

-Patologias relacionadas a canais iônicos  
-Canais iônicos como alvos de Fármacos e Toxinas

- Prof. Ricardo M. Leão
- FMRP - USP



# Canais iônicos são alvos de drogas e toxinas



# As toxinas alfa de escorpião inibem a inativação dos canais de sódio voltage-dependentes

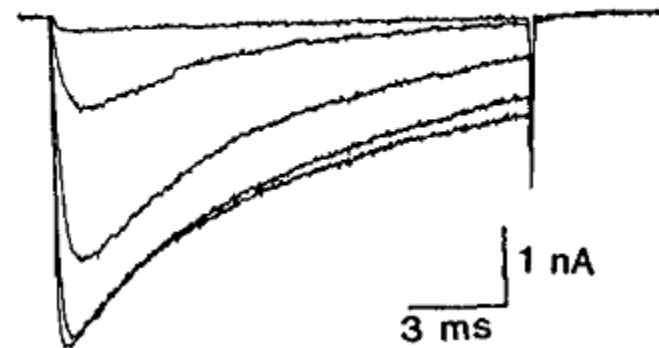
Modification of Na Channel Gating  
by an  $\alpha$  Scorpion Toxin  
from *Tityus serrulatus*

G. E. KIRSCH, A. SKATTEBØL, L. D. POSSANI, and A. M. BROWN

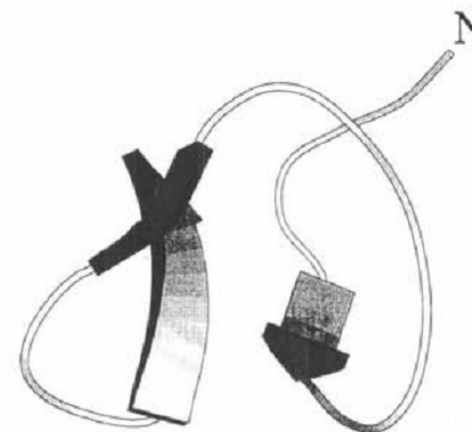
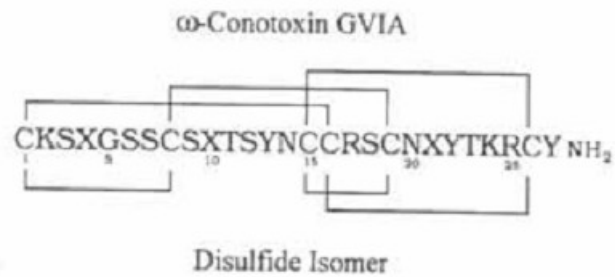
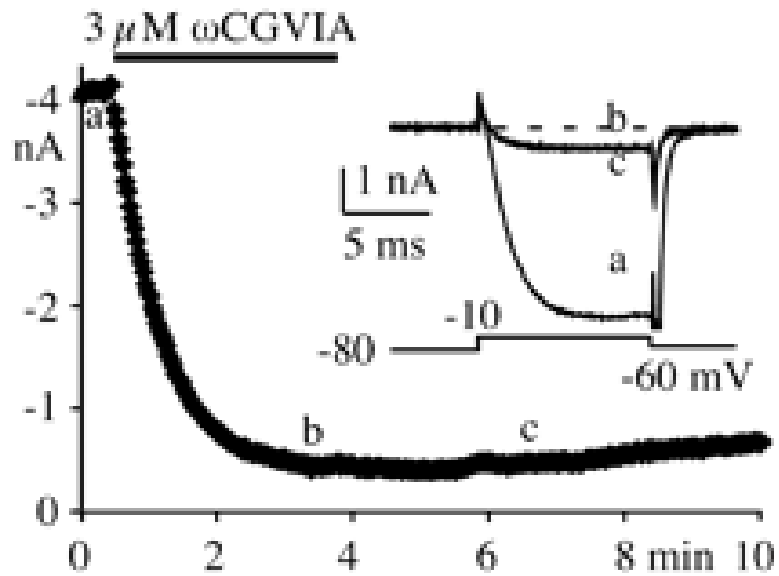
A Control



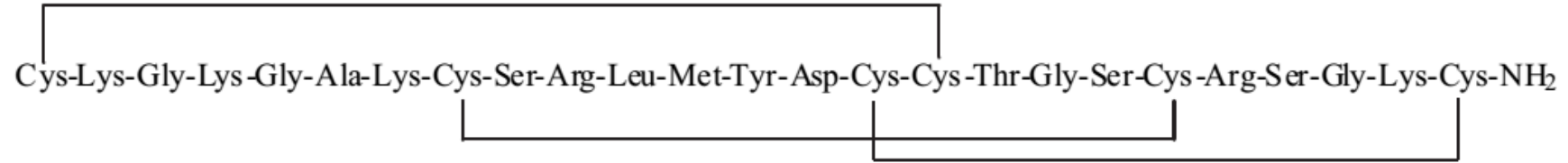
B Tox



As omega-conotoxinas, presentes no veneno dos moluscos do genero *Conus*, inibem vários canais de cálcio voltage-dependentes



Ziconotide (SNX-111), é a forma sintética da omega conotoxina MVIIA que é usada clinicamente para tratamento de dor crônica resistente a morfina



*Current Medicinal Chemistry*, 2004, 11, 3029-3040

3029

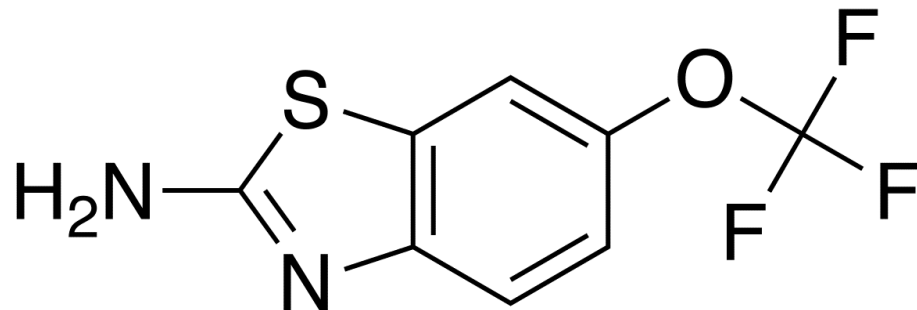
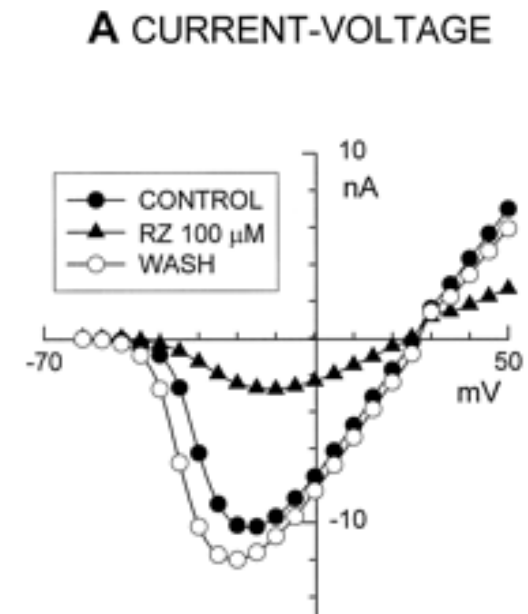
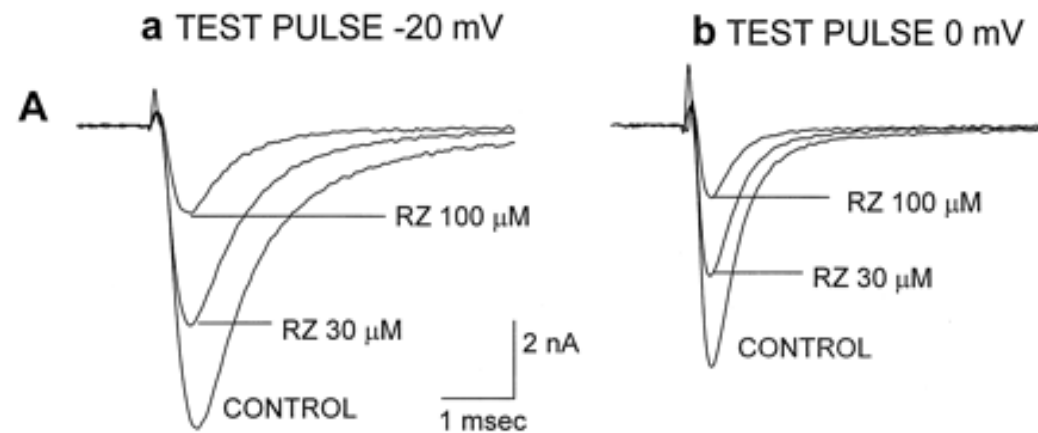
### Ziconotide: Neuronal Calcium Channel Blocker for Treating Severe Chronic Pain

