ANAT 3045 Visual Neuroscience
BIOS 3001 Advanced Visual Neuroscience

UCL

Fundamentals of neuroscience: cells, axons, and synapses

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Institute of Ophthalmology

The Neurone

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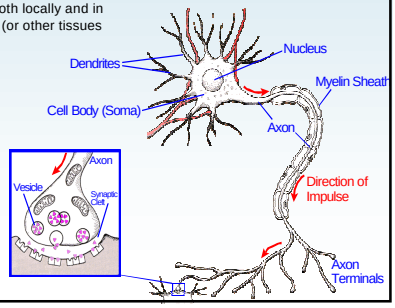
The Nervous system's wiring can be described in terms of neuronal cell types in each of its distinct gray matter regions and their stereotyped pattern of axonal projections to cell types both locally and in other gray matter regions (or other tissues – *eg* muscle)

Grey Matter – areas of neuronal cell bodies
White Matter – areas of nerve fibres (axons)



The Neurone Doctrine

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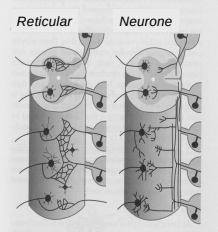
- Santiago Ramon y Cajal ~1890s
  - **Neurone Doctrine**: Each neurone is an individual entity, the basic unit of neural circuitry (*cf* 'reticularist view' of *eg* Camillo Golgi)
- Charles Sherrington ~1897
  - Postulated that neurones functionally contact each other and other cell types (*eg* muscle) via a theoretical structure he termed the "*synapse*".



Functional Polarity Rule

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- Santiago Ramon y Cajal
  - Functional Polarity: The Dendrites and Cell bodies of neurones receive information, whereas the single axon with its collaterals transmits information to other cells.
  - This rule allows prediction of information flow direction through neural circuits based on morphology of individual neurones.
- Functional Polarity was the cornerstone of Charles Sherrington's (1906) revolutionary analysis of mammalian reflex organisation.

Applying the Neurone Doctrine and Functional Polarity

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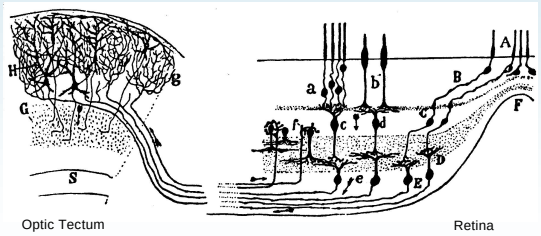
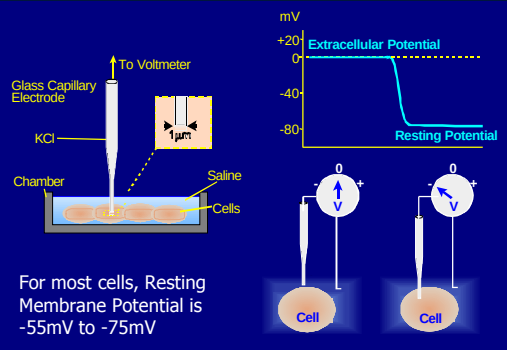
Cajal's (1909-1911) neural architecture drawing based on the Golgi method.



Optic Tectum (superior colliculus)

Retina

Resting Membrane Potential



For most cells, Resting Membrane Potential is -55mV to -75mV

Distribution of Major Ions Across the Membrane of the Squid Giant Axon

Ion	Cytoplasm	Extracellular
K^+	400	20
Na^+	50	440
Cl^-	52	560
	(mM)	(mM)

Resting potential *ca.* -60mV

Distribution of Major Ions Across the Membrane of the Frog Muscle

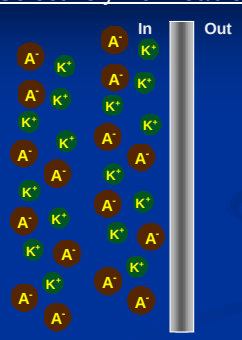
Ion	Cytoplasm	Extracellular
K^+	124	2.3
Na^+	10	109
Cl^-	1.5	78
	(mM)	(mM)

Resting potential *ca.* -100mV

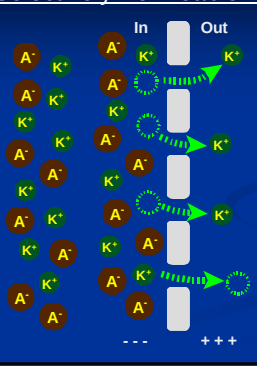
What Forces Govern the Movements of Ions?

