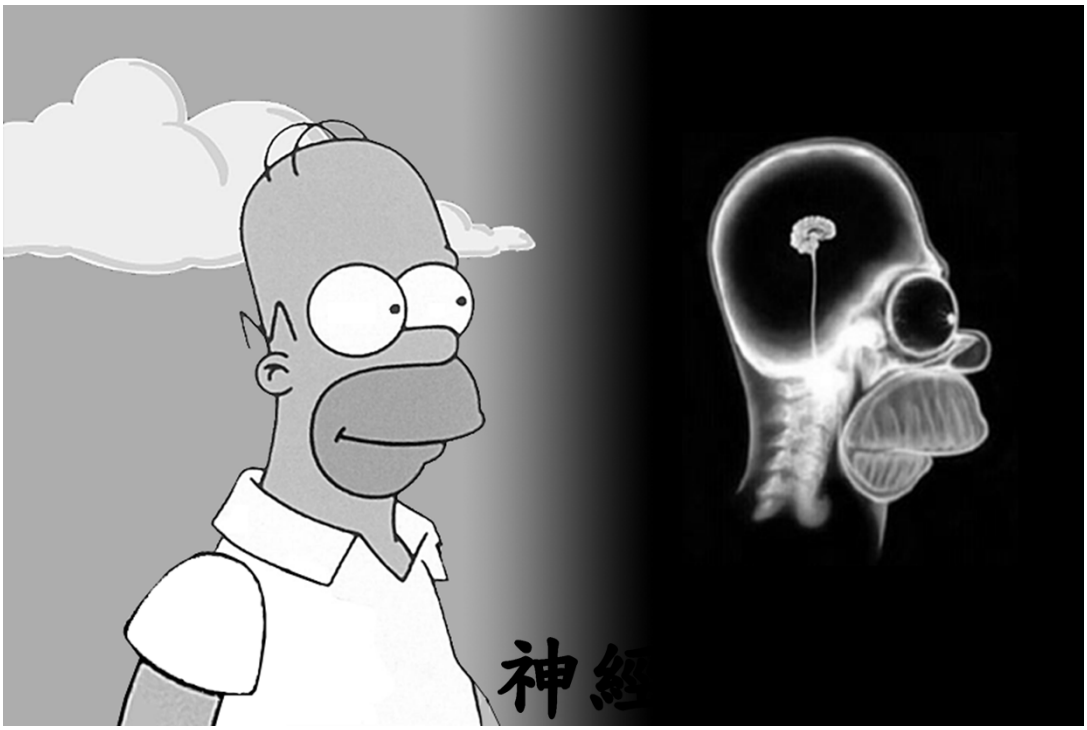


視覺模糊、頭痛、頭昏眼花、嘔吐、癲癇、@※&◎….

685 小孩被送上救護車
大部分人在送醫途中恢復正常

150 小孩需要住院觀察

2 人需住院超過二星期

アニメ ポケモン問題 検証報告

“光敏感性癲癇”

4～14歲的小孩中，大約每1000人有8個人會有這種危險的症狀發生！

生物
vs
無生物

Response to environment

辨識系統

“接受器”

Physical Factors:

Sound

Light

Heat

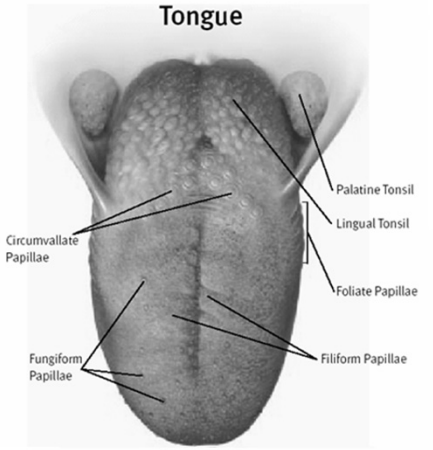
Gravity

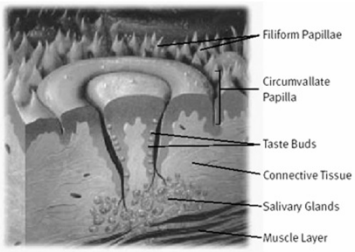
Chemical Factors:

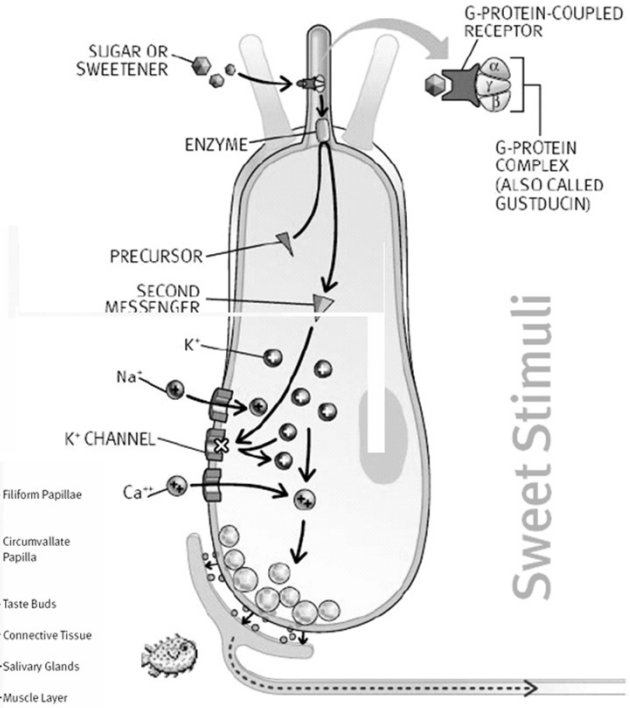
Taste

Odor

Drugs

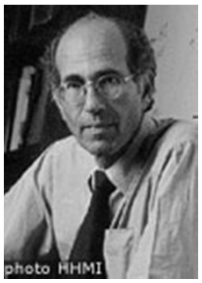






The Nobel Prize in Physiology or Medicine 2004

"for their discoveries of odorant receptors and the organization of the olfactory system"



Richard Axel

USA

Columbia University
New York, NY, USA; Howard Hughes Medical Institute

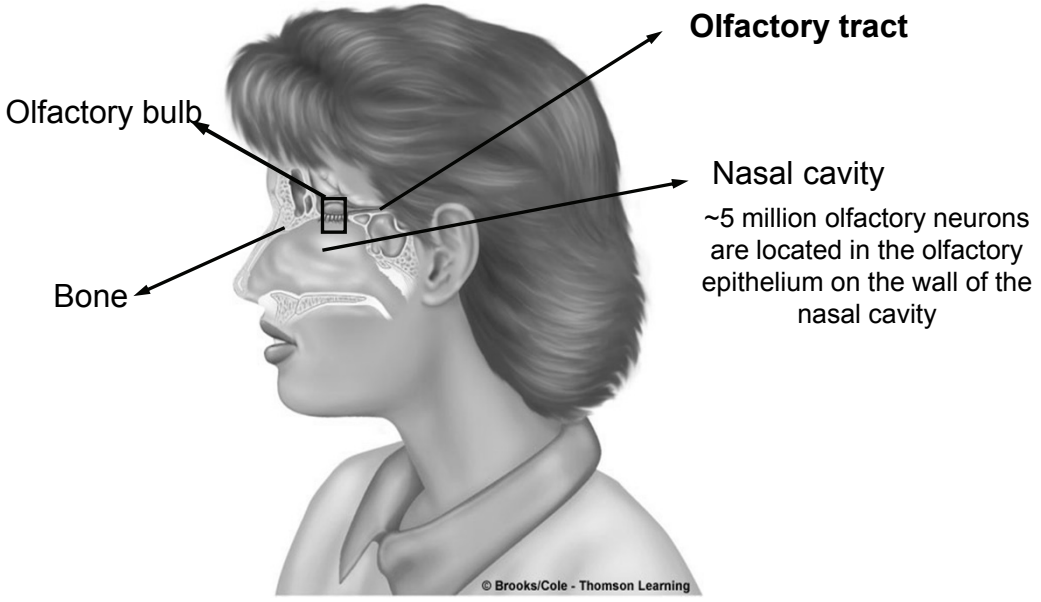
b. 1946

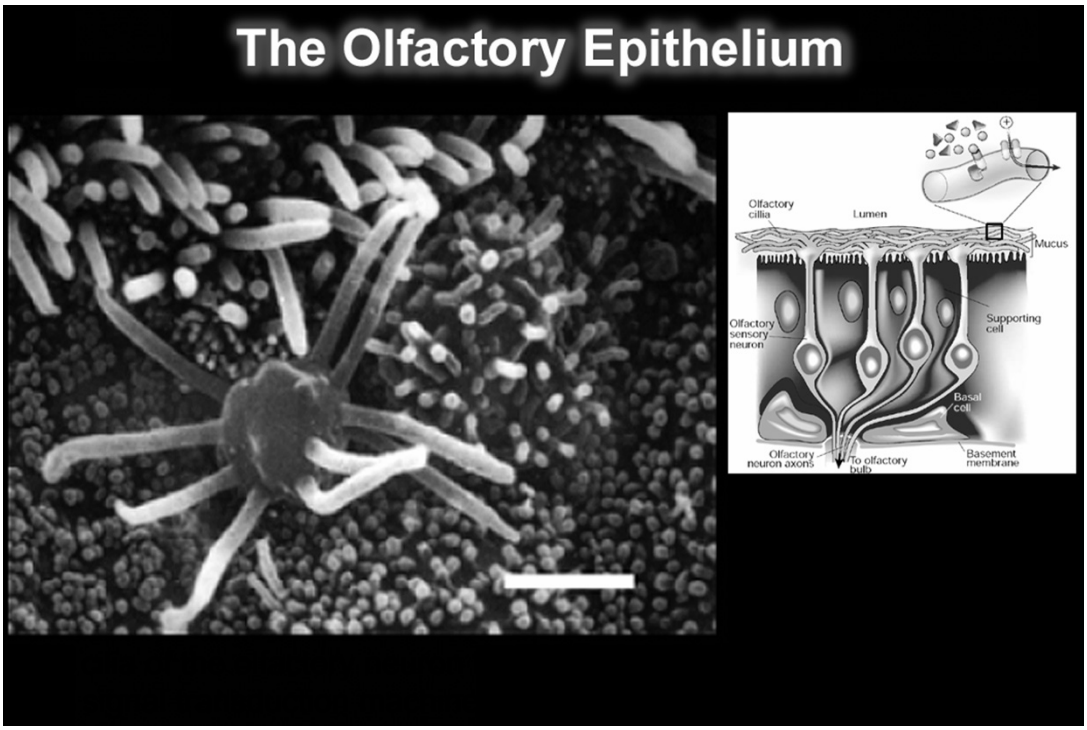
Linda B. Buck

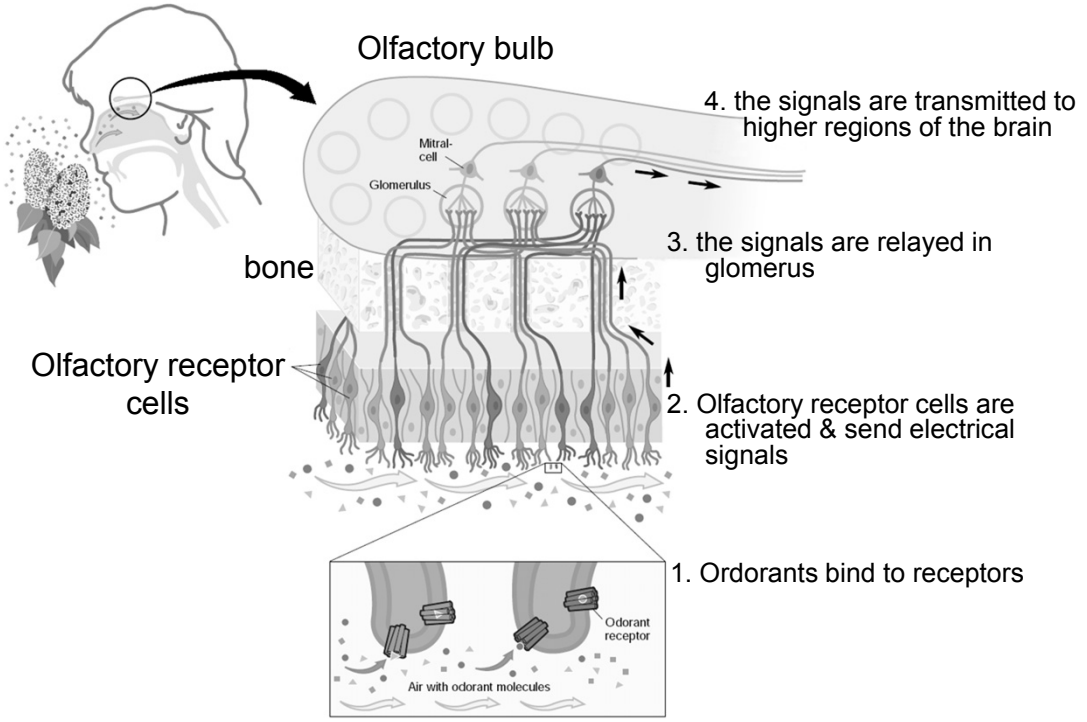
USA

Fred Hutchinson Cancer Research Center
Seattle, WA, USA; Howard Hughes Medical Institute

b. 1947




The Olfactory Epithelium
Olfactory cilia
Lumen
Mucus
Supporting cell
Olfactory sensory neuron
Basal cell
Olfactory neuron axons
To olfactory bulb
Basement membrane


Olfactory bulb
4. the signals are transmitted to higher regions of the brain
Mitral-cell
Glomerulus
3. the signals are relayed in glomerus
bone
Olfactory receptor cells
2. Olfactory receptor cells are activated & send electrical signals
1. Ordorants bind to receptors
Odorant receptor
Air with odorant molecules

神經活動，無所不在！

神經細胞是沙咪碗糕呢？

一般來說，每個神經元的寬度大約是10微米，相當的小。也就是說一公分的長度相當於1000個神經元並排，那一千億個神經元細胞有多長呢?並排起來可以達到1000公里那麼遠呢!

= 100,000,000,000

= 1300 克

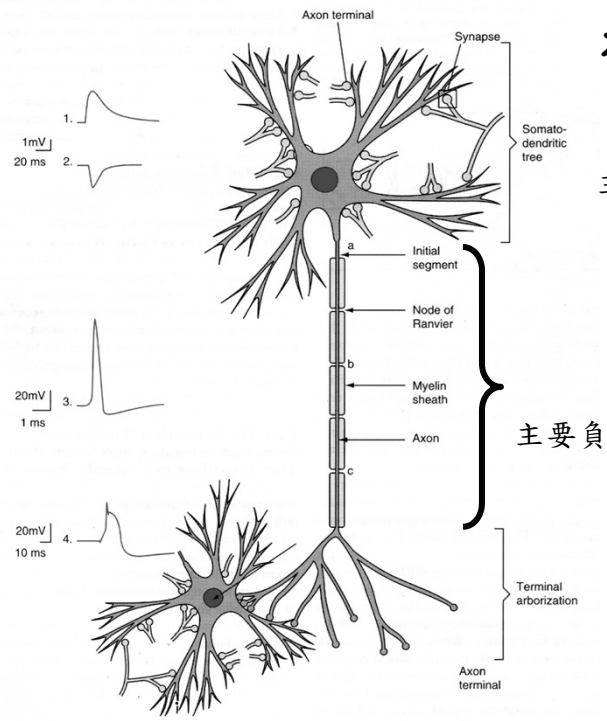
= 體重的 2%

Neurons are the oldest and longest cells in the body !

