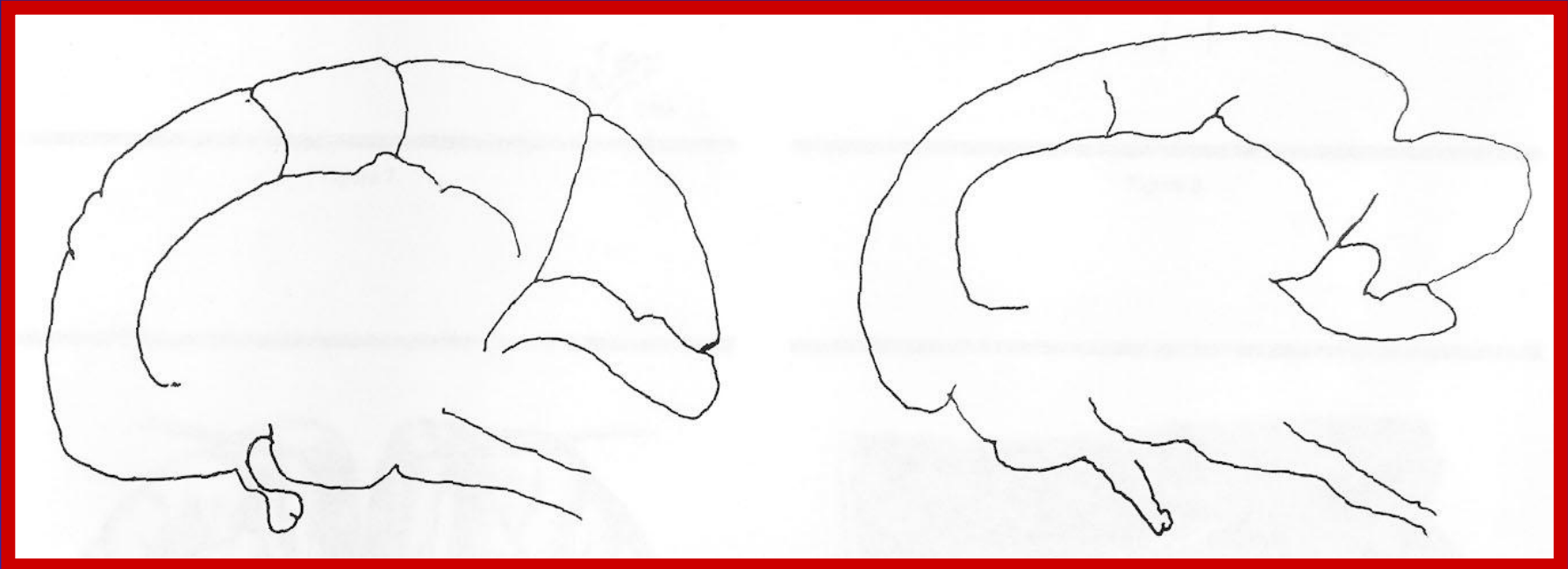
- Learn about neurotransmission via muscle acetylcholine receptor in normals.
- Characterization of pathological changes in acetylcholine receptor using natural toxins.
- Clinical applications/implications of acetylcholine receptor changes.

# Creation of Adam by Michelangelo



- Reproduced from Sistine Chapel, Vatican, Rome

# Outline of Sagittal Section of Brain Vs. Sistine Chapel Painting



Tracing from Frank Netter's  
Neuroanatomy 20<sup>th</sup> Century

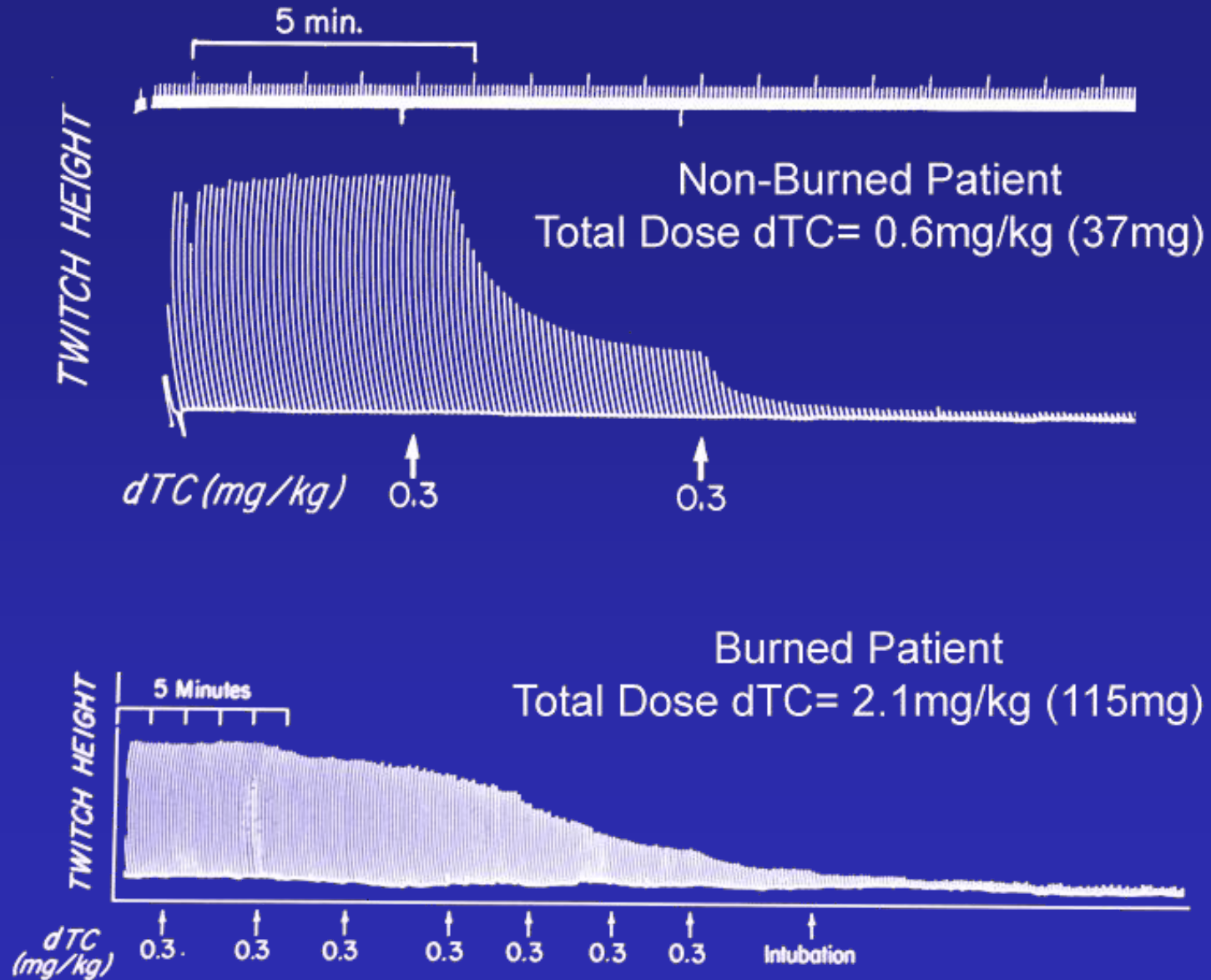
Tracing from Michelangelo's  
Creation of Adam 1508 AD