1. **Concentration Gradients.** i.e. diffusion from high to low concentration areas.
2. **Electric Charge Separation.** i.e. ions tend to move towards regions of opposite electric charge.
3. **Cell Membrane.** i.e. ion movement is restricted by the physical barrier imposed by the cell membrane.

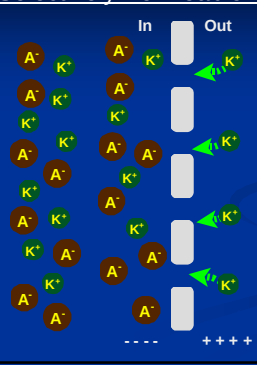
Selectively Permeable Membrane



Selectively Permeable Membrane



Selectively Permeable Membrane



Nernst Equation

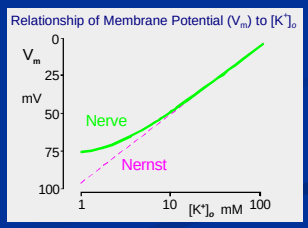
$$E_K = \frac{RT}{ZF} \bullet \ln \frac{[K^+]_o}{[K^+]_i}$$

Substituting,

$$E_K = 26mV \bullet \ln \frac{20}{400} = -75mV$$

Where

E_K	= K^+ Equilibrium Pot'l.
R	= Gas Constant
T	= Absolute Temperature
Z	= Valence of K^+
F	= Faraday Constant
$[K^+]_{o,i}$	=K^+ concentrations



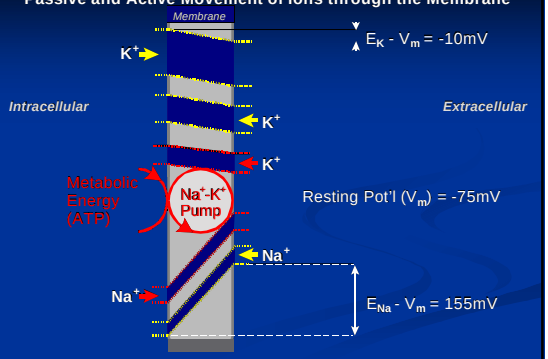
1. How can concentration gradients for Na^+, K^+, and Cl^- all be maintained across the cell membrane?
2. How do these gradients interact to determine the resting membrane potential?

Distribution of Major Ions Across the Membrane of the Squid Giant Axon

Ion	Cytoplasm	Extracellular Fluid	Nernst Potential
K^+	400	20	-75
Na^+	50	440	+55
Cl^-	52	560	-60
	(mM)	(mM)	(mV)

Resting potential *ca.* -60mV

Passive and Active Movement of Ions through the Membrane



GOLDMAN EQUATION

$$V_m = \frac{RT}{F} \bullet \ln \frac{P_K[K^+]_o + P_{Na}[Na^+]_o + P_{Cl}[Cl^-]_i}{P_K[K^+]_i + P_{Na}[Na^+]_i + P_{Cl}[Cl^-]_o}$$