神經細胞和身體其他的細胞有何差異呢？

- 神經細胞有特殊的形狀及大小
  Neurons have diverse forms
- 神經細胞彼此會藉由形成突觸而互相聯繫
  Neurons communicate with each other at synapses
- 神經細胞具有產生細胞電性差異的能力
  Neurons have ability to generate electricity
- 神經細胞具有極高的代謝活動
  Neurons have high rate of metabolic activity
- 神經細胞具有有效的運輸系統
  Neurons have an efficient transport system

.....族繁，不及備載。



神經細胞的外觀

樹突與細胞體

主要負責接收外界的傳入訊號

軸突

主要負責將興奮的訊號傳遞到軸突末梢

軸突末梢

主要負責將興奮的訊號傳遞給後面的動器（如另一個神經細胞或肌肉細胞）

The Somato-dendritic Tree

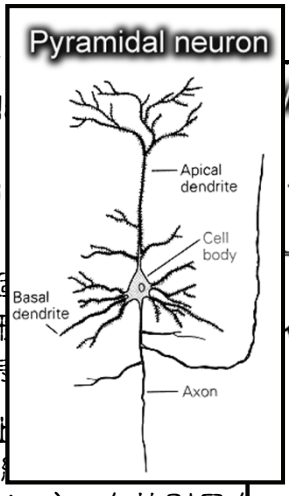
細胞體形狀：多樣化的

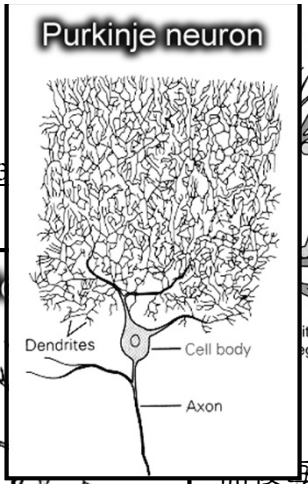
錐狀（大腦皮質及海馬回中的 Pyramida
neurons）

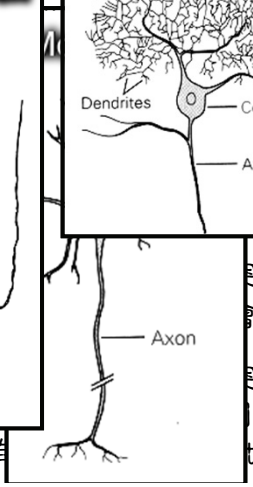
軟圓形（小腦皮質

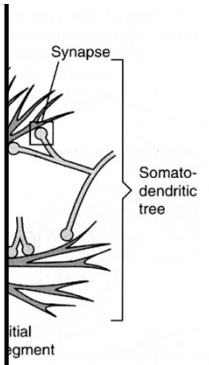
紡垂狀的（pallid
元細胞）

星狀的（脊髓中的

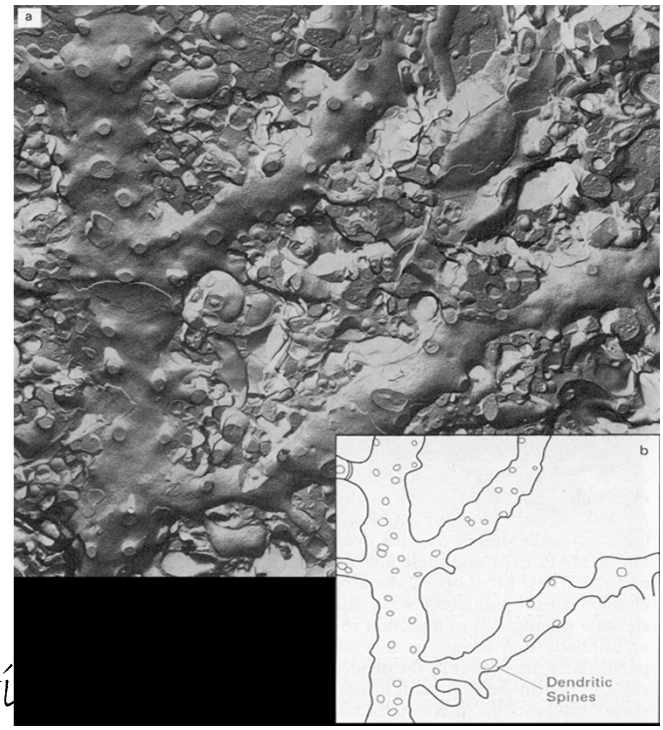




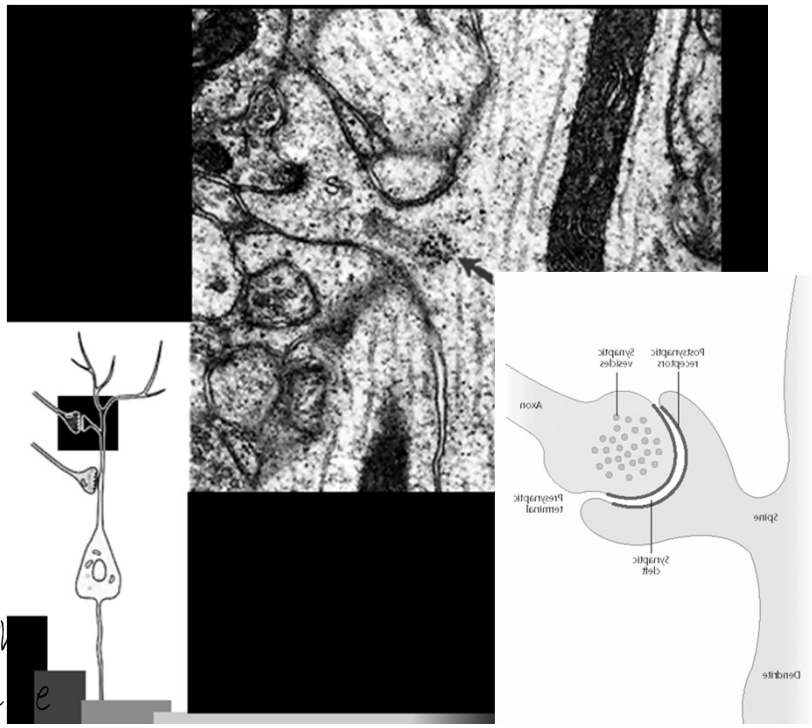




- 一般來說，每個 …每條一級樹突在繼續分支而形 …的形狀較不規則，刪由細胞體分出時 …會便得越細。
- 在樹突樹突之上 …突出物，稱爲dendritic spine，每個神經 …不盡相同，有的高達4萬~10萬個(spiny)，有的則只有 …te spine (smooth)。



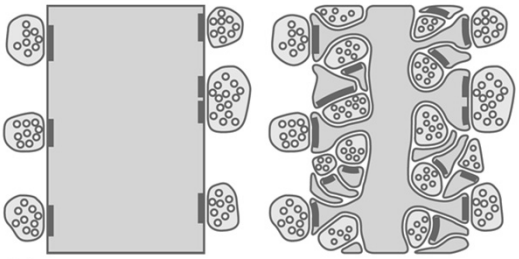
Dendrí



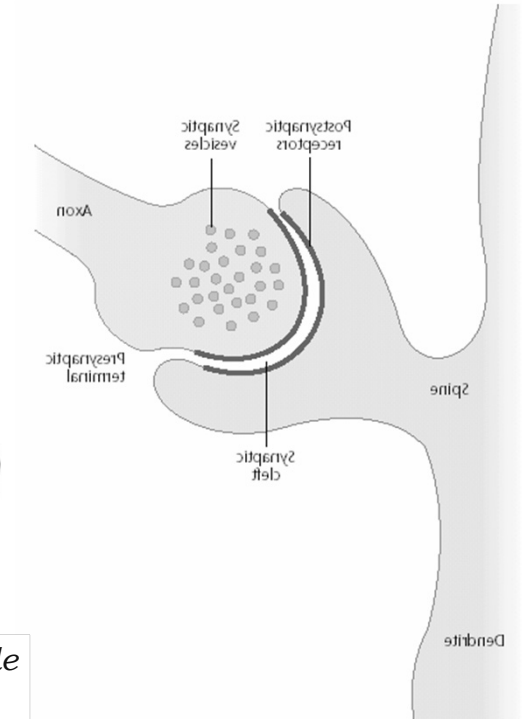
Th

Dendrite Spi e

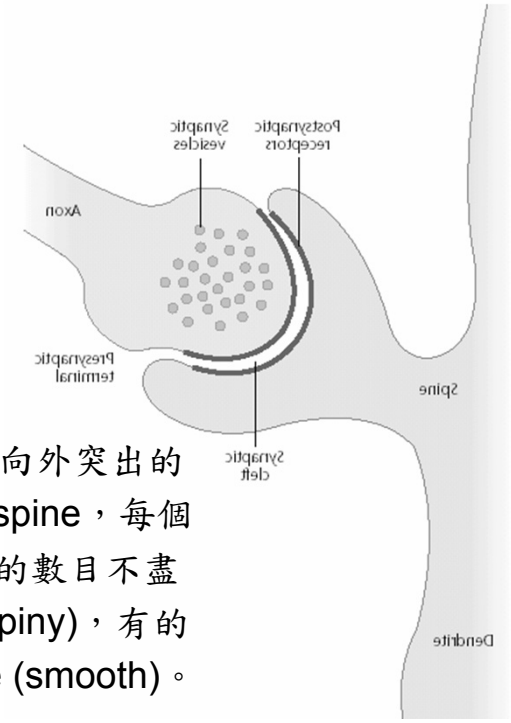
THE Dendrite Spine



increase the surface area available for new synapses to form

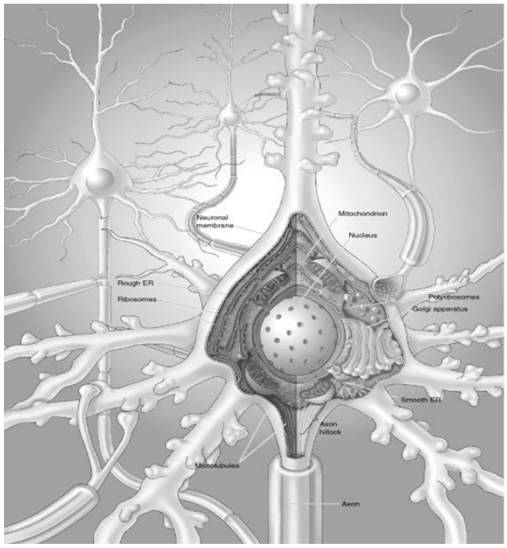


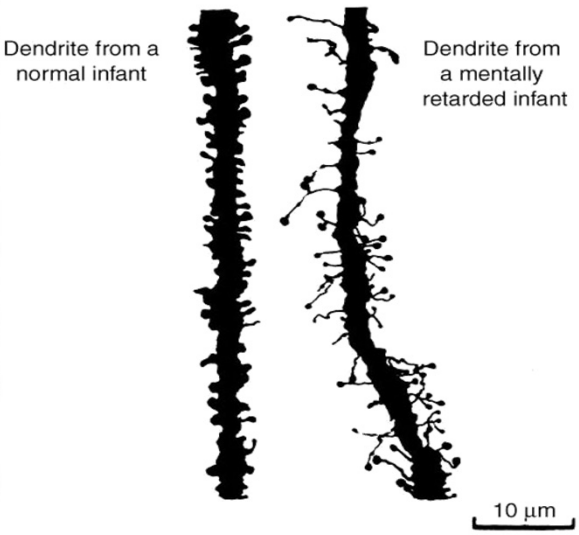
Dendritic Spine



- 在樹突樹突之上可以看到許多向外突出的卵圓形突出物，稱為dendritic spine，每個神經元細胞上dendritic spine 的數目不盡相同，有的高達4萬~10萬個(spiny)，有的則只有極少數的dendritic spine (smooth)。

Normal and Abnormal Dendrite



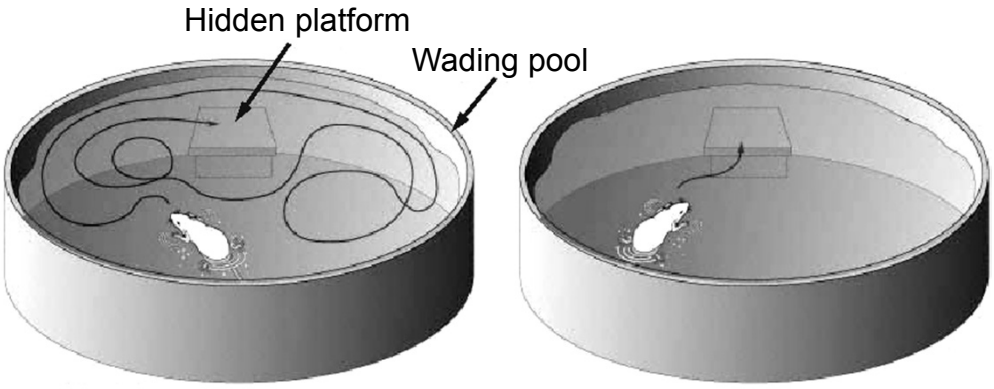


Long-term potentiation (LTP) or learning induces morphological changes in dendritic spines.

Most excitatory synapses in the brain terminate on

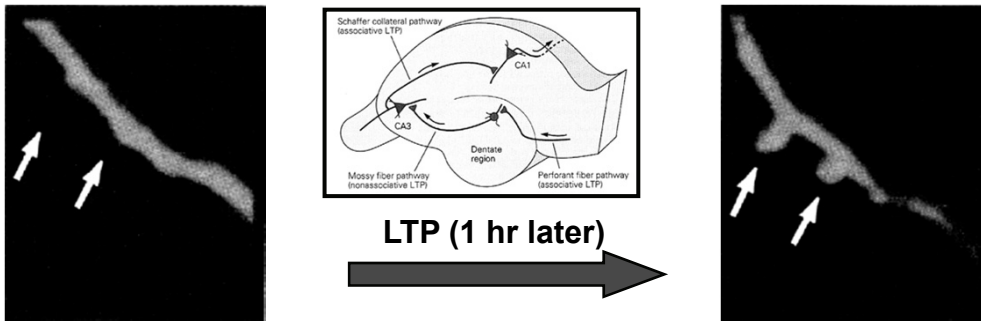
dendritic spines

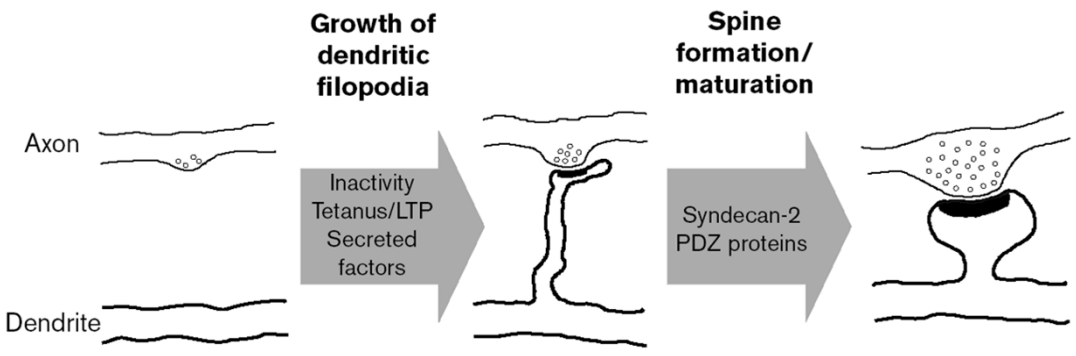
Morris water maze (by Richard Morris): spatial memory



Before learning

After learning

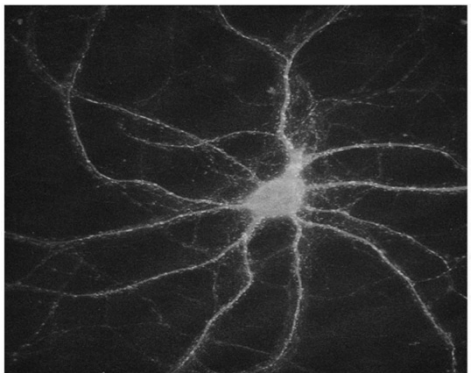


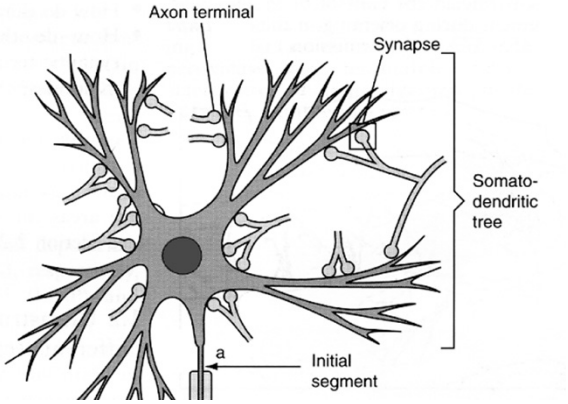


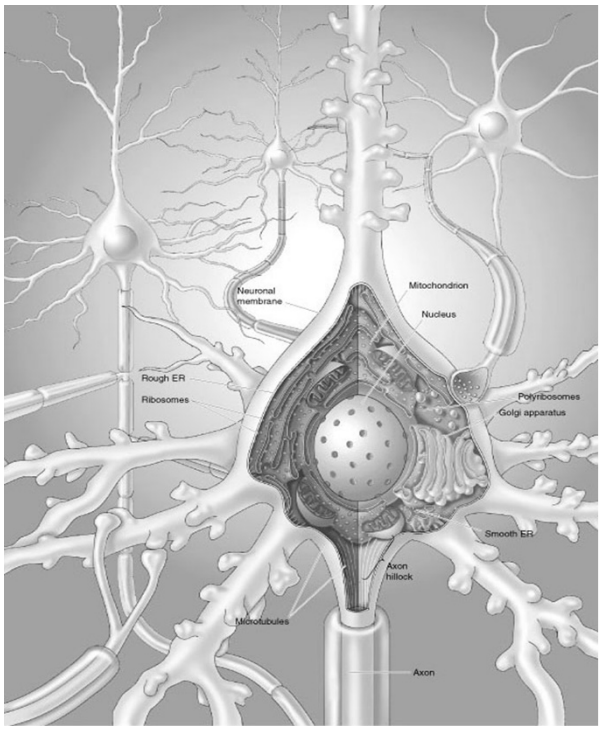
The Somato-dendritic Tree is the neuron's Receptive Pole

功能：

- 接受外來的訊號，有的神經甚至可與傳入神經建立高達一萬個突觸!!
- 整合外界所傳來的興奮性(EPSP)或抑制性(IPSP)訊號，若訊號總和超過一個特定的閥值，則會引發動作電位。



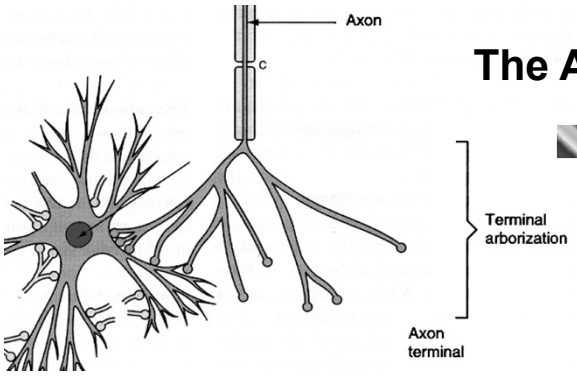




Soma:

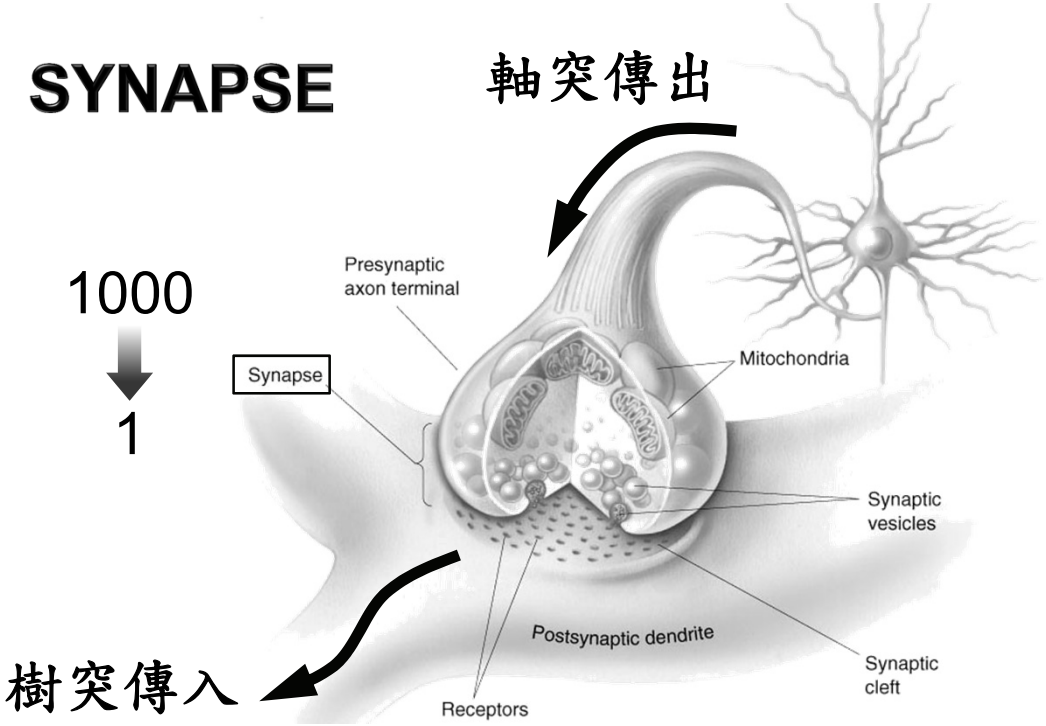
(neuronal cell body)
the metabolic center

- 與身體其他細胞具有相同的胞器，如細胞核、高基氏體、核糖體，粒腺體、內質網等等，可合成蛋白質，爲細胞的代謝中樞。



The Axon & axonal collaterals

- 和樹突比較起來，軸突具有平滑的外觀，且整條軸突自soma 起始端到末梢的直徑很均一。軸突的長度隨著神經的種類差異很大，在某些神經其長度甚至可長達一公尺以上。
- 有些神經的軸突會被膠質細胞（glia cell）所包覆而形成髓峭，軸突在兩段髓峭間未被包覆的區域稱爲蘭氏結（Nodes of Ranvier）。
- 神經軸突的末梢會特化成synaptic buttons，藉由這些特化組織，軸突可以和其他神經或標的細胞（如肌肉細胞）形成突觸（synapse），達到聯繫的作用。



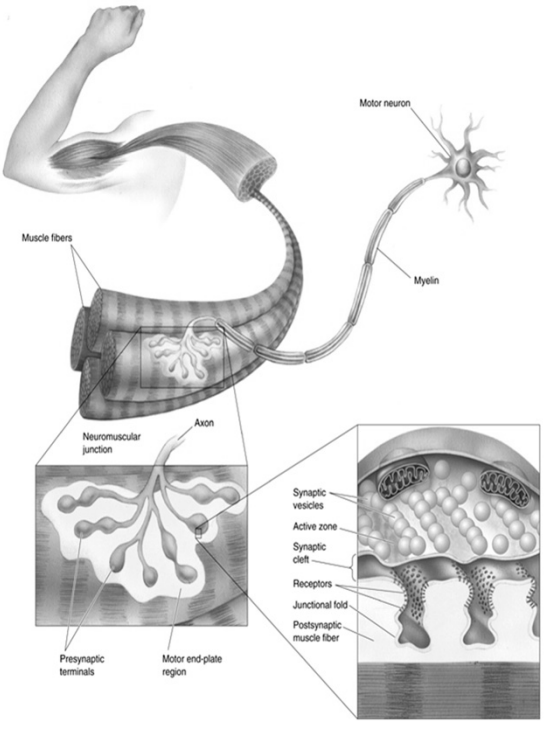
Synapse = Syn + haptein

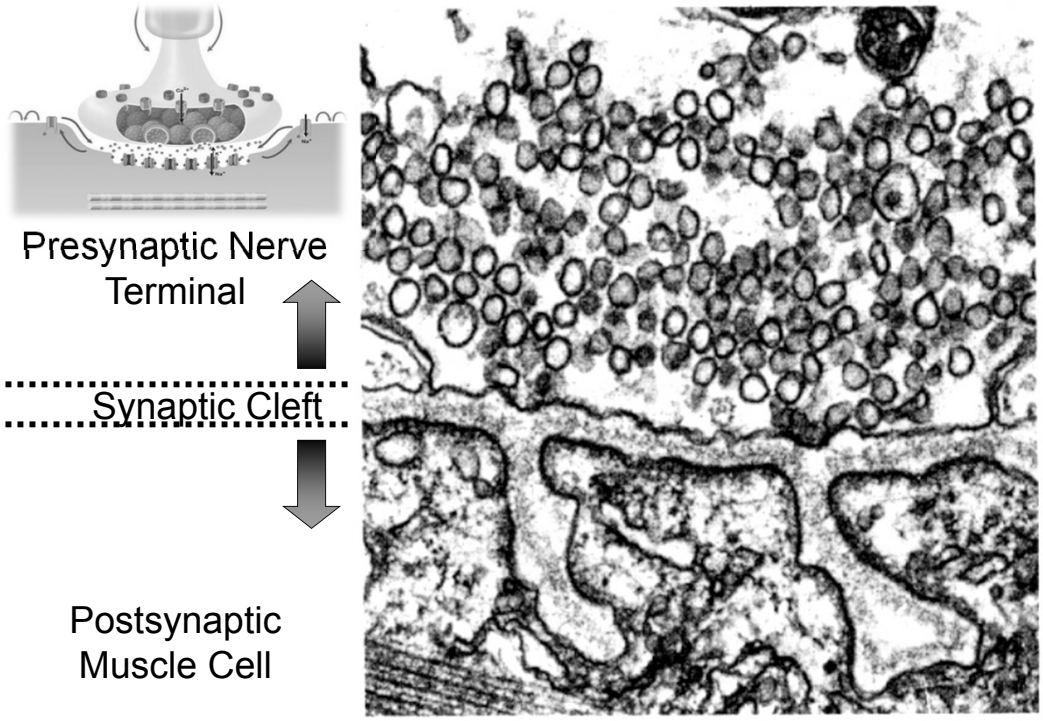
together clasp

113Years Old

Since 1897

Michael Foster & Charles Sherrington

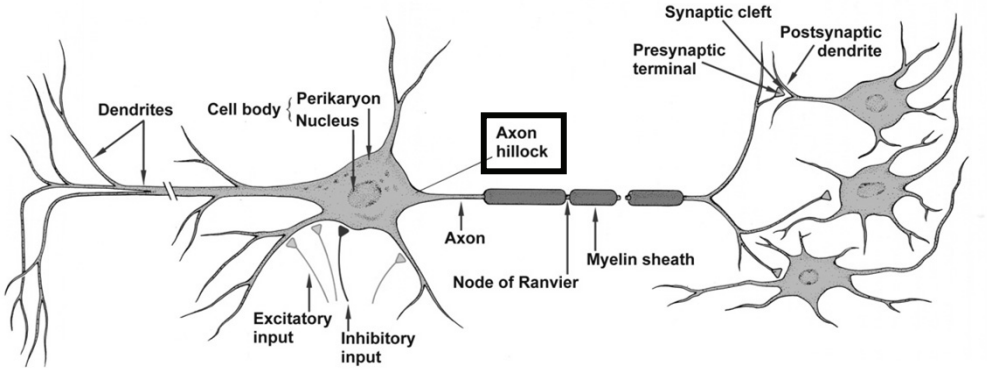


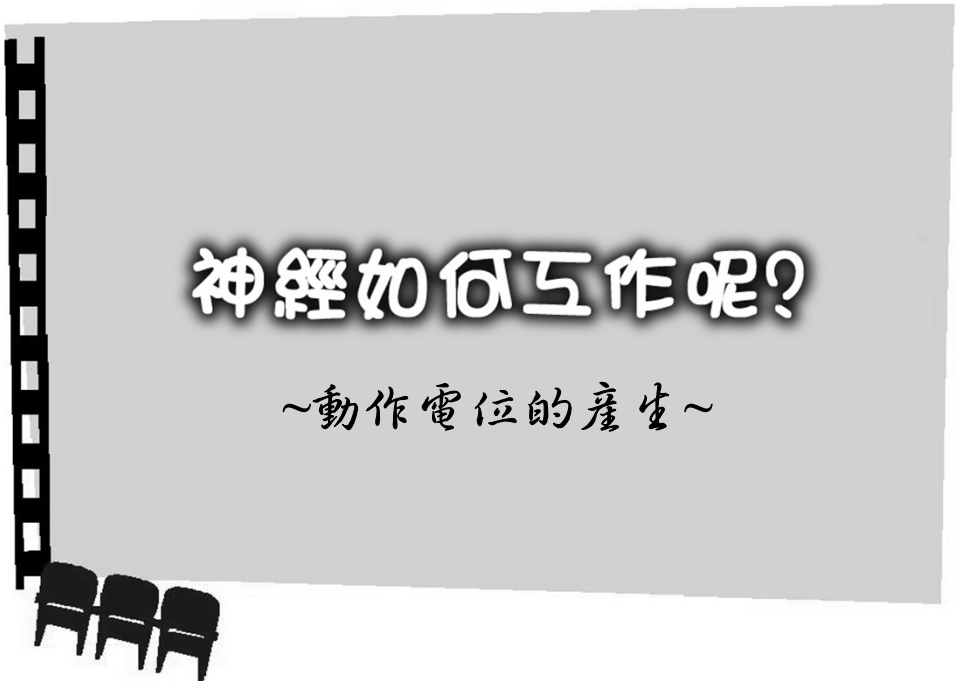


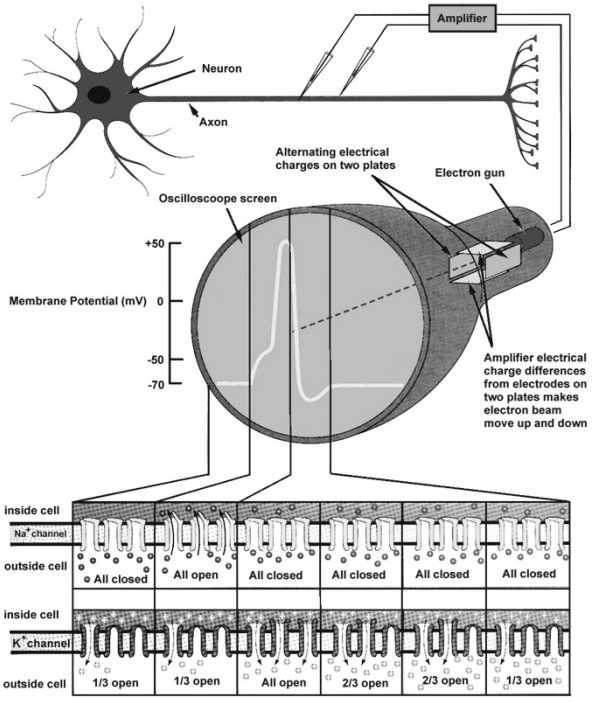
The Axon & axonal collaterals are the neuron's Transmitter Pole

功能:

- 誘發動作電位(Trigger action potential)
- 以不失真的方式來將動作電位傳遞到神經末梢
- 特化的軸突末端可以感應動作電位的來臨而釋放出神經傳遞物質來影響突觸後的神經或標的細胞







- 神經活性的誘導係因為神經本身細胞膜電位由於細胞外及細胞內各種離子經由離子通道的流動所引發而造成動作電位

- 動作電位：

去極化：鈉離子流入細胞內

再極化：鉀離子流出細胞外

"Ion channel" is....

Hodgkin & Huxley, 1950s

...the fluxes of Na^+ and K^+ ions are through "holes" in the membrane

Awardees of the 1963 Nobel Prize

The Nobel Prize in Physiology or Medicine 1963

"for their discoveries concerning the ionic mechanisms involved in excitation and inhibition in the peripheral and central portions of the nerve cell membrane"

Sir John Carew Eccles

1/3 of the prize

Australia

University College London, United Kingdom

b. 1903
d. 1997

Alan Lloyd Hodgkin

1/3 of the prize

United Kingdom

University of Cambridge Cambridge, United Kingdom

b. 1914
d. 1998

Andrew Fielding Huxley

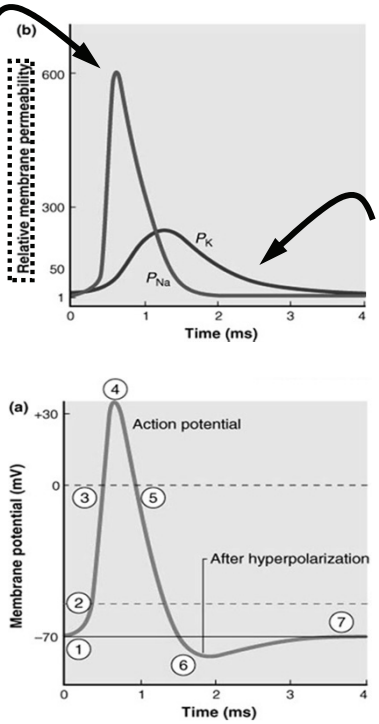
1/3 of the prize

United Kingdom

University College London, United Kingdom

b. 1917

The rapid opening of voltage-gated Na^+ channels allows rapid entry of Na^+, moving membrane potential closer to the Na^+ equilibrium potential (+60 mv)



The slower opening of voltage-gated K^+ channels allows K^+ exit, moving membrane potential closer to the K^+ equilibrium potential (-90 mv)

神經細胞如何能產生訊號以便將所接收的訊號往下傳達呢?

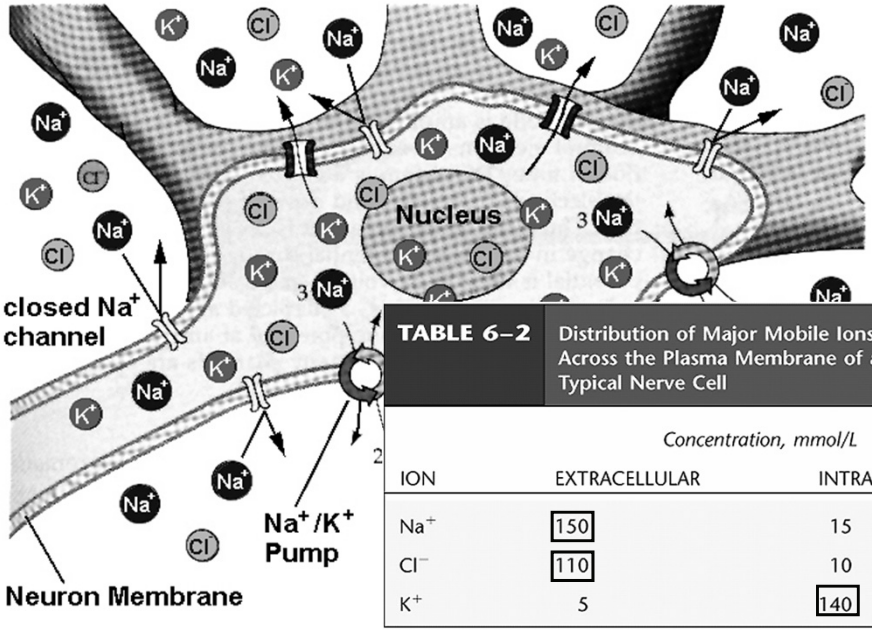
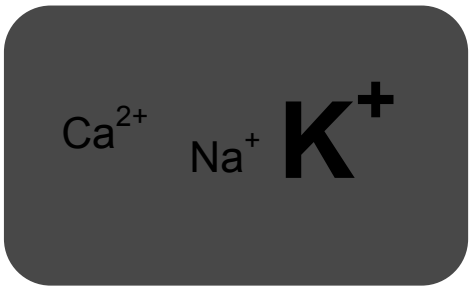
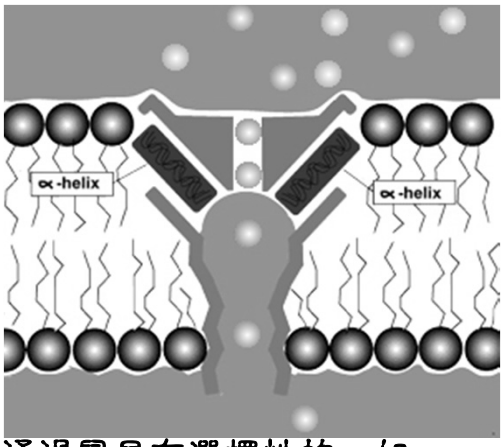


TABLE 6–2 Distribution of Major Mobile Ions Across the Plasma Membrane of a Typical Nerve Cell