# “The Doctor”

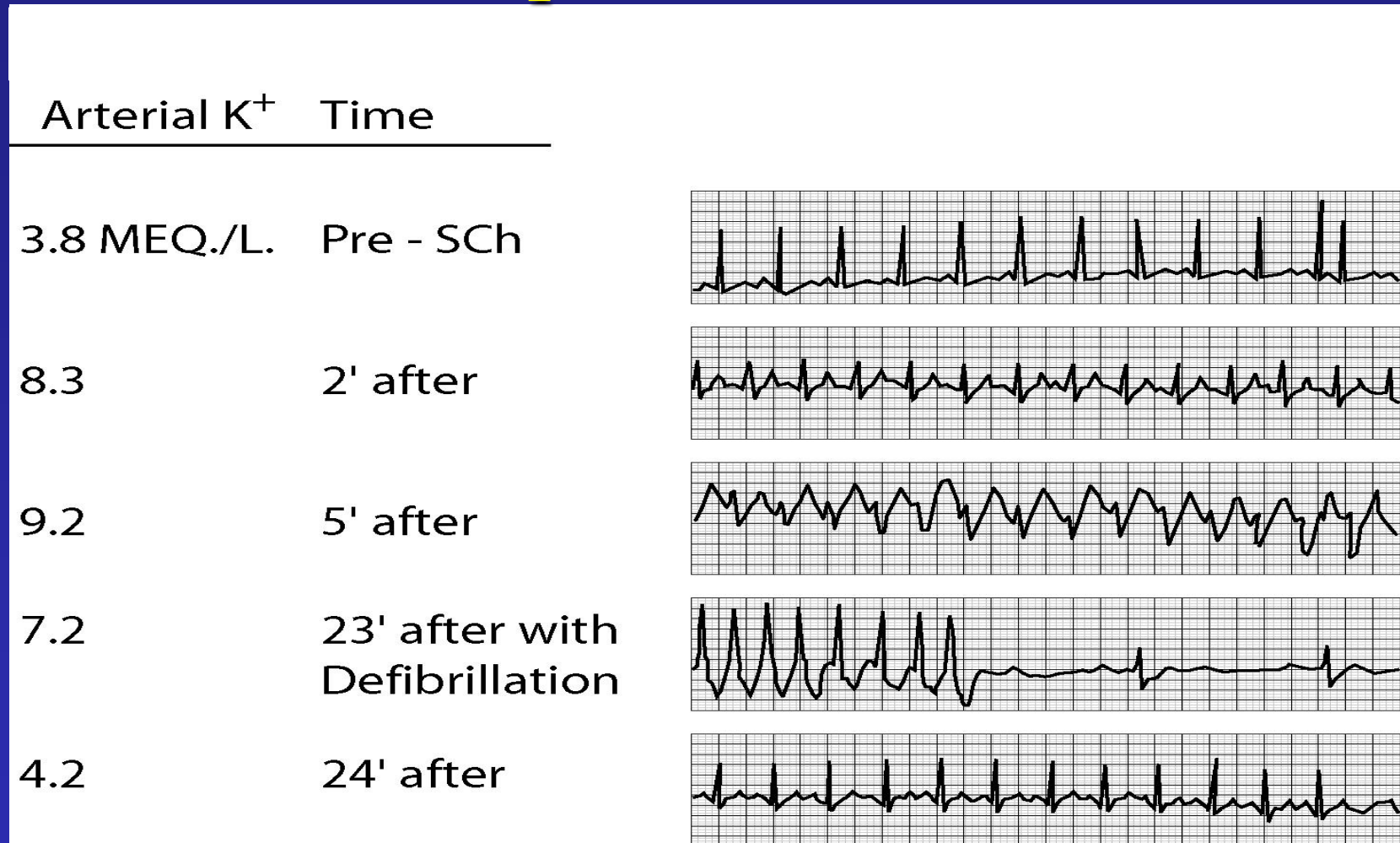


Painted by Sir Luke Fildes in 1891. On Display at the Tate Gallery, London

# Curare-Induced Muscle Paralysis: Burn Vs. Non Burn



# Hyperkalemia with Succinylcholine in a Susceptible Individual

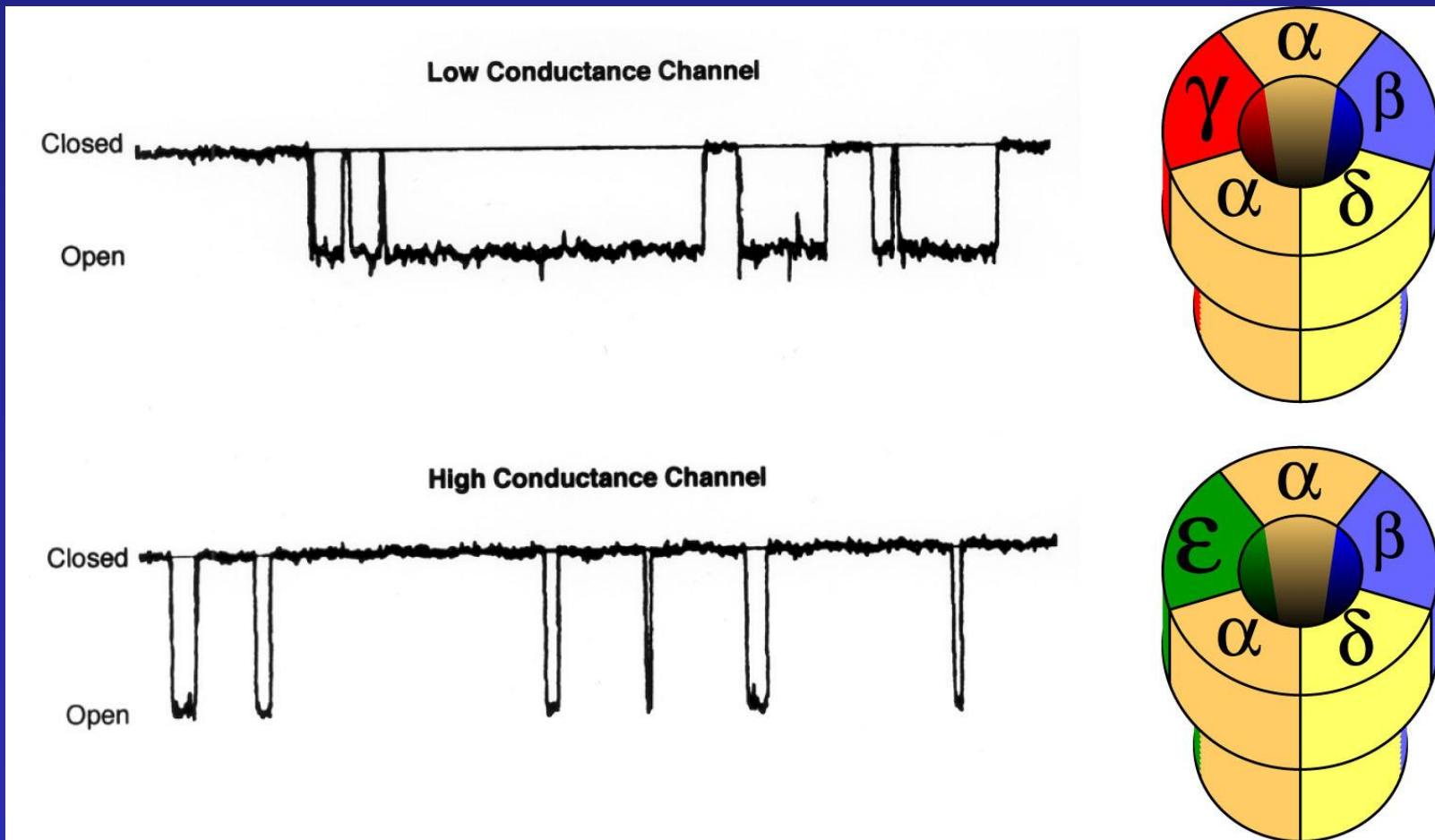


# Overview of the Lecture

## (Focusing mostly on Disuse Atrophy)

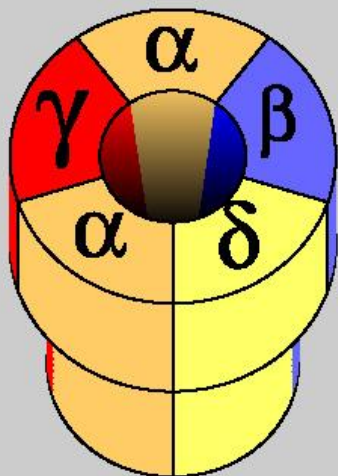
- 1) Describe the normal physiology of neurotransmission
- 2) Characterize function of AChR subtypes during disease
- 3) Use of natural toxins to study muscle function