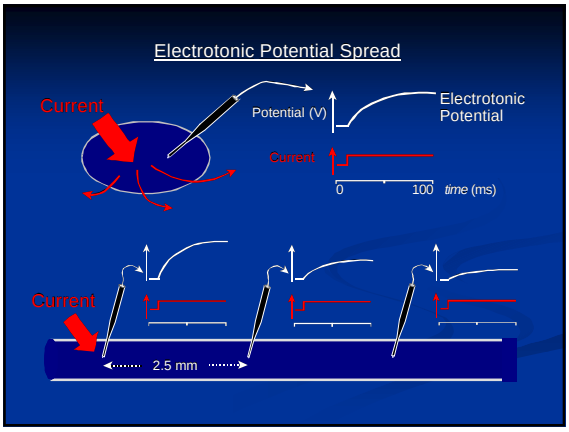
where P = Permeability

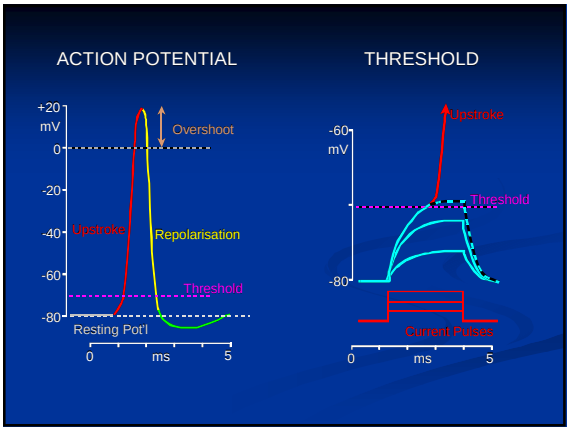
If $P_K >> P_{Na}$ and P_{Cl},

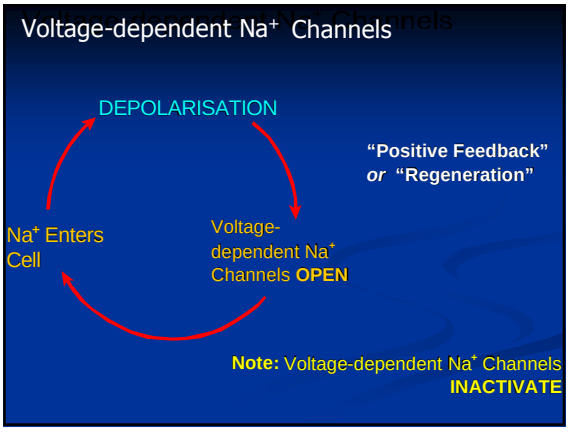
$$V_m \approx \frac{RT}{F} \bullet \ln \frac{P_K[K^+]_o}{P_K[K^+]_i}$$

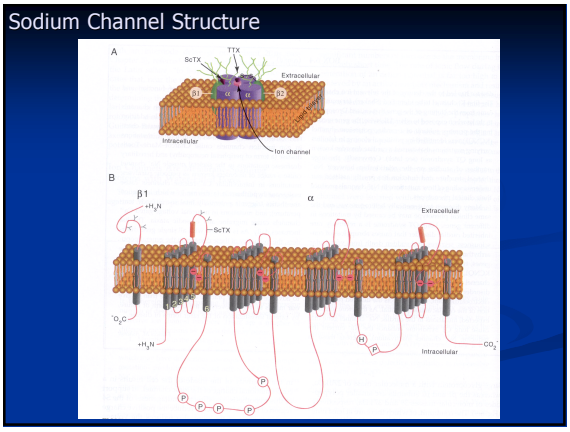
Therefore,
The greater the permeability and concentration of an ion, the greater will be its contribution to V_m.

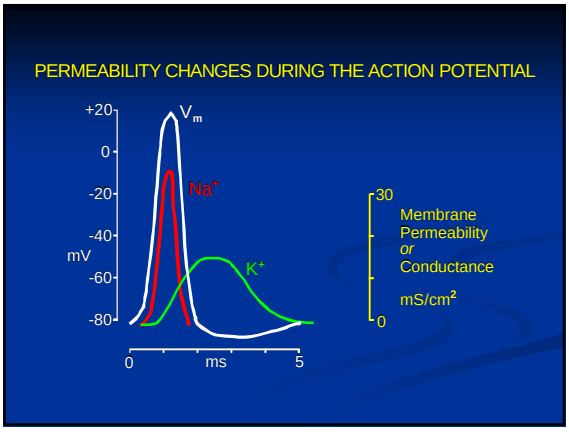
- Membrane potential (Vm) is determined primarily by K+ and Na+.
- Membrane potential will be closest to the Nernst (Equilibrium) Potential of the ion with the greatest concentrations and membrane permeability.
- At Rest, Membrane Potential is close to the potassium equilibrium potential (EK+) because the membrane is most permeable to K+.
- At Rest, as EK+ is slightly more negative than Vm, there is a steady K+ efflux, balanced by a steady Na+ influx. These two passive fluxes are balanced by active pumping of Na+ and K+ in the opposite directions. Note: this is a steady state, not an equilibrium.
- Under most physiological conditions the bulk concentrations of Na+, K+ and Cl- inside and outside of the cell remain constant.