G.P. Miljanich\*

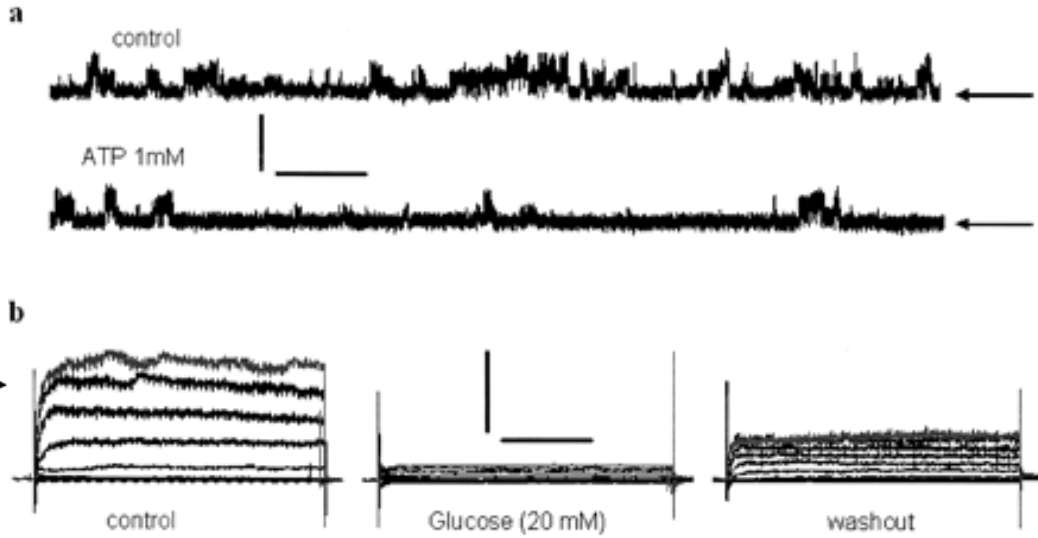
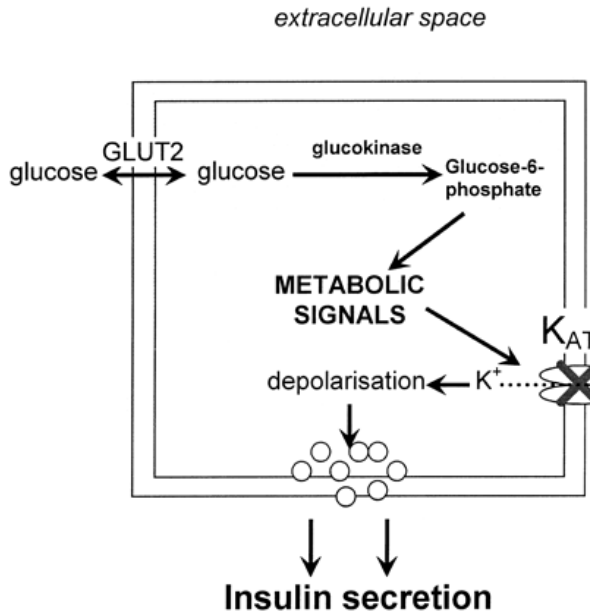
*Elan Pharmaceuticals, Inc., 7475 Lusk Boulevard, San Diego, CA, 92121, USA*



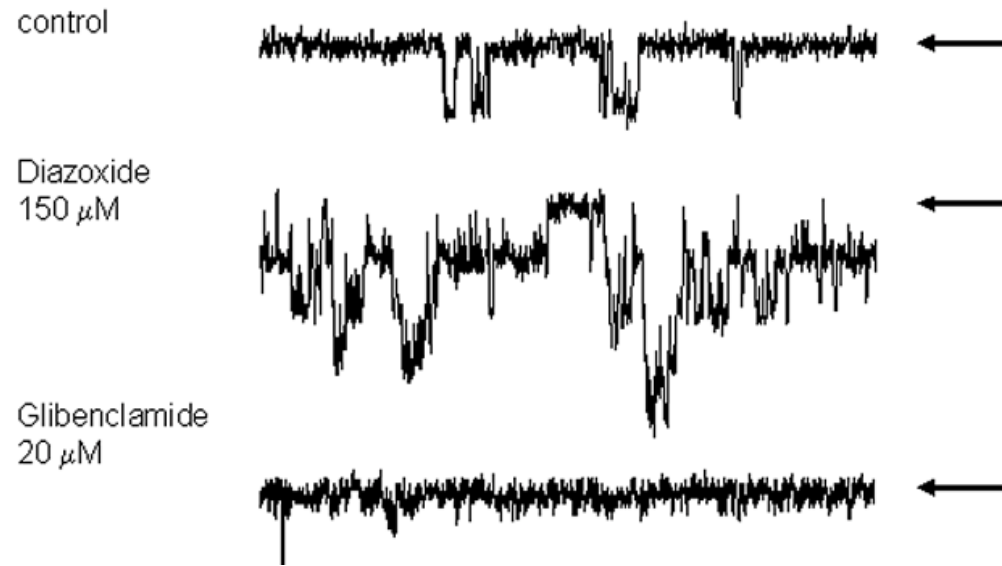
Riluzol, uma droga **neuroprotetora e antiepilética** inibe canais de sódio voltage-dependentes



Canais de potássio sensíveis ao ATP intracelular regulam a secreção de insulina na célula beta-pancreática.

