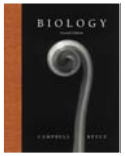
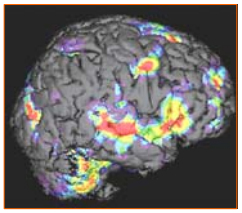
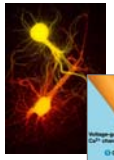


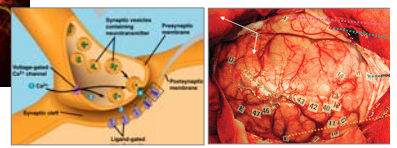
bs148h 25 October 2007
Read: Text ch 48

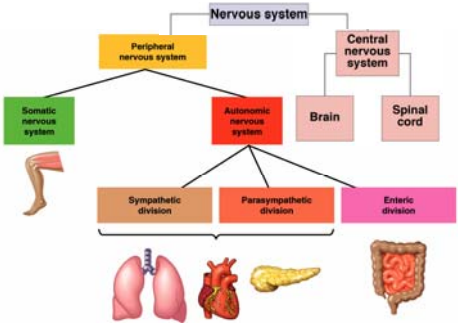
- nervous systems
- neurons
- info processing - reflexes
- resting & action potentials
- synapses & mechanisms
- transmitters
- autonomic NS
- CNS
- depression
- addiction
- synaptic plasticity & learning
- sex differences



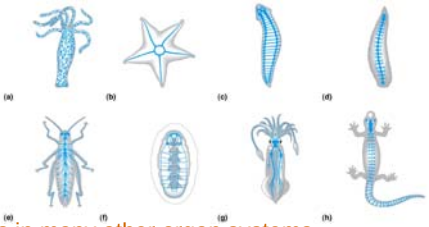


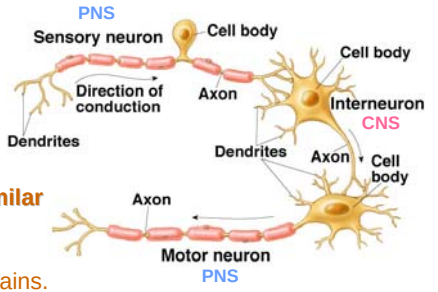
Nervous Systems:
(from molecules to mind)





Animal survival & reproduction
depend on rapid & flexible responses.
A diversity of nervous systems has evolved
in various animal phyla. *{except sponges}*



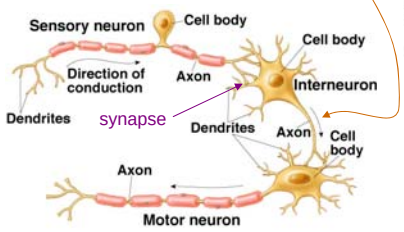


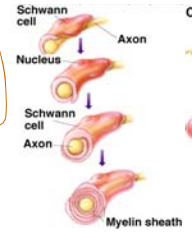
As in many other organ systems,
animal nervous systems are remarkably similar at the cellular level - how neurons work –
but differ at higher levels of organization,
such as the structure and function of their brains.

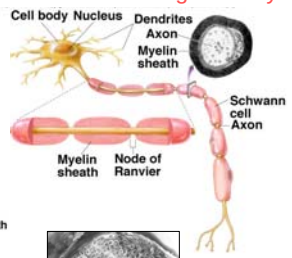
Neurons & nerves

Myelinated CNS = 'white matter'
unmyelinated CNS = 'gray matter'

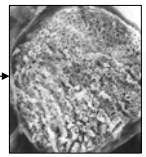
oligidendrocytes & glia: CNS neuroglia → myelin
Schwann cells: PNS neuroglia → myelin

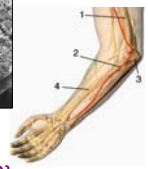






Peripheral nerves are cable-like collections of axons,
electro-chemically isolated inside myelin sheaths





ulnar nerve relays sensation from the little & ring fingers
and activates many of the small muscles in the hand.
If pinched against elbow - '**crazy bone:**' depolarizes all axons;
{later: can action potential go backwards up axon? – across synapse?}

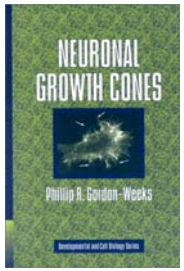
MS National Multiple Sclerosis Society

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

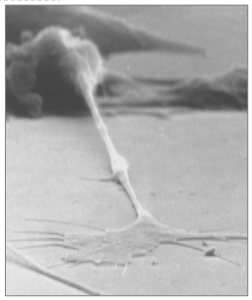
Glial cells are important in neural development and neural activity