- 4) Novel role for  $\alpha 7$ AChRs during disease in neurotransmission and control of inflammation in muscle

# Subunit Composition of AChR in Muscle: Fetal or Denervated vs. Mature

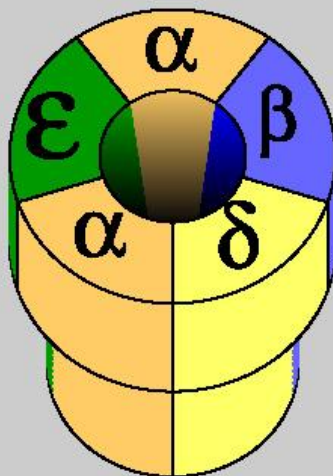


# Acetylcholine Receptors (AChRs) Expressed in Muscle

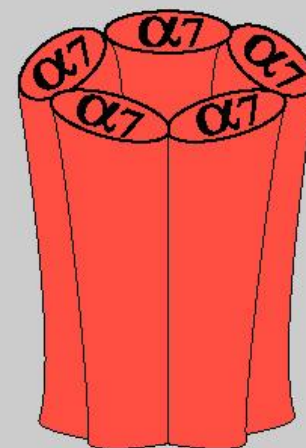
**Fetal/Denervated**



**Mature/Innervated**



**Denervated/? Other Pathologies**



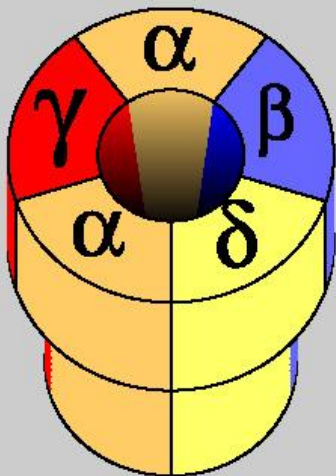


## **Waorani Indian, Southeast Ecuador.**

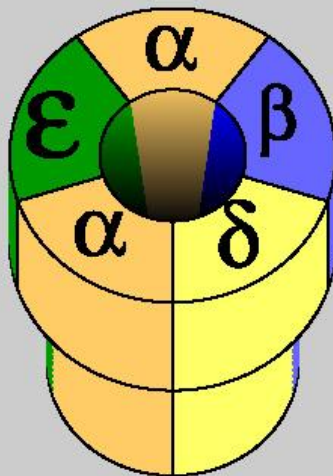
Curare poison from a plant in Amazon jungles is used in blow guns or arrows to paralyze animals (arrow poison).

