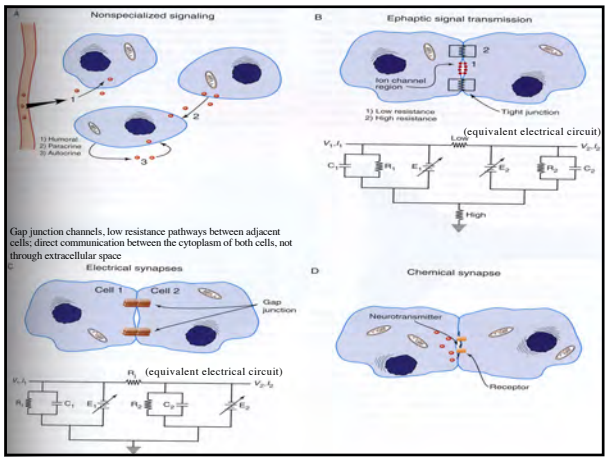
Advanced Neurobiology

Course No: BSE1012
Credits: 3.00

Tuesday: 9:30am – 12:30pm

3. Neurotransmitters

Prof. Dr. Klaus Heese



Criteria for a Neurotransmitter

Neurotransmitter are endogenous substances that are released from neurons, act o receptor sites that are typically present on membranes of postsynaptic cells, an produce a functional change in the properties of the target cell:

1) A neurotransmitter must be synthesized by and released from neurons. This mean that the presynaptic neuron should contain a transmitter and the appropriat enzymes need to synthesize the neurotransmitter. Synthesis in the axon terminal not an absolute requirement. For example, peptide transmitters are synthesized i the cell body and transported to distant sites, where they are released.
2) The substance should be released from nerve terminals in a chemically pharmacologically identifiable form. Thus, one should be able to isolate th transmitter and characterize its structure using biochemical or other techniques.
3) A neurotransmitter should reproduce at the postsynaptic cell the specific even (such as changes in membrane properties) that are seen after stimulation of th presynaptic neuron.
4) The effect of a putative neurotransmitter should be blocked by competitiv antagonists of the transmitter in a dose-dependent manner. In addition, treatmen that inhibit synthesis of the transmitter candidate should block the effects presynaptic stimulation.
5) There should be active mechanisms to terminate the action of the putativ neurotransmitter (enzymatic or reuptake by neuron / glia).

The Process of Chemical Neurotransmission can be Divided into Five Step

1) Synthesis of the neurotransmitter in the presynaptic neuron
2) Storage of the neurotransmitter and/or its precursor in the presynaptic nerv terminal
3) Release of the neurotransmitter into the synaptic cleft
4) Binding and recognition of the neurotransmitter by target receptors
5) Termination of the action of the released transmitter

Classical Neurotransmitters

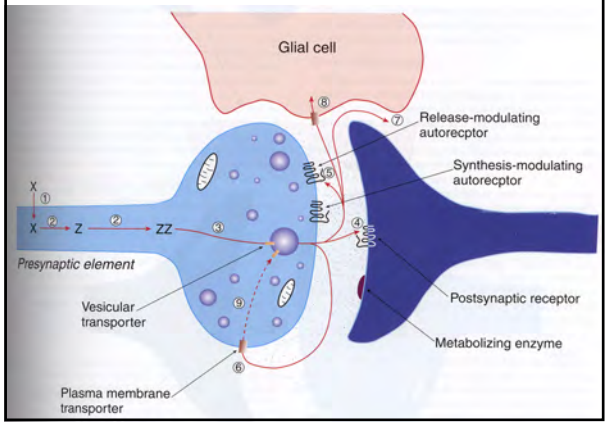
1) Acetylcholine, biogenic amines, amino acids
2) Others

Storage vesicles for classical transmitters are smaller,

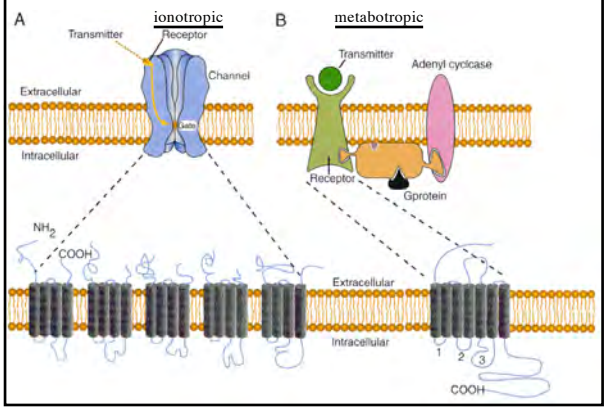
classical transmitters are subject to active reuptake by presynaptic cell an thus can be viewed as homoeostatically conserved; in contrast, there is n energy-dependent, high-affinity reuptake process for non-classic transmitters.

Most classical transmitters are synthesized in the nerve terminal b enzymatic action;
peptides, however, are synthesized in the soma from a precursor protei and are then transported to the nerve terminal.

Life cycle of a Classical Neurotransmitter

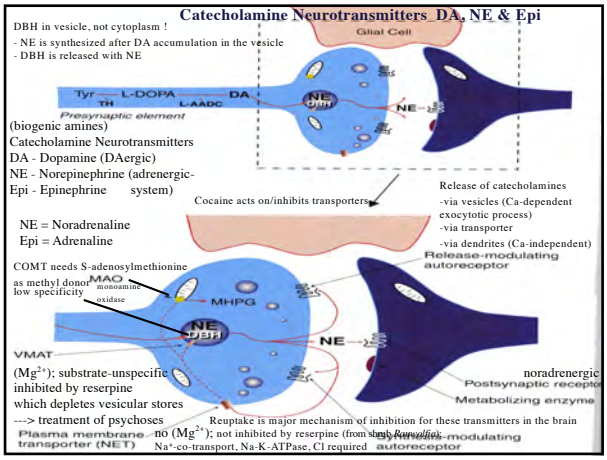


Neurotransmitter Receptors



Catecholamine Neurotransmitters DA, NE & Epi

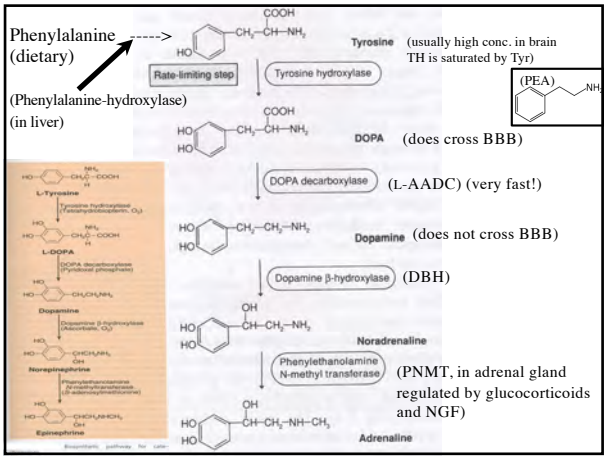
Catecholamine Neurotransmitters DA, NE & Epi



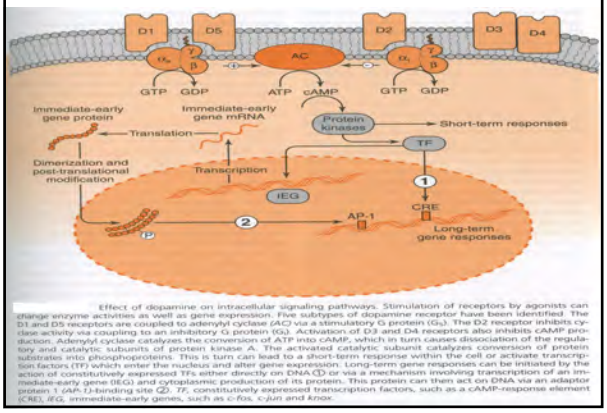
Dopamine

&

NA-system

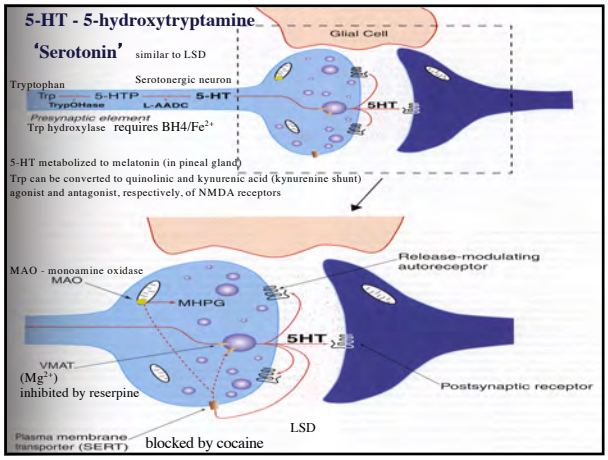


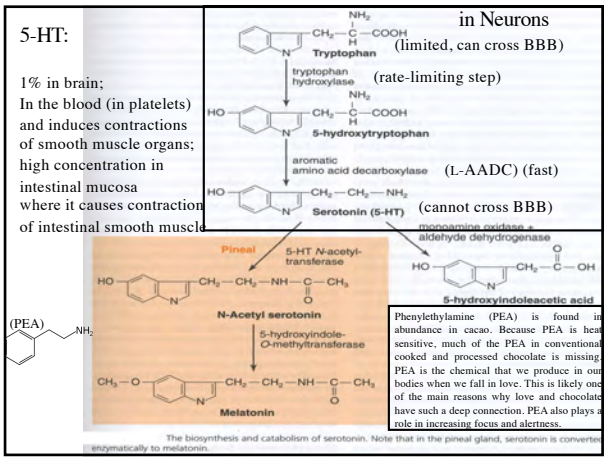
Dopamine Receptors



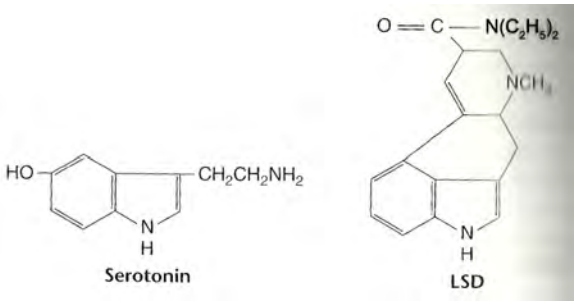
Effect of dopamine on intracellular signaling pathways. Stimulation of receptors by agonists can change enzyme activities as well as gene expression. Five subtypes of dopamine receptor have been identified. The D1 and D5 receptors are coupled to adenylyl cyclase (AC) via a stimulatory G protein (G_s). The D2 receptor inhibits cyclase activity via coupling to an inhibitory G protein (G_i). Activation of D3 and D4 receptors also inhibits cAMP production. Adenylyl cyclase catalyzes the conversion of ATP into cAMP, which in turn causes dissociation of the regulatory and catalytic subunits of protein kinase A. The activated catalytic subunit catalyzes conversion of protein substrates into phosphoproteins. This is turn can lead to a short-term response within the cell or activate transcription factors (TF) which enter the nucleus and alter gene expression. Long-term gene responses can be initiated by the action of constitutively expressed TFs either directly on DNA (1) or via a mechanism involving transcription of an immediate-early gene (IEG) and cytoplasmic production of its protein. This protein can then act on DNA via an adaptor protein 1 (AP-1)-binding site (2). *TF*, constitutively expressed transcription factors, such as a cAMP-response element (CRE); *IEG*, immediate-early genes, such as *c-fos*, *c-jun* and *knox*.