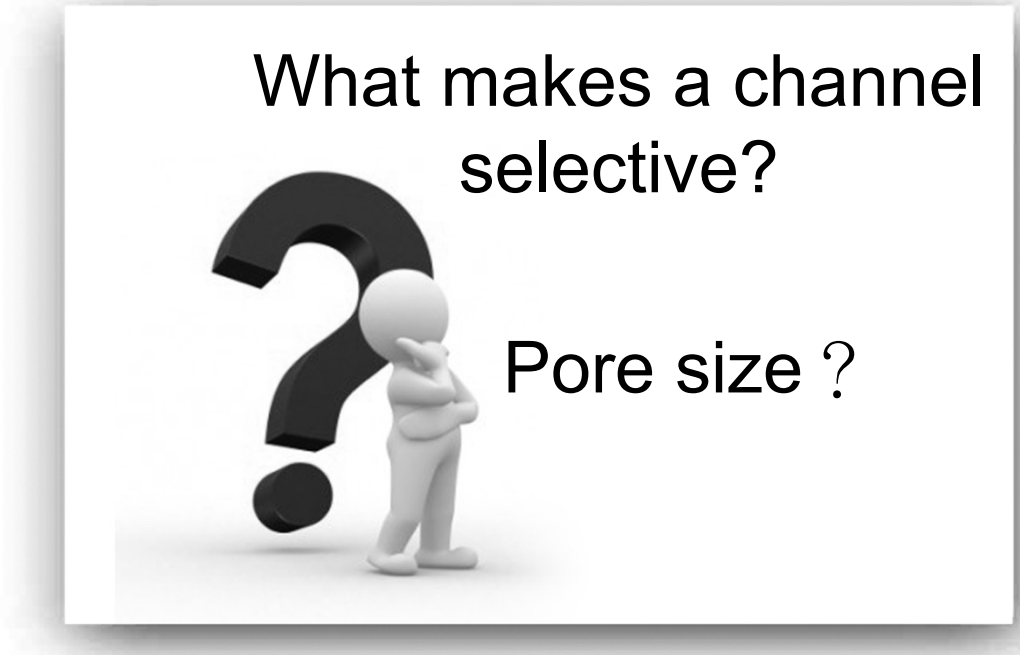
	Concentration, mmol/L	
ION	EXTRACELLULAR	INTRACELLULAR
Na^+	150	15
Cl^-	110	10
K^+	5	140

Ca^{2+} Na^{+} K^{+}

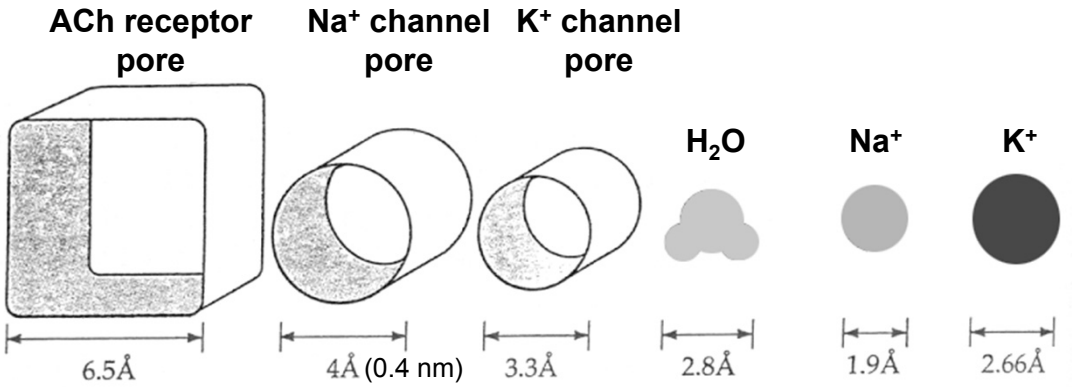




大體來說，離子通道對離子的通過是具有選擇性的。如：Na^+ 離子通道打開時對 Na^+ 的通透性要比 K^+ 高10~20倍；而 K^+ 離子通道打開時對 K^+ 的通透性要比 Na^+ 高100倍以上。

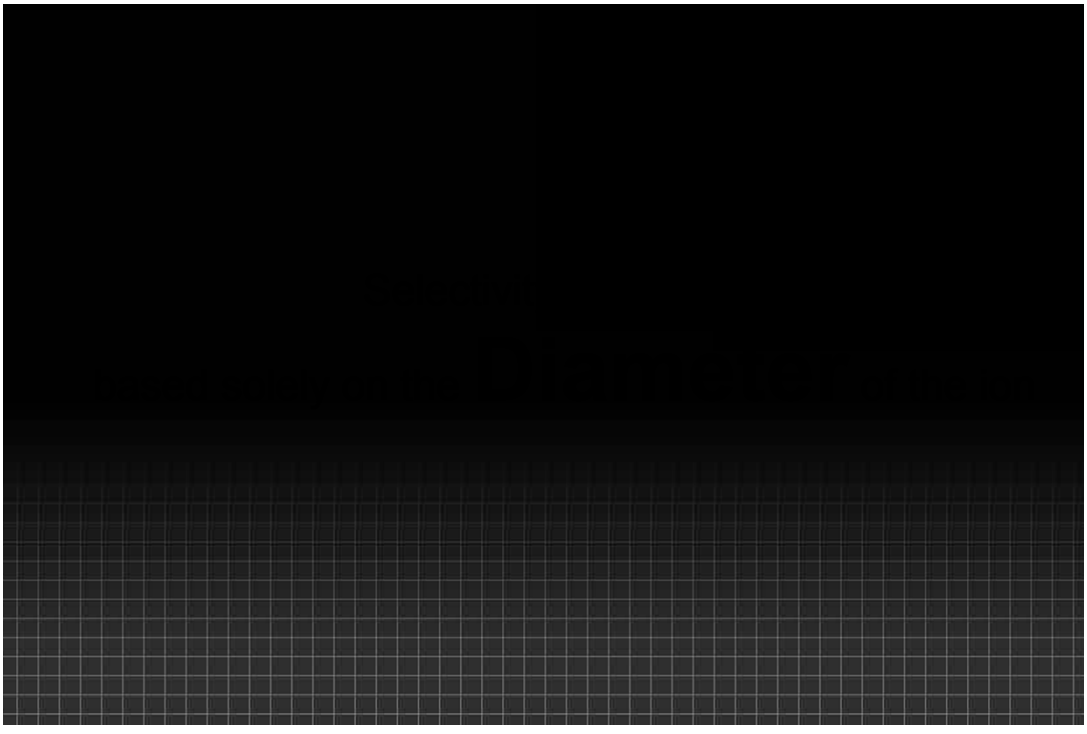


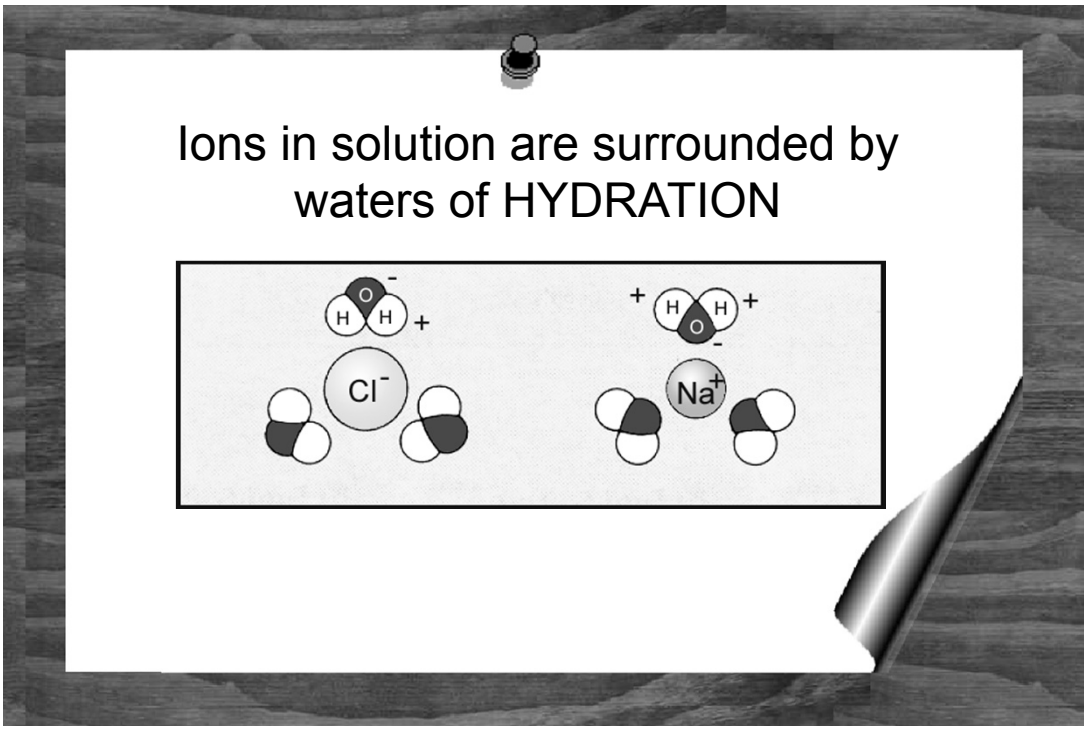
酵素藉由形成不同的結合位來辨識其受質，離子通道用什麼方法來辨識各種離子呢？
例如具有相同形狀與相同電荷的 Na^+ 及 K^+ 呢？

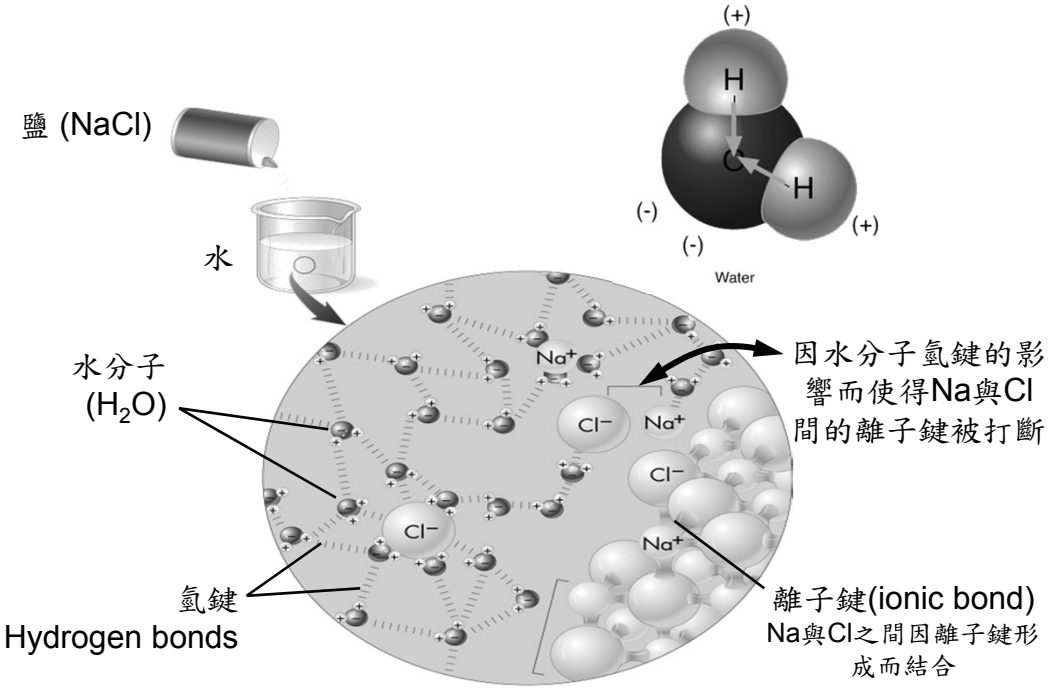


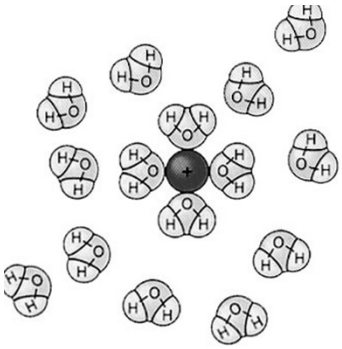
Molecular Neurobiology, P.88

K^+ channel，可以讓K^+ (2.66) 通過，卻不能讓Na^+(1.9) 通過呢？




Ions in solution are surrounded by waters of HYDRATION
Cl⁻
Na⁺


鹽 (NaCl)
水
水分子 (H_2O)
氫鍵
Hydrogen bonds
(+)
H
O
H
(-)
(-)
(+)
Water
因水分子氫鍵的影響而使得Na與Cl間的離子鍵被打斷
離子鍵(ionic bond)
Na與Cl之間因離子鍵形成而結合
Na⁺
Cl⁻



The ease with which an ion moves in solution depends on its *size together with the shell of water surrounding it*

Ions in solution are surrounded by waters of hydration

↓

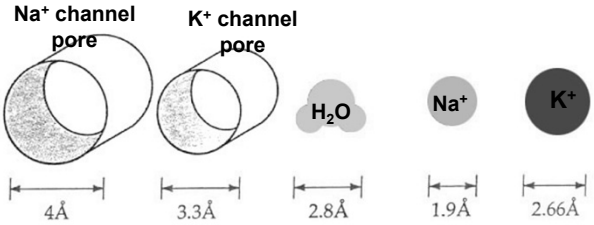
Small ions have stronger effective electric fields

↓

Smaller ions attract water more strongly

↓

The smaller the ion, the lower its mobility



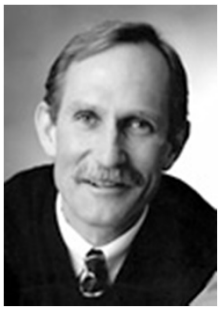
For K^+
$2.66 + n*2.8 > 3.3$ (K channel)

For Na^+
$1.9 + n*2.8 > 4$ (Na channel)

Principal of Neural Science p.106

The Nobel Prize in Chemistry 2003

*"for discoveries concerning **channels in cell membranes**"*



Peter Agre

USA

Johns Hopkins University School of Medicine
Baltimore, MD, USA

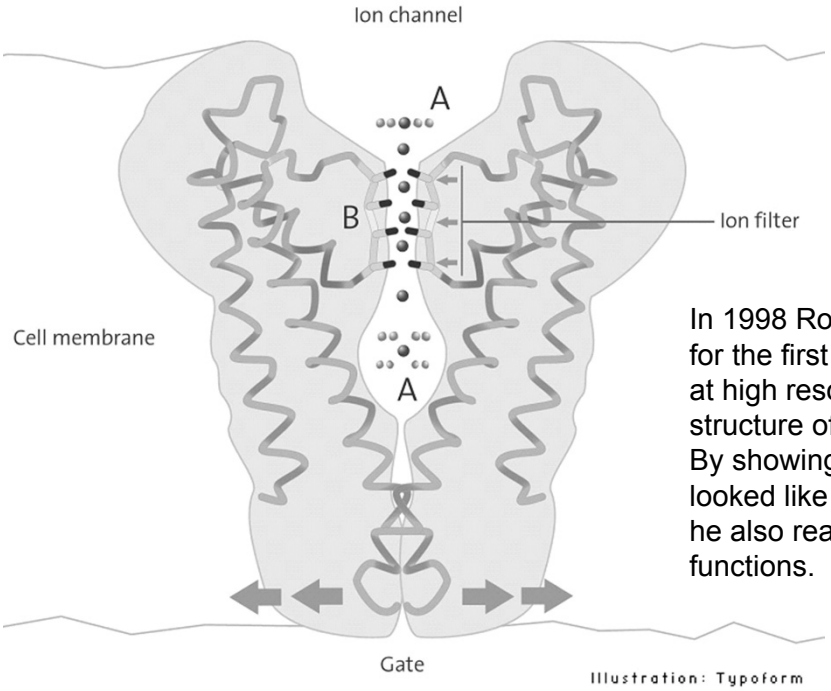
b. 1949

Roderick MacKinnon

USA

Rockefeller University
New York, NY, USA; Howard Hughes Medical Institute

b. 1956

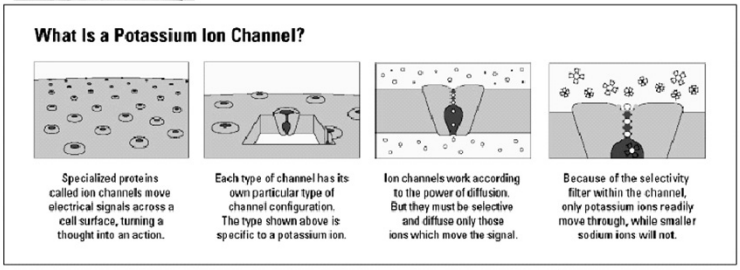


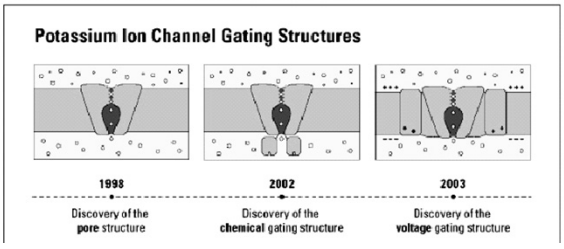
In 1998 Roderick MacKinnon for the first time determined at high resolution the structure of an ion channel. By showing what the protein looked like at the atomic level, he also realized how it functions.

2003 NOBEL PRIZE

Research illustrations

Roderick MacKinnon, M.D.
John D. Rockefeller Jr. Professor
Laboratory of Molecular Neurobiology and Biophysics
Investigator, Howard Hughes Medical Institute





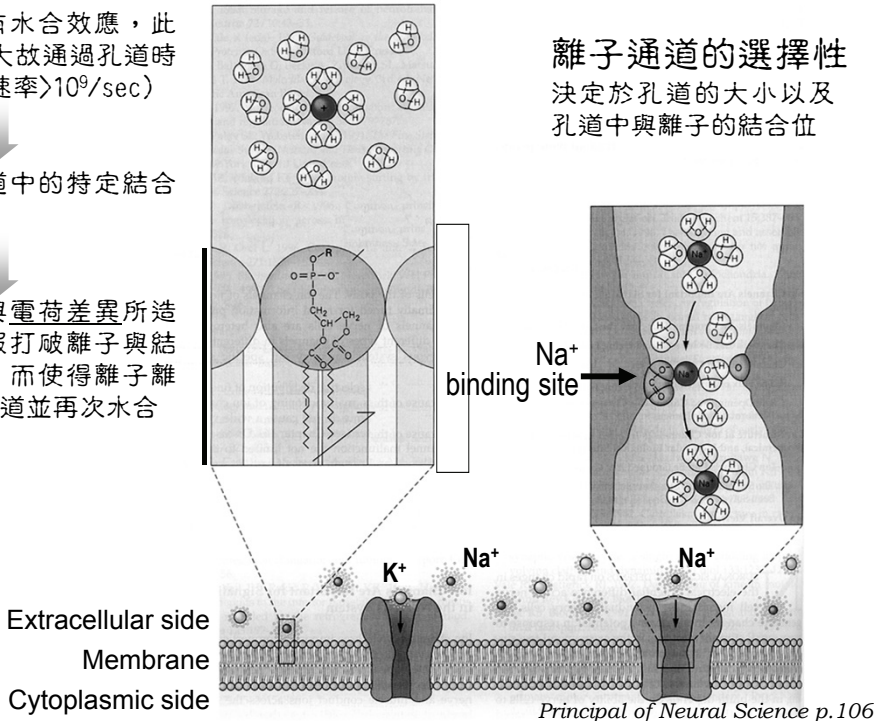
離子在水中會有水合效應，此時size 比孔道大故通過孔道時必需先去水合(速率>10^9/sec)

離子與離子通道中的特定結合位結合

離子濃度梯度與電荷差異所造成的驅動力克服打破離子與結合位的鍵結能，而使得離子離開結合位通過孔道並再次水合

離子通道的選擇性

決定於孔道的大小以及孔道中與離子的結合位



Principal of Neural Science p.106

神經細胞如何能產生訊號以便將所接收的訊號往下傳達呢?

