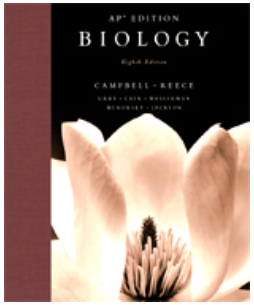
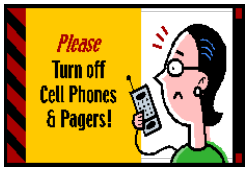


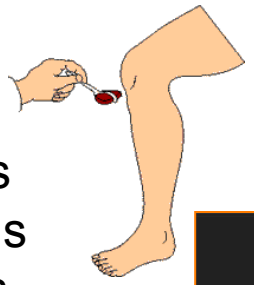
Overview of Lecture: Nervous systems.

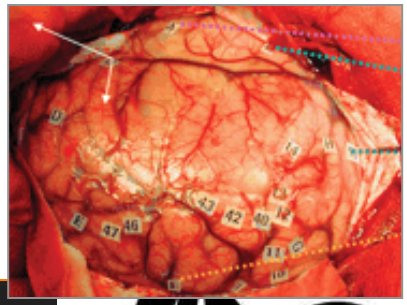
Read: Text ch 48 & 49.

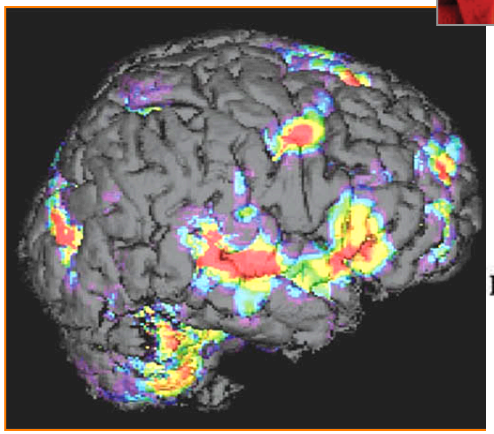
Bullet Points:

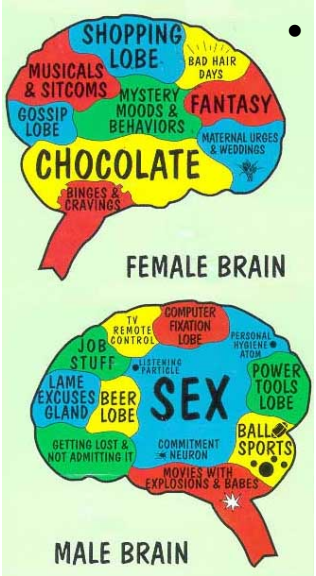
- nervous systems
- neurons
- info processing - reflexes
- resting & action potentials
- synapses & mechanisms
- transmitters
- autonomic NS
- CNS
- depression
- addiction
- synaptic plasticity & learning
- sex differences