5-HT-system

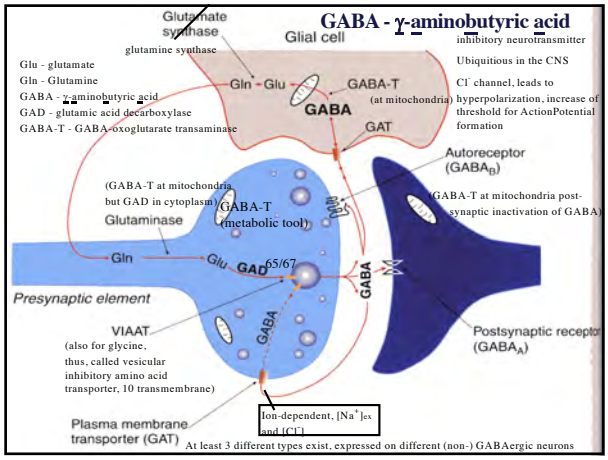




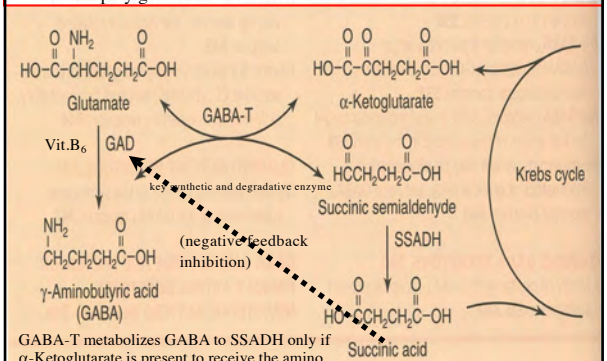
LSD, a hallucinogetic drug



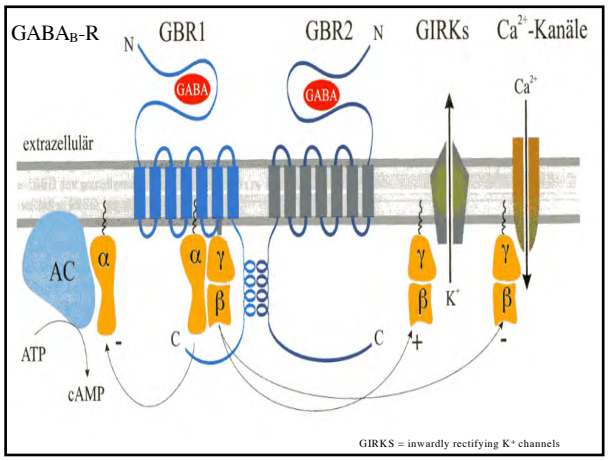
GABA-system



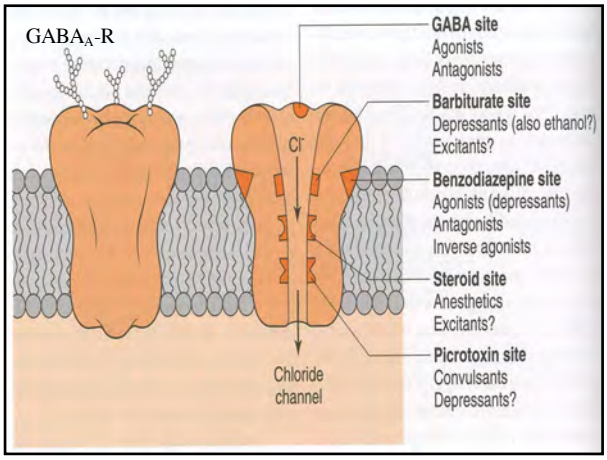
Major difference between catecholamines and amino acid neurotransmitters
the latter are derived from glucose metabolism and
are taken up by glia and neurons



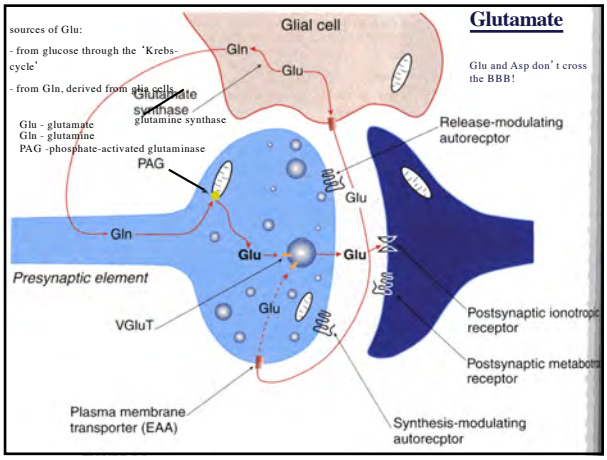
GABA-T metabolizes GABA to SSADH only if
α-Ketoglutarate is present to receive the amino
group from GABA (to generate then Glu)



GIRKS = inwardly rectifying K+ channels



Glutamate-system

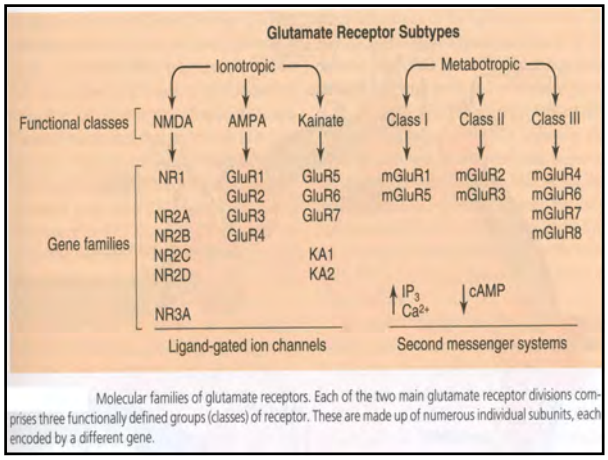


sources of Glu:

- from glucose through the 'Krebs-cycle'
- from Gln, derived from glia cells

Glu - glutamate
Gln - glutamine
PAG -phosphate-activated glutaminase

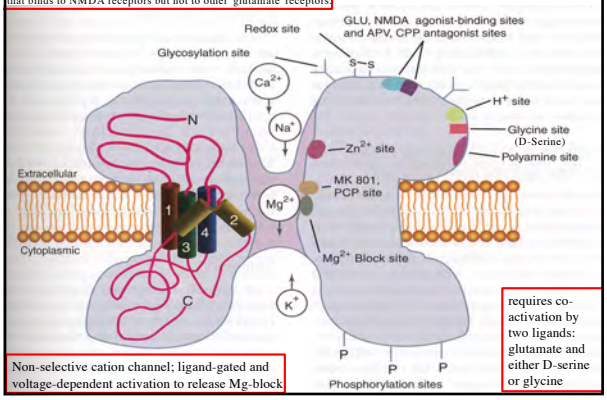
Glu and Asp don't cross the BBB!



Molecular families of glutamate receptors. Each of the two main glutamate receptor divisions comprises three functionally defined groups (classes) of receptor. These are made up of numerous individual subunits, each encoded by a different gene.

NMDA-receptor, binds NMDA, ionotropic

NMDA (N-methyl-D-aspartate) is the name of a selective agonist that binds to NMDA receptors but not to other 'glutamate' receptors.

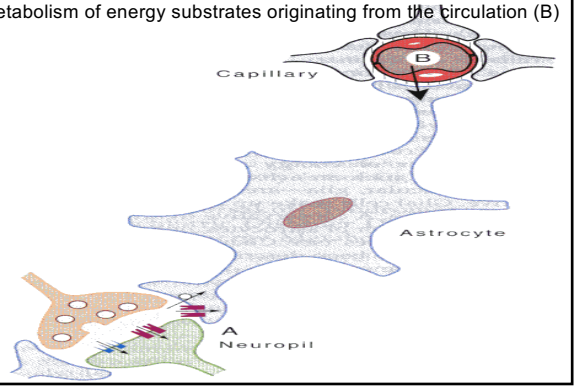


Non-selective cation channel; ligand-gated and voltage-dependent activation to release Mg-block

requires co-activation by two ligands: glutamate and either D-serine or glycine

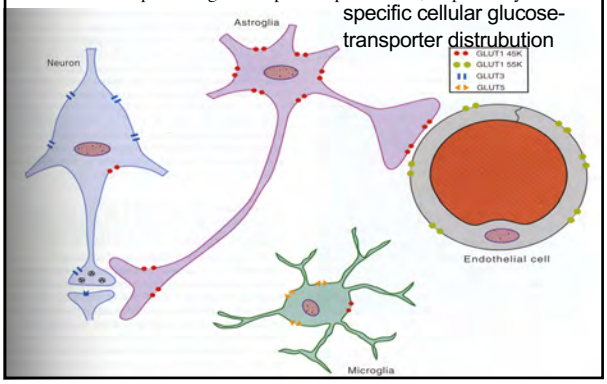
Astrocytes as mediators between capillaries and neuropil