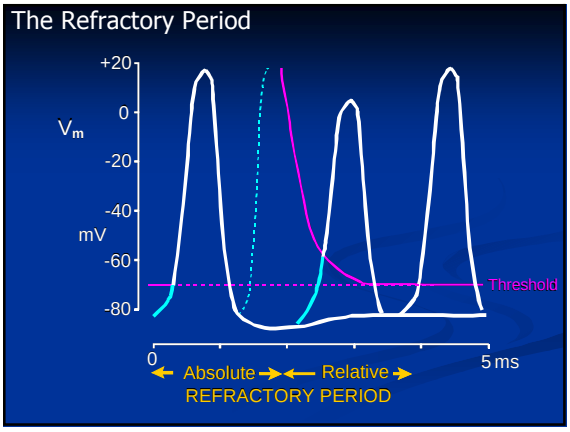

Electrotonic Potential Spread
Current
Potential (V)
Electrotonic Potential
Current
0
100
time (ms)
Current
2.5 mm


ACTION POTENTIAL
THRESHOLD
+20
mV
0
-20
-40
-60
-80
Overshoot
Upstroke
Repolarisation
Threshold
Resting Pot'l
0
ms
5
-60
mV
-80
Upstroke
Threshold
Current Pulses
0
ms
5


Voltage-dependent Na+ Channels
DEPOLARISATION
"Positive Feedback"
or "Regeneration"
Na+ Enters Cell
Voltage-dependent Na+ Channels OPEN
Note: Voltage-dependent Na+ Channels INACTIVATE


Sodium Channel Structure
A
TTX
ScTX
Extracellular
β1
α
β2
Intracellular
Ion channel
B
β1
α
Extracellular
ScTX
Intracellular


PERMEABILITY CHANGES DURING THE ACTION POTENTIAL
+20
0
-20
-40
mV
-60
-80
Vm
Na+
K+
0
ms
5
30
Membrane Permeability
or
Conductance
mS/cm²
0


The Refractory Period
+20
0
-20
-40
mV
-60
-80
Vm
Threshold
0
5 ms
Absolute
Relative
REFRACTORY PERIOD

PROPAGATION OF THE ACTION POTENTIAL - 1

Unmyelinated nerve membrane

PROPAGATION OF THE ACTION POTENTIAL - 1

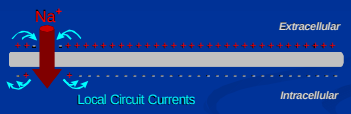
Unmyelinated nerve membrane

Note

- No significant change in ionic concentrations during the action potential.
- No change in Na^+ Pump activity during the action potential.

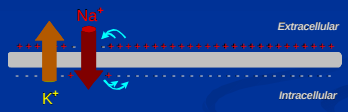
PROPAGATION OF THE ACTION POTENTIAL - 1

Unmyelinated nerve membrane



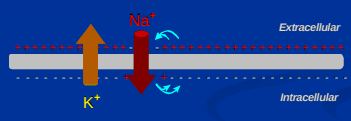
PROPAGATION OF THE ACTION POTENTIAL - 2

Unmyelinated nerve membrane



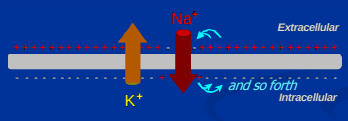
PROPAGATION OF THE ACTION POTENTIAL - 3

Unmyelinated nerve membrane



PROPAGATION OF THE ACTION POTENTIAL - 3

Unmyelinated nerve membrane



Note

- An action potential is triggered in each portion of the membrane
- The action potential can travel in all directions from the initial triggering point.
- The action potential cannot immediately reinvade a portion of membrane, because of the *refractory period*.

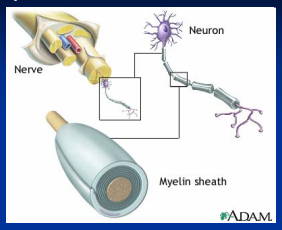
The Erlanger / Gasser Classification of Nerve Fibres