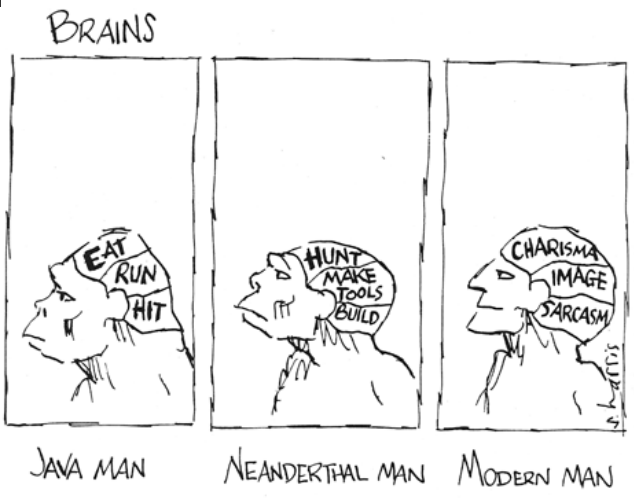




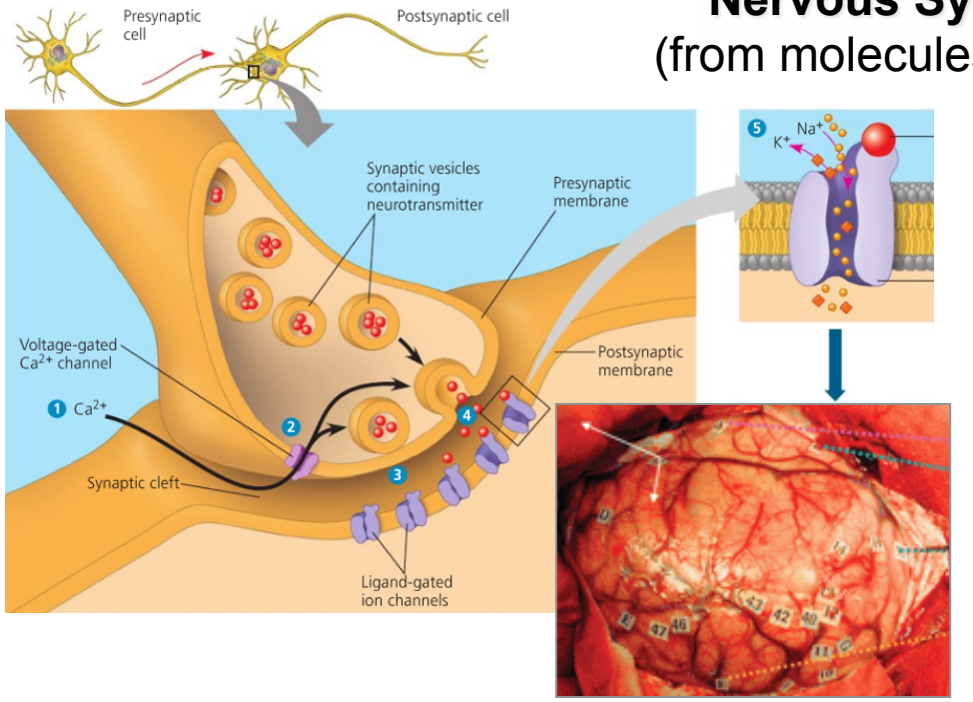


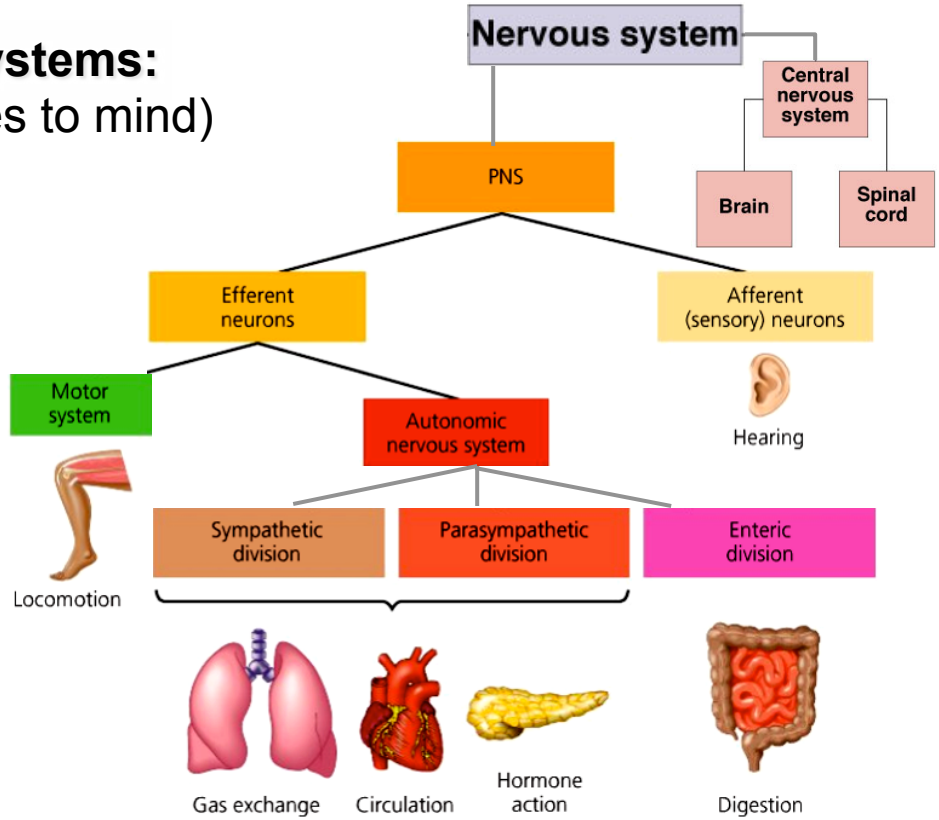


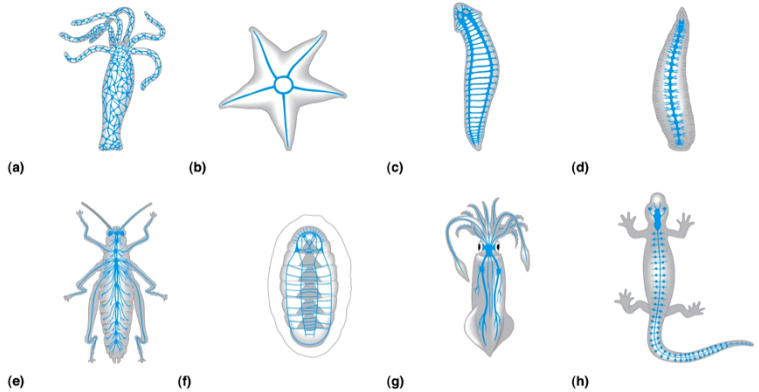


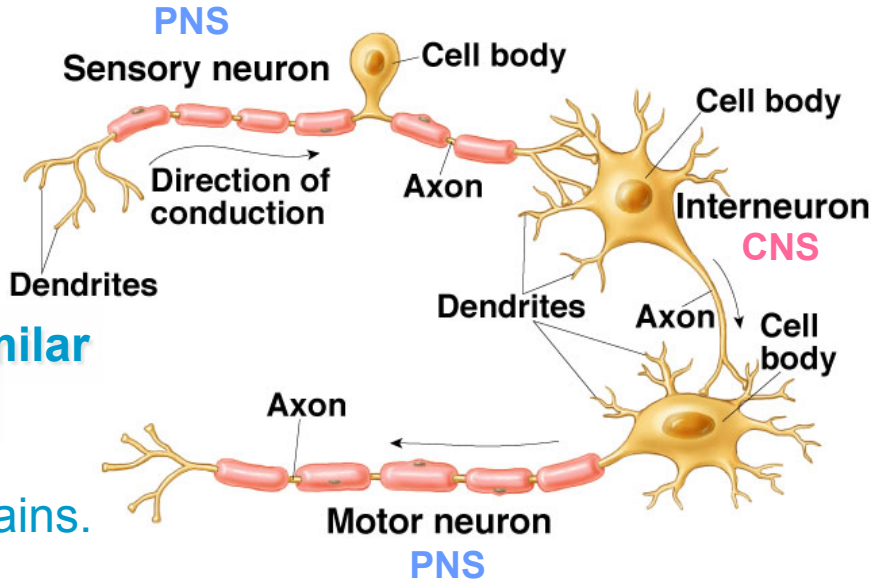


Nervous Systems:
(from molecules to mind)









Animal nervous systems are remarkably similar at the cellular level - how neurons work –

but differ at higher levels of organization, such as the structure and function of their brains.

Science 26 October 2012:
Vol. 338 no. 6106 pp. 475-476
PERSPECTIVE Scott W. Emmons

The Mood of a Worm

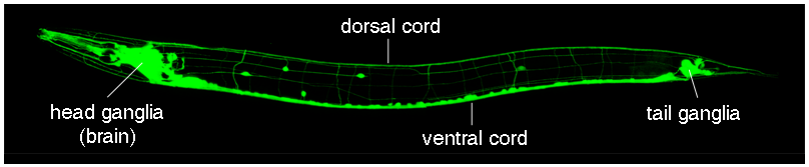
Nervous system function may be understood as the emergent collective property of a network rather than as the sum of individual circuits. **+ interactions**

The human nervous system is a vastly complex network of functionally interconnected cells whose detailed structure is at present beyond reach.

All our actions, calculations, feelings, memories, dreams—consciousness itself—emerge from its workings. To understand this colossal, enigmatic structure, experimentally amenable model animals with tractable nervous systems many orders of magnitude smaller are studied.

A popular choice has been the worm **Caenorhabditis elegans**, a nematode 1 mm long with a nervous system containing fewer than 400 neurons. …

http://www.sfu.ca/biology/faculty/hutter/hutterlab/research/Ce_nervous_system.html



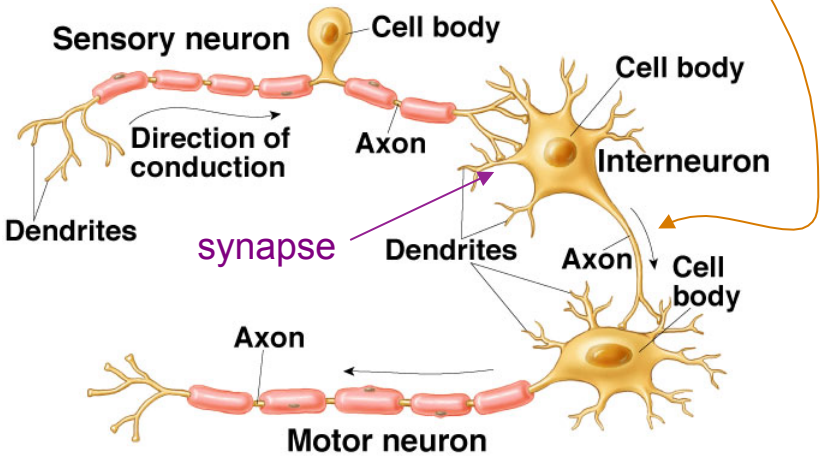
Although **it is a mistake to consider small invertebrates as primitive, their systems may be closer to the ancestral condition than those of their larger cousins.**

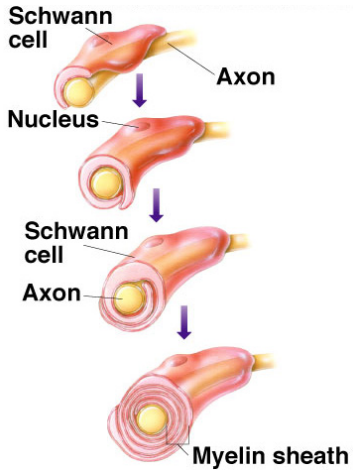
Insights into that ancestral condition can help us understand function today.

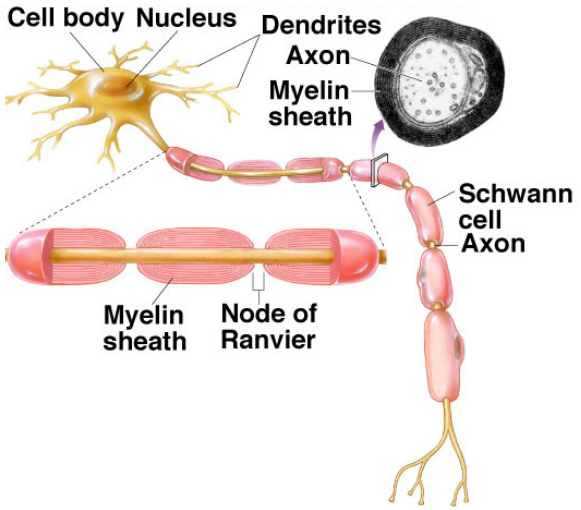
Garrison et al. (1) and Beets et al. (2), add to a growing body of evidence that **even at the highest levels of coordinating fundamental and complex behaviors,**

Neurons & nerves

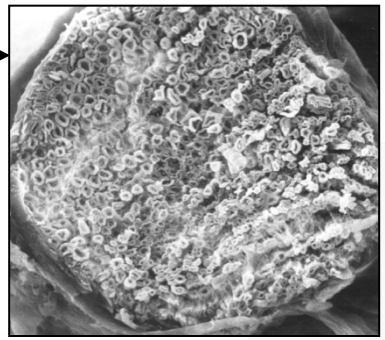
oligodendrocytes & glia: CNS neuroglia → myelin
Schwann cells: PNS neuroglia → myelin



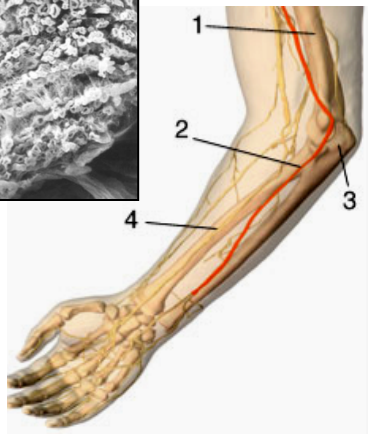




Peripheral nerves are cable-like collections of axons, electro-chemically isolated inside myelin sheaths
{which also provide nourishment to neurons}



ulnar nerve
afferent: relays sensation from the 4th & 5th fingers
efferent: motor to small muscles in the hand.
If pinched against elbow - '**crazy bone:**' depolarizes all axons;
{later: can action potential go backwards up axon? – across synapse?}

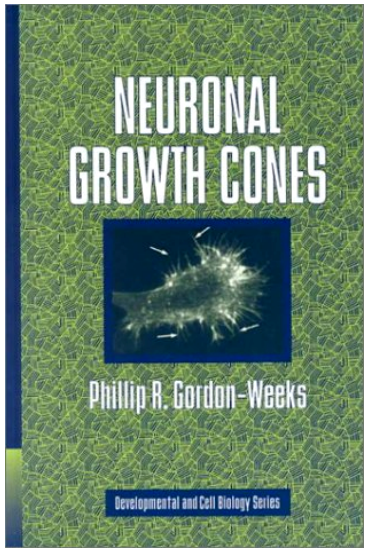


NATIONAL MULTIPLE SCLEROSIS SOCIETY

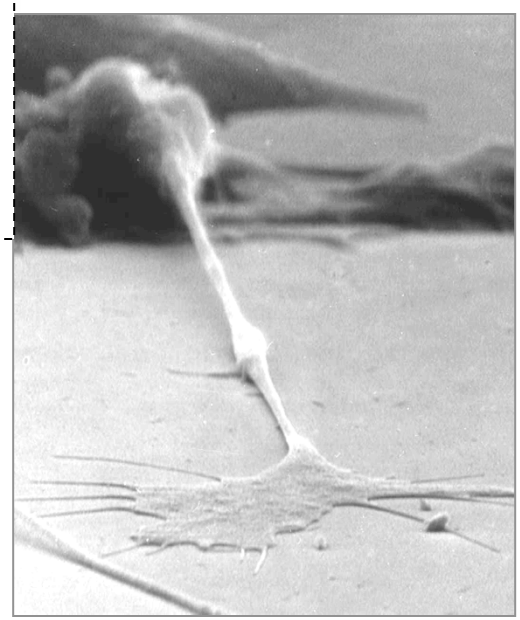
Multiple sclerosis (MS) results from
impulse speed is reduced; electro-chemical 'cross-talk' between axons.