Astrocytes sense synaptic activity (A) and couple it with uptake and metabolism of energy substrates originating from the circulation (B)

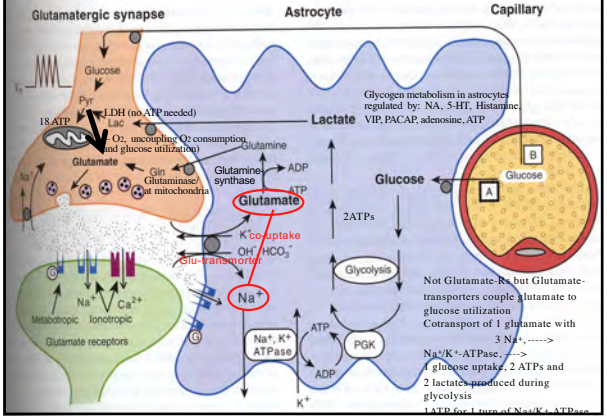


in brain: ~ 0.5-2.0 mM glucose in extracellular space; basal rate of glucos utilization is higher in astrocytes than in neurons, with values of about 20 and 6 nmol per milligram of protein per minute, respectively.

specific cellular glucose-transporter distrubution

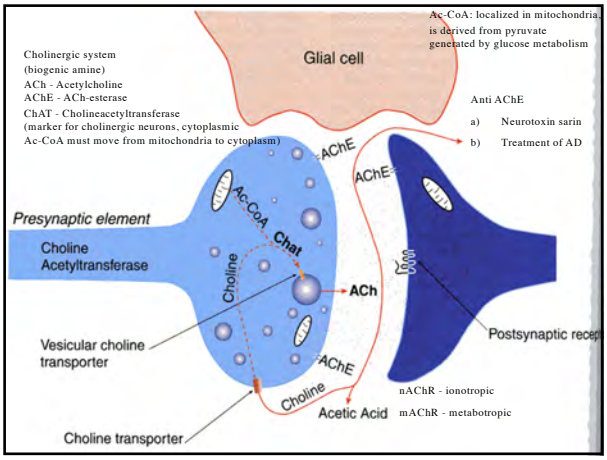


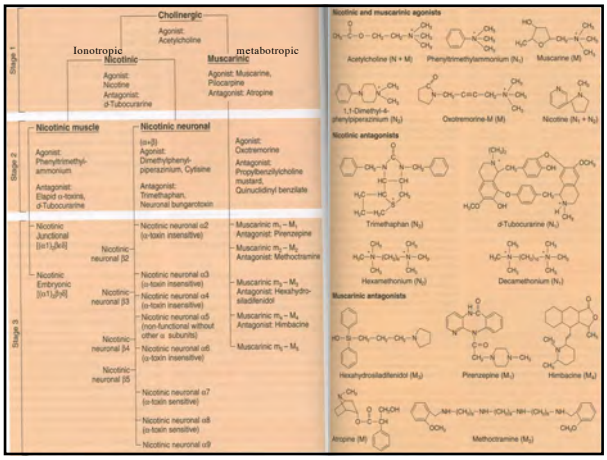
Coupling of Glutamate Action and Glucose Utilization

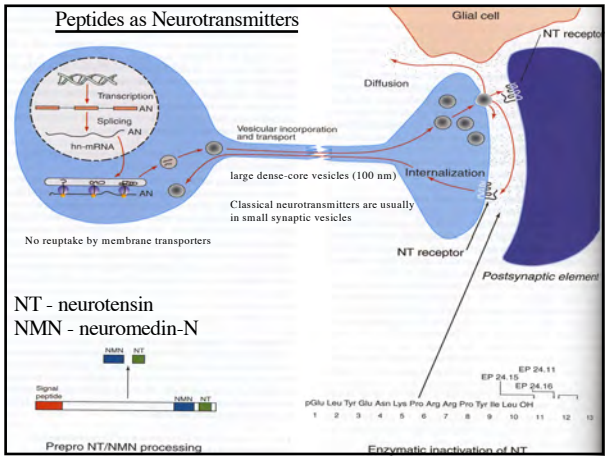


Acetylcholine (ACh)

Important Neurotransmitter in CNS and of e.g.: motorneurons, preganglionic sympathetic neurons, and neurons innervating sweat glands







Major differences between 'classical' (Glu, GABA and ACh)- and peptide (for instance neurotensin (NT)) neurotransmitters:

In most cases, genes encoding peptide transmitters give rise to prohormone which is incorporated into secretory granules afte transcription, it is then acted on by peptidases to form the peptid transmitter, thus, peptide transmitters differ from classical transmitter by being synthesized in the soma rather than axon terminal. The activ transmitter thus must be transported in vesicles to the nerve terminal.
Termination of peptide transmitter action differs from that of classica transmitters, being achieved mainly by enzymatic means and diffusion Peptides: lack of a specific high-affinity active reuptake process an there is much less specificity in the enzymatic inactivation of peptid transmitters. [For example, a metalloendopeptidase that inactivate enkephalins, small pentapeptide opioid-like transmitters, is frequentl called enkephalinase but is also critically involved in he inactivation c several other neuropeptides.]

Major differences between 'classical' (Glu, GABA and ACh)- and peptide (for instance neurotensin (NT)) neurotransmitters:

Termination (inactivation) of classical transmitters (small molecule that are derived from either amino acids (Glu, GABA) or intermediar metabolism; usually synthesized by the sequential action of ke enzymes, in the general vicinity of where they are to be released) take place by a specific high-affinity active reuptake mechanism (Glu GABA) to remove the transmitter from the extracellular space, and b enzymatic means (ACh), or both mechanism.
One final difference in the inactivation of peptide and classica transmitter is the product. Once classical transmitters are catabolizec the resultant metabolites are inactive at the transmitter receptor.
However, certain peptide fragments derived from the enzymati 'inactivation' of peptide transmitters are biologically active. A example is angiotensinI ---> II (more active than I).
It is therefore sometimes difficult to distinguish between syntheti processing and inactivation.

Major differences between 'classical' (Glu, GABA and ACh)- and peptide (for instance neurotensin (NT)) neurotransmitters:

The peptide that is stored in vesicles and then released is therefor considered the transmitter, although the actions of certain peptidase may lead to other biologically active fragments later on/upon release.

five major steps involved in neurotransmission at CNS synapses
(1) Invasion of action potential into presynaptic terminal.
(2) Ca2+ influx into the nerve terminal through activation (opening) of voltage-dependent (gated) Ca2+ channels (VGCC).
(3) Docking (fusion) of synaptic vesicles with the terminal membrane (Exocytosis) and discharge of vesicular contents (neurotransmitters)
(4) Diffusion of neurotransmitters into the synaptic cleft and activation of (binding to) postsynaptic receptors.
(5) Diffusion and/or uptake (enzymatic inactivation) of neurotransmitters to terminate their actions.

the major ions that contribute to shape the action potential and the basic properties of their channels.
(1) Na+ and K+ ions are responsible for shaping the action potential. The Na+ current underlies the rising phase of action potential, whereas the K+ current is responsible for the decaying phase (re-polarization) of action potential.
(2) The properties of Na+ channels:
a. The Na+ channel displays threshold where activation starts to occur.
b. The Na+ channel shows the regenerative activity (self-reinforcing) that underlies an overshoot of action potentials. Because of this property, the action potential can conduct along the axon and muscle fibers without attenuating its amplitude.
c. The Na+ channel exhibits an inactivation process, which determines the refractory period of action potential regeneration.
d. Tetrodotoxin (TTX) and cocaine selectively block the Na+ channel activation.
(3) The properties of K+ channels:
a. The activation of K+ channels proceeds depending on the membrane depolarization.
b. The K+ channels does not exhibit an inactivation with maintained membrane depolarization, which is in a sharp contrast to the Na+ channel activation.

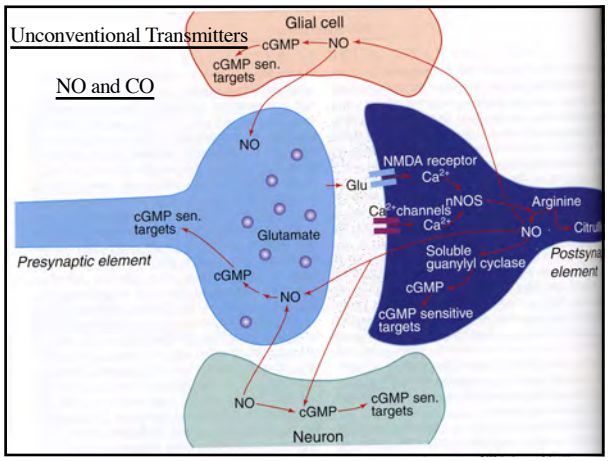
the three major types of synaptic connections and two other forms of synaptic interactions
(1) Axo-somatic synapses.
(2) Axo-dendritic synapses.
(3) Axo-axonic synapses.

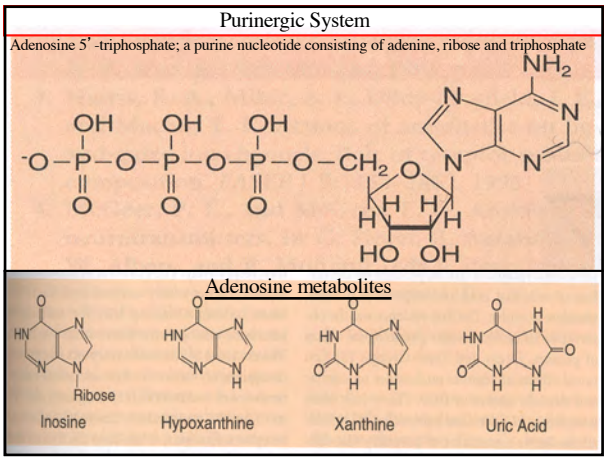
(4) Dendro-dendritic interactions (Dendritic release of neurotransmitters).
(5) Retrograde interactions (signaling/transmission).