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,

for making these connections.
... **consistent with observations made in vertebrates and highlights the importance of glial cells in specifying precise neural connectivity.**



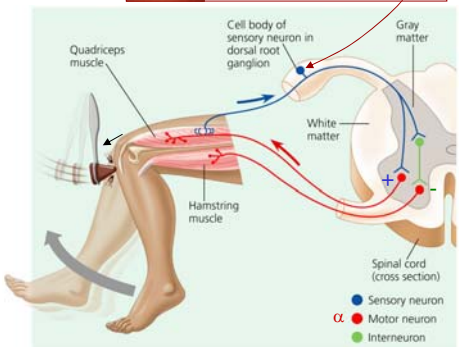
Glia Promote Local Synaptogenesis
Through UNC-6 (Netrin) Signaling in C. elegans
DA Colón-Ramos et al. 2007. Science 318: 103 – 106.

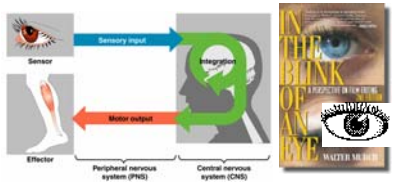


A cultured sensory neuron extending a growth cone with long thin filopodia, photo by Ken Balazovich

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

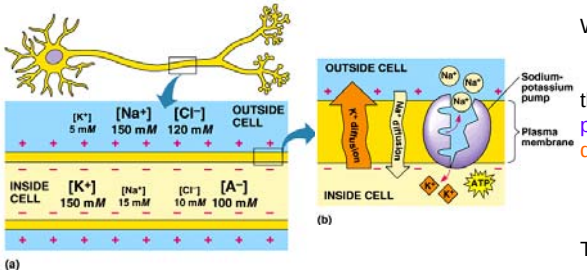
Activation of these receptors initiates **the postural reflex**: motor neurons of synergists are activated (+) & those of antagonists are inhibited (-).

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)

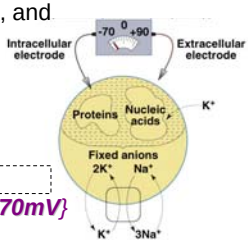
The K^+ & Na^+ gradients are created by

and some back-flow diffusion through ion



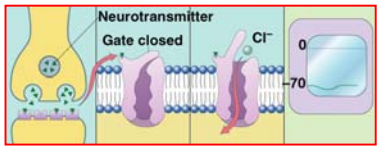
Water-soluable Ions cannot dissolve in the phospholipid plasma membrane; they must either be pumped by membrane proteins or diffuse through ion channels, which are aqueous pores made of specific transmembrane protein molecules.
These molecular channels are selective for specific ions.

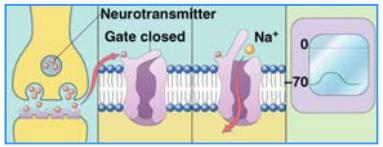
Membrane potentials are determined by
(a) the ionic concentration differences across the membrane, and
(b) the membrane's relative permeabilities to different ions.
Plasma membrane Na,K-ATPase pumps maintain intracellular sodium concentration low and potassium high.
In almost all resting cells, the plasma membrane is much more permeable to K^+ than to Na^+;
the membrane potential is close to that is, the inside is negative relative to the outside. ***{about -70mV}***

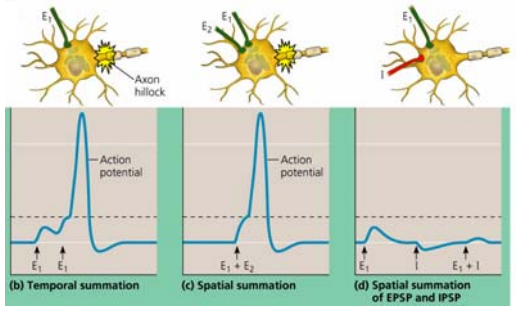


http://www.mhhe.com/biosci/ap/vander/student/olc/index.htm

Within neurons, **graded potentials integrate inputs** (like AM, adding analog signals)
and (like FM, w/o degradation)



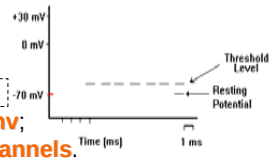




At **inhibitory synapse**: an inhibitory postsynaptic potential (**IPSP**) ***{hyperpolarization}*** results when **ligand-gated chloride channels are opened.** (ex by glycine or GABA)

At **excitatory synapse**: an excitatory postsynaptic potential (**EPSP**) ***{depolarization}*** results when **ligand-gated** (ex by glutamate)