# Acetylcholine Receptors (AChRs) Expressed in Muscle

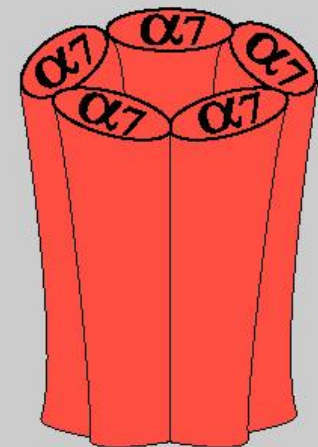
**Fetal/Denervated**



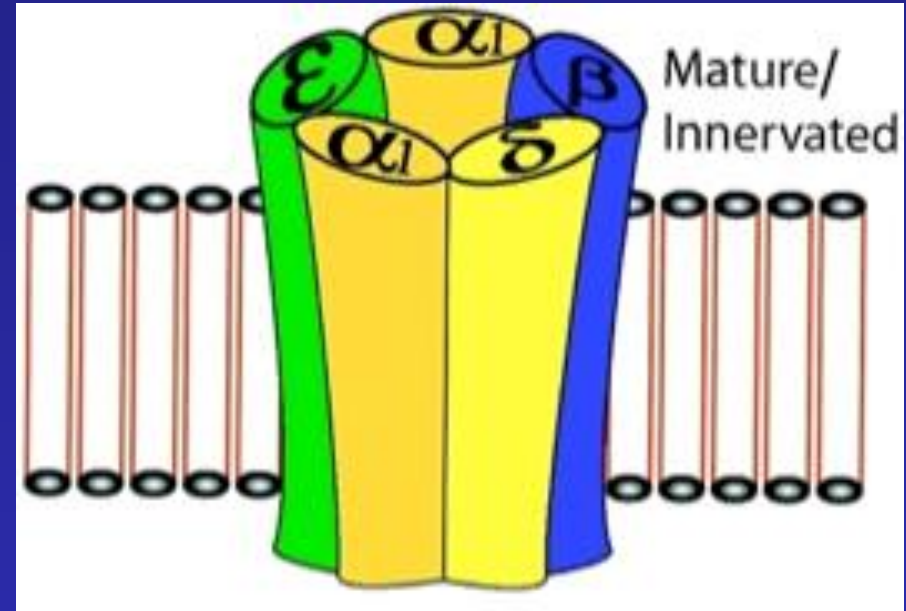
**Mature/Innervated**



**Denervated/? Other Pathologies**



# Waglerin-1 (Neurotoxin) from Trimeresurus Viper, a Specific Mature Receptor Blocker (Antagonist)



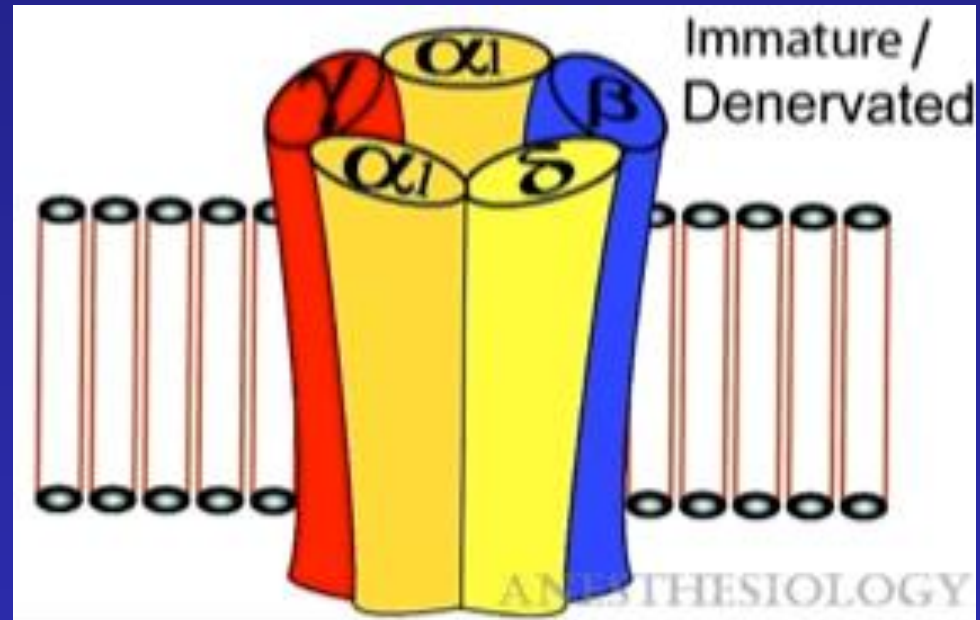
Trimeresurus wagleri

# Conotoxin $\alpha$ A-OIVA from Marine *Conus* Snails, a Specific Immature Receptor Blocker



Conus pergrandis (left)

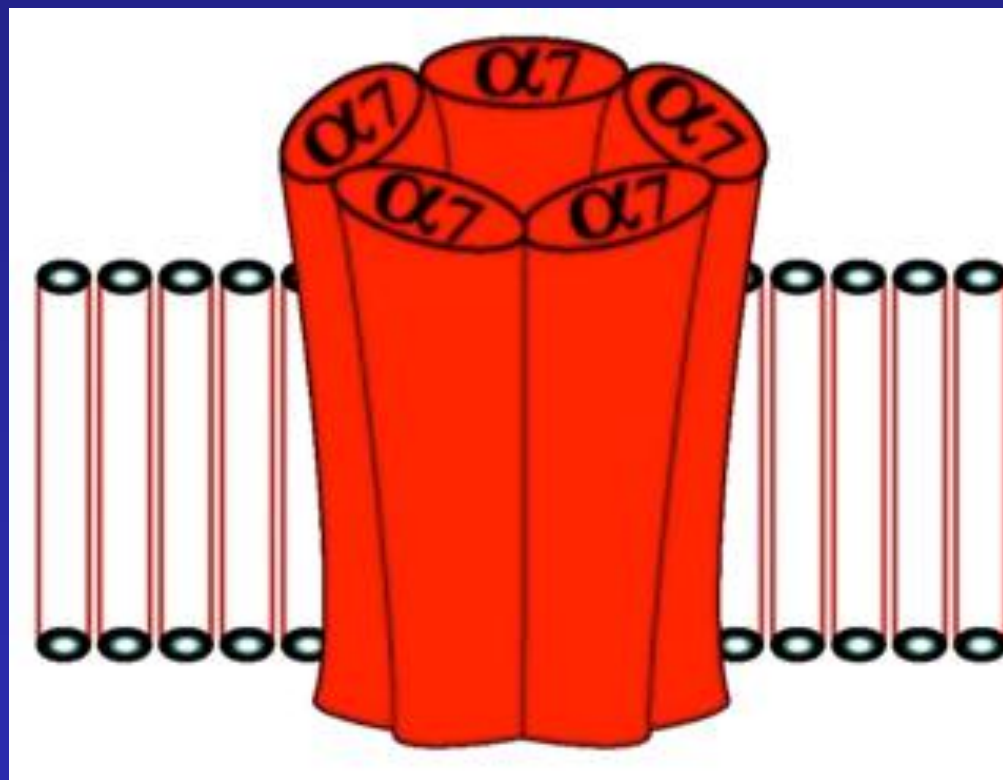
Conus obscurus (right)