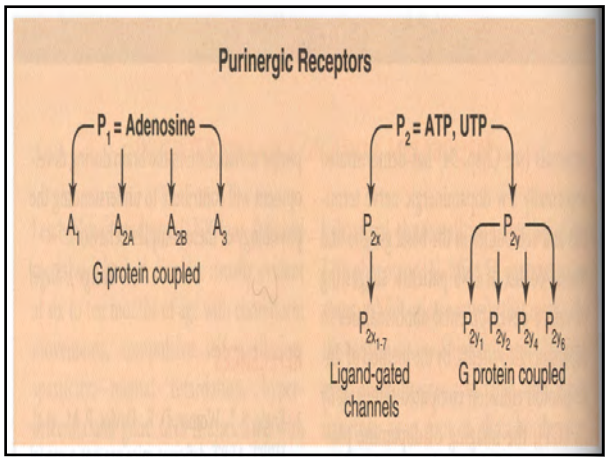
(6) Heterosynaptic interactions (Spillover transmission).
(7) Receptor cross-talks.

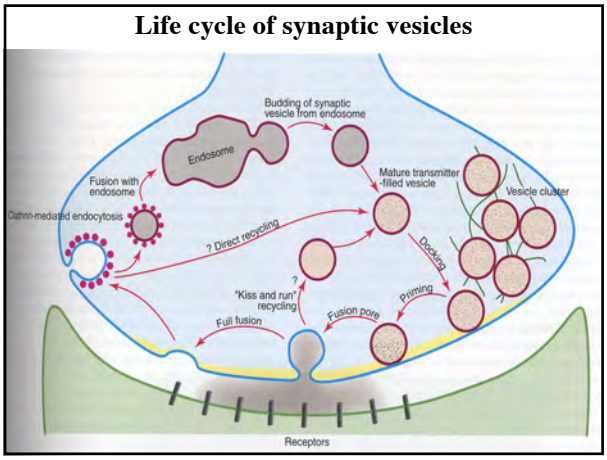
the three possible mechanisms that underlie modulation (i.e., gain changes) of neurotransmission at CNS synapses
(1) Presynaptic mechanisms: either increase or decrease of neurotransmitter release. Monoamines, such as serotonin (5-HT), nor-adrenaline and dopamine, modulate the release of neurotransmitters.
(2) Postsynaptic mechanisms: (a) receptor efficacy can be changed by protein phosphorylation, and (b) the number of receptors at the synaptic site can be changed by enhanced or decreased trafficking (exocytosis or endocytosis) of receptor molecules through intracellular Ca^{2+}-dependent signaling pathways, such as CaMKII-mediated protein phosphorylation.

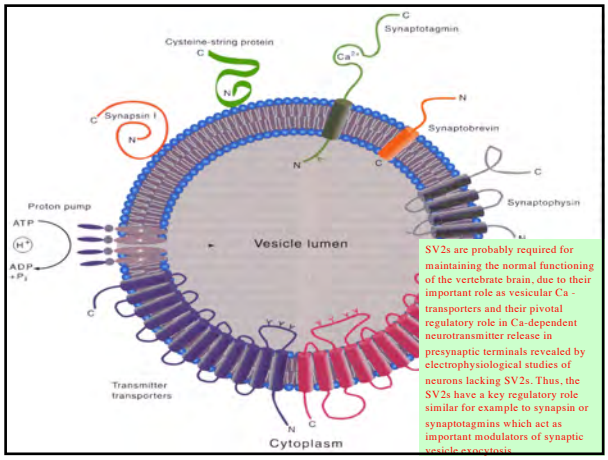
the differences between ionotropic and metabotropic receptors.
(1) The ionotropic receptor consists of a binding site for the neurotransmitter and an ionophore (ion pore) for allowing ion permeability (influx or efflux) within a single receptor molecule. Therefore, the ionotropic receptor is suitable for direct transmission which allows a fast point-to-point signaling at morphologically defined synapses.
(2) The metabotropic receptor has a binding site for the neurotransmitter and activates a GTP-binding protein, thereby coupling to modulation of the membrane ion channel activity (direct channel modulation) and/or intracellular signaling pathways (short-term action and long-term action via changes in transcription). Therefore, the metabotropic receptor is suitable for slow indirect transmission which allows integration (modulation) of

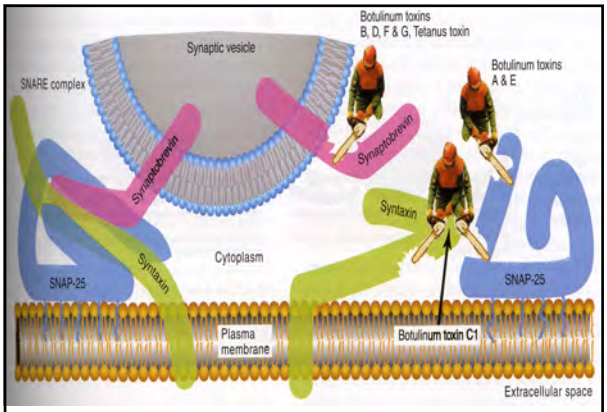




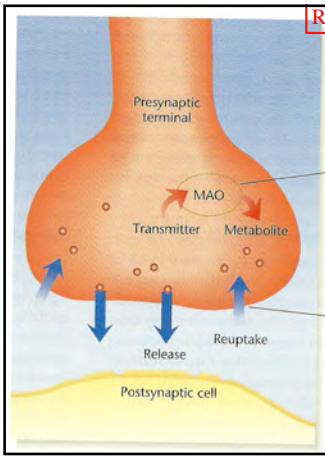








Tetanus toxins and the botulinum toxins, proteases that cleave specific SNARE proteins as shown, can block transmitter release.



Routes of action of antidepressants

Tricyclics block the uptake of dopamine, norepinephrine, or serotonin. SSRIs specifically the reuptake of serotonin (5-HT).

MAOIs block the enzyme MAO, prevent it from breaking transmitters into inactive metabolites

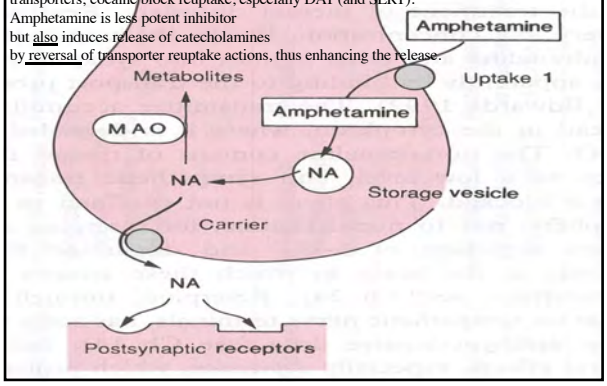
Tricyclics: e.g. imipramine, trade name Tofranil

Tricyclic drugs and SSRIs block reuptake

MAOIs block the enzyme MAO, which converts dopamine, norepinephrine, or serotonin into inactive chemicals. Atypical antidepressant have varying effects.

Amphetamine and cocaine block catecholamine and 5-HT transporters; cocaine block reuptake, especially DAT (and SERT). Amphetamine is less potent inhibitor but also induces release of catecholamines by reversal of transporter reuptake actions, thus enhancing the release.

Amphetamine action



Drugs	Main Effects on Behavior	Main Effects on Synapses
Amphetamine	Excitement, alertness, elevated mood, decreased fatigue	Increases release of dopamine and several other neurotransmitters
Cocaine	Excitement, alertness, elevated mood, decreased fatigue	Blocks reuptake of dopamine and several other neurotransmitters
Methylphenidate	Increased concentration	Blocks reuptake of dopamine and others, but more gradually than cocaine does
Nicotine	Mostly stimulant effects	Stimulates nicotinic-type acetylcholine receptor, which (among other effects) increases dopamine release in nucleus accumbens
Opiates	Relaxation, withdrawal, decreased pain	Stimulates endorphin receptors
Cannabinoids (marijuana)	Intensified sensory experiences, distorted sense of time, decreased pain and nausea	Excites negative-feedback receptors on presynaptic cells; thereby puts the brakes on release of either glutamate or GABA
LSD	Distorted sensations	Stimulates serotonin type 2 receptors (5-HT_2)
Alcohol	Relaxation, decreased attention	Facilitates $GABA_A$ receptor

Taking home message:

- Classical Neurotransmitters vs peptides
- Unconventional Transmitters
- Major difference between catecholamines and amino acid neurotransmitters
- Criteria for a neurotransmitter?
- Process (steps) of chemical neurotransmission?
- neuronal activity coupled to energy supply and controlled by by astrocytes

Advanced Neurobiology

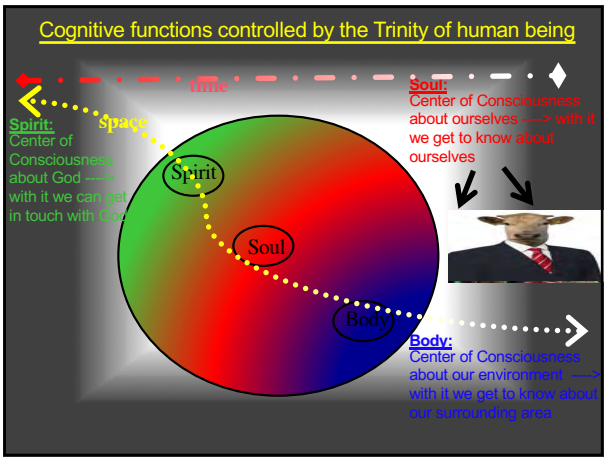
Course No: BSE1012
Credits: 3.00

Tuesday: 9:30am – 12:30pm

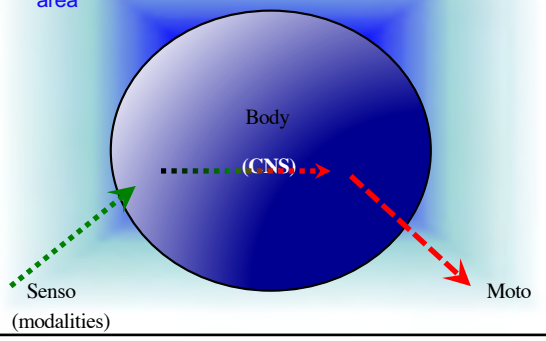
5. Cognitive Neuroscience: Memory & Learning processes