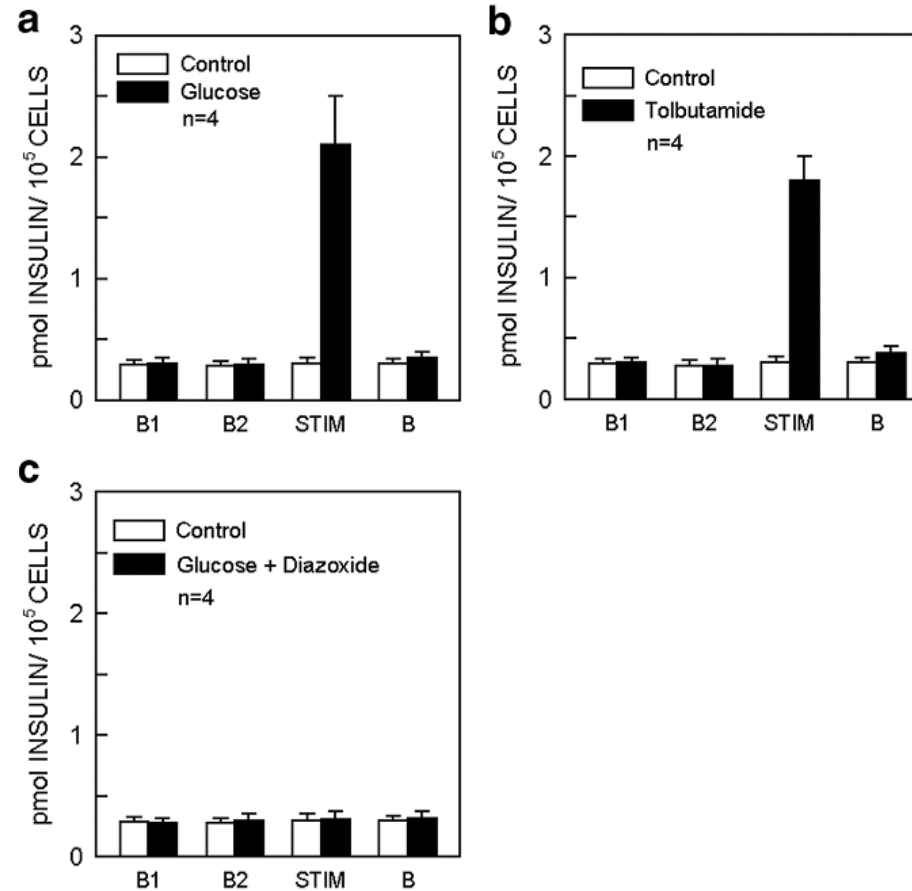


Os hipoglicemiantes orais inibem os canais de potássio sensíveis ao ATP, aumentando a secreção de insulina



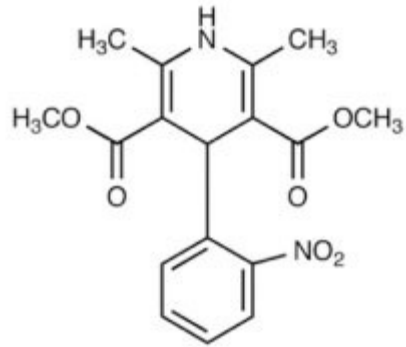


Os hipoglicemiantes orais inibem os canais de potássio sensíveis ao ATP, aumentando a secreção de insulina

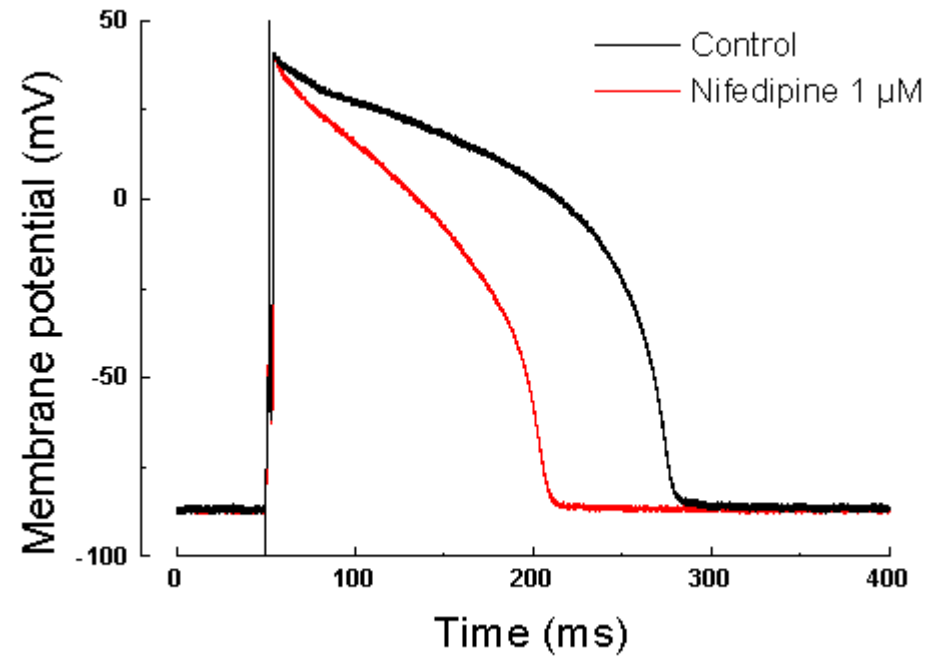


**Figure 6.** Static stimulation of insulin secretion in cultures of HEPG2ins/g cells. Secretion of insulin from HEPG2ins/g cells in response to (a) 20 mM glucose, (b) 100  $\mu$ M tolbutamide, and (c) 20 mM glucose + 150  $\mu$ M diazoxide. Cells were incubated in basal medium for two consecutive 1-h periods before being exposed to the stimulus for 1 h (solid bars); cells in the control group were treated throughout with basal medium (unfilled bars). n, Number of experiments; B1, first basal period; B2: second basal period; B3: basal period following stimulation; S: stimulation period. Values are expressed as means  $\pm$  SE.

A dihidropirindina **nifedipina** inibe o canal de cálcio cardíaco e diminui a duração do potencial de ação cardíaco