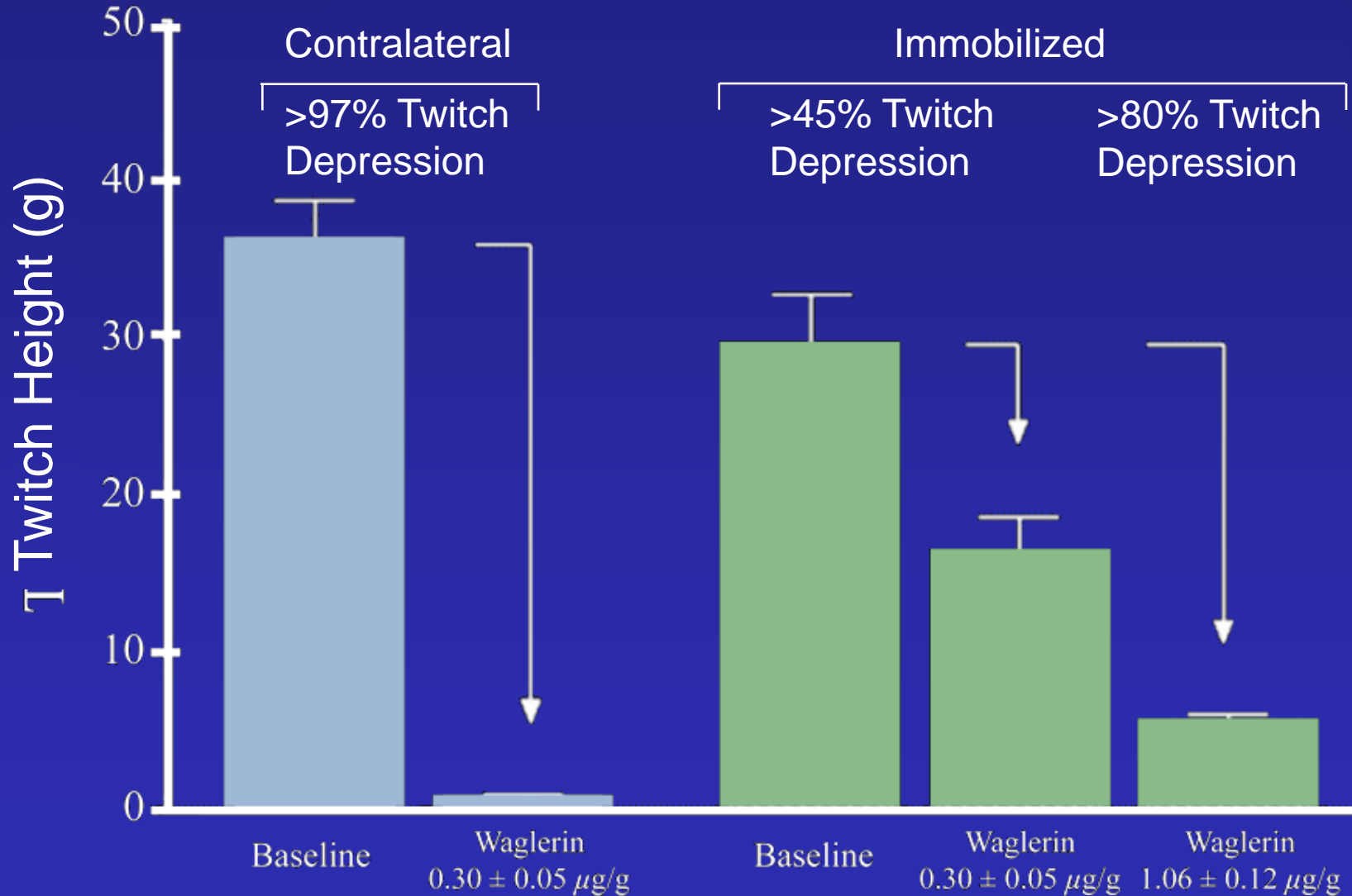
Methyllycaconitine (MLA) from Delphinium Plant,  
a Specific Blocker of  $\alpha 7$ AChRs