Prof. Dr. Klaus Heese

Cognitive functions controlled by the Trinity of human being



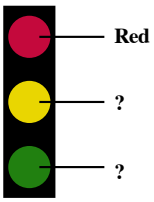
Body:
Center of Consciousness about our environment ----> with it we get to know about our surrounding area



Cognitive Neuroscience ----> Neuropsychology ----> Memory & Learning

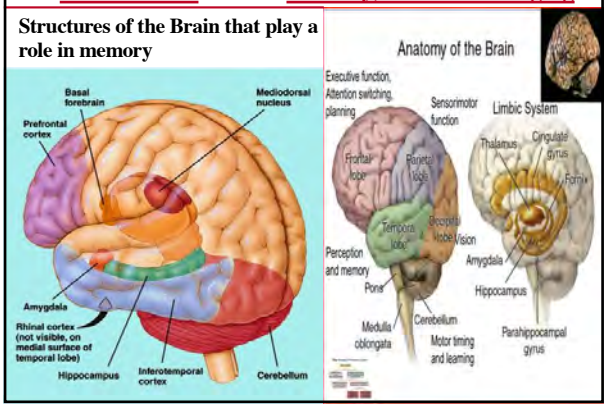
Genes, environment & education ----> behavior

environment and education: mechanisms: learning and memory



Introduction: Memory, Dementia & Aging

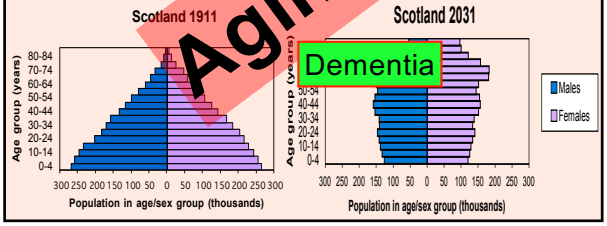
Structures of the Brain that play a role in memory

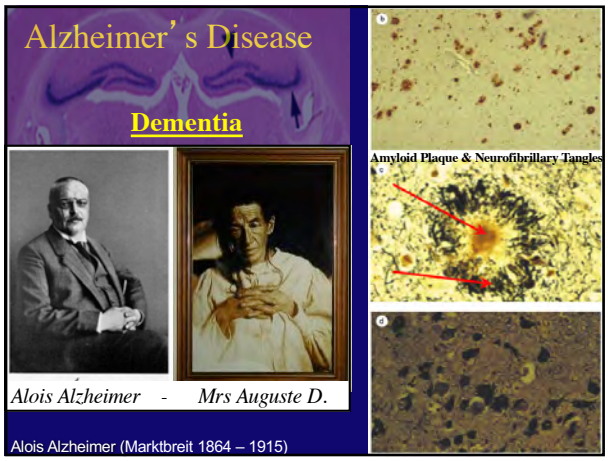


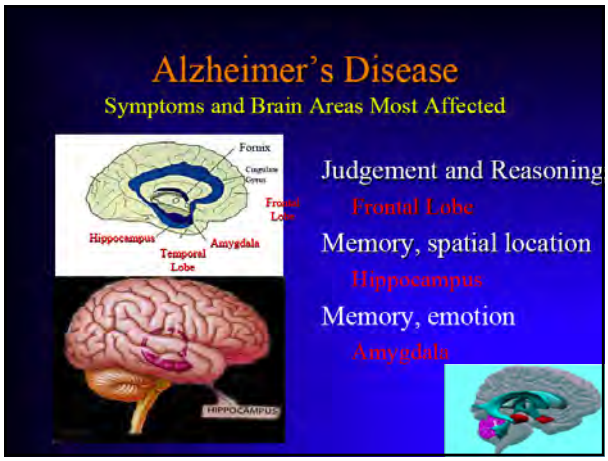
The Queen's Birthday Telegrams to people reaching the age of 100

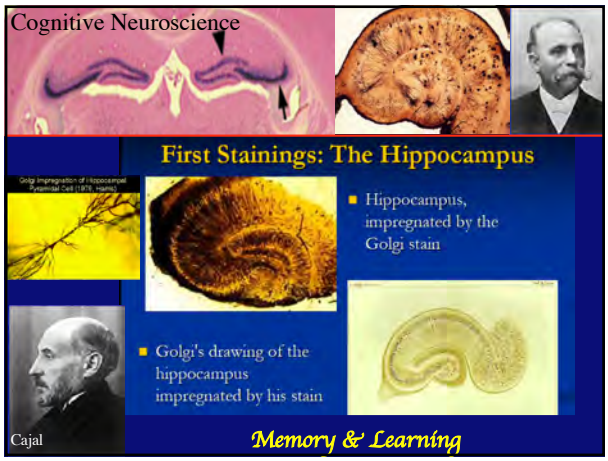
However, sadly……memory and other cognitive functions do begin to fail in certain neurological diseases that tend to occur in older age.

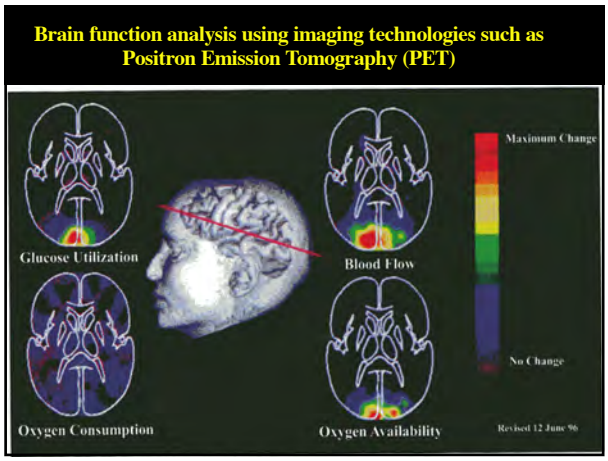
1962 200 telegrams
2002 3800 telegrams

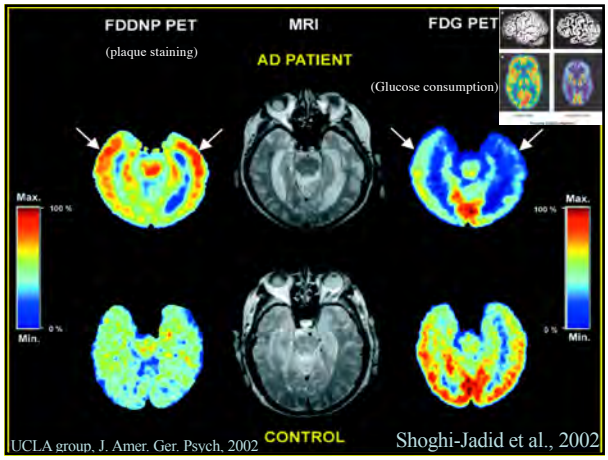












Different categories/types of Memory

1. When did you last ride a bicycle?
2. What is a bicycle?
3. How do you ride a bicycle? Knowing How vs Knowing That

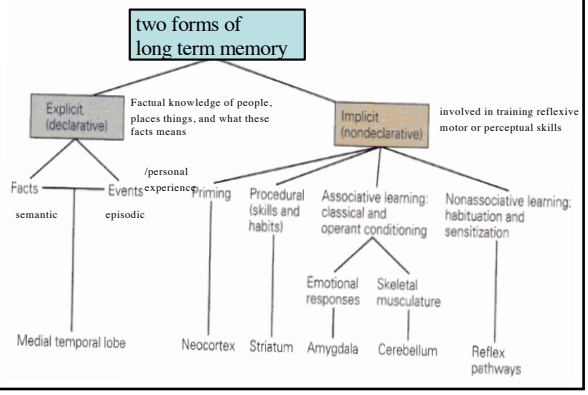
These questions reveal the different "types" of long term memories we are capable of accessing.

1. Requires conscious recollection of unique temporally distinct past experience
2. Requires conscious recollection of knowledge, but no unique "experience"
3. Unanswerable - unconscious learning

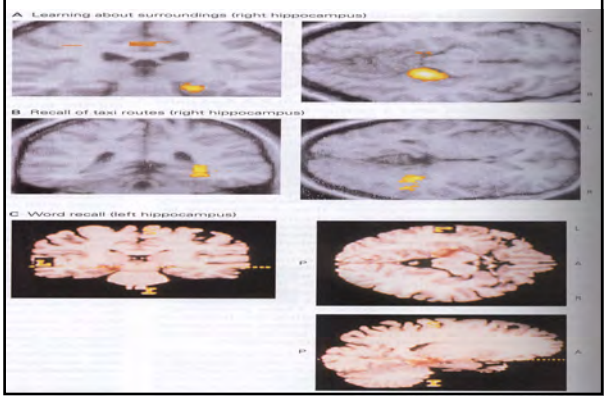
Researchers have developed a number of different ways to conceptualise these differences.