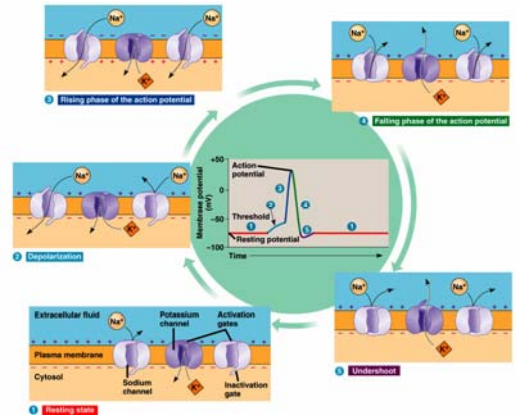
The postsynaptic cell's membrane potential is the result of of the **EPSPs** and **IPSPs** at the many excitatory and inhibitory synapses on the cell.



This **integrates information**; **a 'decision' at** 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^+ & K^+ channels

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

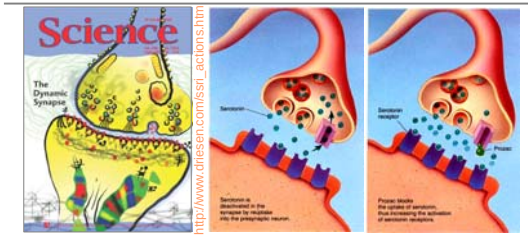


In **myelinated axons**, APs manifest saltatory *{skippy}* conduction; allows small diameter axons to be fast; myelin lost in multiple sclerosis (MS)

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;
information encoded by

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



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

SSRIs like Prozac are **Selective**

interfere w/ reuptake transporter, but not w/ receptor protein

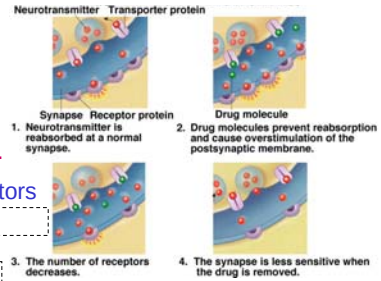
Extasy (MDMA) is a serotonin reuptake inhibitor

The signal from a pre- to a postsynaptic neuron (or effector muscle) is a **neurotransmitter** stored in presynaptic vesicles.

Depolarization of the axon terminal, opens calcium gates & lets in Ca^{++}, causes the release of neurotransmitter into the synaptic cleft (Fig 48.17).

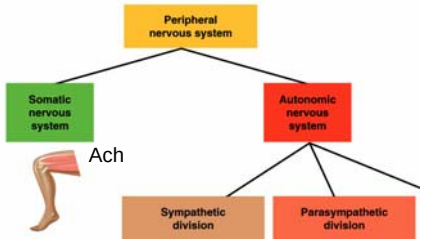
The neurotransmitter diffuses across the cleft & [ ] on the postsynaptic cell; opens ligand-gated ion channels.

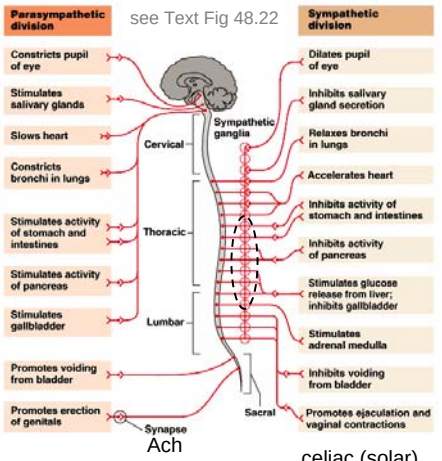
Pre-synaptic [ ] remove neurotransmitter from cleft, turning the signal off (information requires on-off).



Prolonged **hyper-stimulation** of receptors **often results in** the number of receptors - **sets the stage for** [ ]

The **autonomic nervous** system innervates cardiac & smooth muscle, glands





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

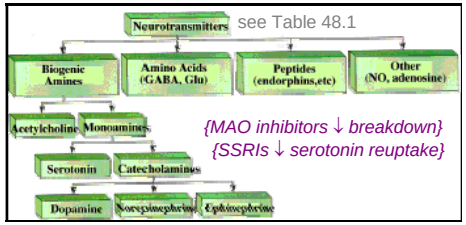
The preganglionic neurons in both divisions release **acetylcholine (Ach)**;

the postganglionic parasympathetic neurons release mainly [ ]

the postganglionic sympathetic neurons release mainly [ ]

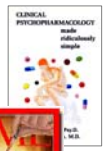
Effector organs innervated by the autonomic nervous system generally receive dual innervation. *{push-pull control}*