*Figure 1. Chemical structure of nifedipine*

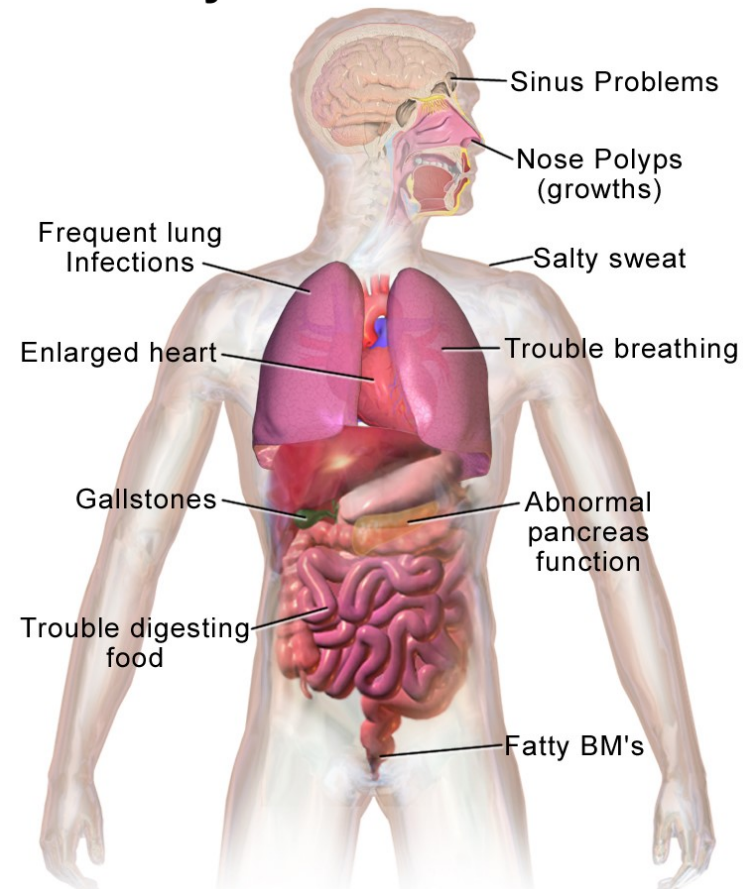


# Canalopatias

Patologias relacionadas a mutações em canais iônicos

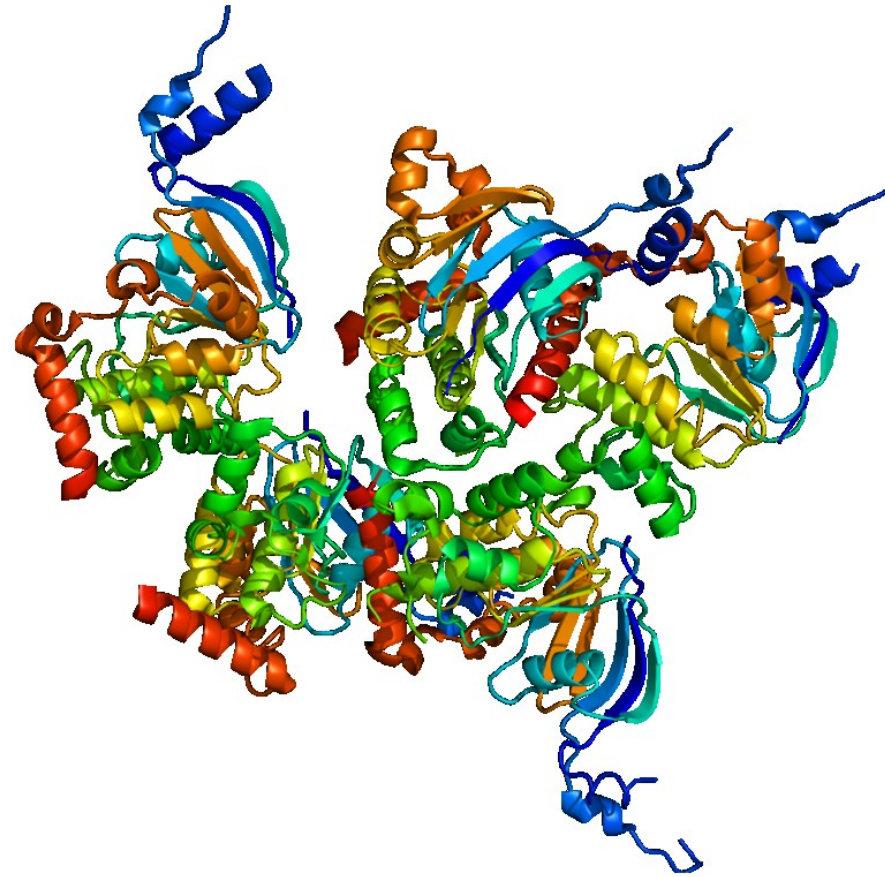
# A FIBROSE CÍSTICA É UMA CANALOPATIA

## Health Problems with Cystic Fibrosis



A FIBROSE CÍSTICA É CAUSADA POR UM DEFEITO EM UM CANAL PARA CLORETO EPITELIAL.

Foi a primeira canalopatia de origem genética a ser identificada.



# Muitas canalopatias afetam o Sistema Nervoso

1824

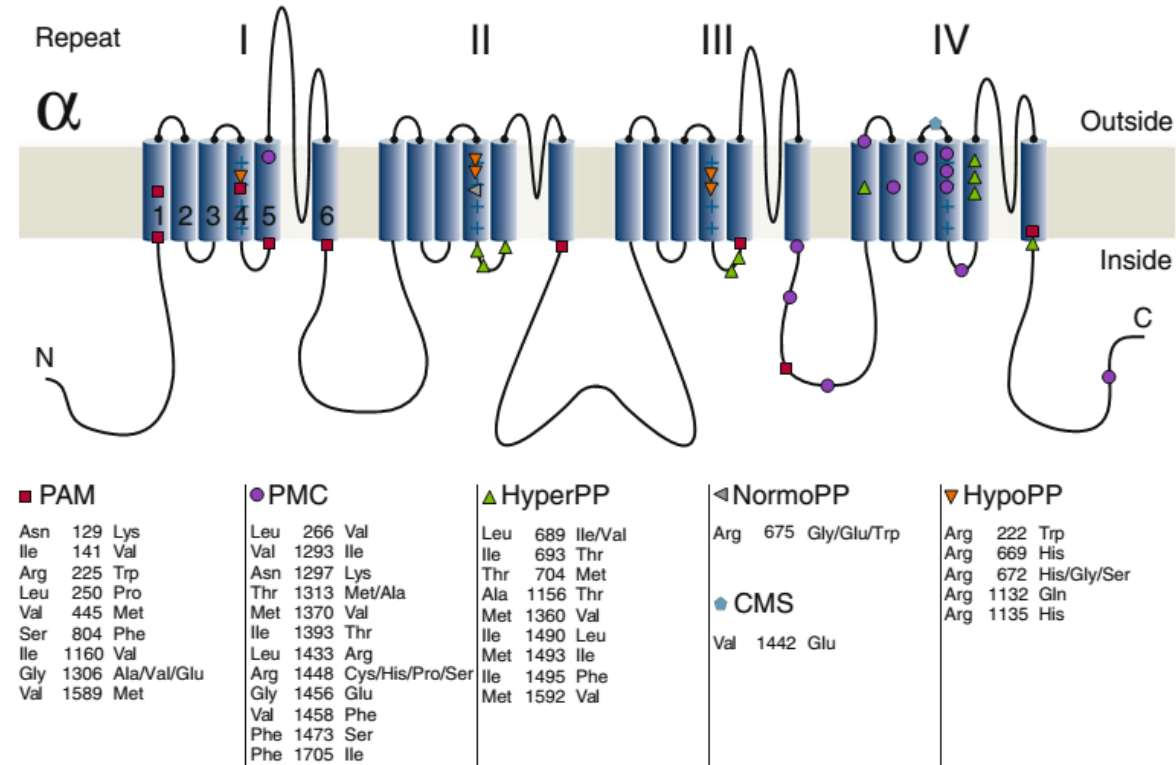
D. M. Kullmann and S. G. Waxman

*J Physiol* 588.11

**Table 1. The neurological channelopathies**

		Gene	Channel subunit	Disease
CNS	Sodium channels	<i>SCN1A</i>	$\alpha$ subunit of Nav1.1	Epilepsy, migraine
		<i>SCN1B</i>	$\beta$ 1	Epilepsy
		<i>SCN2A</i>	$\alpha$ subunit of Nav1.2	Epilepsy
	Potassium channels	<i>KCNQ2</i>	Kv7.2	Epilepsy
		<i>KCNQ3</i>	Kv7.3	Epilepsy
		<i>KCNMA1</i>	BK	Epilepsy with dyskinesia
		<i>KCNA1</i>	Kv1.1	Episodic ataxia
		<i>KCNC3</i>	Kv3.3	Ataxia
	Calcium channels	<i>CACNA1H</i>	$\alpha$ 1H subunit of Cav3.2	Epilepsy
		<i>CACNA1A</i>	$\alpha$ 1A subunit of Cav2.1	Episodic or progressive ataxia, migraine, epilepsy
	GABA <sub>A</sub> receptors	<i>GABRA1</i>	$\alpha$ 1	Epilepsy
		<i>GABRB3</i>	$\beta$ 3	Epilepsy
		<i>GABRG2</i>	$\gamma$ 2	Epilepsy
	Nicotinic ACh receptors	<i>CHRNA2</i>	$\alpha$ 2	Epilepsy
		<i>CHNRA4</i>	$\alpha$ 4	Epilepsy
		<i>CHRNB2</i>	$\beta$ 2	Epilepsy
	Glycine receptors	<i>GLRA1</i>	$\alpha$ 1	Hyperekplexia
<i>GLRB</i>		$\beta$	Hyperekplexia	
Peripheral nerve	Sodium channel	<i>SCN9A</i>	$\alpha$ subunit of Nav1.7	Excessive pain, insensitivity to pain
Muscle	Sodium channel	<i>SCN4A</i>	$\alpha$ subunit of Nav1.4	Periodic paralysis, myotonia
	Potassium channels	<i>KCNJ2</i>	Kir2.1	Periodic paralysis
		<i>KCNJ18</i>	Kir2.6	Periodic paralysis
	Calcium channel	<i>CACNA1S</i>	$\alpha$ 1S subunit of CaV1.1	Periodic paralysis
	Chloride channel	<i>CLCN1</i>	CLC-1	Myotonia
	Nicotinic ACh receptors	<i>CHRNA1</i>	$\alpha$ 1	Congenital myasthenic syndromes
		<i>CHRNB1</i>	$\beta$ 1	Congenital myasthenic syndromes
		<i>CHRNG</i>	$\gamma$	Congenital myasthenic syndromes
		<i>CHRND</i>	$\delta$	Congenital myasthenic syndromes
<i>CHRNE</i>		$\epsilon$	Congenital myasthenic syndromes	