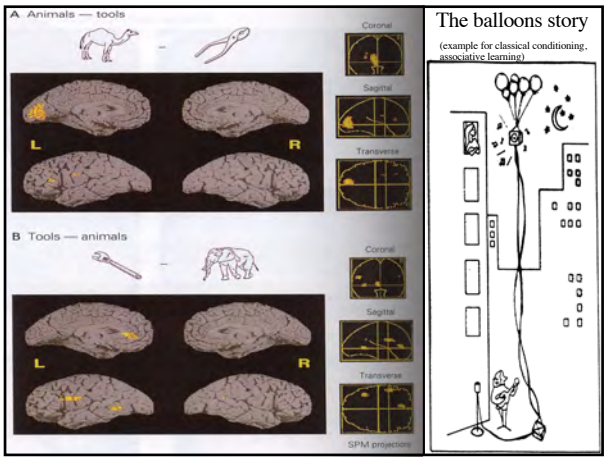
The critical question is whether these "types" of memories reflect the operation of different memory systems, or whether they reflect different ways of accessing a unitary LTS (long term store)

A Taxonomy of Long-term Memory



Brain Areas involved in Memory & Learning processes

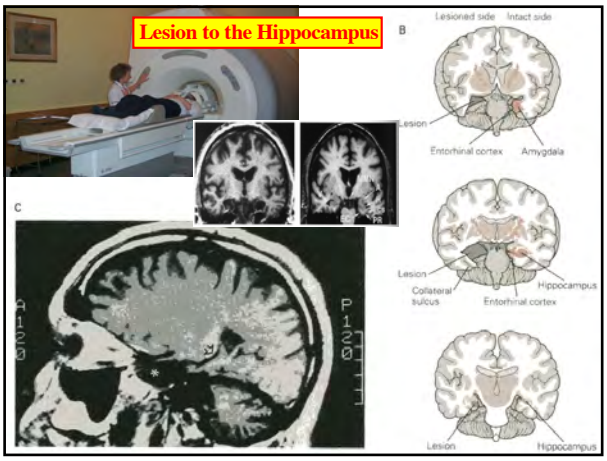




The balloons story

(example for classical conditioning, associative learning)

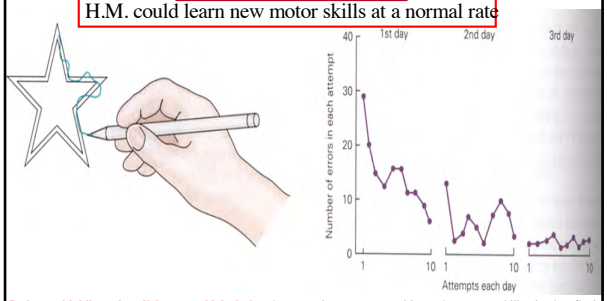
Lesion to the Hippocampus



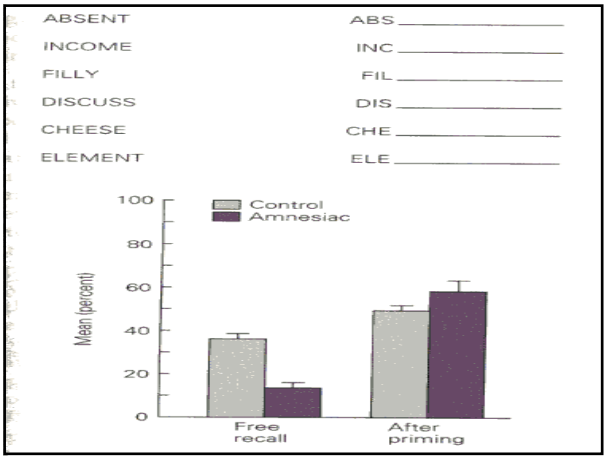
Lesion to the Hippocampus

Explicit vs Implicit Memory

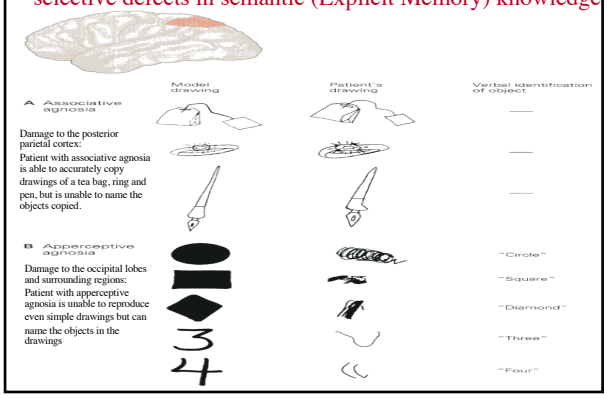
H.M. could learn new motor skills at a normal rate



Patients with bilateral medial temporal lobe lesions have certain memory capacities such as: motor skills, simple reflexiv learning, including habituation, sensitization, classical conditioning, and operant conditioning; and they are able to improve their performance on certain perceptual tasks. The memory capability that is spared in patients with bilateral lesions of the temporal lobe typically involves learned tasks that have two things in common. A) the tasks tend to be reflexive rather than reflective in nature and involve habits and motor or perceptual skills. B) they do not require conscious awareness or comple cognitive processes, such as comparison and evaluation. The patient needs only to respond to a stimulus or cue, and need no to remember anything. (puzzle)



Selective lesions in the posterior parietal cortex produce selective defects in semantic (Explicit Memory) knowledge



Explicit Memory

declarative memory that comprises factual knowledge o people, places and things, and what these facts mean. This i recalled by a deliberate, conscious effort. Explicit memory i highly flexible and involves the association of multiple bit an pieces of information. In contrast, *implicit memory* is mor rigid and tightly connected to the original stimulus condition under which the learning occurred.

Explicit memory is stored in Association Cortices

can be further classified as

episodic (a memory for events and personal experience) or

semantic (a memory for facts)

Semantic (factual) knowledge is stored in a distributed fashion in the Neocortex. Semantic memory is that type of long-term memory that embraces knowledge of objects, facts, and concepts as well as words and their meaning. It includes the naming of objects, the definitions of spoken words, and verbal fluency.

We build up semantic knowledge through association over time. Different aspects (representations) of an object are stored separately. When we recall the object it comes to mind in one smooth and continuous operation. Semantic knowledge is not stored in a single region. Damage to a specific cortical area can lead to loss of specific information and therefore a fragmentation of knowledge.

Hippocampus is a temporary way station for long-term memory

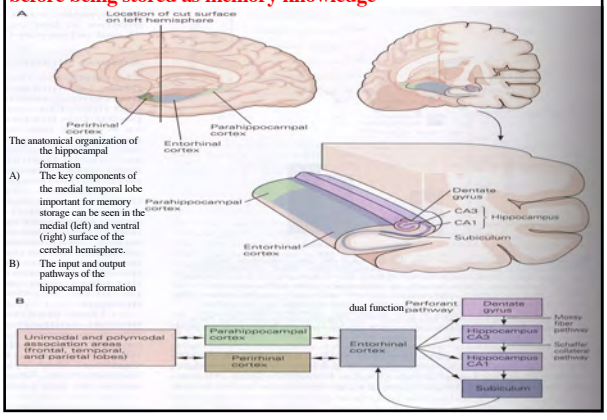
Hippocampus slowly transfers information to the neocortical storage system

Patients with lesions in association areas have difficulty in recognizing faces, objects, and places in their familiar world.

Conceptualizing Memory Processes

Explicit knowledge **involves at least** ***four distinct processes.***
Semantic and episodic knowledge**:**
- there is not a single, all purpose memory store
- any item of knowledge has multiple representations in the brain, each o which corresponds to a different meaning and can be accessed independentl (by visual, verbal or other sensory clues).
- both, semantic and episodic knowledge are the result of at least four relate but distinct types of processing: ***encoding, consolidation, storage, an retrieval.***
Encoding**: processes by which newly learned information is attended to an processed when first encountered.**
Consolidation**: involves already gene expression and protein synthesis (an structural changes).**
Storage*: organize and retain information,* **mechanism by which memory i retained over time - long-term storage seems to have unlimited capacity. I contrast, short-term working memory is very limited.**
Retrieval**: Recall and use of stored information. Retrieval involves bringin different kind of information together that are stored separately in differen storage sites. It is a constructive process and therefore subject to distortion.**

Information must be passed through the hippocampal pathways before being stored as memory knowledge



Implicit Memory

driving a car

playing soccer

learning a language

→ learning motor skills

Memory storage does indeed involve many different regions of the brain, but these regions are not equally important.

Implicit memory: non-declarative memory, memory that is recalled unconsciously, typically involved in training reflexive motor or perceptual skills.

Implicit memory is stored in *perceptual, motor, and emotional circuits*

Does not depend directly on conscious processes nor does recal require a conscious search of memory. This type of memory builds u slowly, through repetition over many trials.
E.g.: perceptual and motor skills and the learning of certain types p procedures and rules.
Different forms of implicit memory are acquired through differen forms of learning and involve different brain regions.

Fear (emotion) ---> amygdala,
Operant conditioning ---> striatum, cerebellum
Classical conditioning, sensitization, habituation ---> sensory and motor systems

Implicit memory can be Non-associative or Associative.

Implicit Memory: Associative or Non-Associative

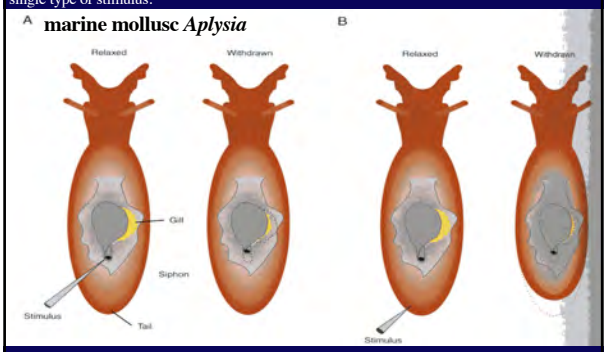
Non-Associative Learning

Habituation is defined as a reduction in the response to a stimulus that is delivered repeatedly.

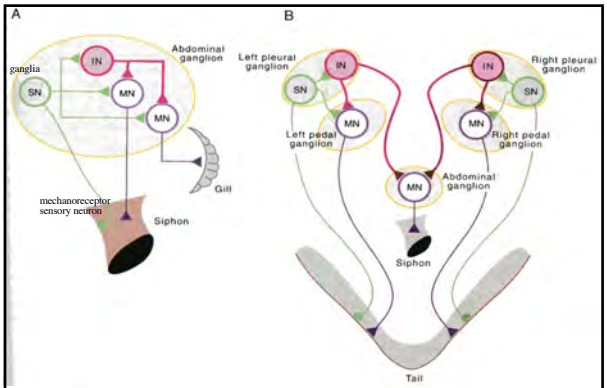
Dishabituation refers to the restoration or recovery of a habituated response due to the presentation of another, typically strong, stimulus to the subject.

Sensitization is an enhancement or augmentation of a response produced by the presentation of a strong stimulus.

Implicit Memory: Non-associative learning: sensitization and habituation
Non-associative learning results when an animal or person is exposed once or repeatedly to a single type of stimulus.