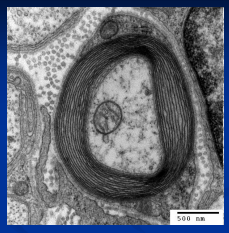
Fibre Type	Function (examples)	Avg. Fibre Dia. (μm)	Avg. Cond. Vel. (m/s)
$A\alpha$	Primary Muscle Spindle Afferents Motor to Skeletal Muscles	15	100 (70-120)
$A\beta$	Cutaneous Touch and Pressure Afferents	8	50 (30-70)
$A\gamma$	Motor to Muscle Spindles	5	20 (15-30)
$A\delta$	Cutaneous Temperature and Pain Afferents	< 3	15 (12-30)
B	Sympathetic Preganglionic	3	7 (3-15)
C	Cutaneous Pain Afferents	1	1 (0.5-2)
	Sympathetic Postganglionic	(unmyelinated)	

The Lloyd Hunt Classification of Nerve Fibres

Group	Function (examples)	Avg. Fibre Dia. (μm)	Avg. Cond. Vel. (m/s)
I	Primary Muscle Spindle Afferents Afferents from Tendon Organs	13	75 (70-120)
II	Cutaneous Mechano-receptors	9	55 (25-70)
III	Deep Pressure Sensors in Muscle	3	11 (10-25)
IV	Unmyelinated Pain Afferents	1	1 (0.5-2)

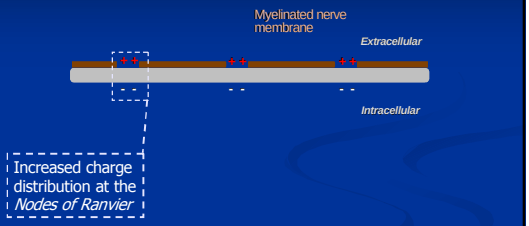
Myelinated Nerve Fibres



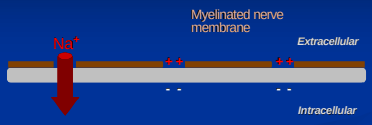


- Conduction velocity increases with fibre diameter, but the greatest influence is whether or not an axon is *myelinated*.
- Myelin sheath consists of membranes of *Schwann Cells* wrapped around the axons. This wrapping is periodically interrupted at what are termed the *Nodes of Ranvier*.
- The effect of this sheath is to increase the resistance across the cell membrane from the inside of the axon to the extracellular space, and to concentrate charge distribution at the Nodes of Ranvier.

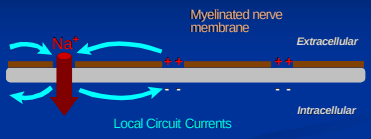
Action Potential Propagation in Myelinated Axons



Action Potential Propagation in Myelinated Axons

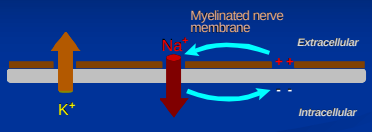


Action Potential Propagation in Myelinated Axons

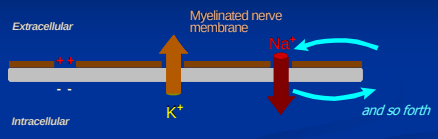


local circuit current flow is from one Node of Ranvier to the next

Action Potential Propagation in Myelinated Axons



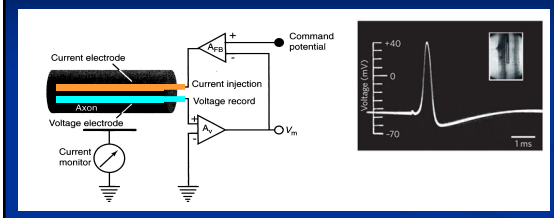
Action Potential Propagation in Myelinated Axons



- Effectively the action potential is propagated from one node of ranvier to the next. This is referred to as *Saltatory Conduction.*
- The net result of this is that an action potential can travel more quickly by jumping along a myelinated axon rather than by being conventionally propagated along an umyelinated axon.