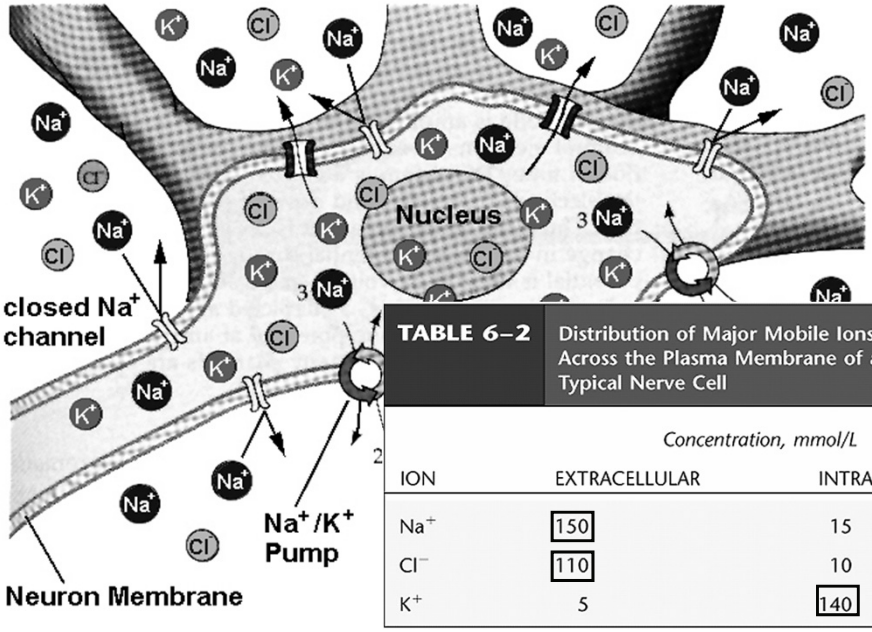
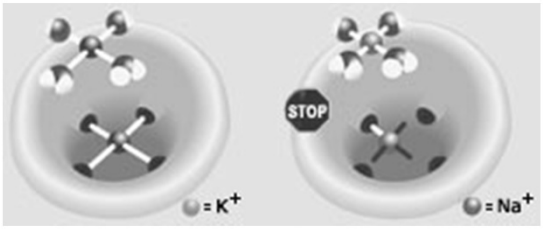
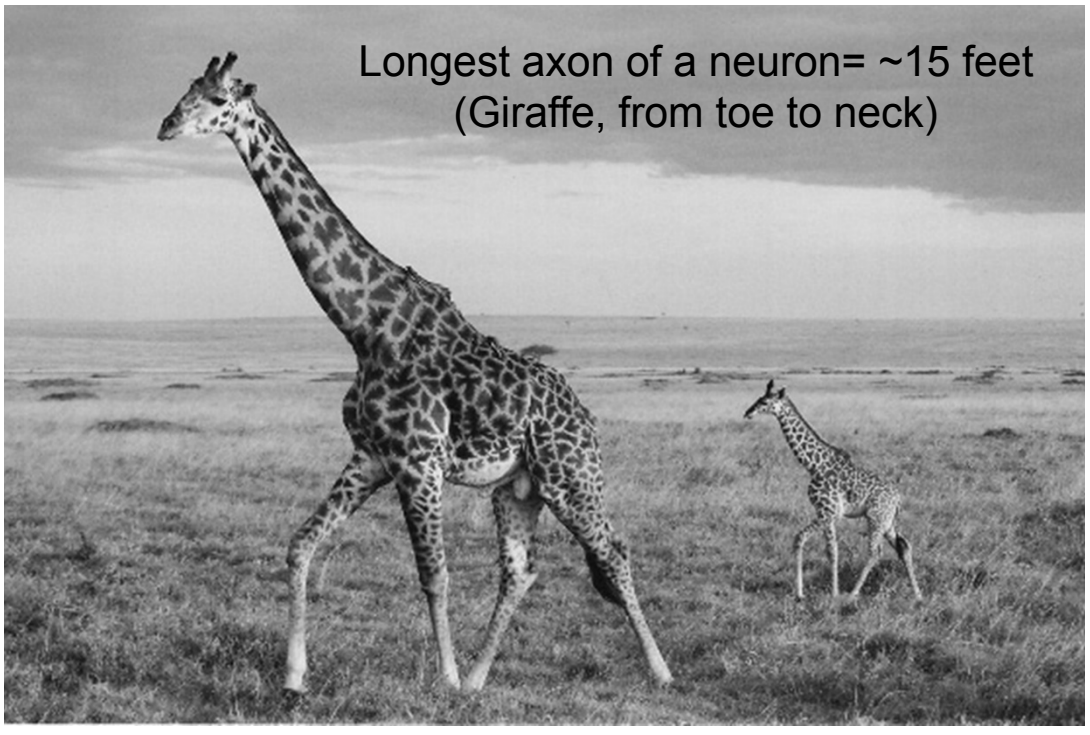


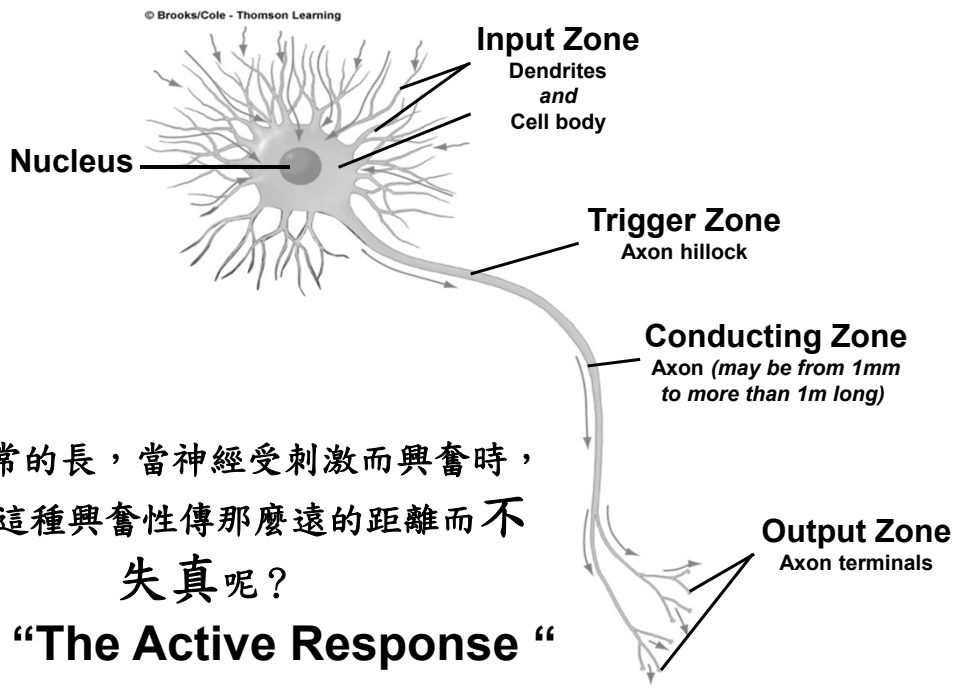
TABLE 6–2 Distribution of Major Mobile Ions Across the Plasma Membrane of a Typical Nerve Cell

	Concentration, mmol/L	
ION	EXTRACELLULAR	INTRACELLULAR
Na^+	150	15
Cl^-	110	10
K^+	5	140

In case of K^+ channel…



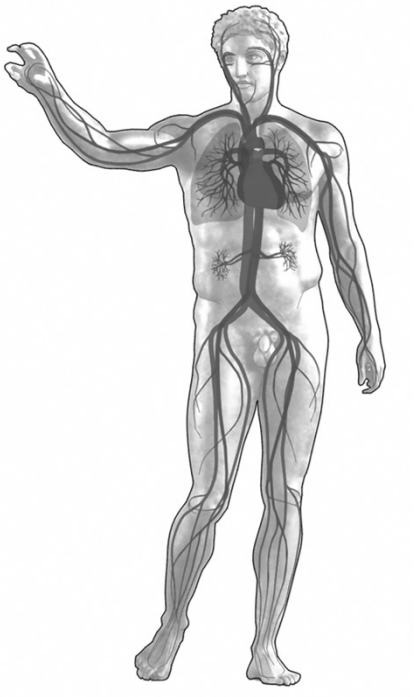




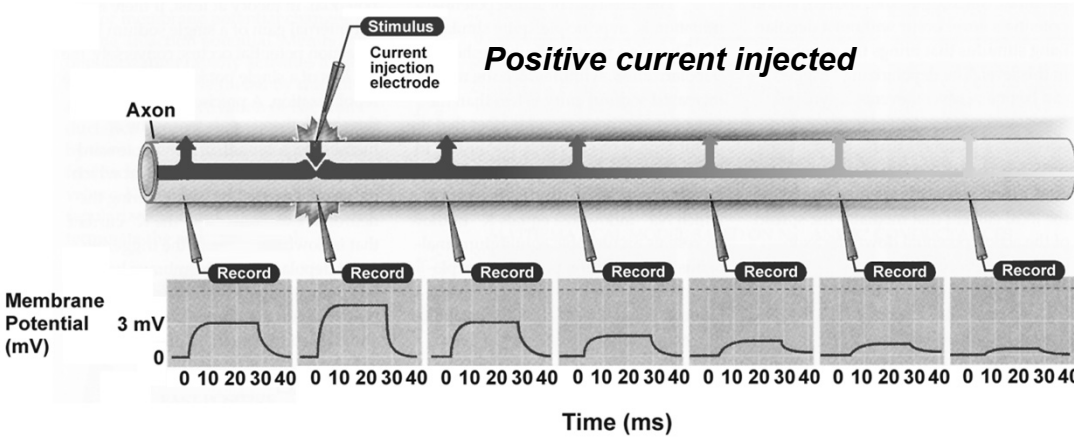
神經非常的長，當神經受刺激而興奮時，如何將這種興奮性傳那麼遠的距離而不失真呢？

“The Active Response “

能量在傳遞過程中會逐漸喪失！

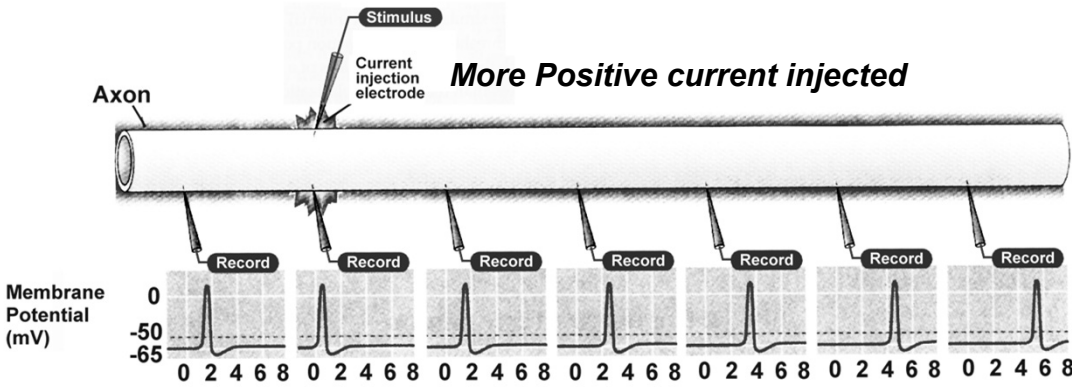


Passive Current Flow in an Axon



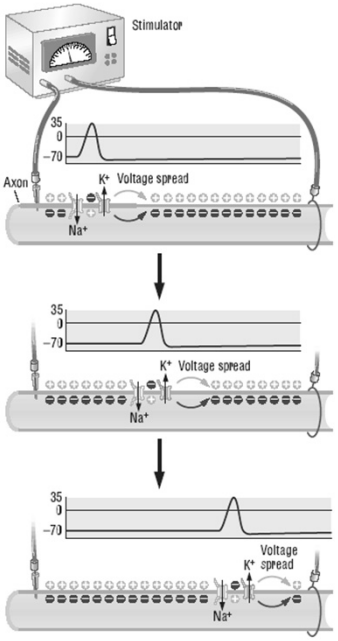
Neuroscience p.62

Active Responses to large depolarizing stimuli

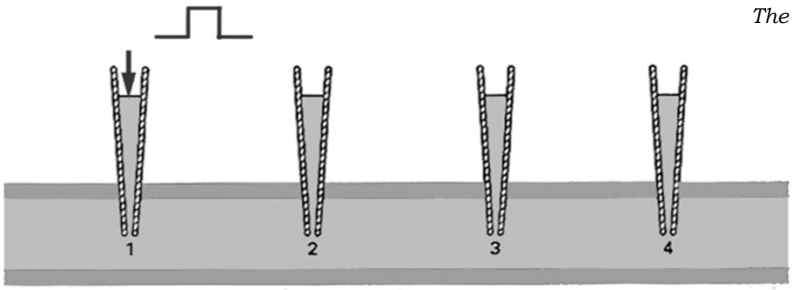


Neuroscience p.63

The Domino Effect

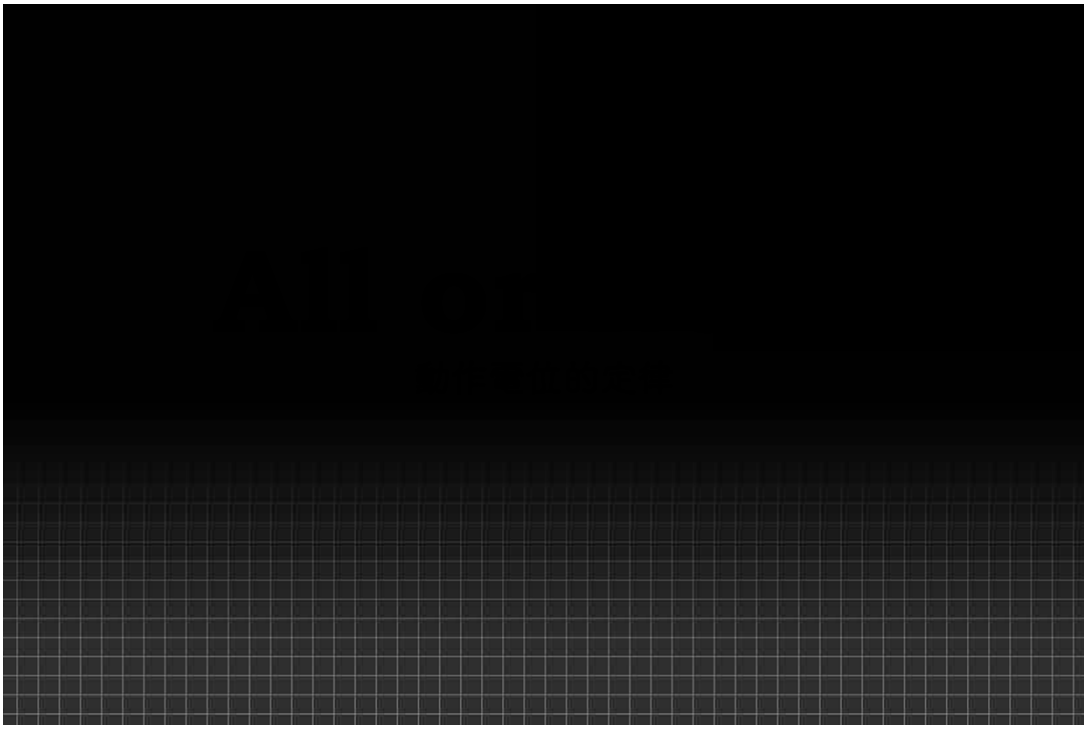


The Neuron p.58

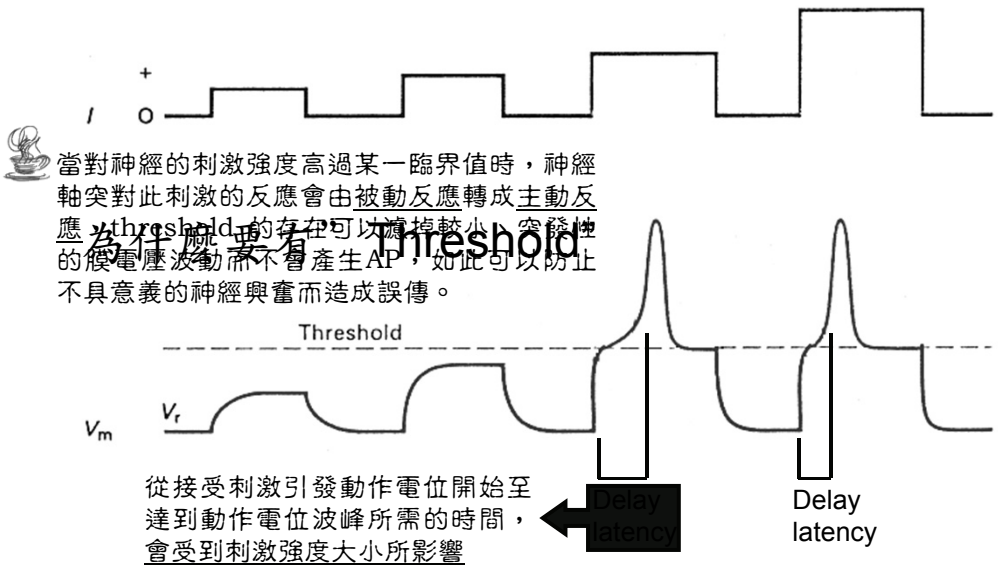


Active response-- 鄰近的Na^+ channel打開-- regenerate energy
Passive response-- 鄰近的Na^+ channel不打開--No regenerate energy