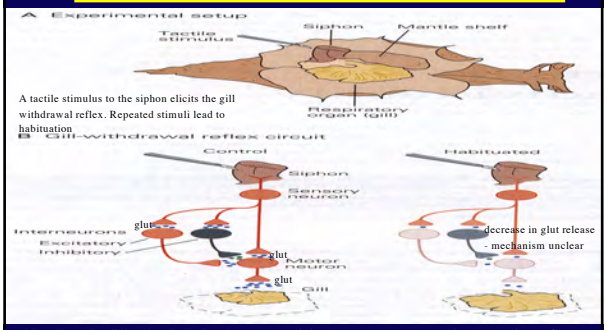


The siphon-gill and tail-siphon withdrawal reflex of *Aplysia* ***(invertebrate)***
(defensive reflexes)

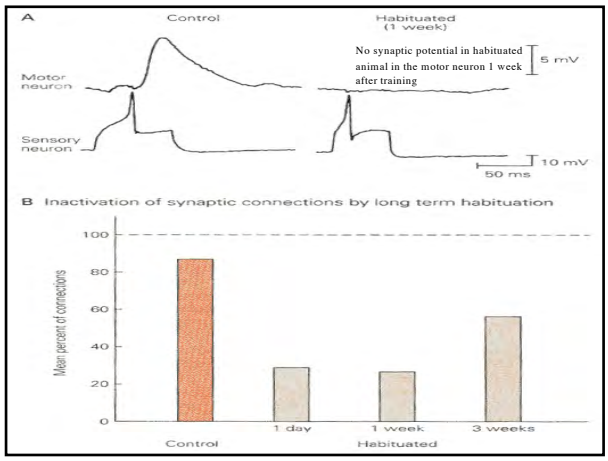


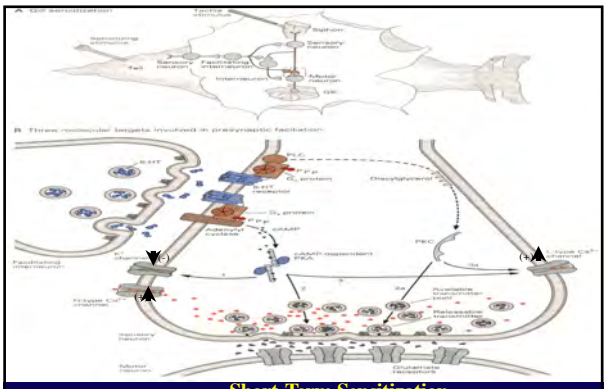
Simplified circuit diagrams of siphon-gill (A) and tail-siphon (B) withdrawal reflexes. SN sensory neuron (mechanoreceptor), IN = interneuron, MN = motor neuron. (No modulatory / facilitating interneuron (5-HT-release and acting on SN-axon) shown here)

Cellular mechanisms of non-associative learning



Habituation (implicit learning) involves an activity-dependent pre-synaptic depression of synapt transmission. Habituation: if the stimulus is neither beneficial nor harmful, the animal learns, after repeate exposure, to ignore it. Postsynaptic (non-) NMDA-receptor sensitivity unchanged - neurotransmitter releas reduced = cellular mechanisms mediating the short term memory for habituation; homosynaptic process; t decrease in synaptic strength is a direct result of activity in the sensory neurons and their central connectio in the reflex pathway.

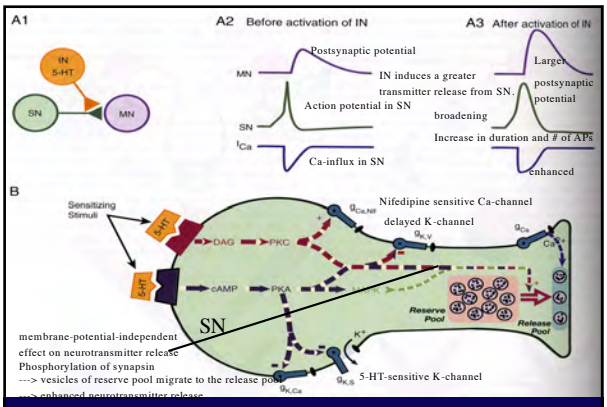




Short-Term Sensitization

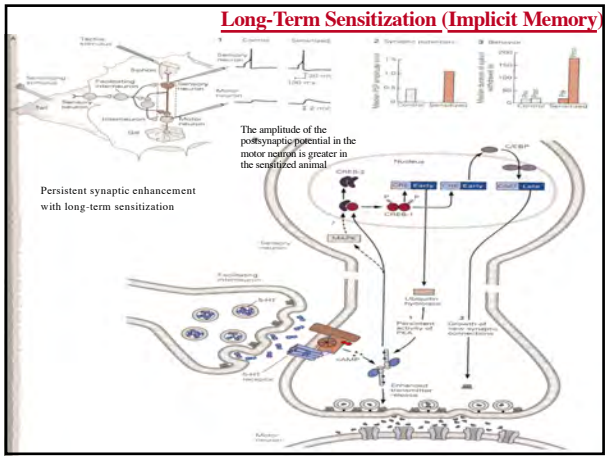
Applying a noxious (or tetanus) stimulus to another part of the body (tail) ---> axoaxonic synapse ---> facilitating interneuron enhances transmitter release from the sensory neuron.

Short-term sensitization **(minutes) is induced when a single brie train of shocks to the body wall results in the release of modulator neuro-transmitters, such as 5-HT, from a separate class o interneurons referred to as facilitatory neurons. These facilitator neurons regulate the properties of the sensory neurons and th strength of their connections with postsynaptic interneurons an motor neurons through a process called heterosynaptic facilitation.**

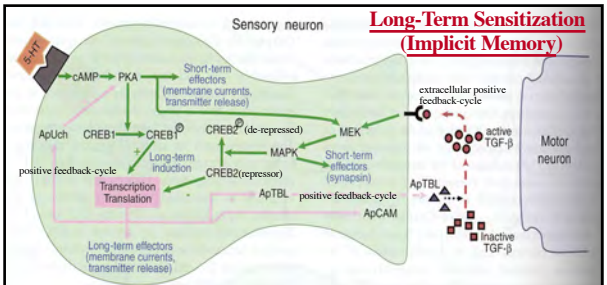


Model of short-term heterosynaptic facilitation of the sensorimotc connection that contributes to short- and long-term sensitization in Aplysia

Long-Term Sensitization (Implicit Memory)



Long-Term Sensitization (Implicit Memory)

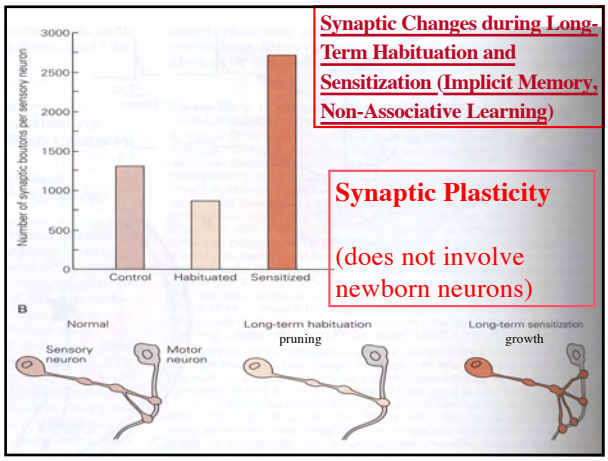


Simplified scheme of mechanisms in sensory neurons that contribute to long-term sensitizatio CREB2 - repressor; synthesis of ApUch leads to degradation of PKA-regulatory subunit --- enhanced PKA activity (catalytic subunit) ---> activation of CREB1 ---> gene transcriptio activation; ApCAM= Aplysia homologue of NCAM (neuronal cell adhesion molecule) is dow regulated ---> regulating growth processes associated with long-term facilitation (neuronal plasticity ApTBL=Aplysia tolloid/BMP-like protein, functions as secreted Zn proteases ---> activation of TGF- ---> mimics effect of 5-HT. Positive feedback loop to consolidate the memory. ApUch=Aplysia ubiquitin hydrolase (involved in intracellular positive feedback-loop). In CNS: enhanced re-uptake of neurotransmitter (glutamate) ---> vesicle-reserve-/release-pool sho higher efficacy.

Long-term sensitization **(at least 24 hrs) requires a more extensiv training period over an hour or more.**

Long- **and** ***short-term sensitization*** **share** common cellular pathway **during their induction, but in the long-term form activation o cAMP/PKA induces gene transcription, new protein synthesis an growth*(pruning(habituation))* of synaptic connections.**

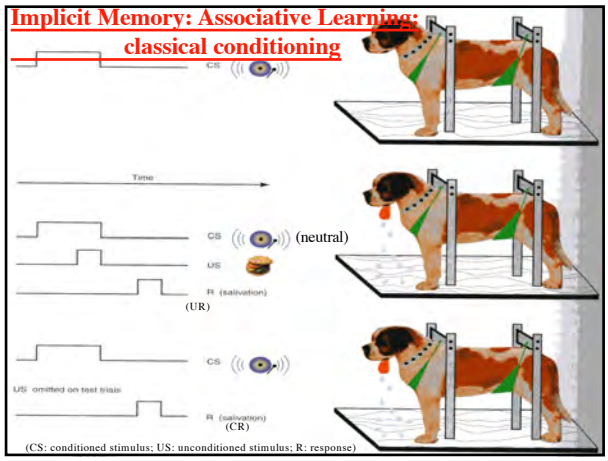
The process by which transient short-term memory is converte into a stable long-term memory is called consolidatio Consolidation of long-term implicit memory for simple forms o learning involves gene transcription, new protein synthesis an growth*(pruning(habituation))* of synaptic connections.