Glial cells are important in neural development of functional connections

Neuronal Roadmap
As the neural system develops,
a distinctive network of interneuron connections is created.
Neural circuit formation requires an intricate orchestration of ...
cell migration, axon guidance, dendritic growth,
synaptic target selection, and synaptogenesis.
Colón-Ramos et al. (p. 103) find that,
in the nematode worm C. elegans,



Glia Promote Local Synaptogenesis
Through UNC-6 (Netrin) Signaling in C. elegans
DA Colón-Ramos et al. 2007. Science 318: 103 – 106.



A cultured sensory neuron extending a growth cone with long thin filopodia, photo by Ken Balazovich

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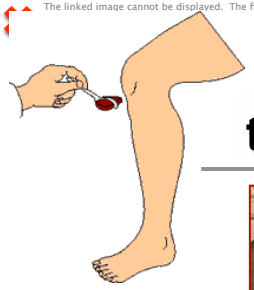
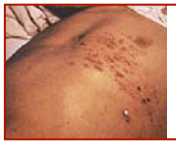
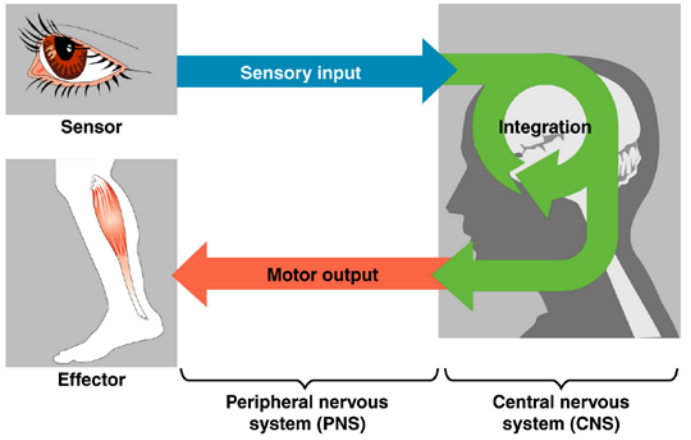
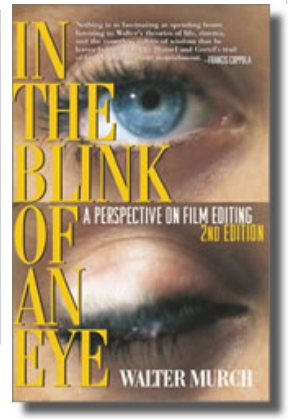


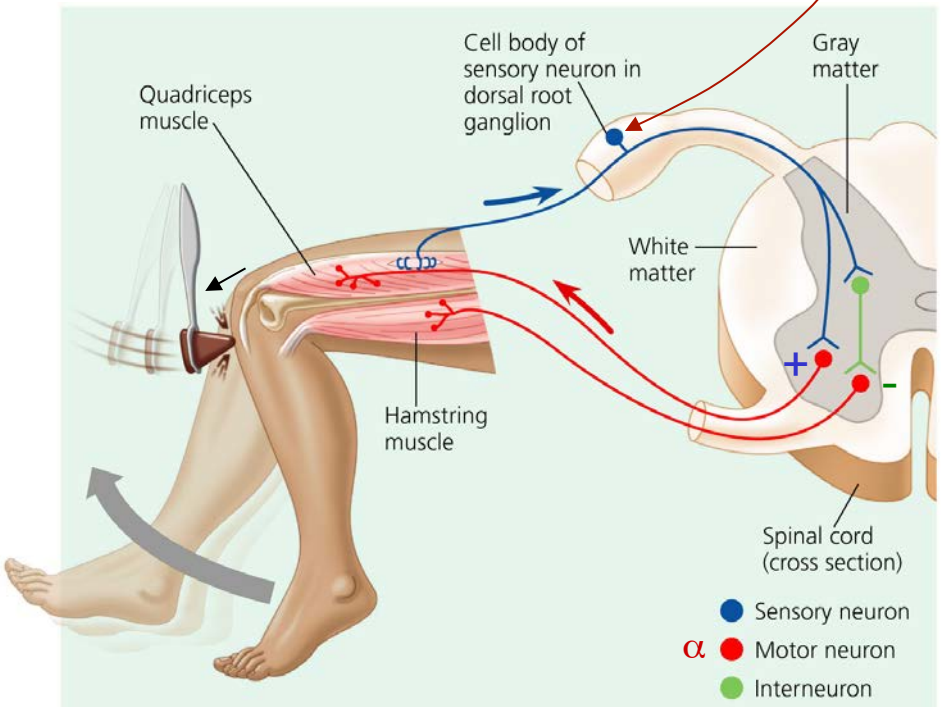
A simple functional network: **the Patellar postural reflex**;



latent chicken pox emerge from **dorsal root ganglia** to become shingles







So, how can you move?

Voluntary contraction

Dendrites of alpha (α) motor neuron
can have ~50k incoming synapses from brain.

Gamma neurons
to spindles (not shown)
inhibit the postural reflex,
allowing muscle contraction.

Muscle length & velocity are monitored by

different reflexes mature at diff times

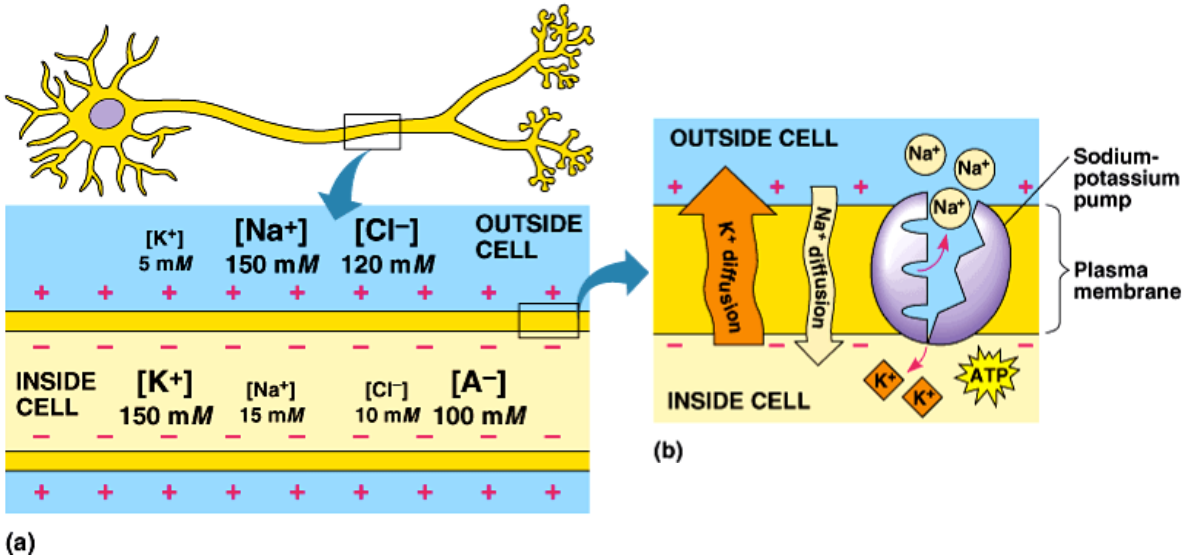
http://en.wikipedia.org/wiki/Reflex

Adult human reflexes

Baby reflexes not seen in adults

All cells have a **resting potential** (ionic gradients) across the plasma membrane,
but neurons have voltage-sensitive permeability (**voltage-gated ion channels**)

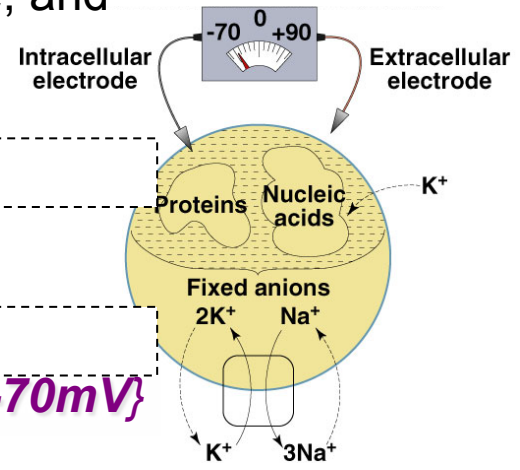
and some back-flow diffusion through ion **leak channels** (more by K^+). (Fig 48.6)



Water-soluable Ions
cannot dissolve in the phospholipid plasma membrane;
they must either be
pumped by membrane proteins or
diffuse through ion channels,
which are aqueous pores made of specific transmembrane protein molecules.
These molecular channels
are selective for specific ions.

Membrane potentials are determined by
(a) the ionic concentration differences across the membrane, and
(b) the membrane's relative permeabilities to different ions.