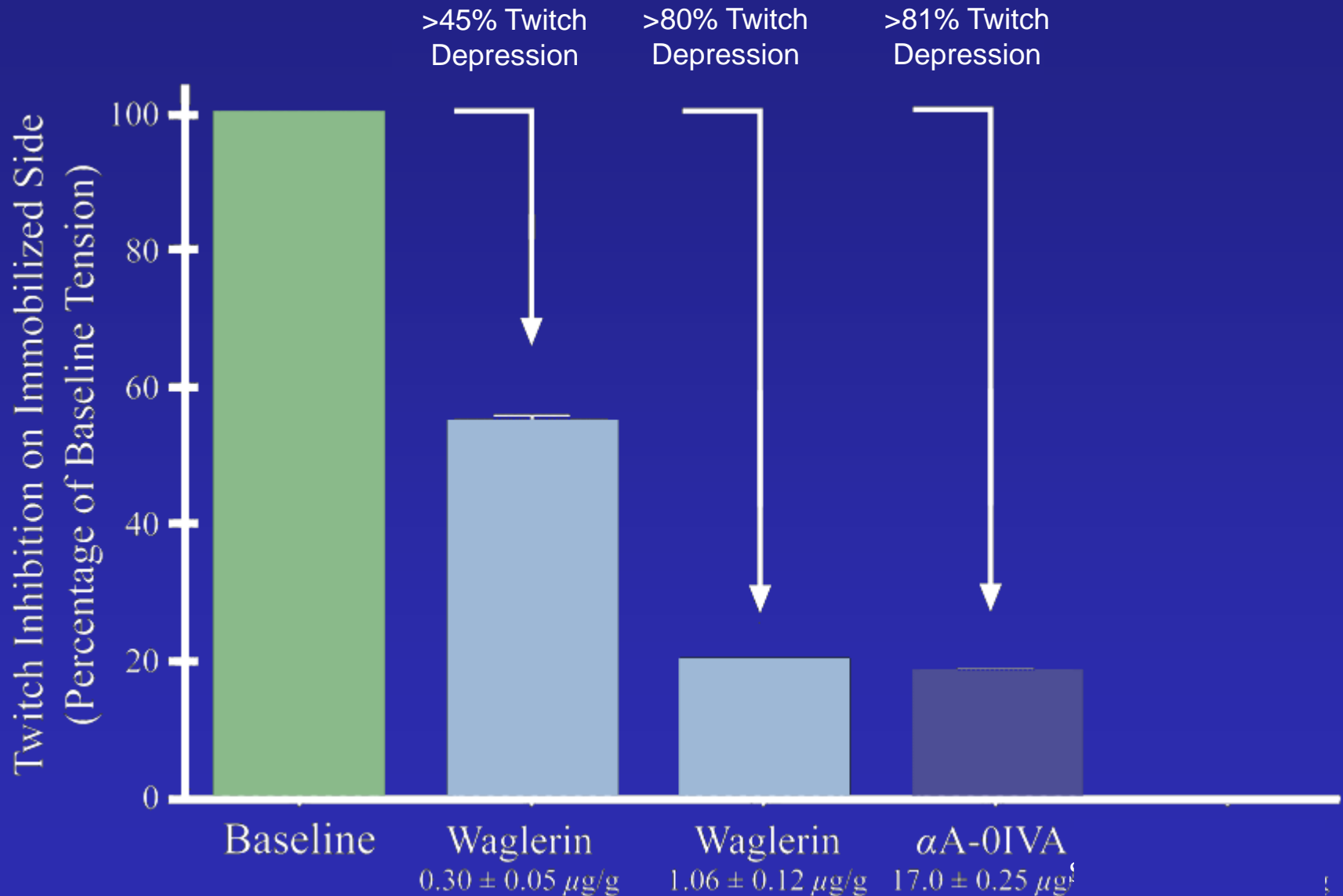
Delphinium Alkaloid



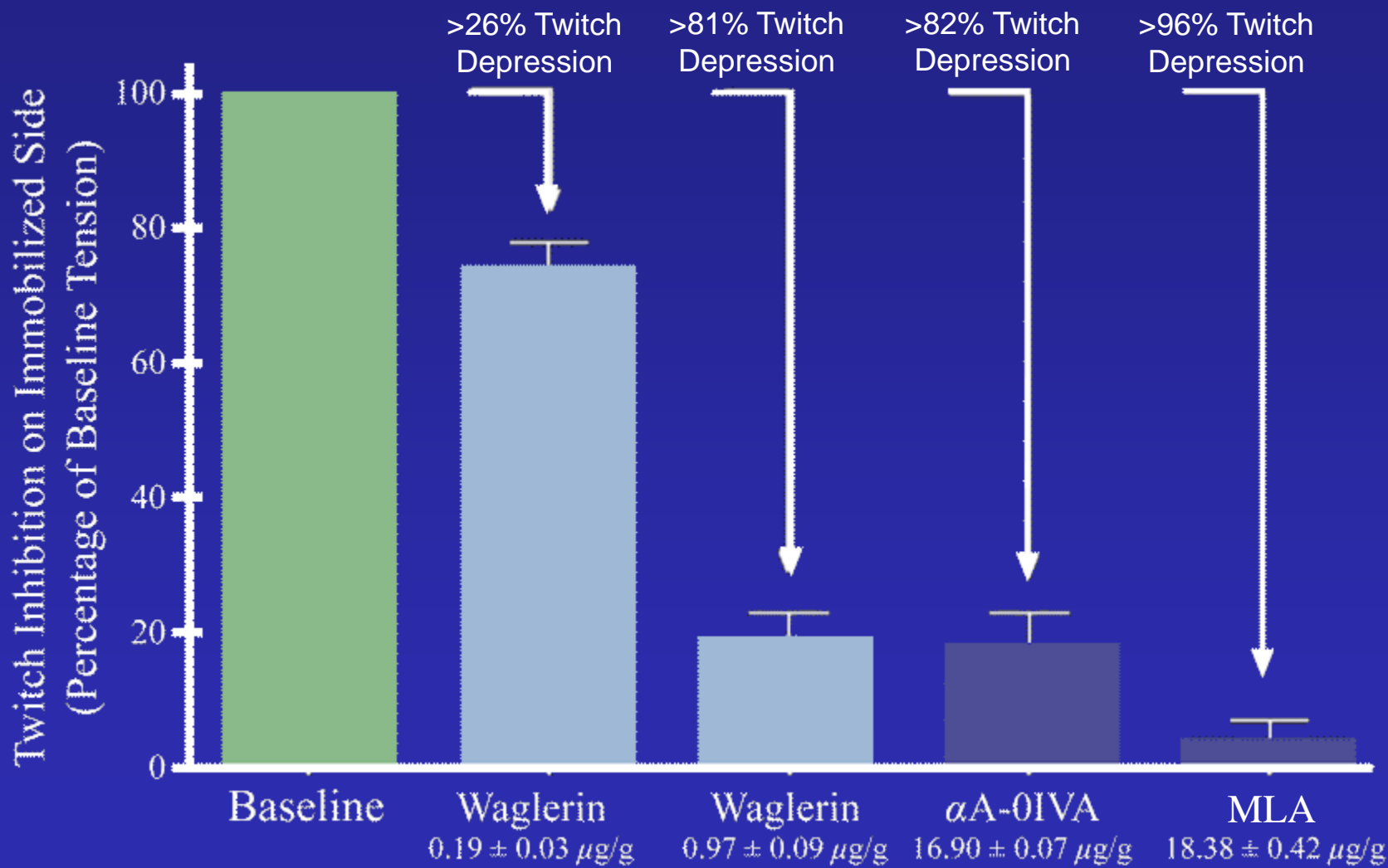
# Waglerin-1 (Mature AChR Blocker) Cannot Cause Complete Twitch Inhibition on Immobilized Side