# Mutações nos canais de sódio $Na_v1.4$ musculares levam a várias canalopatias



PAM = miotonia agravada pelo potássio

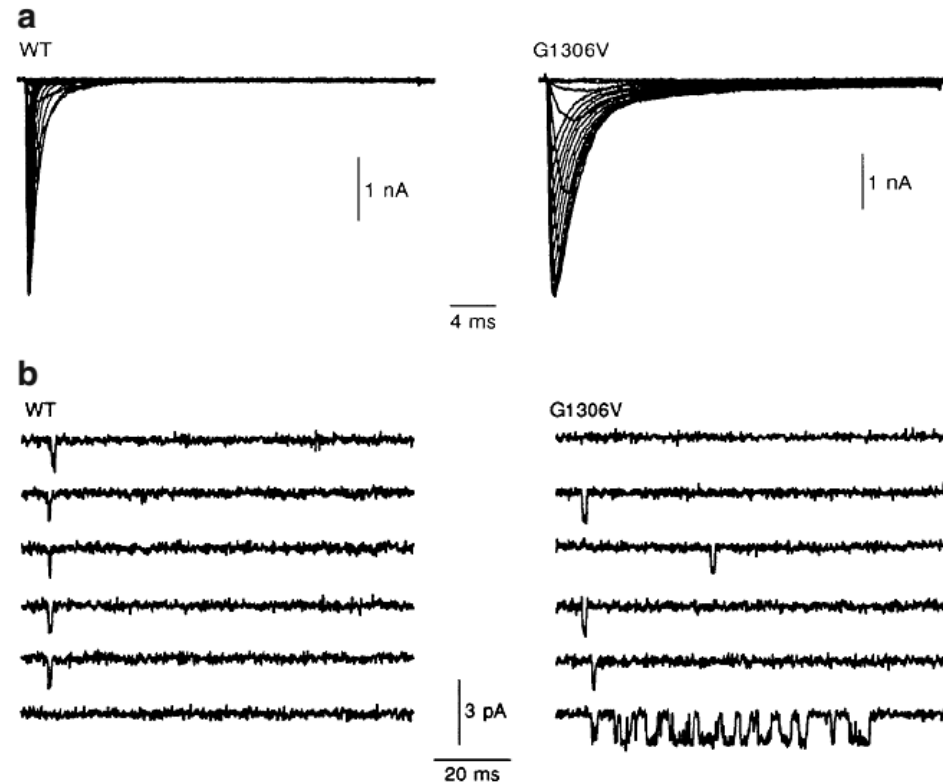
PMC = paramiotonia congênita

HyperPP = paralisia periódica hipercalêmica

HypoPP = paralisia periódica hipocalêmica

CMS = síndrome miastênica congênita

# Exemplo de uma mutação causadora de miotonia\*



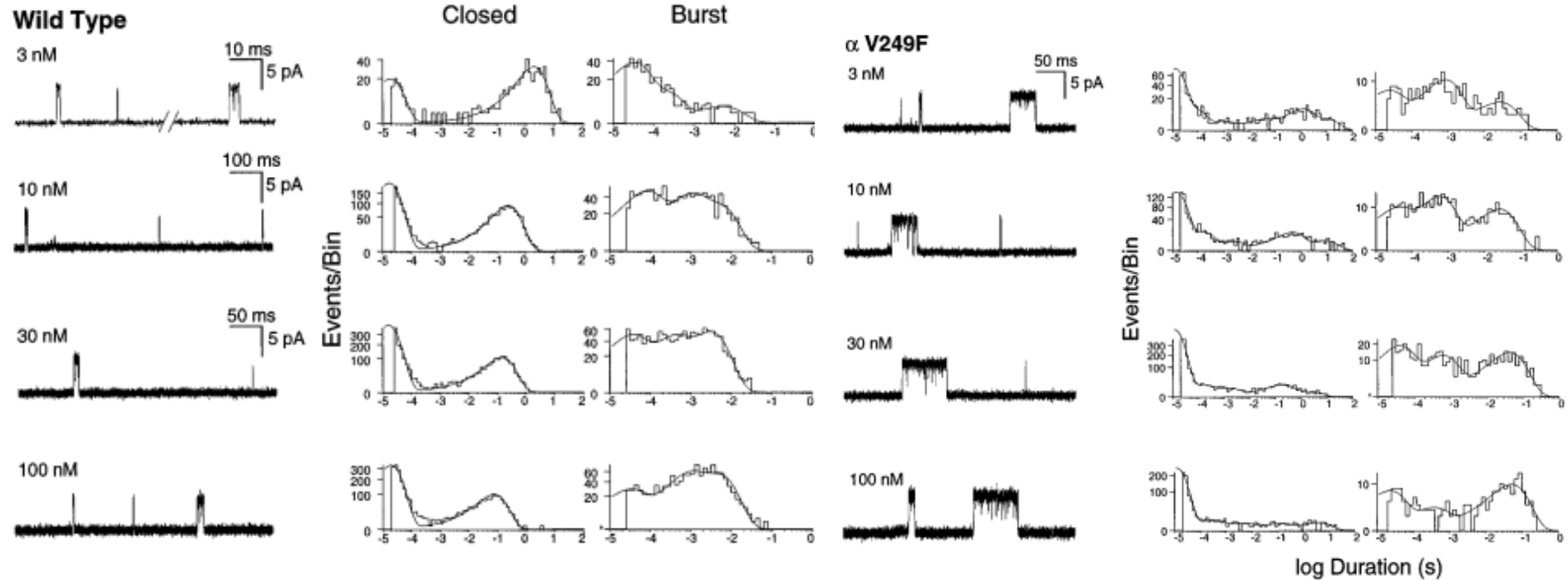
\*miotonia = contração prolongada do músculo