Plasma membrane Na,K-ATPase pumps maintain

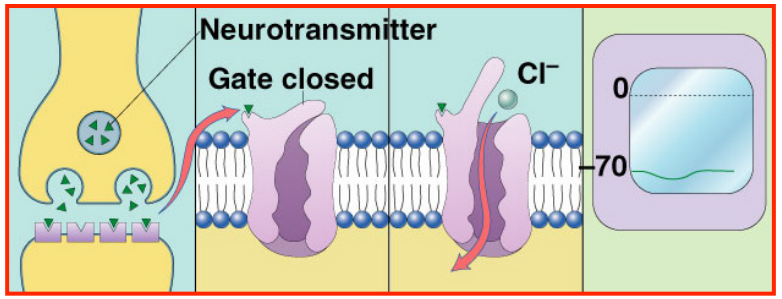


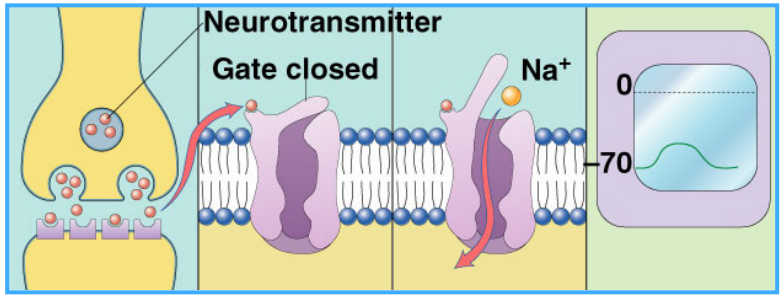
In almost all resting cells, the plasma membrane
is much more permeable to K^+ than to Na^+;

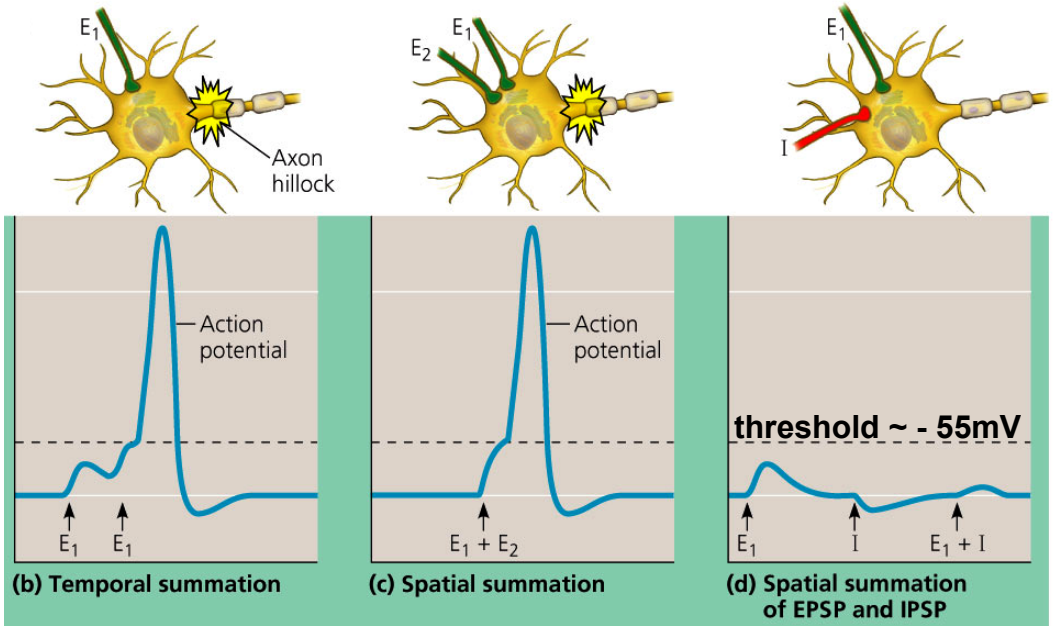
that is, the inside is negative relative to the outside. ***{about -70mV}***

http://www.mhhe.com/biosci/ap/vander/student/olc/index.htm

Within neurons, _____ (*like AM, adding analog signals*)
and _____ (*like FM, w/o degradation*)



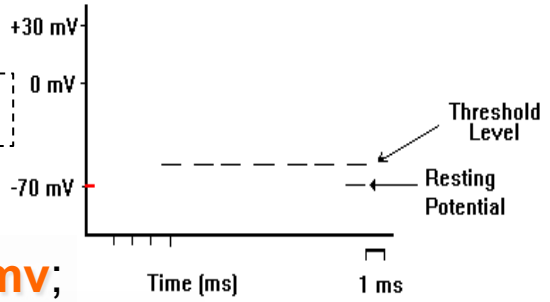




At **inhibitory synapse**: an inhibitory postsynaptic potential (**IPSP**) ***{hyperpolarization}*** results when **ligand-gated chloride channels are opened.** (ex by glycine or GABA)

At **excitatory synapse**: an excitatory postsynaptic potential (**EPSP**) ***{depolarization}*** results when _____

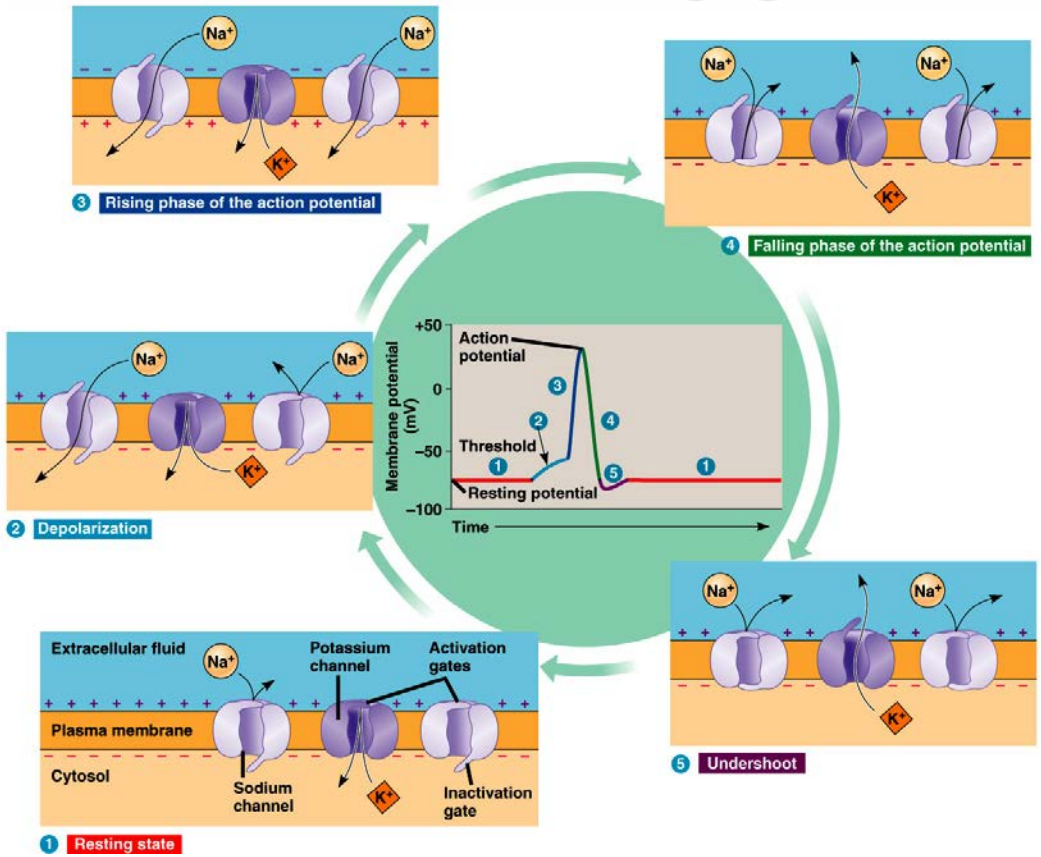
The postsynaptic cell's membrane potential is the result of _____ at the many excitatory and inhibitory synapses on the cell.

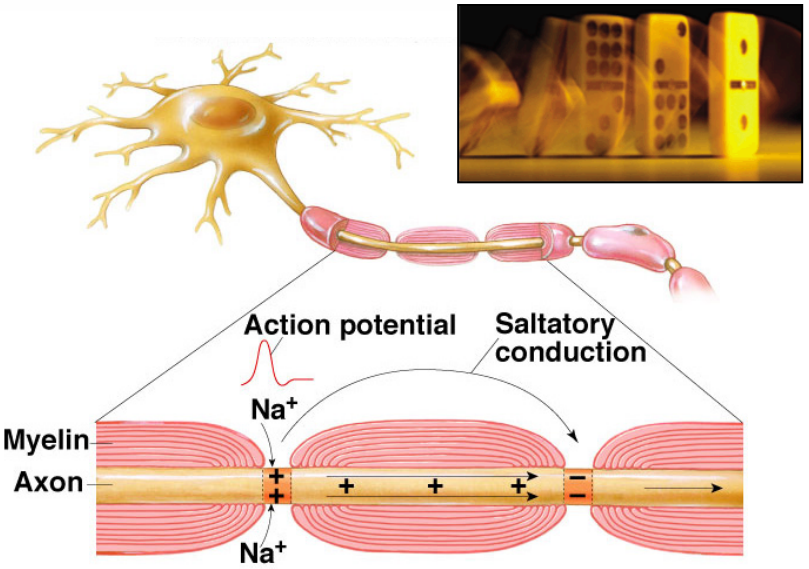


This **integrates information**; **a 'decision' at axon hillock** corresponds to whether **depolarization > threshold ~ - 55mv**; if yes, **triggers +FB opening of voltage-gated Na^+ & K^+ channels**.