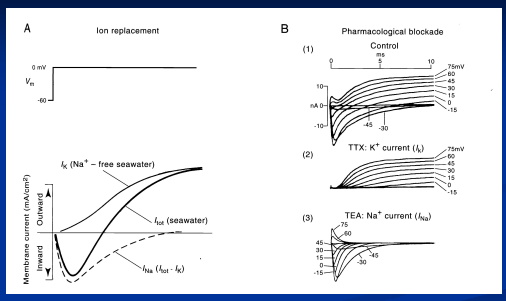
Voltage Clamp

Two-electrode voltage clamp of squid axon, after Hodgkin & Huxley



The voltage-clamp technique keeps the voltage across the membrane constant so that the amplitude and time course of of ionic currents can be measured

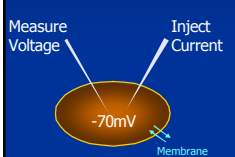
Voltage Clamp Reveals Ionic Currents



TEA - TetraEthylAmmonium – blocks K^+ currents
TTX - TetrodoToXin – blocks Na^+ currents

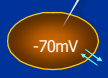
Voltage Clamp recordings from Cells

Two electrode voltage clamp (large cells *eg* oocytes)

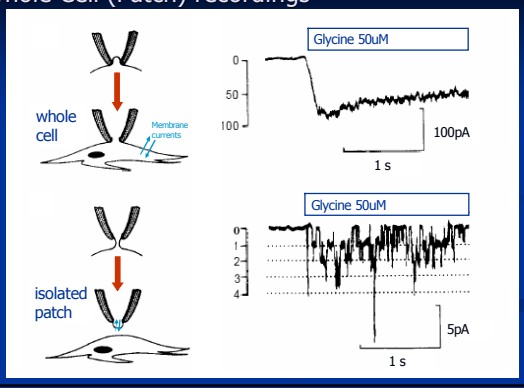


Single electrode voltage clamp (neurones)

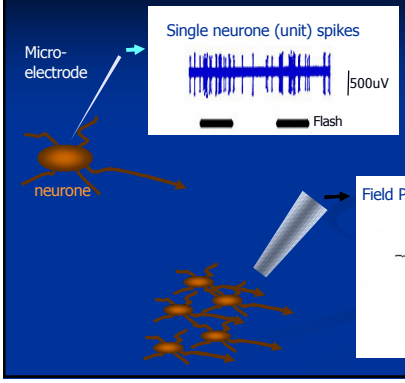
- Measure voltage
- is it what we want ?
- Pass current to adjust voltage



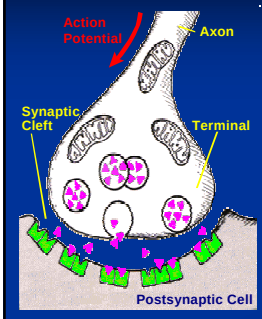
Whole Cell (Patch) recordings



Extracellular Recording methods



CHEMICAL SYNAPSES

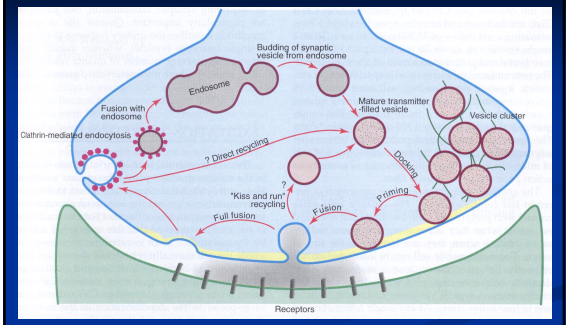


- Action Potential Propagated to the Nerve Terminal.
- Arrival of an Action Potential leads to release of a chemical (*i.e.* the **Neurotransmitter**) from the terminal.
- Neurotransmitter diffusses to the Postsynaptic Membrane.
- Binding of Transmitter molecule to **Receptors** causes a postsynaptic effect (*e.g.* Membrane Depolarisation).

Process of Chemical Neurotransmission

- Synthesis of neurotransmitter in the presynaptic neurone
- Storage of the neurotransmitter and/or its precursor in the presynaptic nerve terminal
- Release of the neurotransmitter into the synaptic cleft
- Binding and recognition of the neurotransmitter by target receptors
- Termination of action of the released transmitter

Life Cycle of Synaptic Vesicles



The "vesicle hypothesis"

TYPES OF NEUROTRANSMITTER

Amines

Acetycholine
Noradrenaline
Dopamine
Serotonin (5HT)

Peptides

Enkephalins
Substance P
Somatostatin
Cholecystokinin

Excit. Amino Acids

L-Glutamic Acid
L-Aspartic Acid
L-Homocysteic Acid

Purines

Adenosine
ATP

Inhibitory Amino Acids

Glycine
GABA

Free Radicals

Nitric Oxide (NO)

Lipids

Cannabinoids
Vanillinoids