# Síndromes miastênicas\* também podem estar relacionadas a mutações nos receptores colinérgicos

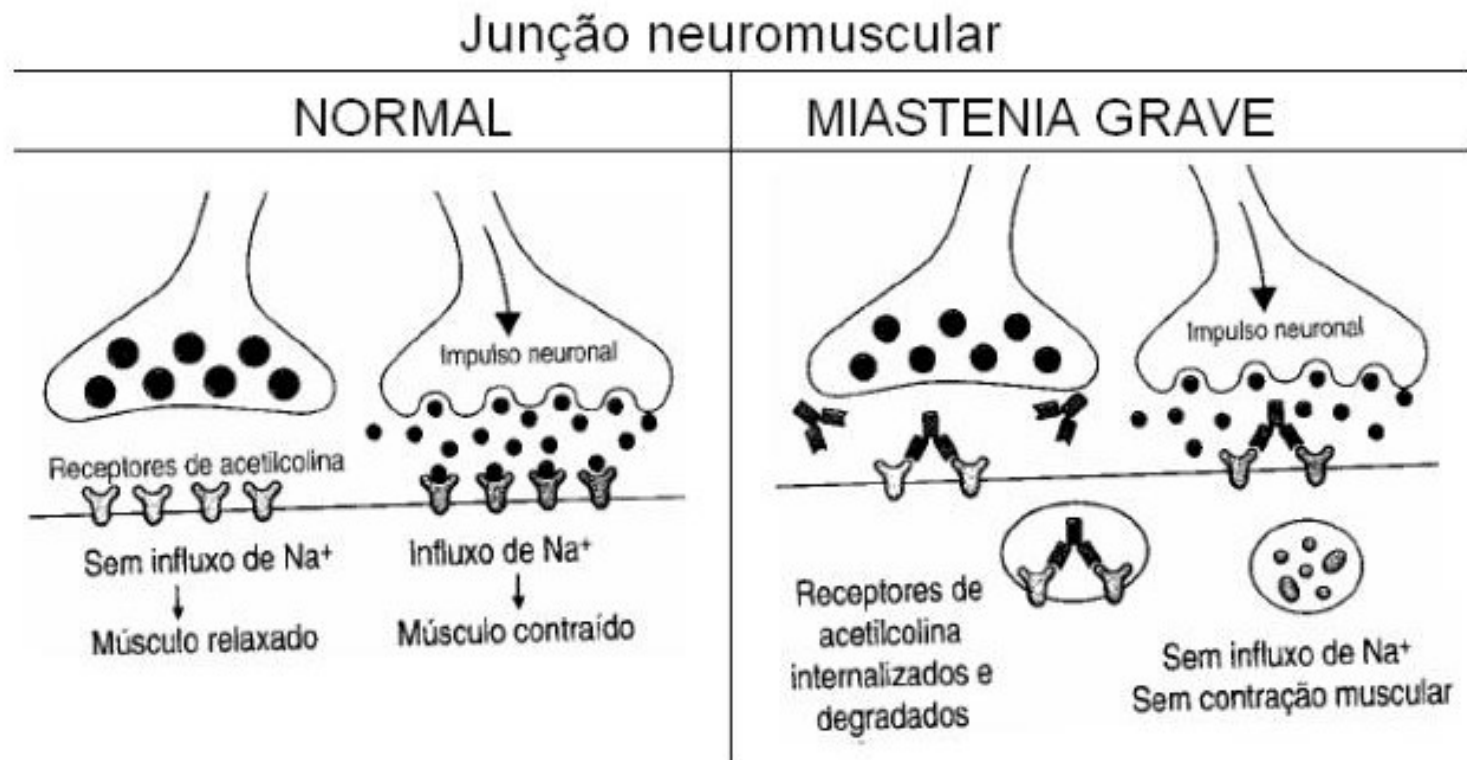
Milone et al. • Myasthenic Syndrome Caused By AChR  $\alpha$  Subunit Mutation

J. Neurosci., August 1, 1997, 17(15):5651-5665 5657



\*Miastenia = síndrome de fraqueza muscular

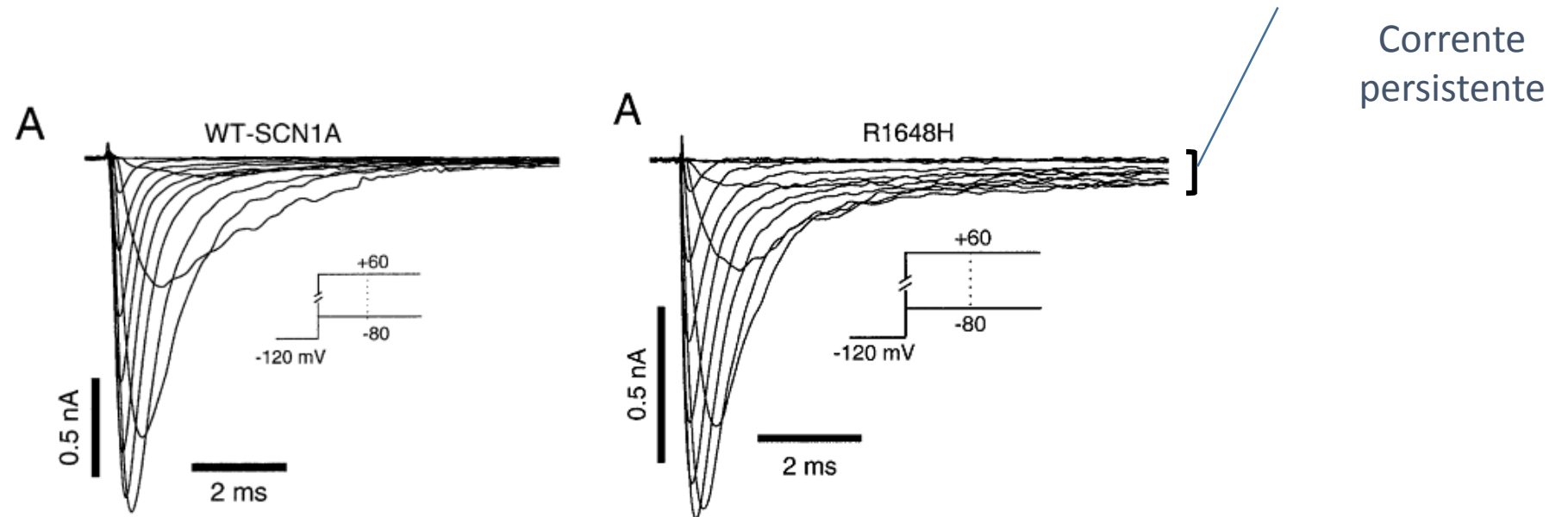
A miastenia grave é uma doença autoimune que ataca os receptores nicotínicos da placa motora, causando fraqueza muscular.



# Mutações nos canais de sódio $\text{Na}_v1.1$ (SCN1A) neuronais estão relacionadas a síndromes epilépticas

Neuron, Vol. 34, 877-884, June 13, 2002, Copyright ©2002 by Cell Press

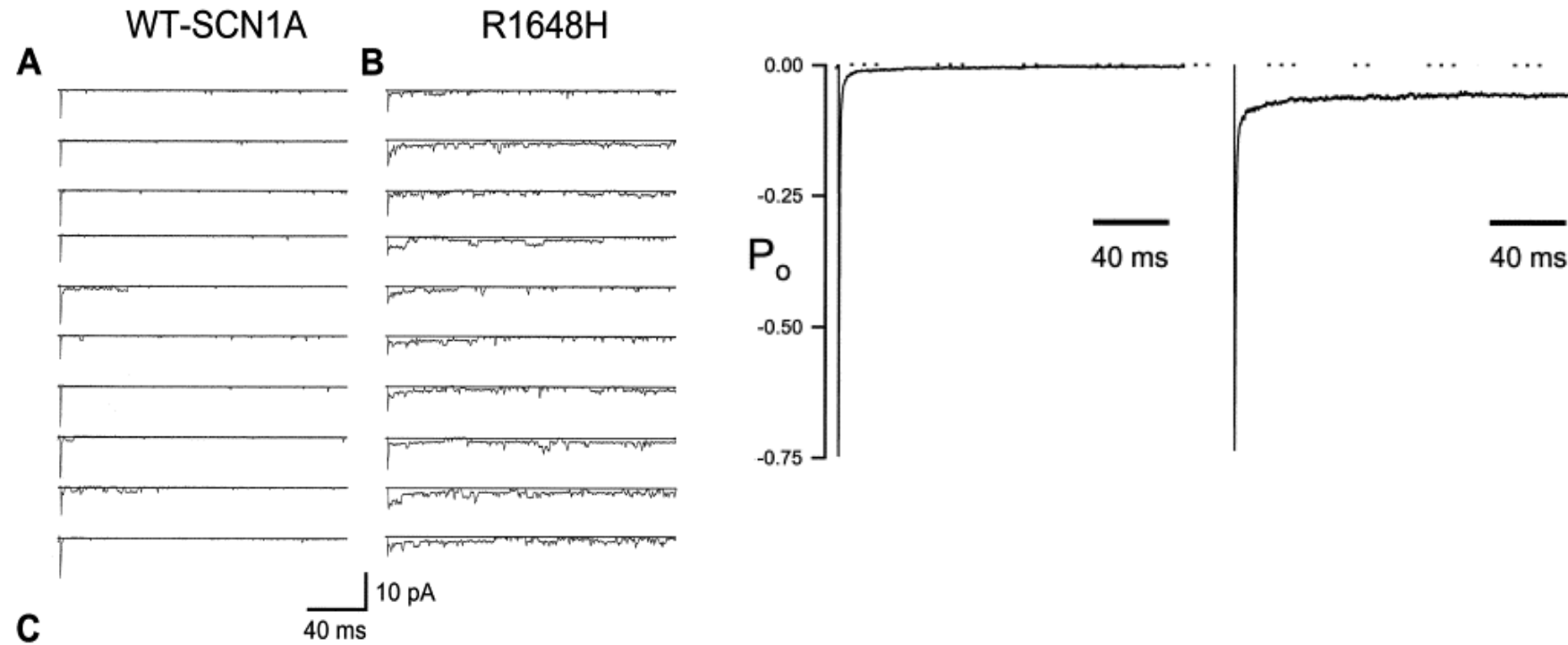
## Molecular Basis of an Inherited Epilepsy