Action potentials: +FB opening of voltage-gated Na^+ then K^+ channels (Fig 48.10)

An **action potential (AP**; 2-5) is a **self-propagating unidirectional wave** of opening & closing of **voltage-gated Na^+ and then K^+ ion channels**,



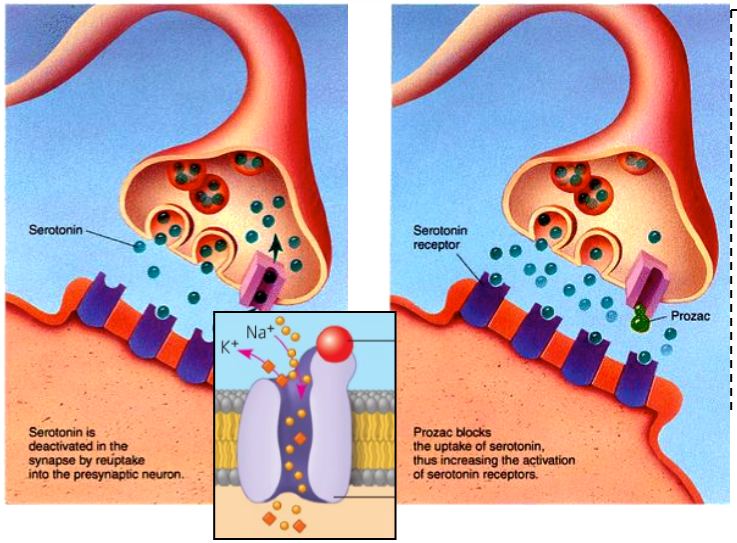


In **myelinated axons**, APs manifest saltatory *{skippy}* conduction; allows small diameter axons to be fast; myelin lost in multiple sclerosis (MS)

Depolarization sends electrical field loops ahead and behind.
The **unidirectionality** results from hyperpolarization behind (5) but resting (1) in front.
Consider 'crazy-bone' initiation of AP in middle of axon – direction?

APs: long-distance transmission of information w/o degradation (or processing);

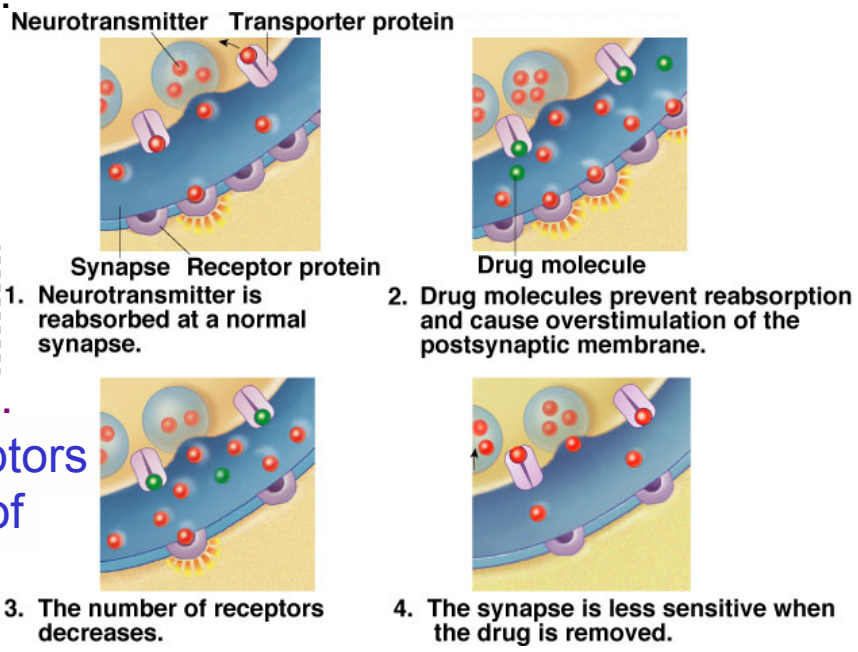
Most graded signals originate at **synapses** on the dendritic tree



http://www.driesen.com/ssri_actions.htm

Extasy (MDMA)
is a serotonin reuptake inhibitor;
cocaine
is a dopamine reuptake inhibitor

The signal from a pre- to a postsynaptic neuron
is a chemical **neurotransmitter**
stored in presynaptic vesicles (see Table 48.1).
Depolarization of the axon terminal
causes the release of neurotransmitter
into the synaptic cleft (Fig 48.15).
The neurotransmitter diffuses across the cleft



Receptors move in and out of plasma membrane.
Prolonged **hyper-stimulation** of receptors
often results in down-regulation of
the number of receptors
- **sets the stage for addiction**.

Science 26 October 2012:
Vol. 338 no. 6106 pp. 482-483
NEUROSCIENCE Chris J. McBain

Decoding the Neuronal Tower of Babel

Individual neurons in the mammalian central nervous system communicate with their downstream targets by means of subcellular specializations in their axon.

Arranged like pearls on a necklace, these **presynaptic terminals enable the rapid release of neurotransmitter in response to an electrical action-potential wave front that travels from the cell body to the far reaches of the axon.**

A single axon may contact hundreds of downstream targets …

each of these presynaptic release sites is often tuned … such that transmission may be robust onto one particular cell type yet weak at another, despite all terminals sensing the same action-potential waveform.

This arrangement allows different terminals in the axon to behave independently …

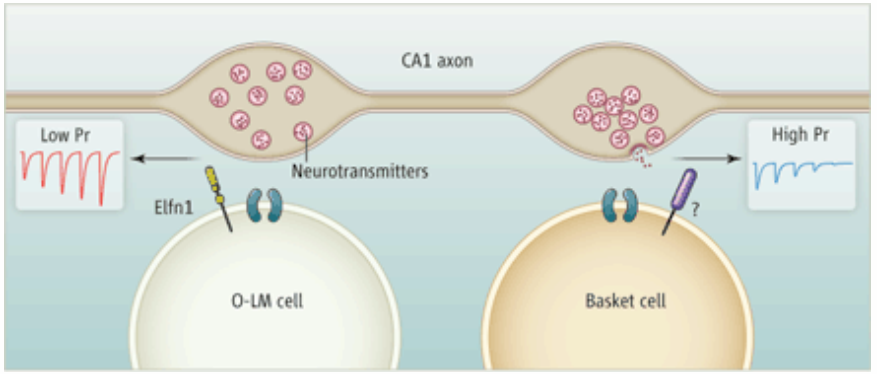
On page 536 in this issue, Sylwestrak and Ghosh (4) show that

postsynaptic expression of … {*a protein 'badge'*} (Elfn1) plays an important role in establishing **target-specific differential transmission**. {*bi-directional signaling*}

Tailoring one neuron to two synapses.

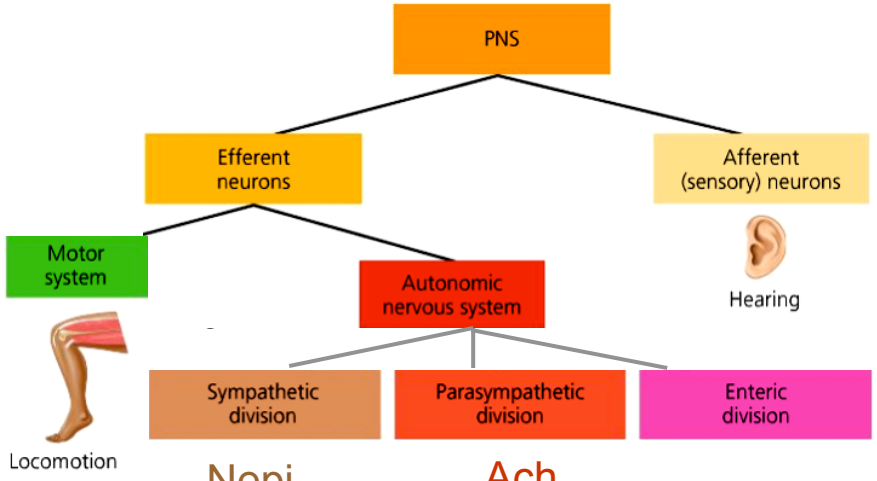
In the hippocampus … cells receive common afferent input from CA1 pyramidal neurons.

The postsynaptic expression of … Elfn1 … acts to set the presynaptic initial transmitter release probability (Pr) low …