神經軸突所具有的 active spread 特性以及當他受到超過閥值的刺激後遵循 all or none 定律來引發動作電位的結果，使得神經興奮後可以將這種興奮性不失真的傳遞很遠，直到神經末梢為止。



Solo Homerun



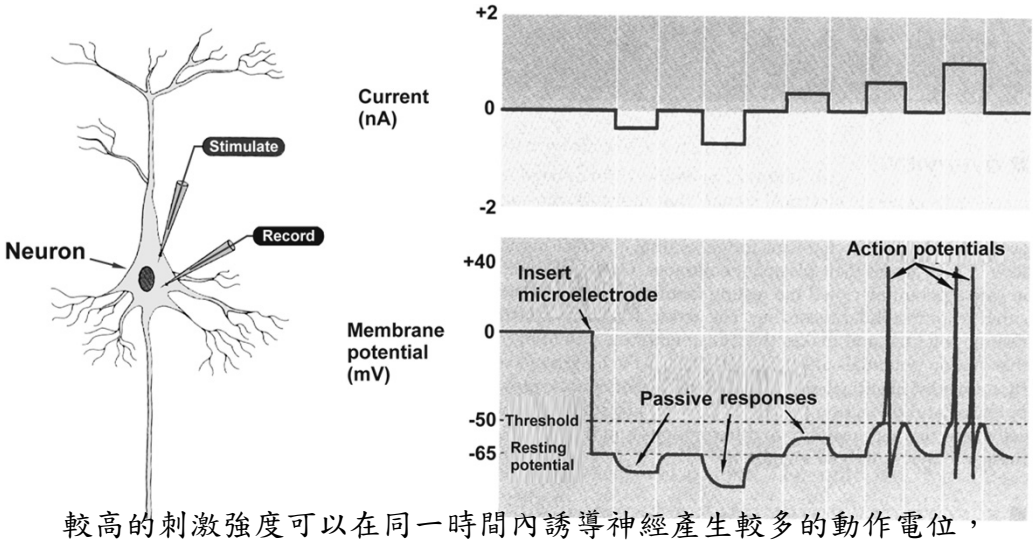
當對神經的刺激強度高過某一臨界值時，神經軸突對此刺激的反應會由被動反應轉成主動反應，threshold的存在可以濾掉較小、突發性的膜電壓波動而不會產生AP，如此可以防止不具意義的神經興奮而造成誤傳。

為什麼要有 threshold

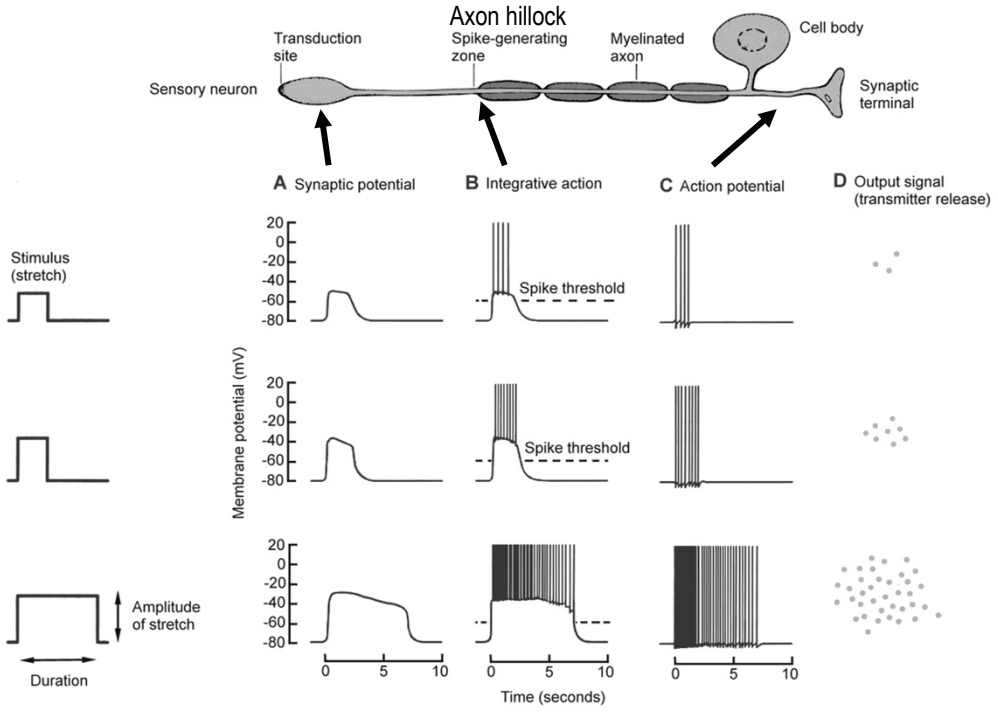
從接受刺激引發動作電位開始至達到動作電位波峰所需的時間，會受到刺激強度大小所影響

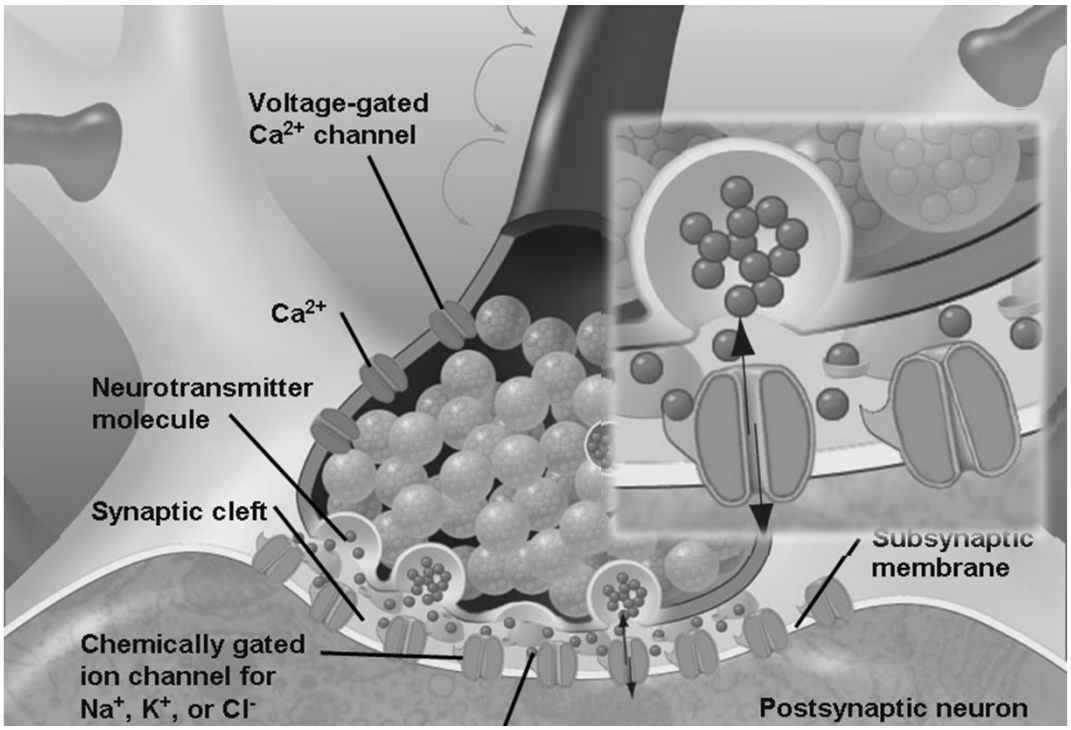
既然所產生的動作電位他們的amplitude 都一樣大，那神經如何區分所受刺激的強度大小呢？

刺激強度和動作電位的amplitude無關，但會影響AP的delay latency 及refractory period

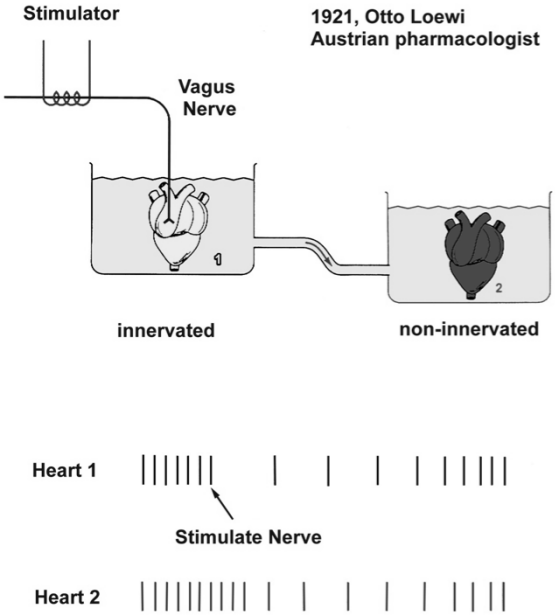


較高的刺激強度可以在同一時間內誘導神經產生較多的動作電位，
也就是神經被興奮的頻率增加了




Voltage-gated
Ca^{2+} channel
Ca^{2+}
Neurotransmitter
molecule
Synaptic cleft
Subsynaptic
membrane
Chemically gated
ion channel for
Na^+, K^+, or Cl^-
Postsynaptic neuron


Discovery
of
Neurotransmitter



- 青蛙的心臟其心跳速率會受迷走神經所控制，刺激迷走神經其心跳速率會減慢
- 迷走神經受刺激之後會釋放出神經傳遞物質Acetylcholine來抑制心臟的收縮速率

The Nobel Prize in Chemistry 1936

"for their discoveries relating to chemical transmission of nerve impulses"

Sir Henry Hallett Dale

United Kingdom

National institute for Medical Research
London, United Kingdom

1875~1968

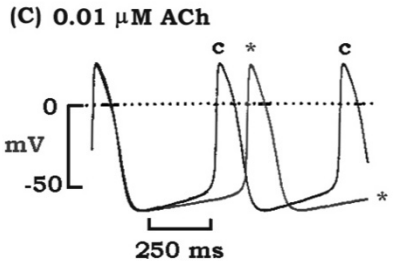
Otto Loewi

Austria

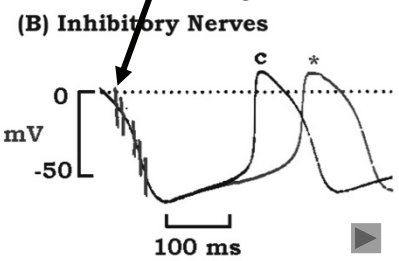
Graz University
Graz, Austria

1873~1961

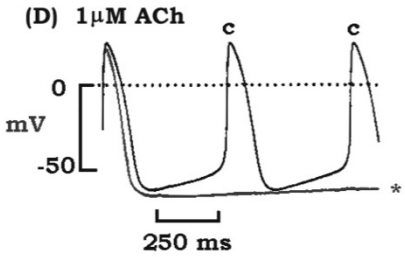
外加 ACh可以比擬刺激迷走神經所造成的心跳速率變慢現象，顯示 ACh 是刺激迷走神經時所釋放出來而改變心跳速率的化學物質。