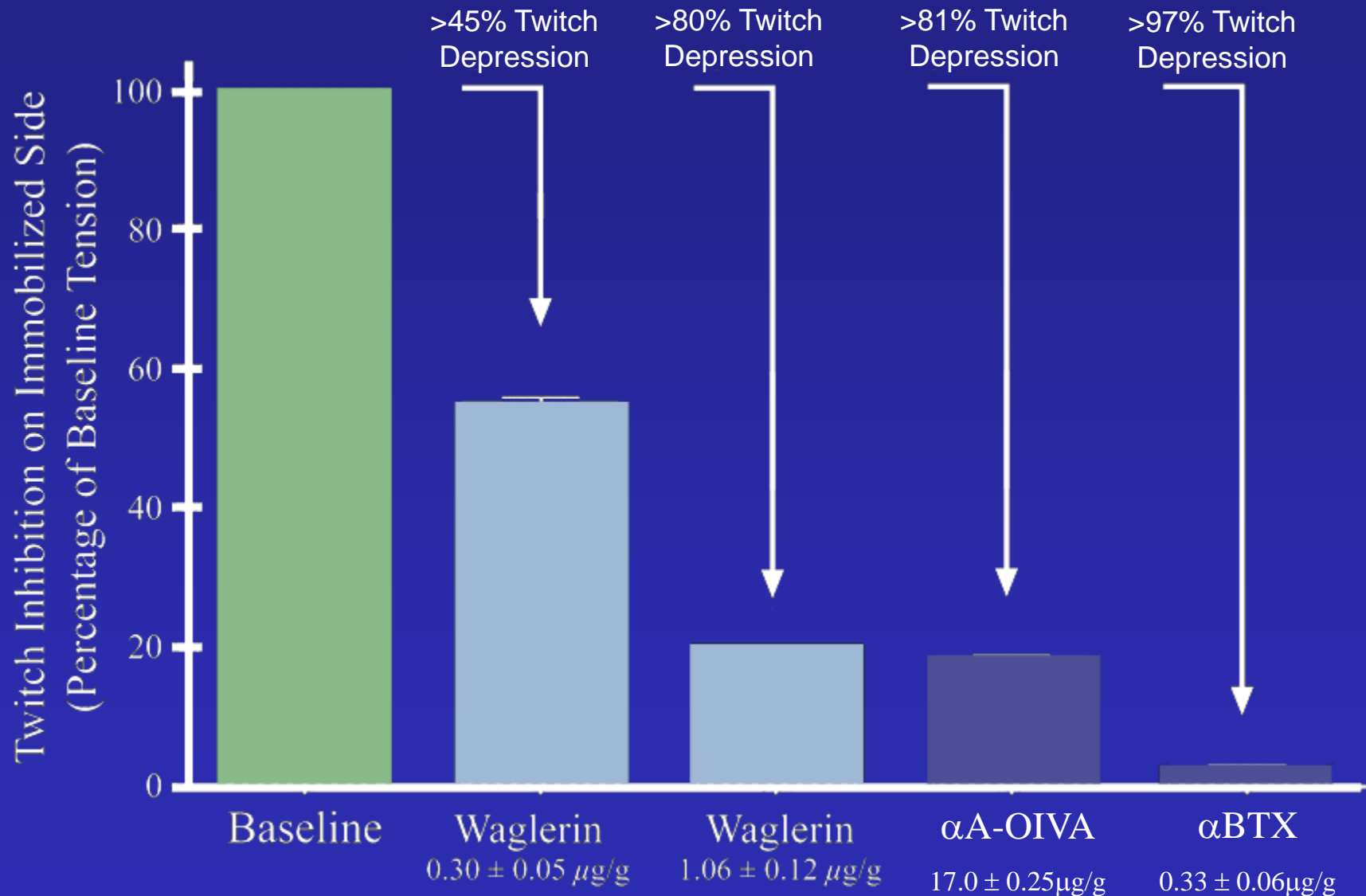
# Immature AChRs Contribute Minimally to Neurotransmission on Immobilized Side



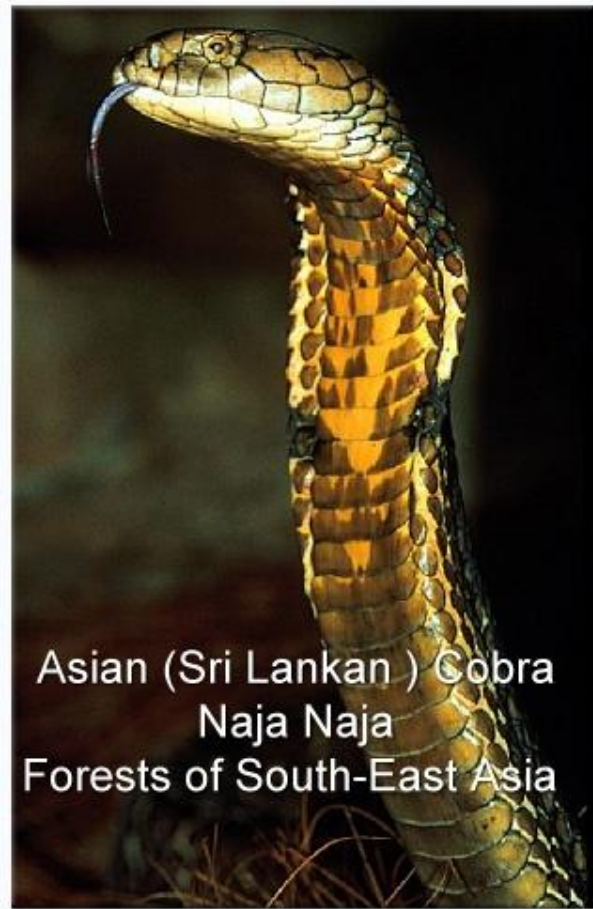
# MLA ( $\alpha 7$ AChR Blocker) Causes Depression of Remaining Tension After Waglerin-1 & $\alpha A$ -OIVA



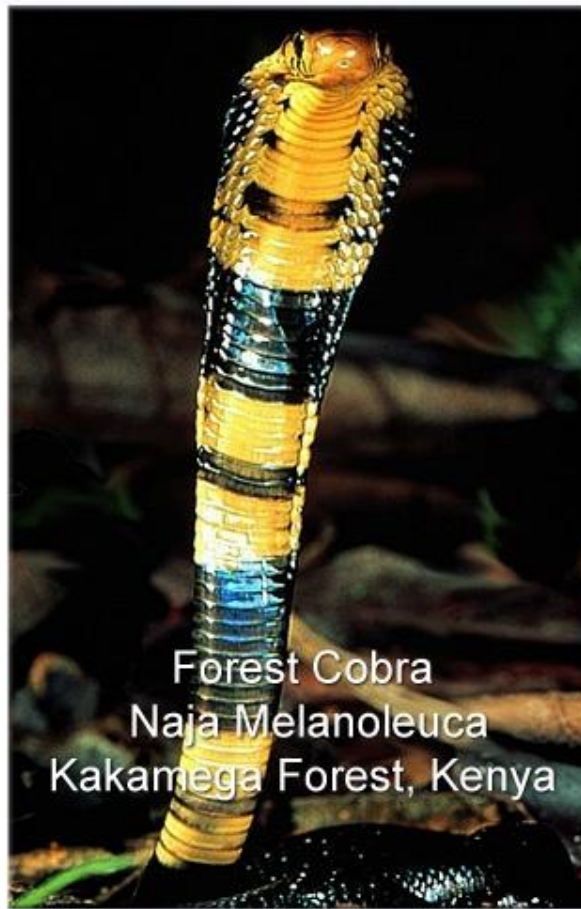
# $\alpha$ -Bungarotoxin ( $\alpha$ BTX) Inhibits Remaining Twitch Height After Waglerin-1