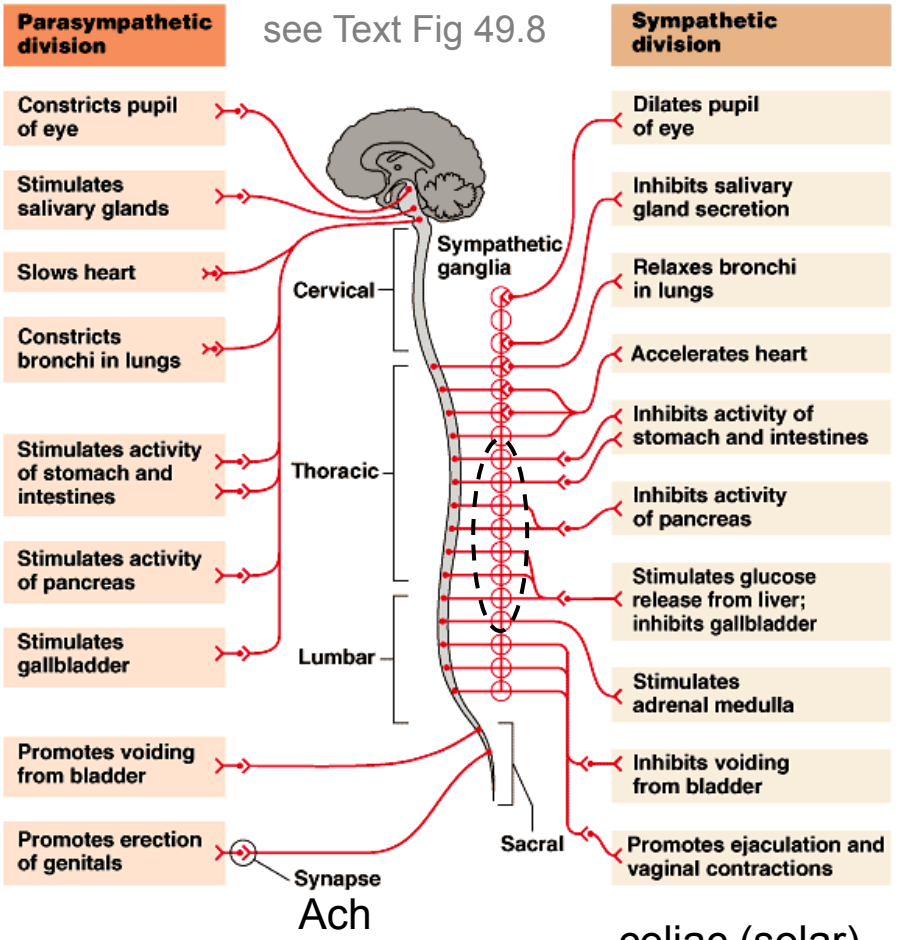


The **autonomic nervous system**

innervates cardiac & smooth muscle, glands



Nepi Ach



Each autonomic pathway consists of
a preganglionic neuron w/ its cell body in the CNS and
a postganglionic neuron w/ its cell body in a ganglion outside the CNS.

celiac (solar) plexus

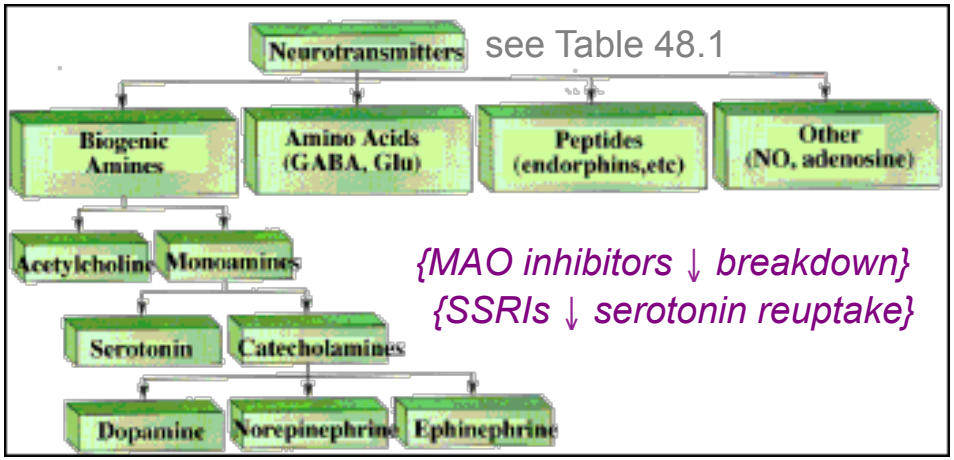
The preganglionic neurons in both divisions release a

the postganglionic parasympathetic neurons release

the postganglionic sympathetic neurons release

Effector organs innervated by the autonomic nervous system
generally receive dual innervation. *{push-pull control}*

http://www.mhhe.com/biosci/ap/vander/student/olc/index.htm

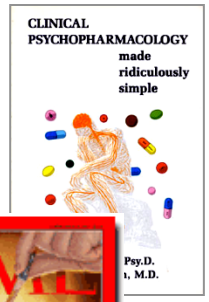


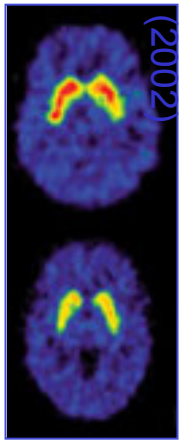
http://www.csuchico.edu/psy/BioPsych/neurotransmission.html

- **Endorphins/Enkephalins** are endogenous opiates found in a variety of places in brain.

They are also released as hormones by the pituitary.
They are involved in pain reduction and pleasure (they enhance the effects of dopamine).

- **NO** *{Viagara}* & **Adenosine** *{caffeine}* **!**





Nature **419**, 872-874 (2002)

- Each time you move a muscle it is because [ ] has been released from a neuron to activate muscle

Alzheimer's Disease is associated with a 90% loss in the brain's production of **Ach** in the basal forebrain and hippocampus.

Nicotine [ ]

- Human mood disorders (depressions) are treated with drugs that [ ] for example fluoxetine (Prozac).

- Cocaine, opiates, nicotine and alcohol produce rewarding effects by promoting the release or inhibiting the presynaptic re-uptake of [ ]

{addiction is associated with reduced density of dopamine receptors:}

Parkinson's Disease (PD) is accompanied by a selective destruction of **dopamine** neurons in the substantia nigra of the midbrain. PD is treated with L-dopa, a precursor of dopamine in the brain.

Schizophrenia is treated with drugs which block the binding of **dopamine** to its postsynaptic receptor sites.

- **GABA** (gamma-aminobutyric acid) is the main inhibitory neurotransmitter in the brain. [ ]

Its actions are mediated at two types of receptor (NMDA and AMPA) involved in **memory formation**

A good source of info: http://en.wikipedia.org/wiki/Neurotransmitter

Perspectives NEUROSCIENCE: **A New Molecule to Brighten the Mood**

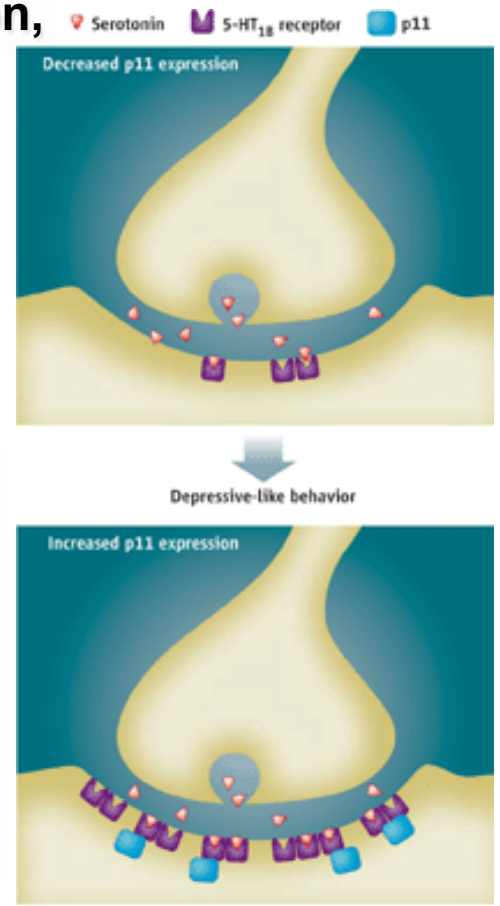
Trevor Sharp *Science* 6 January 2006: Vol. 311. no. 5757, pp. 45 - 46

A popular theory is that **a breakdown in signaling**

is critically involved in the symptoms of clinical depression, but the nature of this defect has proved elusive.

The study by Svenningsson *et al.* (*Science* **311**, 77 2006) identifies an interaction between a brain protein called **p11** and a **serotonin receptor** (**5-HT1B** subtype) that has been previously associated with mood regulation.

... the authors show that



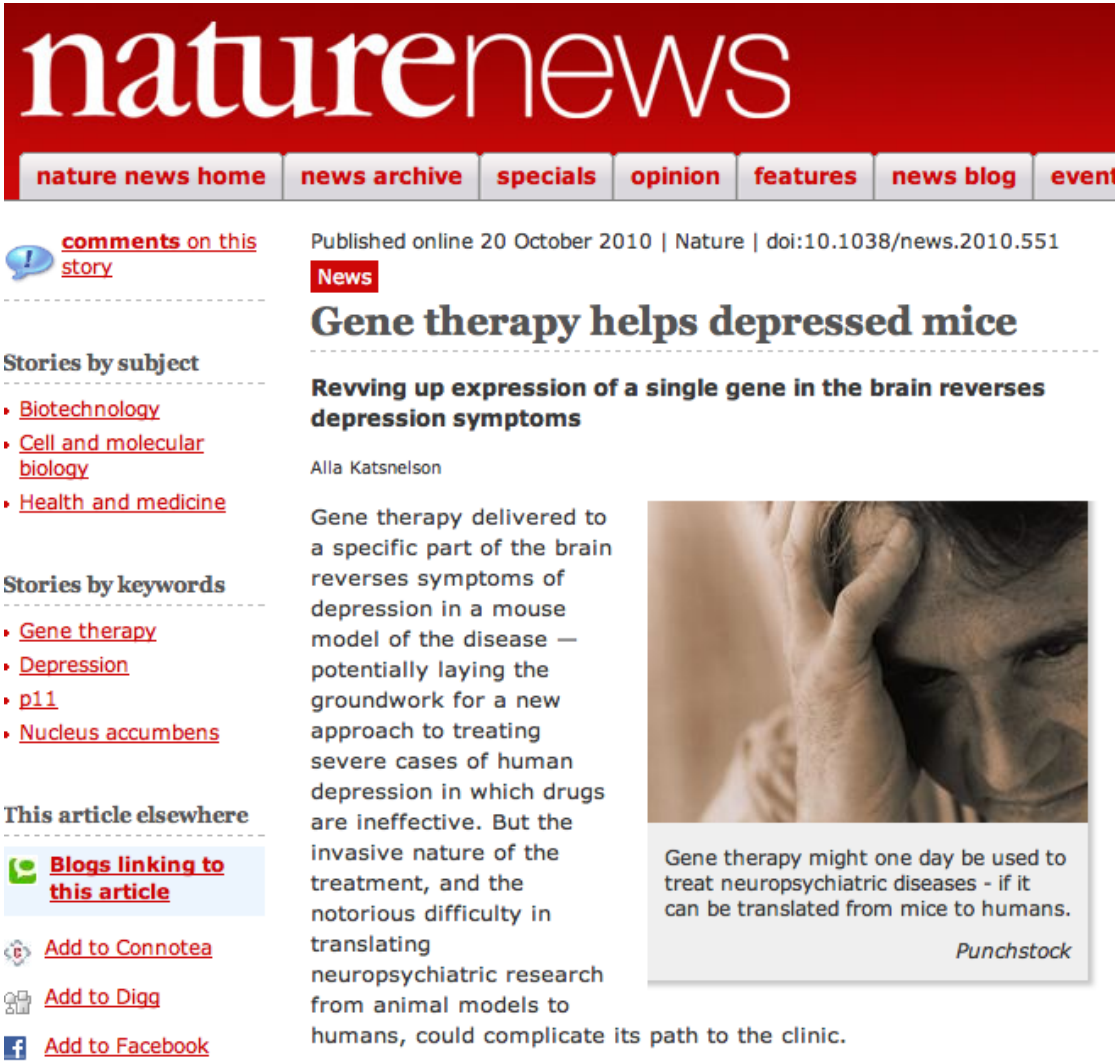
p11 increases delivery of the serotonin 5-HT1B receptor to the neuronal plasma membrane where it can bind to serotonin; increases in p11 can be linked to antidepressant effects