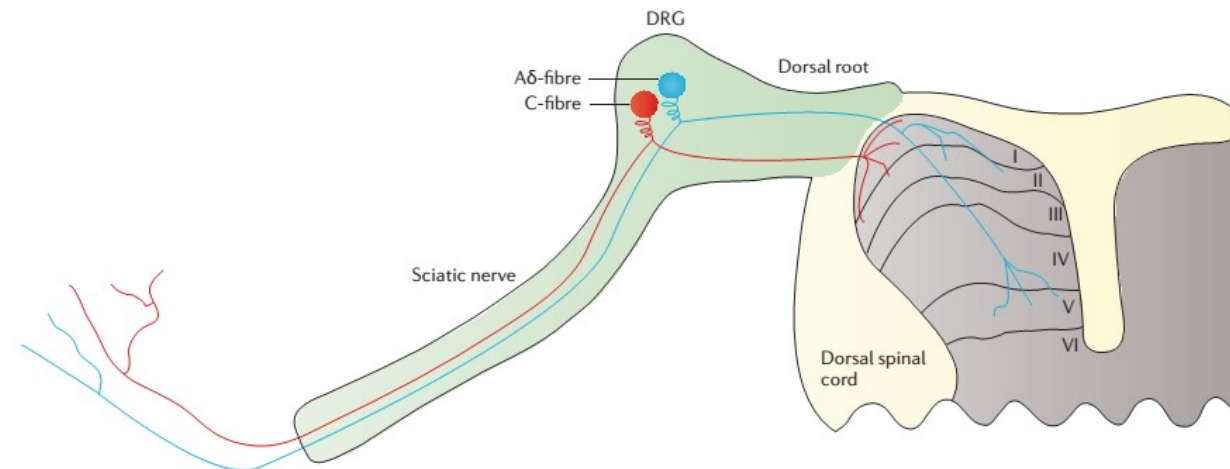
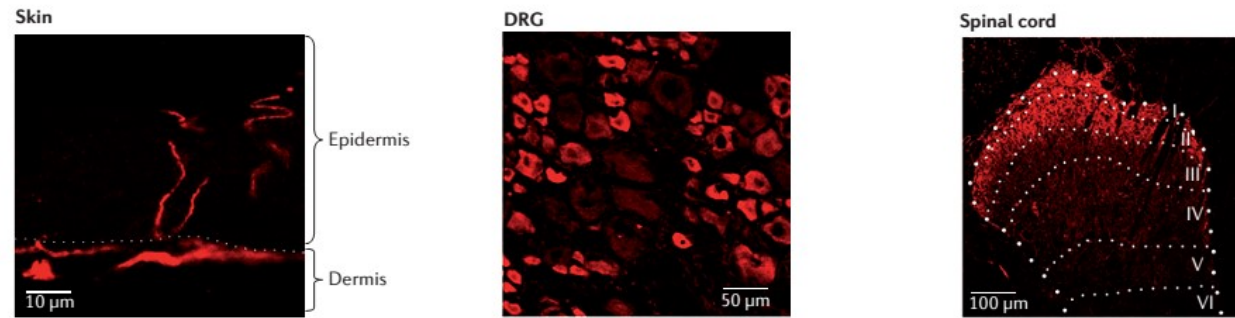
# Mutações nos canais de sódio $\text{Na}_v1.1$ (SCN1A) neuronais estão relacionadas a síndromes epilépticas

Neuron, Vol. 34, 877–884, June 13, 2002, Copyright ©2002 by Cell Press

## Molecular Basis of an Inherited Epilepsy



# Canais de sódio dependentes de potencial $Na_v1.7$ (SCN9A) estão presentes nas vias nociceptivas



# Ausência dos canais de sódio dependentes de potencial Na<sub>v</sub>1.7 (SCN9A) provocam analgesia total

nature

Vol 444 | 14 December 2006 | doi:10.1038/nature05413

## ARTICLES

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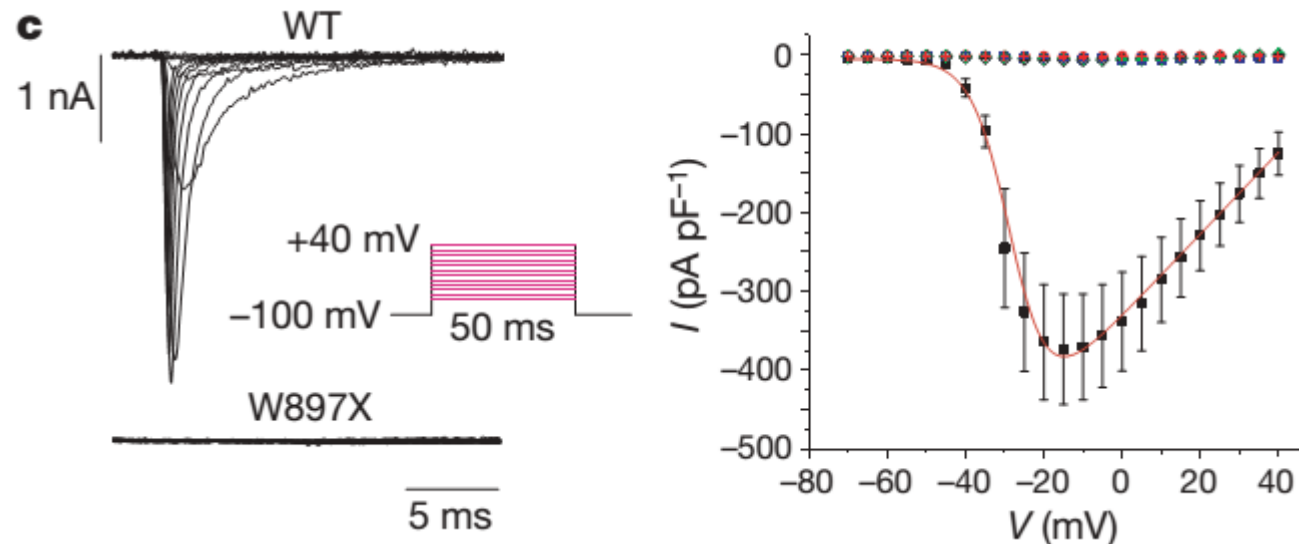
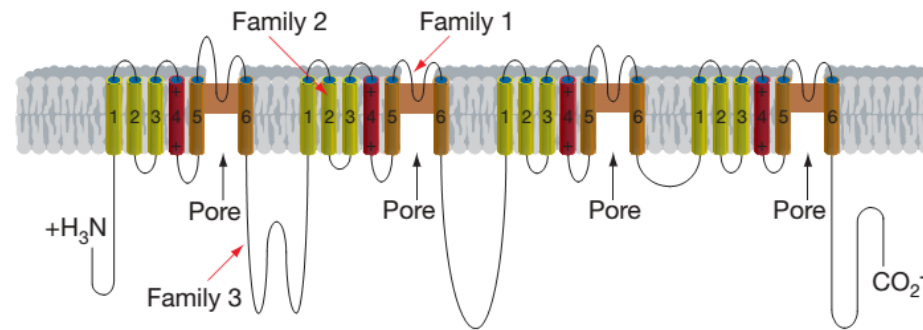
### **An *SCN9A* channelopathy causes congenital inability to experience pain**