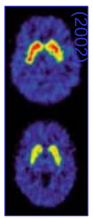
http://www.mhhe.com/biosci/ap/vander/student/olc/index.htm



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 **acetylcholine** (**Ach**) 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 mimics **Ach** at neuromuscular junction, autonomic & CNS.
- Human mood disorders (depressions) are treated with drugs that block the reuptake of **serotonin** (5-HT) into the presynaptic axon terminal, for example fluoxetine (Prozac).
- Cocaine, opiates, nicotine and alcohol produce rewarding effects by promoting the release or inhibiting the presynaptic re-uptake of **dopamine**.
  {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.
- **GLU** (**glutamate**) is the main excitatory 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

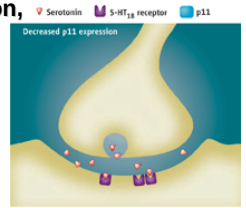
Perspectives NEUROSCIENCE: **A New Molecule to Brighten the Mood**

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

A popular theory is that **a breakdown in signaling by the brain neurotransmitter** [ ] (5-hydroxytryptamine; **5-HT**) **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 **a deficit of p11 is linked to depression**



p11 [ ] **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

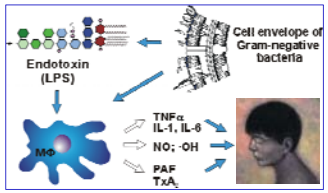
Antidepressants and electroconvulsive therapy (ECT). all caused an increase in the amount of p11 in the brains of mice.

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

Cytokines, stress and depressive illness: brain-immune interactions

Anisman H, Merali Z. 2003 Annals of Medicine 35:2-11



Cytokines, signaling molecules of the immune system,
have been implicated as a contributing factor
for mood disorders such as **depression**.

... lines of evidence ...

1) proinflammatory **cytokines**
(interieukin-1, interleukin-6, tumor necrosis factor)
and bacterial endotoxins **elicit sickness behaviors** (e.g., fatigue, soporific effects)
and symptoms of anxiety/depression *{coming-down-with-something blues}*
that may be attenuated by chronic antidepressant treatment, ...

4) immunotherapy, using interleukin-2 or interferon-a,
promotes depressive symptoms
that are attenuated by antidepressant treatment.

It is argued that cytokine synthesis and release,
elicited upon activation of the inflammatory response system,
provoke neuroendocrine and brain neurotransmitter changes
that are interpreted by the brain as being stressors,
and [ ]

Mild **depressive symptoms are associated with** amplified and prolonged **inflammatory responses** after [ ]

Glaser et al Archives of General Psychiatry 60 (10): 1009-1014 OCT 2003

Perspective: **What Genes Tell Us About Nicotine Addiction**

RC Hogg & D Bertrand 2004 *Science* 306, 983-985.

Nicotine acts on the neuronal nicotinic acetylcholine receptors (nAChRs)
... a family of ligand-gated ion channels widely expressed in CNS & PNS.
Chronic nicotine exposure leads to [ ] & long-term
physiological alterations, including *{downstream effects on other neural circuits}*
Eleven neuronal nAChR subunits have been identified in humans ...
with distinct functional properties and pharmacological characteristics
Tapper *et al*. (*Science* **306**, 1029-1032 (2004) [Full Text]) show that
a mutation in neuronal nAChRs *{in mice}* lowers the threshold for addiction.
{suggesting that there is [ ] *in humans}*

Reduced dopamine D1 receptor **binding in** the ventral striatum of **cigarette smokers.**

Dagher A, et al. SYNAPSE 42 (1): 48-53 OCT 2001

We measured dopamine D1 receptor density in 11 smokers and 18 nonsmokers using
positron emission tomography and the D1 receptor ligand [C-11]SCH 23390 *{a label}*.

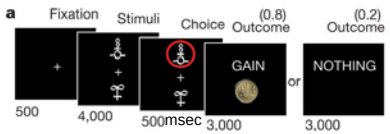
… there was a significant [ ] in [C-11]SCH 23390 binding potential in smokers
compared to nonsmokers in the ventral striatum.
{# D1 dopamine receptors ↓ in smokers & therefore ↓ of the D1 label bound}
Such a hypodopaminergic state may play an important role
in sustaining nicotine-seeking behavior.
{need hyperstimulation of few remaining dopamine receptors in 'pleasure centers'?}
Alternatively, an inherited reduction in dopamine receptors in the striatum
may be associated with an increased risk of addictive behavior. [ ]

nature International weekly journal of science

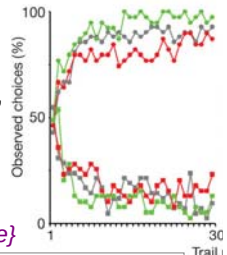
Editor's Summary 31 August 2006

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**.
The precise function of dopamine in humans has remained elusive ...
Using brain imaging technology,
Pessiglione et al. scanned healthy human volunteers
as they gambled for money
after taking drugs ...