U.S. Department of Health and Human Services
NIH News
National Institutes of Health
http://www.nih.gov/news/pr/jan2006/nimh-06.htm

Antidepressants and electroconvulsive therapy (ECT)

So, it's pretty convincing that p11 is associated with the main therapeutic action of antidepressant drugs.

npr
Health & Science
Study Sheds Light on How Depression Drugs Work
Listen by Jon Hamilton



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Published online 20 October 2010 | Nature | doi:10.1038/news.2010.551

News

Gene therapy helps depressed mice

Revving up expression of a single gene in the brain reverses depression symptoms

Alla Katsnelson

Gene therapy delivered to a specific part of the brain reverses symptoms of depression in a mouse model of the disease — potentially laying the groundwork for a new approach to treating severe cases of human depression in which drugs are ineffective. But the invasive nature of the treatment, and the notorious difficulty in translating neuropsychiatric research from animal models to humans, could complicate its path to the clinic.

Gene therapy might one day be used to treat neuropsychiatric diseases - if it can be translated from mice to humans.

Punchstock

http://www.nature.com/news/2010/101020/full/news.2010.551.html#comments

Research published today in Science Translational Medicine
uses a virus to deliver an extra dose of the gene **p11** to the adult mouse brain.
The protein expressed by the gene is thought to
bind to serotonin receptor molecules and ferry them to the cell surface,
positioning them to receive serotonin's signals from neighbouring cells.

Macrophage migration inhibitory factor {MIF}
mediates the antidepressant actions of voluntary exercise

Moon et al. 2012. PNAS 109 (32) 13094-13099

Voluntary exercise is known to have an antidepressant effect.

… the underlying mechanism for this … remains unclear …

We have identified macrophage migration inhibitory factor (MIF) …

A proinflammatory cytokine, **MIF** is expressed in the central nervous system and involved in innate and adaptive immune responses.

… MIF is involved in antidepressant-induced hippocampal neurogenesis …

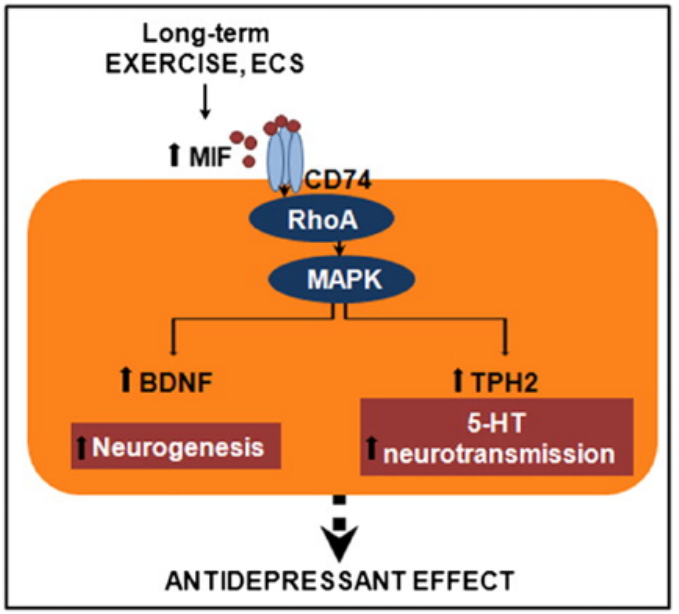
…{tryptophan TPH2} and brain-derived neurotrophic factor (Bdnf) expression was induced after **MIF treatment** in vitro, as well as during both **exercise** and **electroconvulsive seizure** in vivo.

This … was accompanied by increases in the levels of total **serotonin** in vitro.

Experiments in $Mif^{-/-}$ mice revealed depression-like behaviors and a blunted antidepressant effect of exercise …

In addition, administration of recombinant MIF protein produced antidepressant-like behavior in rats …

Taken together**, these results suggest a role of MIF in mediating the antidepressant action of exercise,**



nature International weekly journal of science

Editor's Summary 31 August 2006

Dopamine by Choice

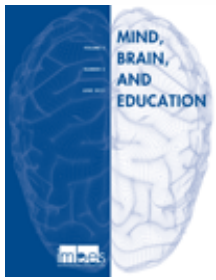
The brain messenger **dopamine** is traditionally known as **the 'pleasure molecule',** linked with our desire for **food** and **sex**, as well as **drug** and **gambling addictions**.

Using brain imaging, Pessiglione et al. (2006) scanned healthy human volunteers as they gambled for money after taking {*dopamine altering*} drugs ...

When dopamine levels were either enhanced or reduced by drugs,
the brain scans showed that both reward-related learning and associated brain activity are modulated, confirming the critical role of dopamine in integrating reward information for generating future decisions. *{ie – anticipated reward-pleasure}*

Dopaminergic Network Differences in **Human Impulsivity**
J.W. Buckholtz, et al. Science 30 July 2010 Vol. 329. no. 5991, p. 532

Associations between dopamine D4 receptor gene variation with both **infidelity and sexual promiscuity**.
(2010) Garcia JR et al. PLoS ONE 5(11):e1412.



EDUCATION

One Size Does Not Fit All

Pamela J. Hines

Some children, particularly those with a more fearful temperament, are more sensitive than others to the influence of parents, teachers, and environment.

Kegel et al. (2011) attempt to link this with a particular genetic polymorphism.

Preschool children played a literacy-geared computer game
that delivered instruction and assignments to all participants,
but differed in whether it delivered feedback about the children's choices.

A feature that distinguished the groups of children was whether they carried the long variant of the dopamine D4 receptor gene, which is associated with lower dopamine reception efficiency.

Children who carried the long {low affinity} **polymorphism**

They outperformed the control group when feedback guided their learning,
and they did worse than the control group when feedback was absent.

In contrast, children with the short {high affinity} **variant of the gene**

For education, just as for shoes, a good fit to the individual produces the best result.

genotype x environment interaction !!!

Differential Susceptibility in Early Literacy Instruction Through Computer Games:
The Role of the Dopamine D4 Receptor Gene (DRD4).
Kegel et al. Mind Brain & Educ. **5**, 71 (2011).

Actin-based **plasticity in dendritic spines**

Matus A SCIENCE 290: (5492) 754-758 OCT 27 2000

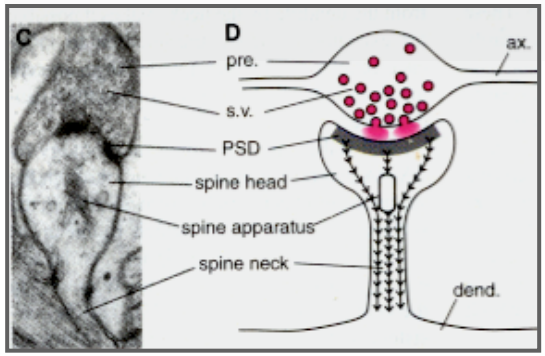
The central nervous system functions primarily
to convert patterns of activity in sensory receptors
into …. **appropriate behavior**.