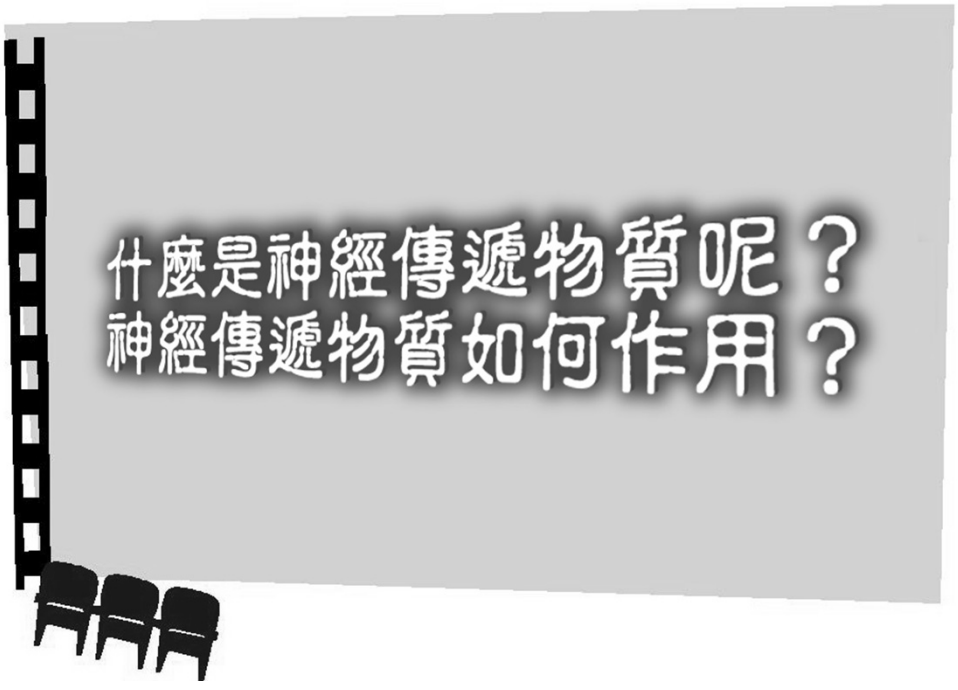
Stimulate vagal nerve



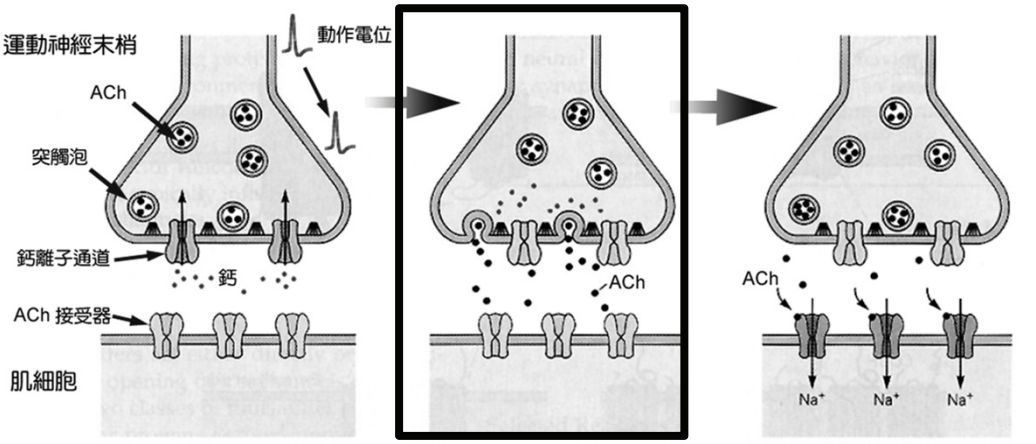
Increase AP interval



AP is abolished



當突觸前神經受到刺激時在突觸會有神經傳遞物質釋放出來

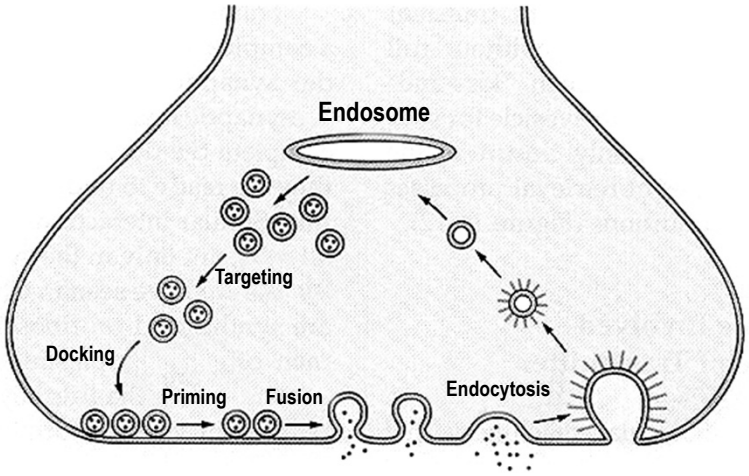


動作電位經Axon 傳到神經末梢造成神經末梢鈣離子通道的打開

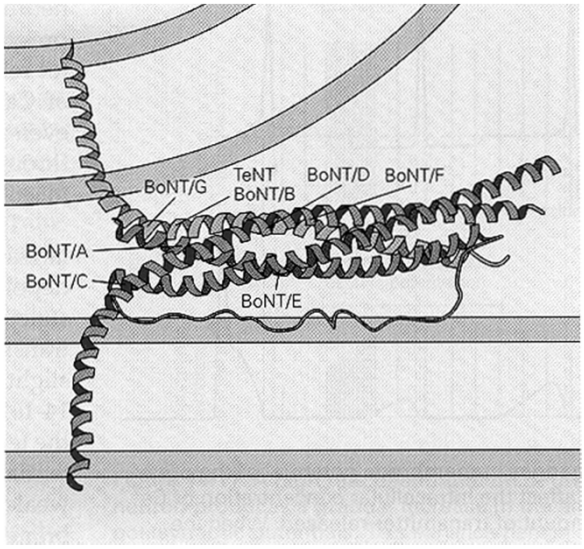
鈣離子流入並造成突觸泡與細胞膜融合破裂而釋放出神經傳遞物質

神經傳遞物質結合並打開離子通道，造成離子流動而促進或抑制突觸後細胞的興奮性

神經末梢突觸泡的循環



Dock the Targeted Vesicles at Active Zone & Prime Them for Fusion

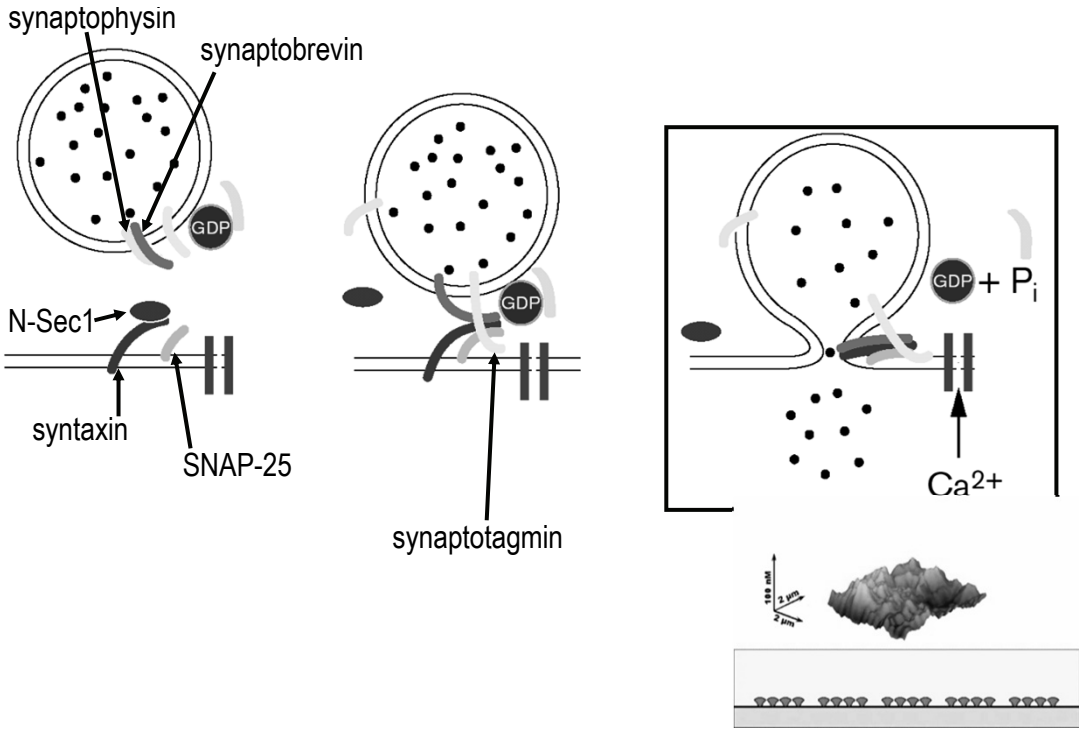


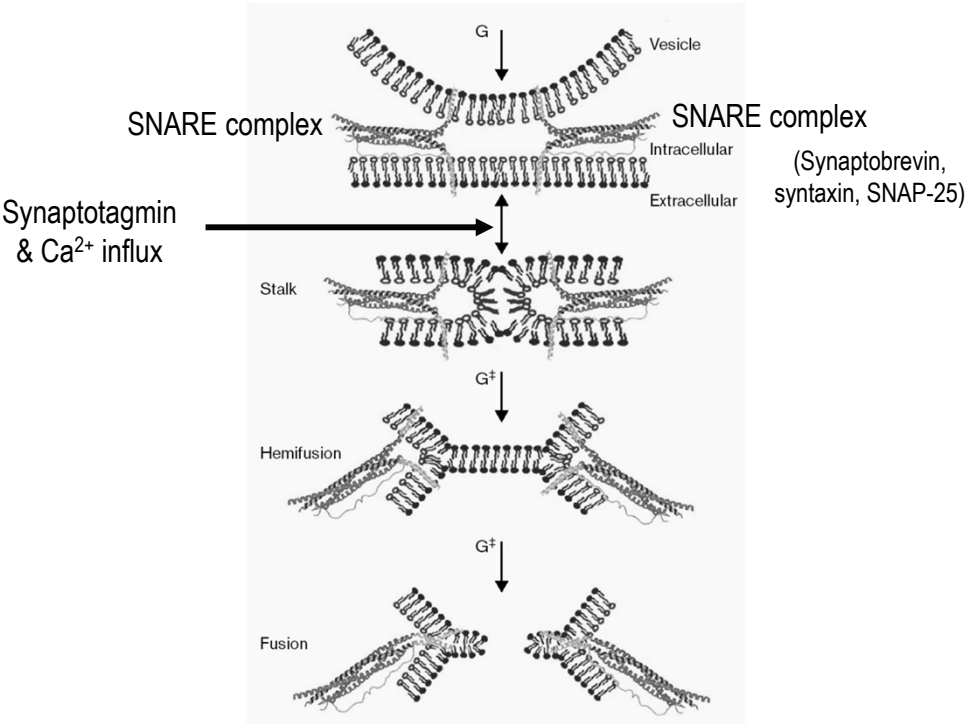
SNARE complex

SNAP-25

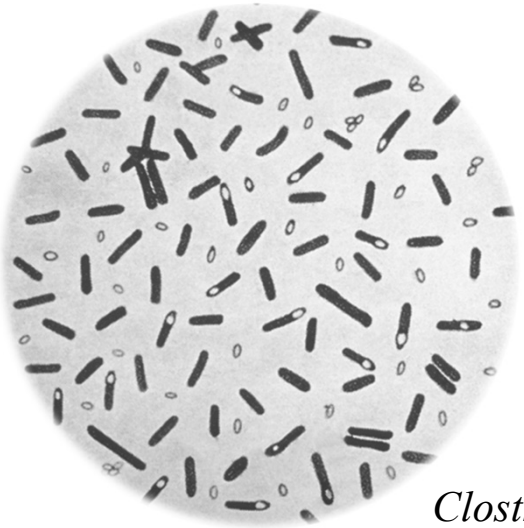
Syntaxin

Synaptobrevin





肉毒桿菌毒素（Botulinum toxin）



視力減退、眼皮下垂、瞳孔散大、語言障礙、吞嚥障礙、唾液分泌障礙，嚴重時會導致呼吸肌受到抑制呼吸衰竭而死亡

Clostridium botulinum

Bioactive peptides:
signaling the future

The current understanding of peptides in cosmetic skincare is generally tied to applications for:

Collagen stimulation

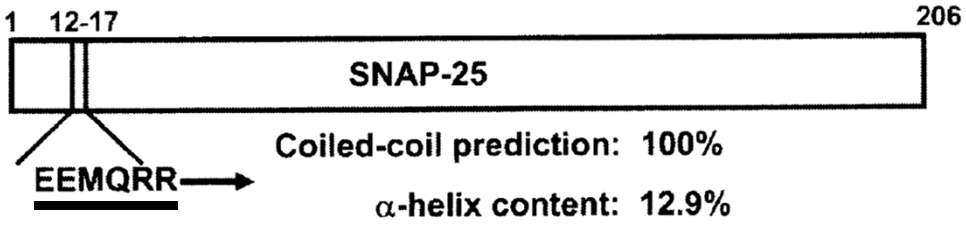
“Botox-like” wrinkle-smoothing effects

Journal of Cosmetic


Botox-like *via*
SNARE inhibition

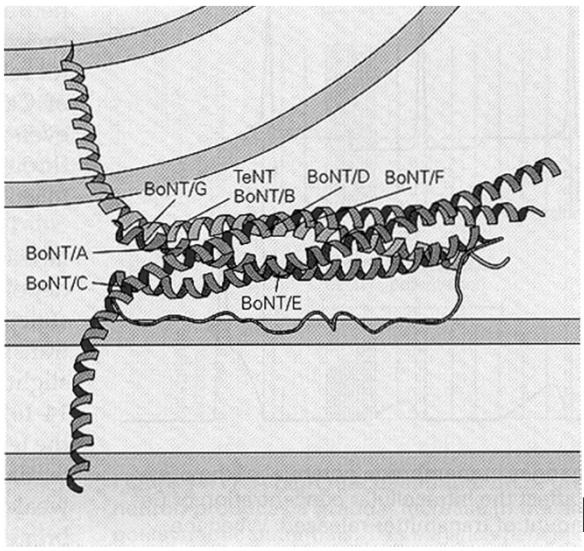

argireline®
(acetyl hexapeptide-3)
ARGIRELINE®
1st. antiexpression wrinkles
www.argireline.com
The First peptide for expression wrinkles

argireline®



Int j cosmet sci 2002;24: 303–10

Dock the Targeted Vesicles at Active Zone & Prime Them for Fusion



SNARE complex

SNAP-25
Syntaxin
Synaptobrevin

Botox-like *via* SNARE inhibition

汞金屬離子中毒事件

時間：1960年左右

地點：日本漁村Minamata Bay

症狀：走路不穩、躺在床上抽動、智商下降等等

汞離子：日光燈、電池.....

鉛離子：油漆、報紙油墨、汽油....

兒童血鉛含量高於歐日

調查單位：高雄醫學大學

取樣來源：高雄市32所小學三年級某班共935人

結果：

1. 血鉛濃度平均值 5.5微克/100毫升，高於臨界質2.5微克/100毫升。
2. 學童血中鉛含量濃度越高者在班上成績名次越後面，尤其與國語、社會等記憶性課程相關性顯著。

鉛的危害：

1. 鉛進入人體以後，90%以上沈積及累積在骨骼系統中，稍後可慢慢釋放到血液中,其半衰期達20年。
2. 對兒童最大的影響是中樞神經的發育。

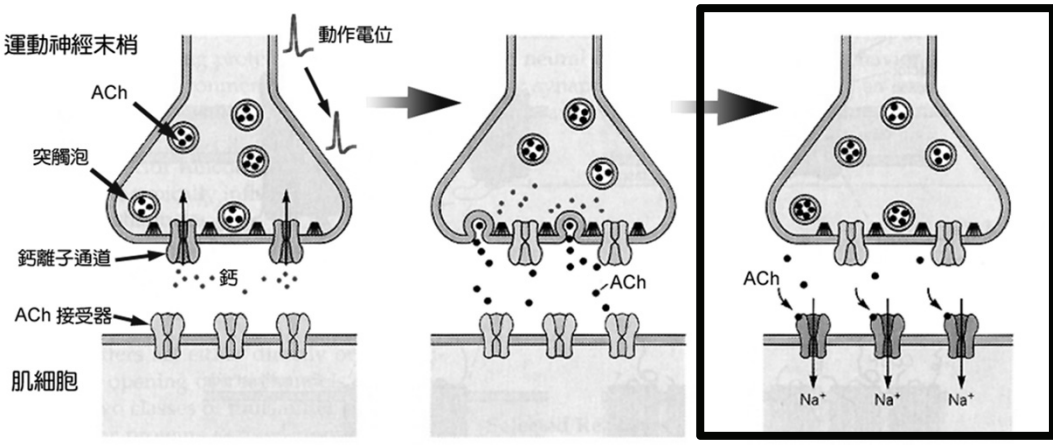
funnel web spider
(*Agelenopsis aperta*)

Agatoxin

Cone snail

***w*-Conotoxin**

當突觸前神經受到刺激時在突觸會有神經傳遞物質釋放出來



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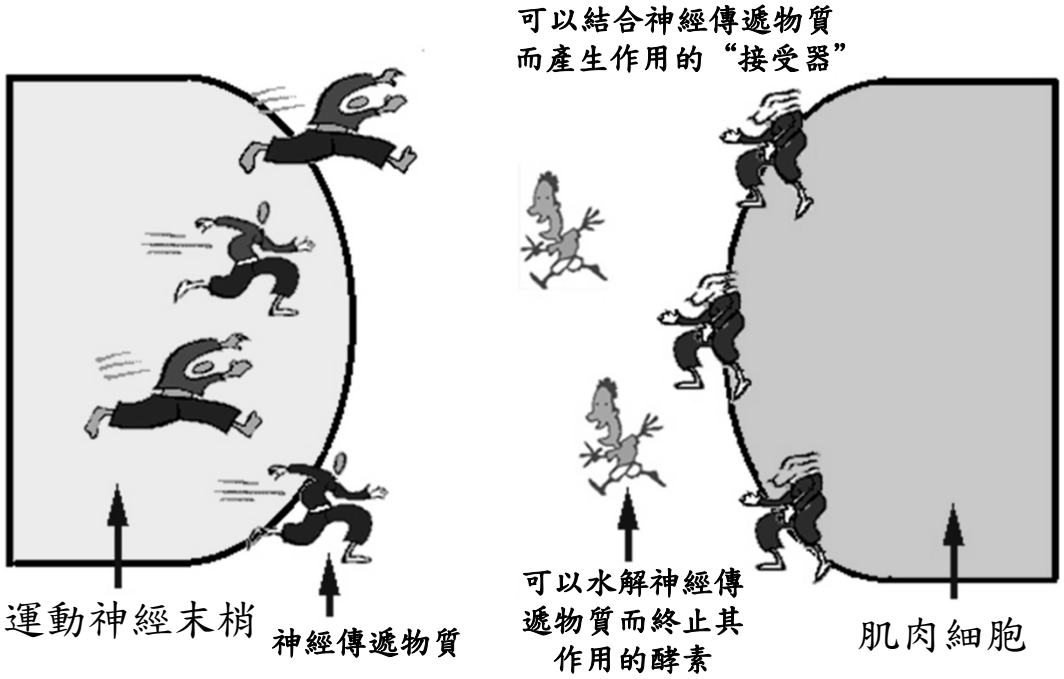
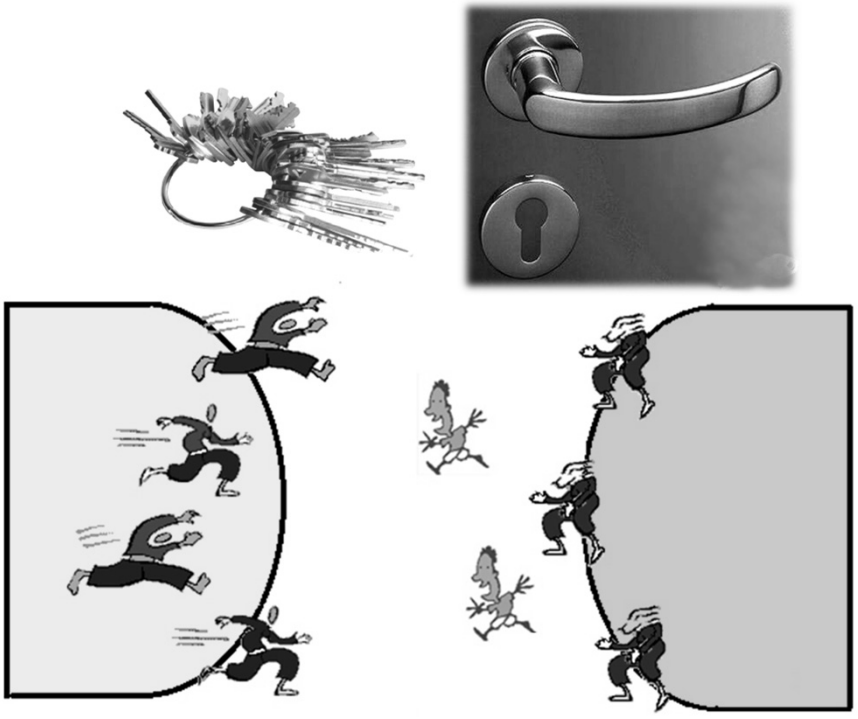
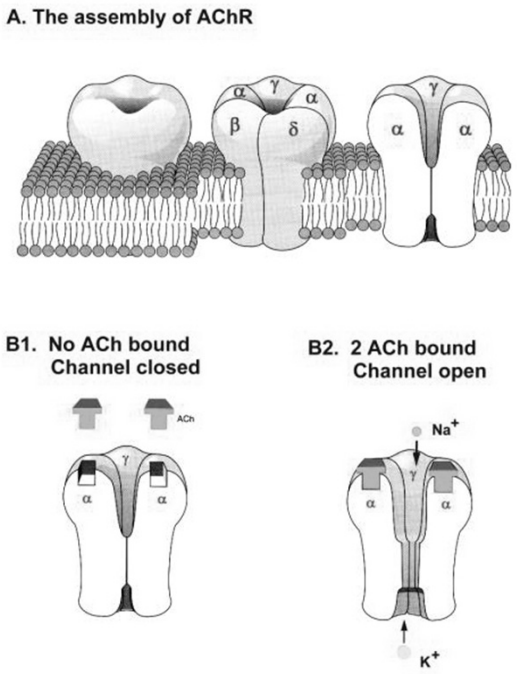
鈣離子流入並造成突觸泡與細胞膜融合破裂而釋放出神經傳遞物質