James J. Cox<sup>1\*</sup>, Frank Reimann<sup>2\*</sup>, Adeline K. Nicholas<sup>1</sup>, Gemma Thornton<sup>1</sup>, Emma Roberts<sup>3</sup>, Kelly Springell<sup>3</sup>, Gulshan Karbani<sup>4</sup>, Hussain Jafri<sup>5</sup>, Jovaria Mannan<sup>6</sup>, Yasmin Raashid<sup>7</sup>, Lihadh Al-Gazali<sup>8</sup>, Henan Hamamy<sup>9</sup>, Enza Maria Valente<sup>10</sup>, Shaun Gorman<sup>11</sup>, Richard Williams<sup>12</sup>, Duncan P. McHale<sup>12</sup>, John N. Wood<sup>13</sup>, Fiona M. Gribble<sup>2</sup> & C. Geoffrey Woods<sup>1</sup>

Ausência dos canais de sódio dependentes de potencial  $Na_v1.7$  (SCN9A) provocam analgesia total



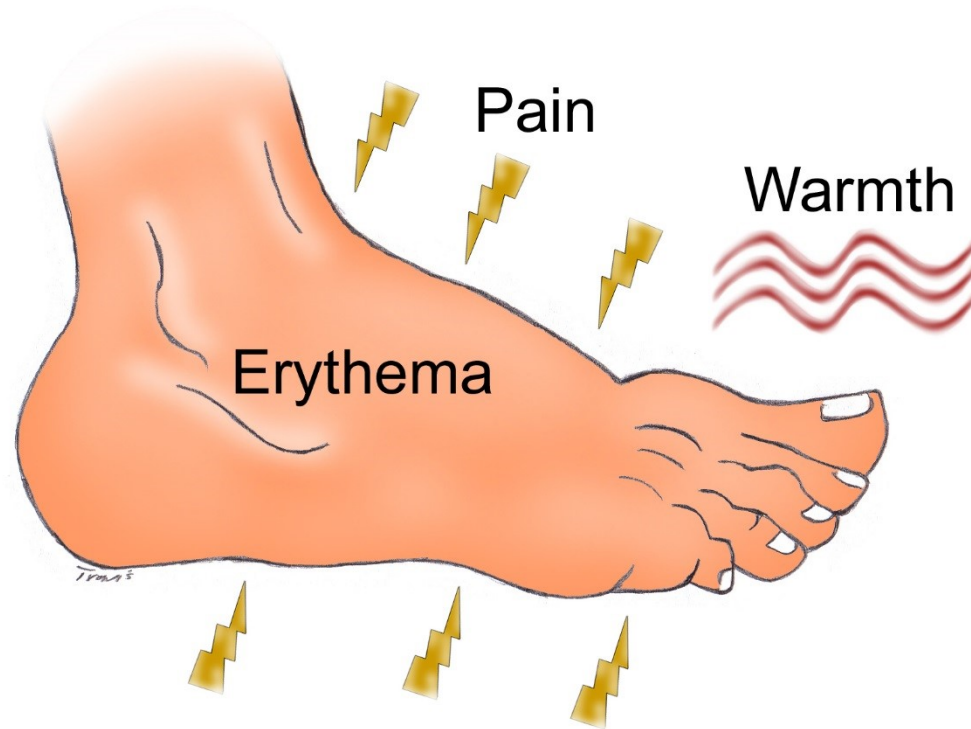
# Ausência dos canais de sódio dependentes de potencial $\text{Na}_v1.7$ (SCN9A) provocam analgesia total



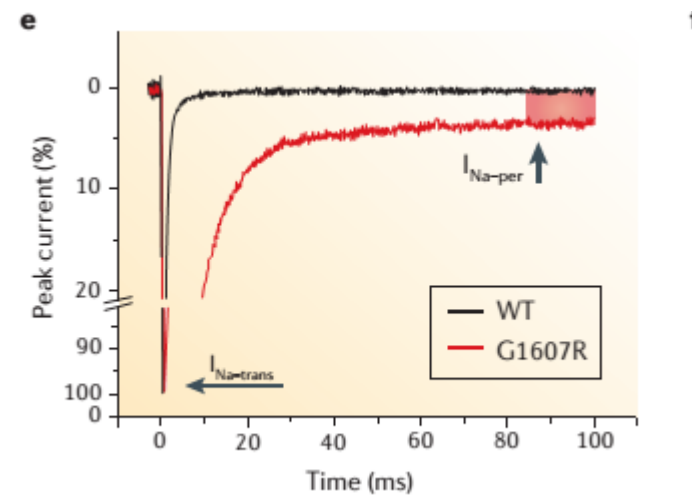
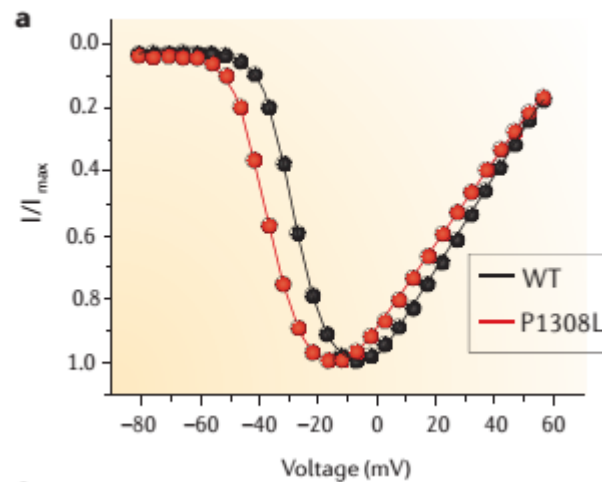
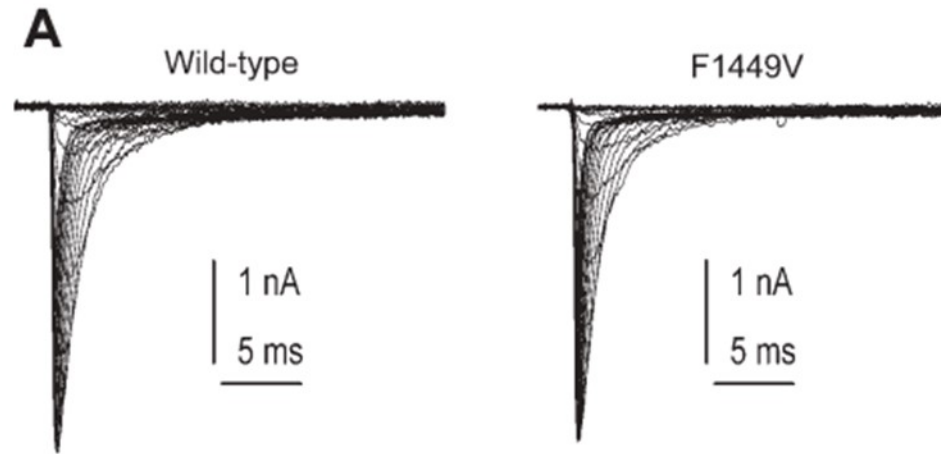


Eritromegalia herdada é uma patologia relacionada a mutações nos canais de sódio dependentes de potencial  $Na_v1.7$  (SCN9A)

### The Cardinal Symptoms of Erythromelalgia



Os canais  $\text{Na}_v1.7$  mutantes da eritromegalia herdada possuem ativação em potencial mais hiperpolarizados e menor inativação



Os canais  $Na_v1.7$  mutantes da eritromegalia herdada diminuem o limiar do potencial de ação dos neurônios nociceptivos e aumentam sua excitabilidade