At the anatomical level this **requires**
two complementary processes:

Evidence has accumulated implicating …
excitatory synapses made onto dendritic spines,
as the sites where connective plasticity occurs. …

Signal-processing machines at the postsynaptic density

Kennedy MB SCIENCE 290: (5492) 750-754 OCT 27 2000



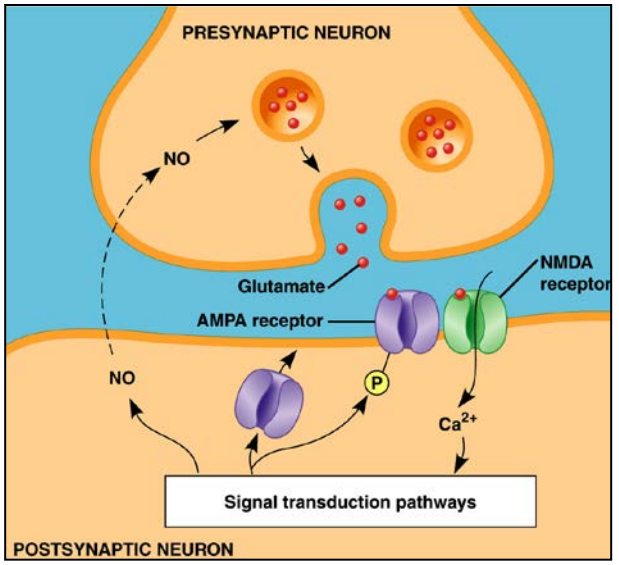
neurotransmitter ***{glutamate GLU}*** **receptors**
are attached to large protein "signaling machines" that
delicately regulate the strength of synaptic transmission.
{The "machines" are in the postsynaptic "spines"}

Glutamate receptor plasticity at excitatory synapses in the brain

D Genoux & JM Montgomery (2007)Clinical & Exp. Pharm. & Phys. 34, 1058-1063.

Significant effort has been focused on determining
the mechanisms of changes in synapse strength.

The present review will focus on
the **changes in the post-synaptic expression**
of {*AMPA* & *NMDA*} glutamate receptors
that **have been shown to occur**
during the expression of synapse plasticity.



Biochemical studies
of excitatory synapses in the central nervous system
have revealed a high concentration ...
at **dendritic spines**.

These proteins appear to **play critical roles in**
synaptic structure, plasticity and in trafficking receptors to synapses.
{"trafficking" means moving receptors into & out of plasma membrane}

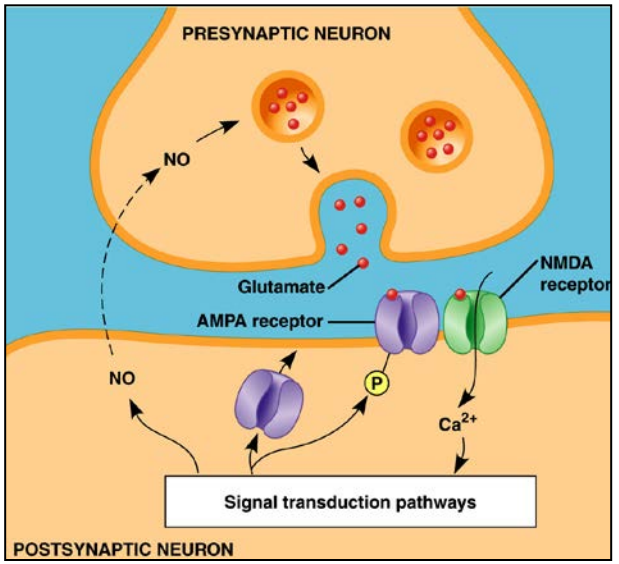
There is growing evidence that **synapse plasticity**
could be the cellular basis of certain forms of learning and memory.

{see Fig 49.20: Long Term Potentiation by recruitment of AMPA glutamate receptors that supplement and potentiate active NMDA glutamate receptors}

Neuroscience: **Memory gene**

Neuron **52**, 437–444; 445–459; 461–474; 475–484 (2006)

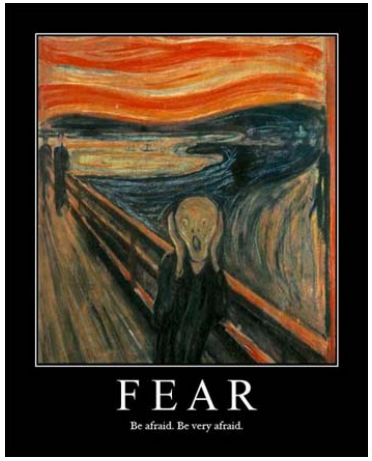
Four papers published in *Neuron* help to demystify
the mechanism of a gene implicated in the consolidation of memories.
The gene, known as *Arc/Arg3.1*, is expressed in the brain during learning.
It has long been used as a marker of neuronal activity,
even though its physiological role was not clear.
The new research shows that
mice with the *Arc/Arg3.1* gene knocked out
fail to form long-lasting memories.
Studies *in vitro* suggest that
the gene controls the appearance and disappearance of
AMPA neurotransmitter receptors
on neuronal surfaces.
Such receptor trafficking
is known to modify
the strength of connections between neurons,
which is fundamental to learning and memory.

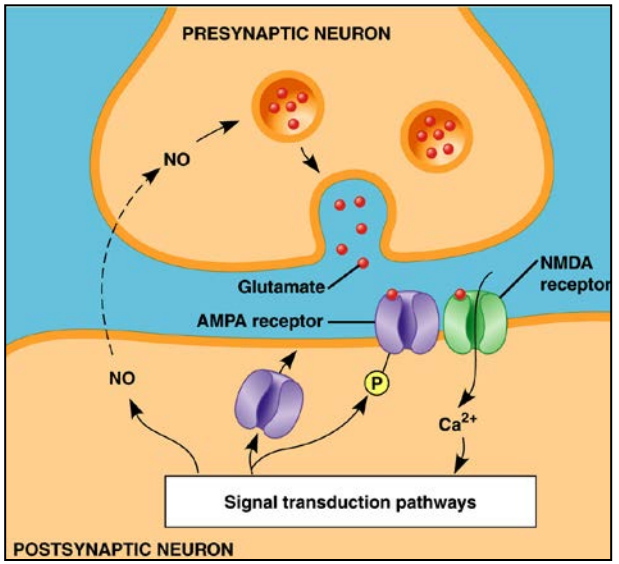


Neuroscience: **Hard to forget**

Cell **131**, 160–173 (2007)

Researchers have unpicked the mechanism by which
memories tied to strong emotions
are recalled with greater clarity.
The effect has been linked to
release of the neurotransmitter noradrenaline
{*aka norepinepherine*} **during emotional situations**.
Now, Roberto Malinow ... and his colleagues have determined that
noradrenaline acts by regulating a class of receptor,
known as GluR1-containing **AMPA receptors**,
that is **involved in learning**.
In mice, both the fear caused by exposure to fox urine
and the experimental injection of adrenaline,
which boosts noradrenaline,
triggered ... phosphorylation ...
GluR1-containing **AMPA receptors**
could be more easily incorporated into synapses,
which improved the animals' learning
in behavioural tests
carried out immediately **after adrenaline injection**.
Noradrenaline had no effect on learning in mice
that contained a mutant GluR1
that lacked the phosphorylation sites.





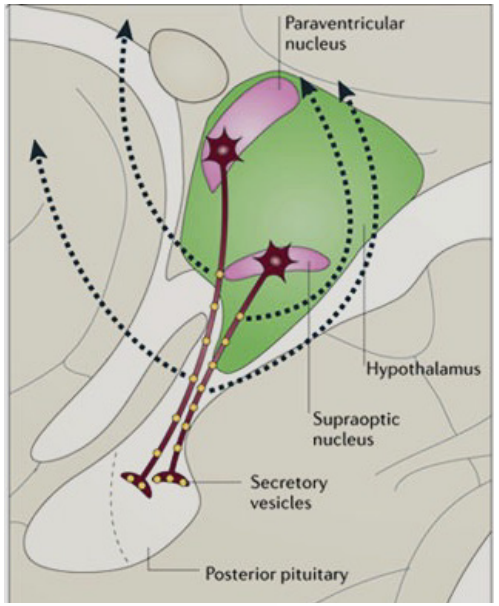
Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine.

Meyer-Lindenberg et al. 2011. *Nature Reviews Neuroscience* **12**, 524-538

For social neuroscience, few molecules could be more important and exciting than the **neuropeptides oxytocin (OXT) and arginine vasopressin (AVP).**

These peptides have had key roles throughout mammalian evolution in the regulation of complex social cognition and behaviours, such as attachment, social exploration, recognition and aggression, as well as anxiety, fear conditioning and fear extinction.

Studies have begun to provide evidence that the function of these neuropeptides is impaired in mental disorders associated with social deficits {*autistic spectrum*}



Oxytocin (OXT) and arginine vasopressin (AVP) are synthesized in neurons in the **hypothalamus**, and are processed along the axonal projections to the **posterior lobe of the pituitary**, where they are stored in secretory vesicles and released into peripheral circulation.

In addition to this release from axonal terminals, **there is dendritic release of OXT and AVP into the extracellular space, resulting not only in local action but also in diffusion through the brain** ....

Furthermore, smaller neurons in the hypothalamus also produce OXT and AVP and **project directly to other regions in the brain**.

Women See Friends, Men See Foes

Gender differences in social behavior are well known. *{duh!}*

Thompson *et al.* (*Proc Natl Acad Sci. USA* **103**,7889 2006)
now show that **arginine vasopressin (AVP),** *{aka ADH}*
which is known to influence the behavior of other mammals,
influences human behavior in a gender-specific manner.

AVP or saline was administered intranasally, and
various responses to faces of the same sex
with happy, neutral, or angry expressions were recorded.

Differences in **the activity of a muscle in the brow**,
the contraction of which is associated with anger or threat,
were increased in men exposed to AVP and shown neutral faces,
{assuming no cosmetic botox injections!}
whereas women exposed to AVP
showed a decrease in the activity of this muscle
in response to happy or angry faces.

Although AVP-treated individuals of both sexes
exhibited increased anxiety,
men reported a decrease in the perceived approachability
or friendliness of people with happy expressions, whereas
women reported an increase in the approachability
or friendliness of people with neutral expressions.

{later – vasopressin and mate fidelity in mice}