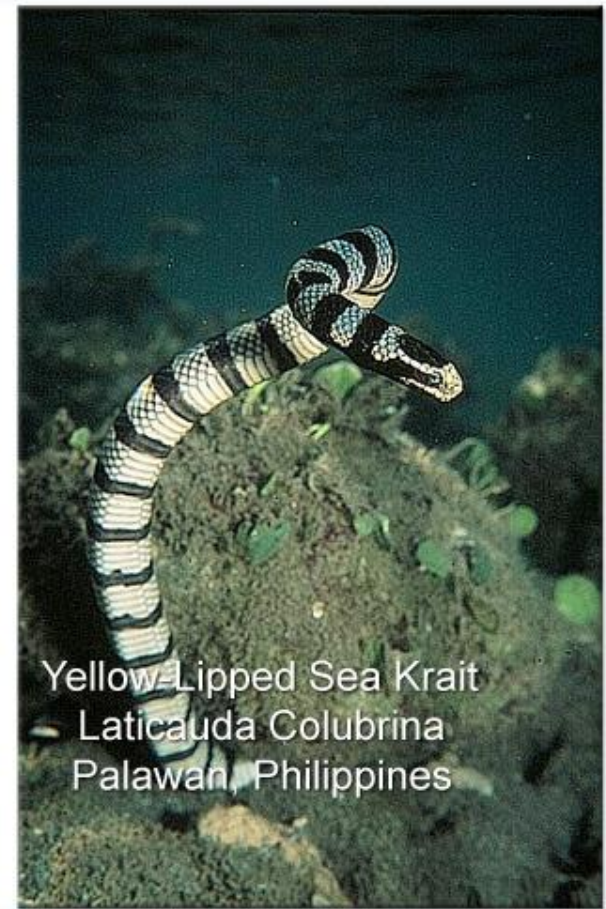
# Elapidae Family of Snakes have $\alpha$ Neurotoxins ( $\alpha$ BTX from Cobra)



Asian (Sri Lankan ) Cobra  
Naja Naja  
Forests of South-East Asia



Forest Cobra  
Naja Melanoleuca  
Kakamega Forest, Kenya

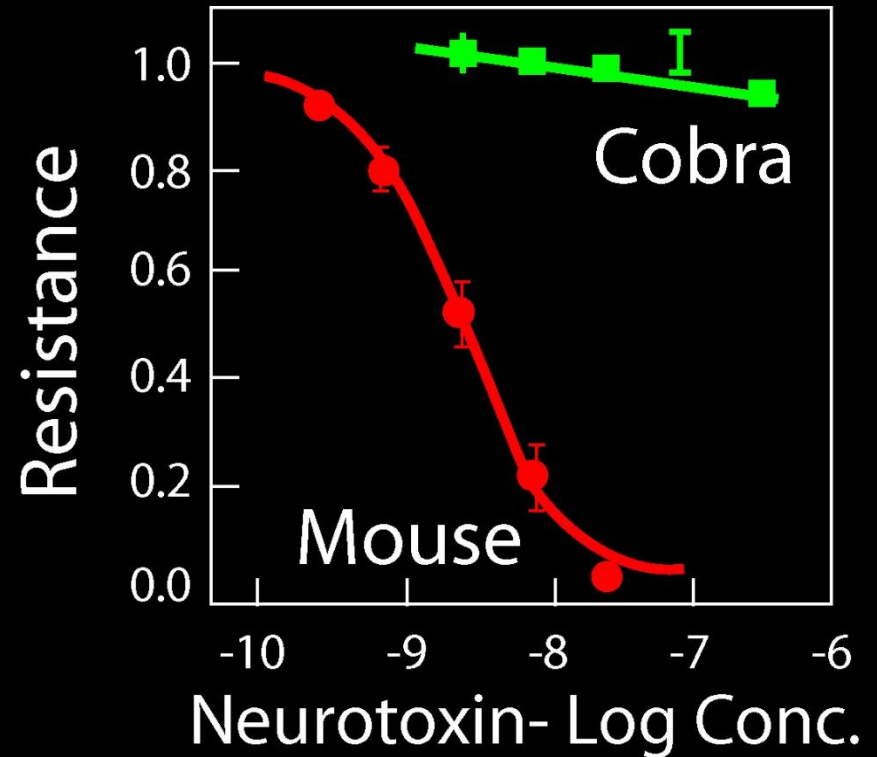
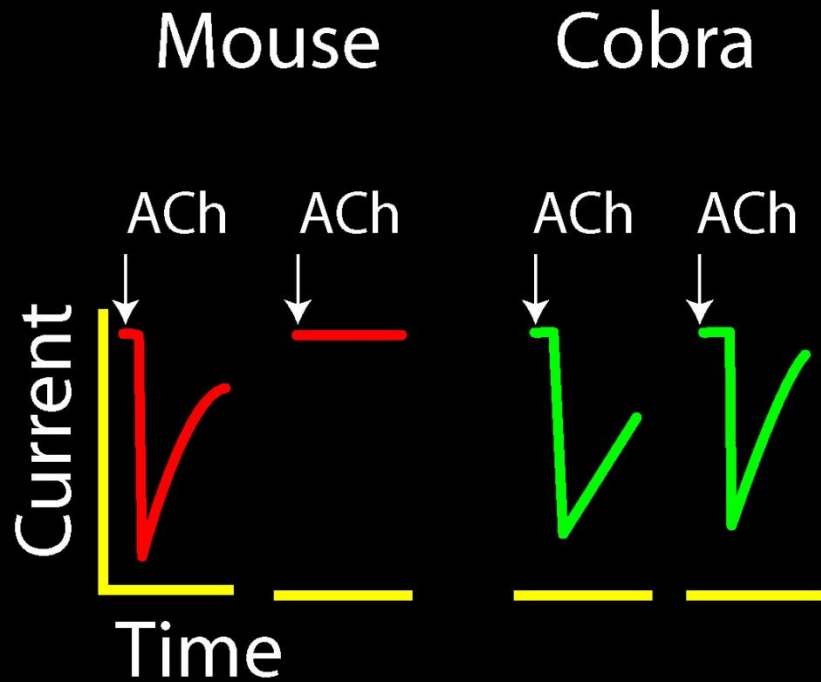


Yellow-Lipped Sea Krait  
Laticauda Colubrina  
Palawan, Philippines

# Gypsy Snake Charmer- Sri Lanka



# Toxicity of Cobra Toxin ( $\alpha$ -Bungarotoxin) to the Mouse vs. Cobra AChR





© John White

**Mongoosees are famous for their snake-fighting ability because of their speed, and agility!**



THANK YOU FOR YOUR ATTENTION