Volunteers with [ ]
(**l-DOPA** a metabolic precursor of dopamine)
became better gamblers
{learned to choose symbol w/ highest probability of reward}
than their [ ] counterparts.
(**haloperidol** blocks dopamine receptors)



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 generation future decisions. *{ie – anticipated reward-pleasure}*

Dopamine-dependent prediction errors
underpin reward-seeking behaviour in humans
Pessiglione, M. et al. 2006 | Full Text | PDF (293K) |

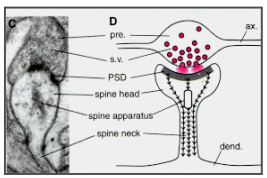
Actin-based **plasticity in dendritic spines**

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:
a set of genetically encoded rules
for building the basic network of connections, and
a mechanism for subsequently fine tuning these
connections on the basis of experience. …
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

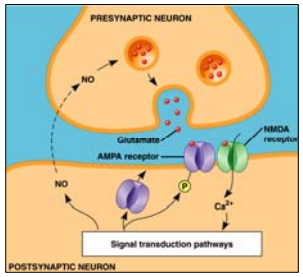


neurotransmitter [ ]
are attached to large protein "signaling machines" that
delicately regulate the strength of synaptic transmission.
{The "machines" are in the postsynaptic "spines"}

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 [ ]
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**.

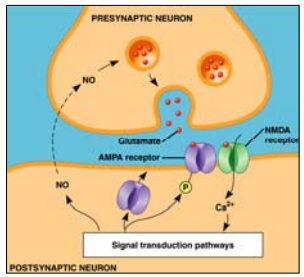


These proteins appear to **play critical roles in**
synaptic structure, plasticity and in trafficking receptors to synapses.
{"trafficking" means [ ]
There is growing evidence that **synapse plasticity**
could be the cellular basis of certain forms of learning and memory.

Neuroscience: **Memory gene**

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

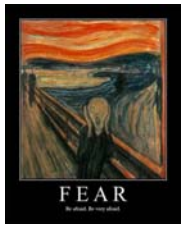
Four papers published in *Neuron* help to demystify
the mechanism of a gene implicated in the consolidation of memories.
The gene, known as *Arc/Arg3.1*, is expressed in the brain during learning.
It has long been used as a marker of neuronal activity,
even though its physiological role was not clear.
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
[ ]
on neuronal surfaces.
Such receptor trafficking
is known to modify
the strength of connections between neurons,
which is fundamental to learning and memory.



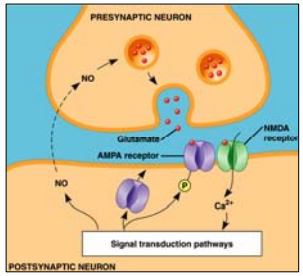
Neuroscience: **Hard to forget**

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 [ ]
during emotional situations.
Now, Roberto Malinow ... and his colleagues have determined that
[ ] **acts by regulating** a class of receptor,
known as GluR1-containing [ ]
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 [ ]
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.



nature
news feature 1 July 2007; Helen Pilcher

Powerful urine is mind-altering

Alpha-male pheromones cause females to [ ]

Urine is rich in the sex pheromones
that many animals use to recognize and choose their mates.
Samuel Weiss ... and his colleagues ...
housed adult female mice with soiled litter for a week.
Animals exposed to urine from dominant males
showed a 25% increase in [ ]
Those exposed to clean bedding, or urine from females or subordinate males
showed no such increase.
[ ] **in the hippocampus,**
a brain region involved in learning and memory,
and the olfactory bulb, which is involved in smell.
Both regions make new neurons throughout life;
We don't know whether pheromones trigger neuron formation in humans ...
whether a subconscious whiff of an alpha-male's urine
could turn a woman's head
is still a matter of speculation.

Mak, G. K. *et al*. *Nature Neuroscience* - **10**, 1003 - 1011 (2007)

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 intra[ ] 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 [ ] exposed to AVP and shown neutral faces, *{assuming no cosmetic botox injections!}* whereas women exposed to AVP showed a [ ] 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 [ ] in the perceived approachability or friendliness of people with happy expressions**, whereas **women reported an [ ] in the approachability or friendliness of people with neutral expressions.**

{later – vasopressin and mate fidelity in mice}