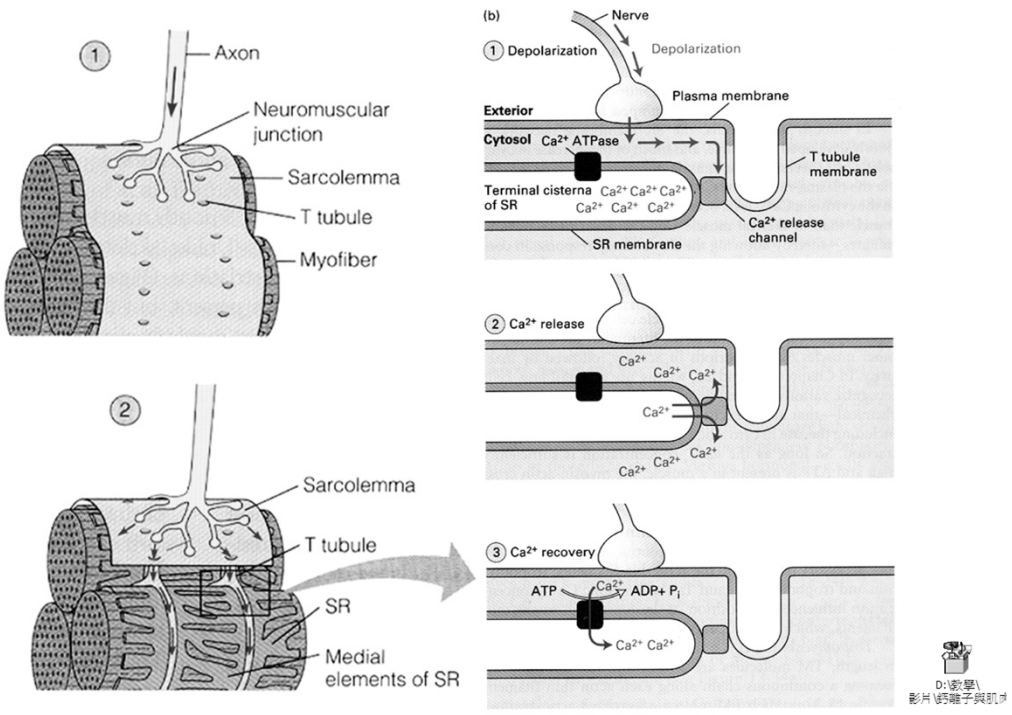
神經傳遞物質結合並打開離子通道，造成離子流動而促進或抑制突觸後細胞的興奮性

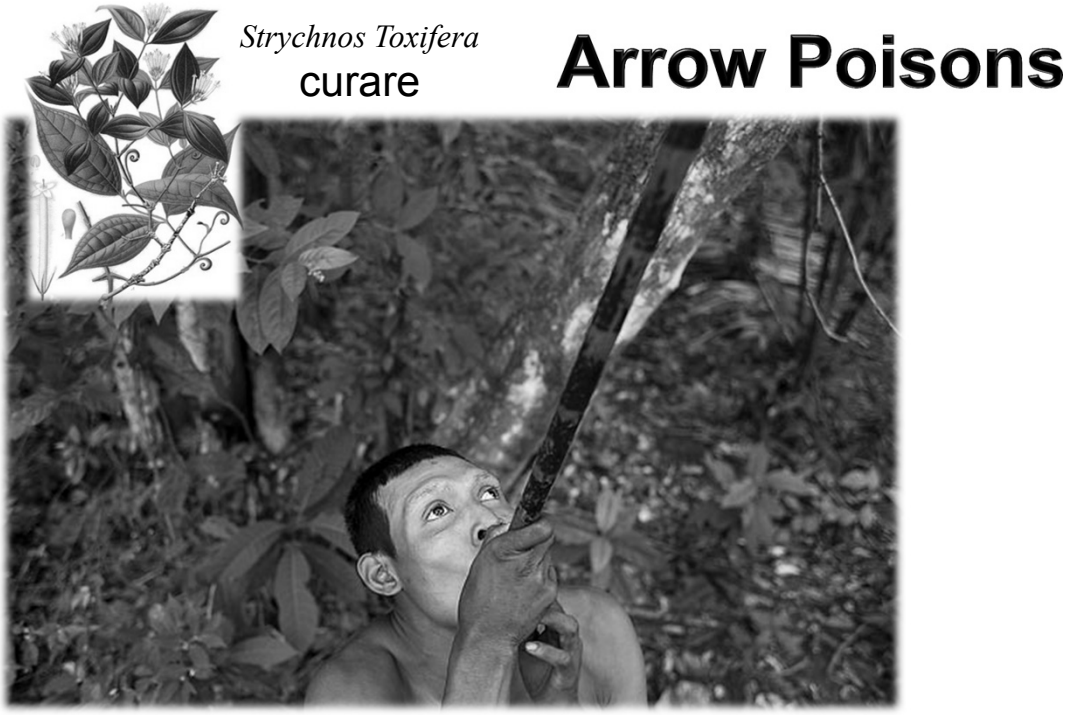

可以結合神經傳遞物質
而產生作用的“接受器”
運動神經末梢
神經傳遞物質
可以水解神經傳
遞物質而終止其
作用的酵素
肌肉細胞



Nicotinic ACh Receptor
(*acetylcholine*)

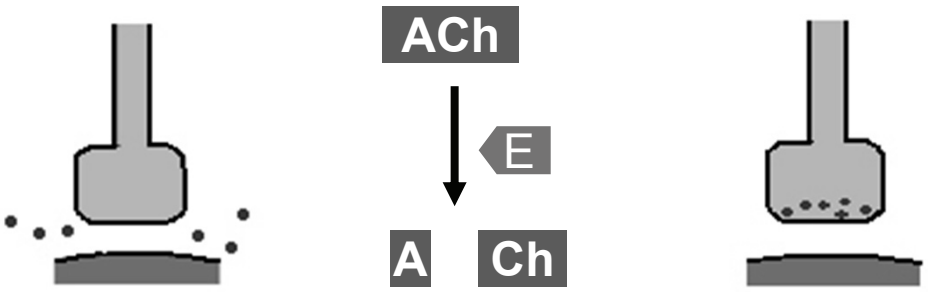






神經傳導物質之去活化

擴 散　　酵素代謝　　回 收



時間：1995年3月20日
地點：東京地下鐵車站
經過：奧姆真理教恐怖份子釋放沙林毒氣
結果：12人死亡，超過5000人中毒身體不適

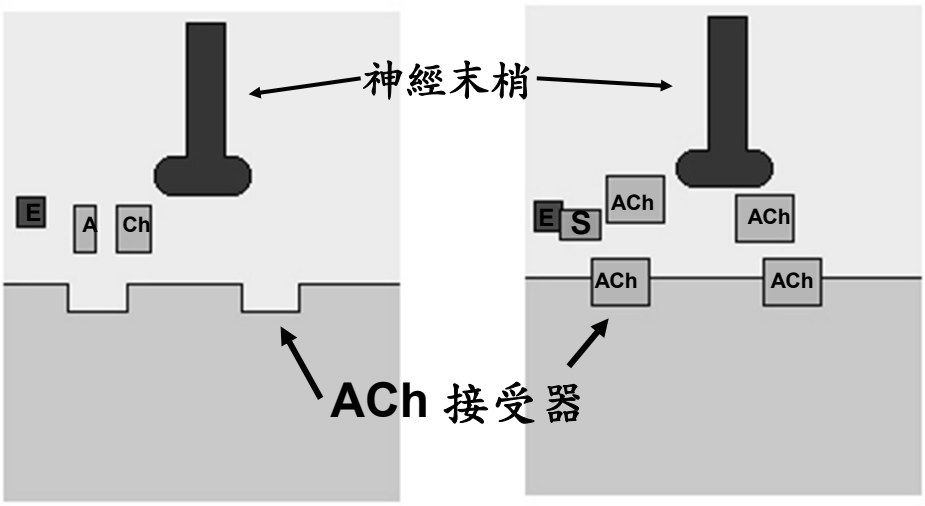
Sarin（沙林）

- 時間：**1938** 年；世界第二次大戰
- 地點：德國
- 人物：德國科學家 **Schrader, Ambros, Ririger** 及 **van der Linde**首次製造
- 特性：無色無味
- 致死劑量：

  吸入**0.075~0.1**克；**15**分鐘內死亡！
  （相當於一顆米大小）

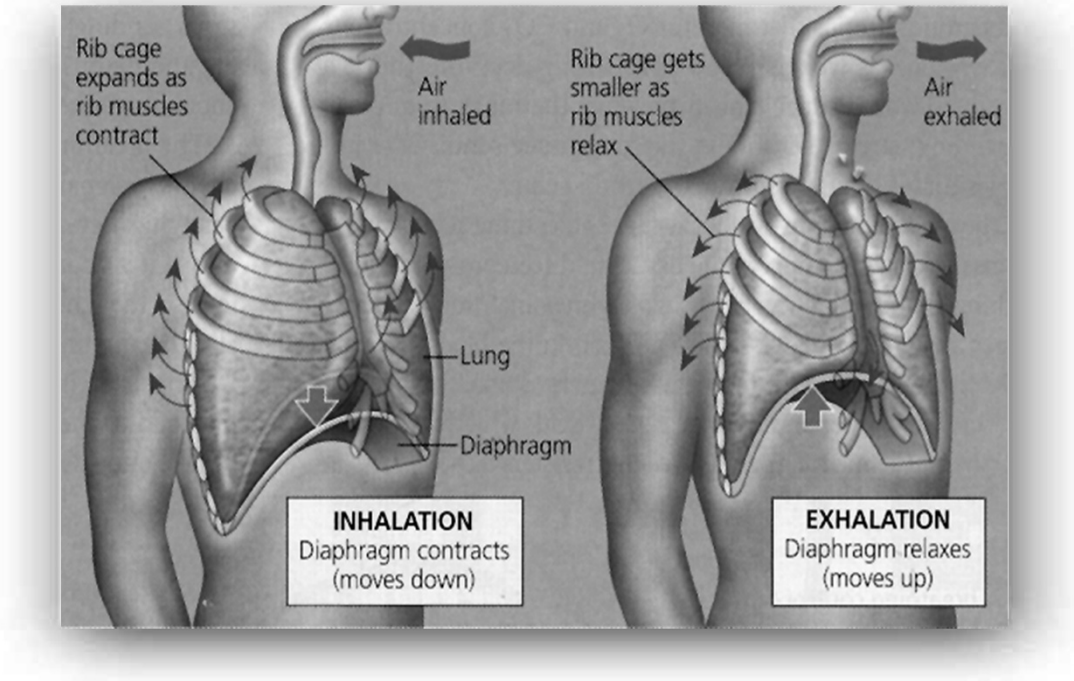
  皮膚接觸**1~1.7**克；**2**分鐘內死亡！

神經毒氣沙林作用機轉

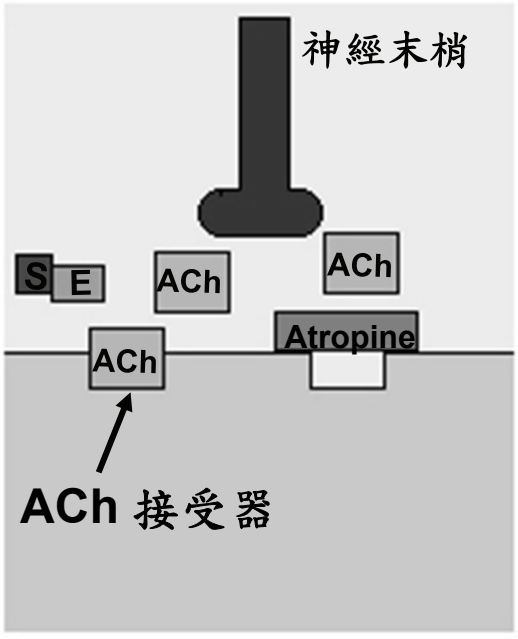


神經毒劑中毒症狀

- 肌肉麻痺、呼吸衰竭
- 視覺模糊、噁心、嘔吐、盜汗
- 頭痛、昏迷、癲癇發作

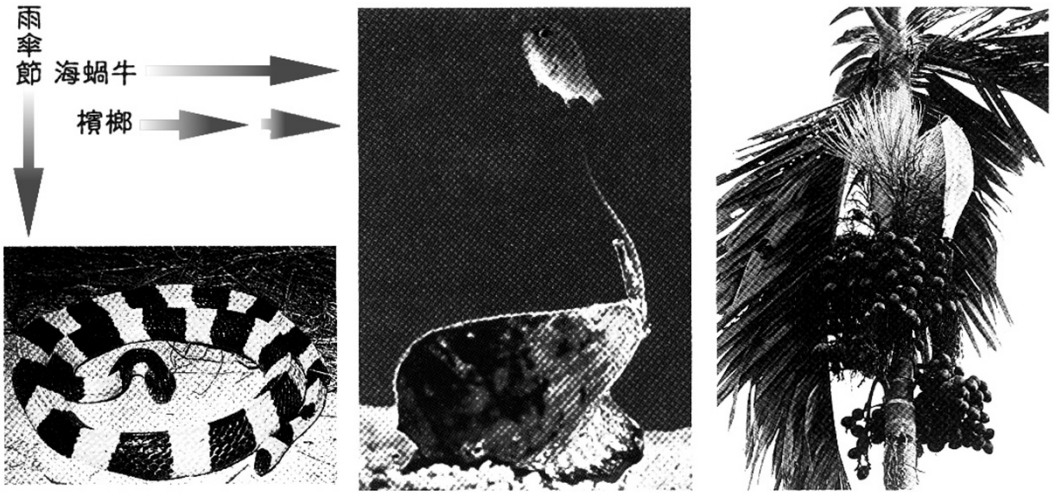


神經毒氣解毒針



影響神經間訊息傳遞而造成毒性的生物

影響神經間訊息傳遞而造成毒性的生物



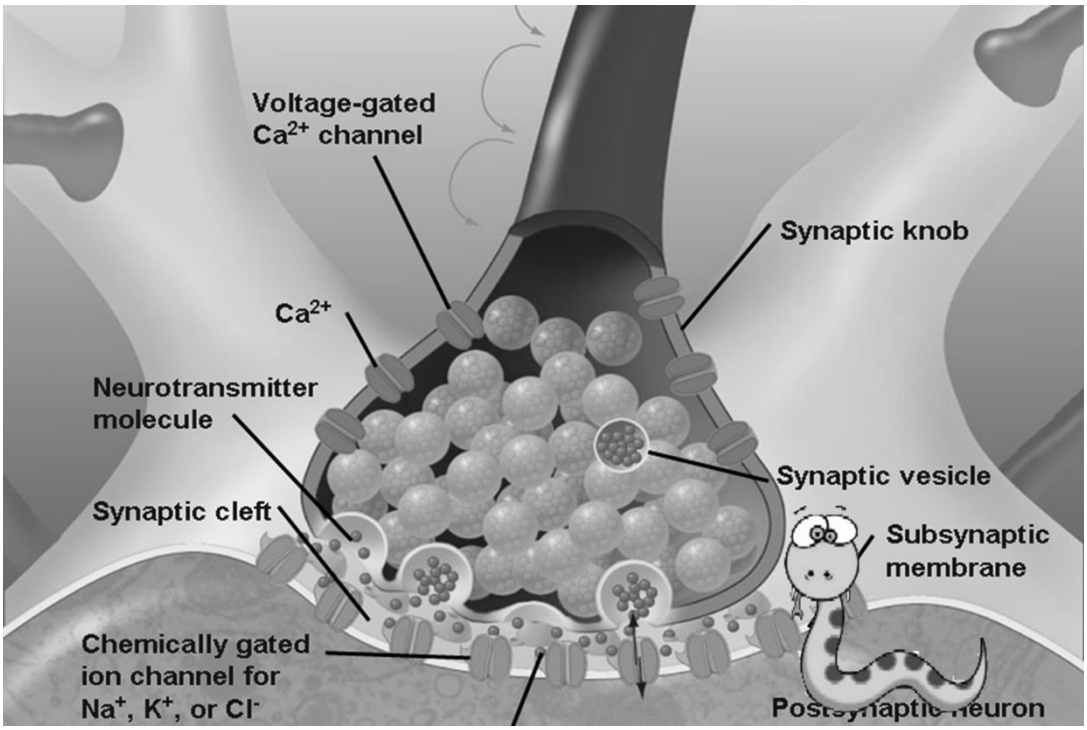
pentapharm
benefiting society through science

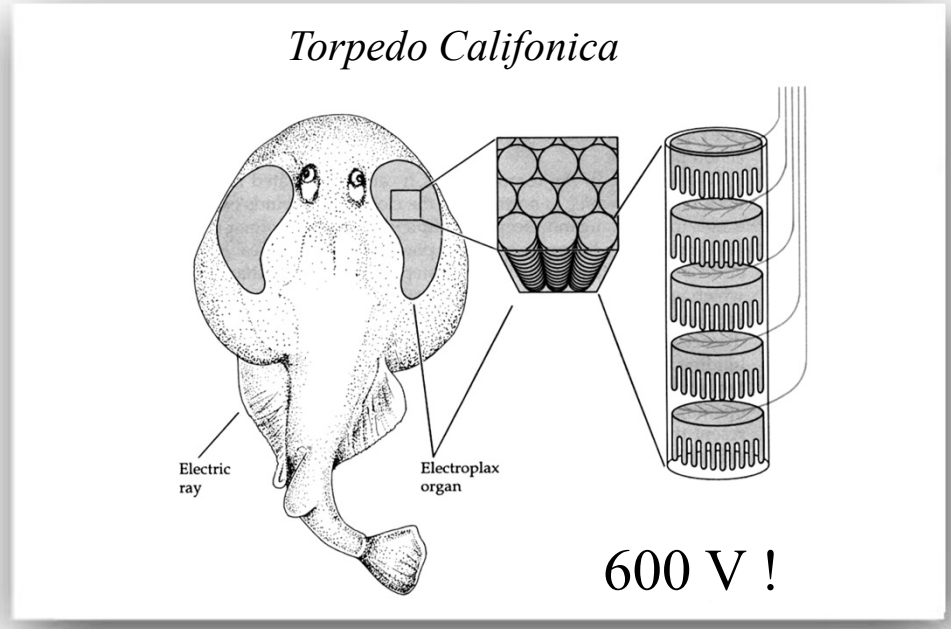
Switzerland based

SYN®-AKE is a small peptide that mimics the activity of Waglerin 1, a polypeptide that is found in the venom of the *Tropidolaemus wagleri* (韋氏竹葉青).

啥咪！

蛇毒也能治皺紋？


Voltage-gated
Ca^{2+} channel
Synaptic knob
Ca^{2+}
Neurotransmitter
molecule
Synaptic vesicle
Synaptic cleft
Subsynaptic
membrane
Chemically gated
ion channel for
Na^+, K^+, or Cl^-


Torpedo Califonica
Electric
ray
Electroplax
organ
600 V !

Electrocyte cells from the electric organ