Synaptic Changes during Long-Term Habituation and Sensitization (Implicit Memory, Non-Associative Learning)

Synaptic Plasticity

(does not involve newborn neurons)



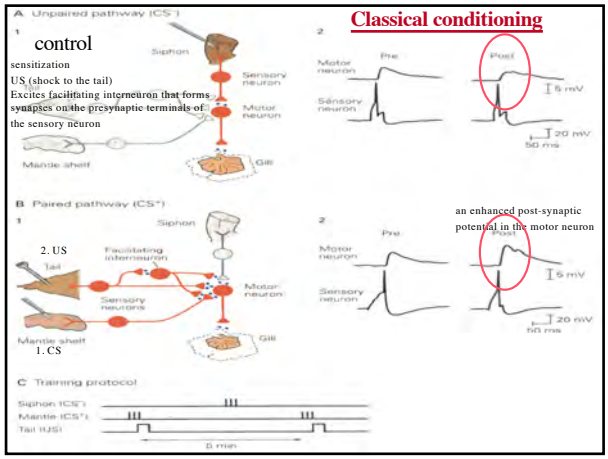
Implicit Memory: Associative Learning: classical conditioning

Implicit Memory: Associative Learning: classical conditioning

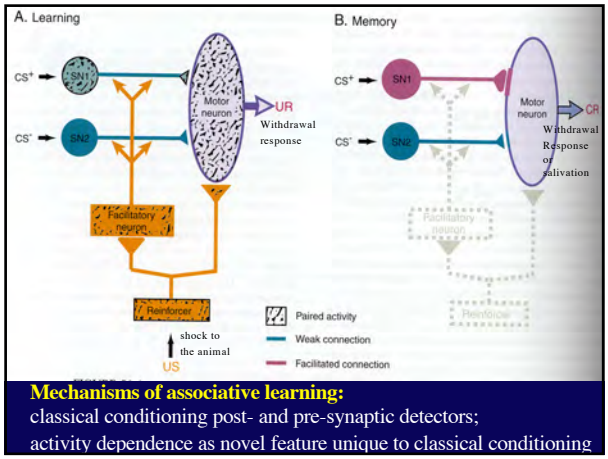
involves the formation of associations among stimuli and/or responses

classical conditioning is induced by neutral stimulus (conditioned stimulus (CS)) and paired with a stimulus that generally elicits a response, termed an unconditioned stimulus (US)) (food <----> salivation (reward classical conditioning)).

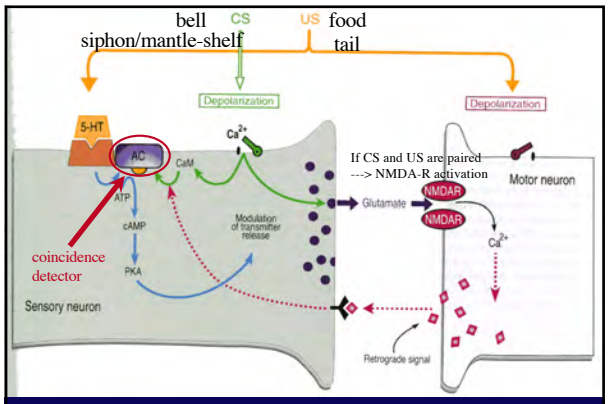
Instrumental (operant) conditioning is a process by which an organism learns to associate consequences with its own behavior. In an operant conditioning paradigm, the delivery of a reinforcing stimulus is contingent upon the expression of a designated behavior. The possibility that this behavior will actually be expressed is then altered.



Classical conditioning



Mechanisms of associative learning:
classical conditioning post- and pre-synaptic detectors;
activity dependence as novel feature unique to classical conditioning



Mechanisms of associative facilitation: post- and pre-synaptic detector for the coincidence of CS and US; plus retrograde signal

Conceptualizing Memory Systems

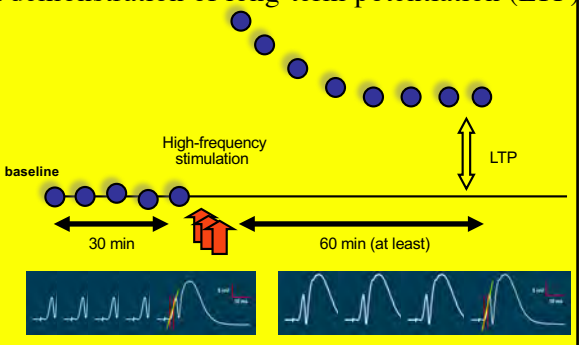
A. Sensory Memory
- Duration: milliseconds
- Capacity: practically unlimited

B. Short-Term Memory (STM)
- Duration: seconds, unless information is rehearsed or otherwise held
- Capacity: limited to 7 ± 2 bits of information

C. Long-Term Memory (LTM)
- Duration: relatively permanent (?)
- Capacity: practically unlimited
- Neuropsychologists are most concerned with LTM

Explicit Memory

A demonstration of long-term potentiation (LTP)

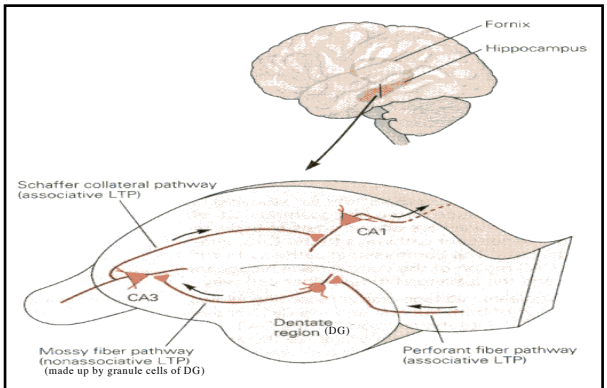


Explicit Memory in Mammals (vertebrate) involves Long-Term Potentiation (LTP) in the Hippocampus

LTP - persistent increase in synaptic strength (as measured by the amplitude of the EPSP) that can be induced rapidly by a brief burst of spike activity in the pre-synaptic afferents. LTP ---> plasticity ---> memory

Long Term Potentiation

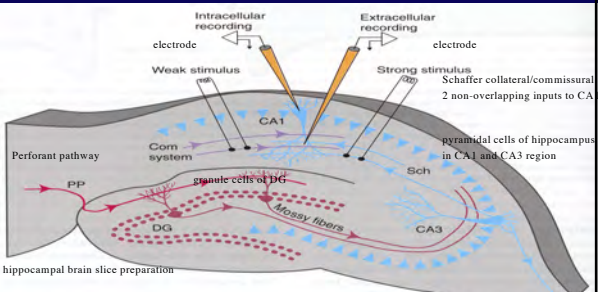
LTP is the term used to describe a remarkably long-lasting (hrs weeks) enhancement of synaptic transmission (persistent increase i synaptic strength as measured by the amplitude of the EPSP in th follower neuron) that occurs at various CNS synapses following short (conditioning) burst (brief train of stimuli, tetanus) o presynaptic stimulation, typically at about 100 Hz for 1 sec..
It increases the excitatory postsynaptic potential in the target neuron This facilitation is called LTP.



Three major afferent pathways in the hippocampus

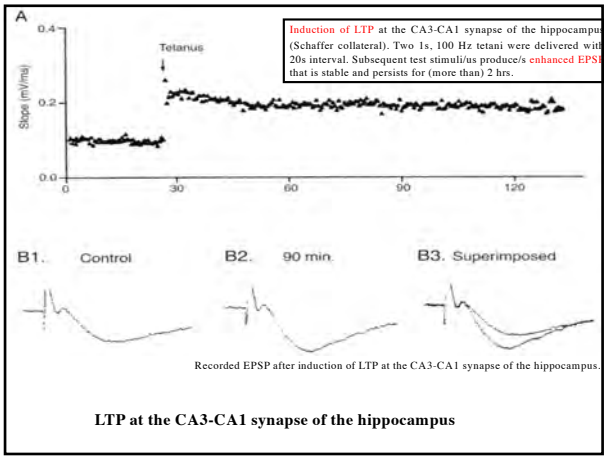
Explicit Memory in Mammals (vertebrate) involves Long-Term Potentiation (LTP) in the Hippocampus

LTP - persistent increase in synaptic strength (as measured by the amplitude of the EPSP) that can be induc rapidly by a brief burst of spike activity in the pre-synaptic afferents. LTP ---> plasticity ---> memory



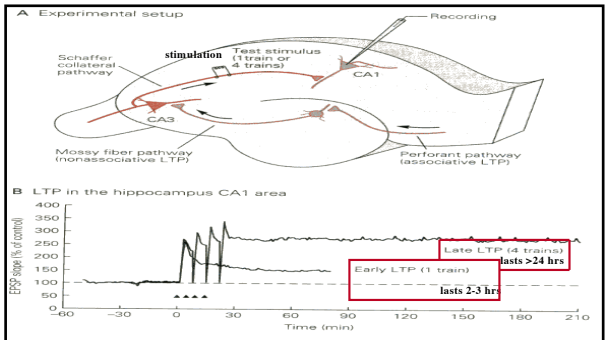
hippocampal brain slice preparation

Brief, high frequency stimulation of the perforant pathway input to the dentate gyrus can produce long-lasting enhancement of the extracellularly recorded field potential. LTP can last for weeks or even months.

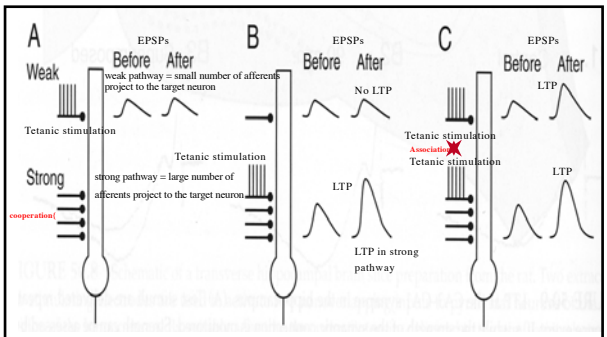


Recorded EPSP after induction of LTP at the CA3-CA1 synapse of the hippocampus.

LTP at the CA3-CA1 synapse of the hippocampus

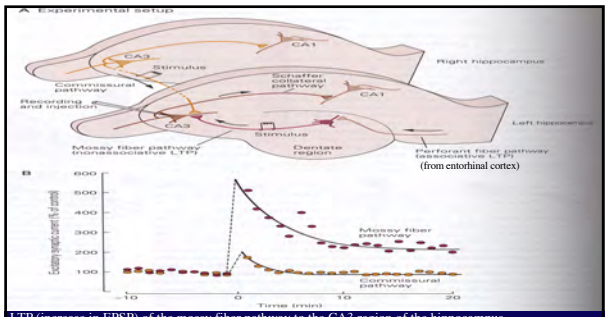


LTP in the Schaffer collateral pathway to the CA1 region of the hippocampus.

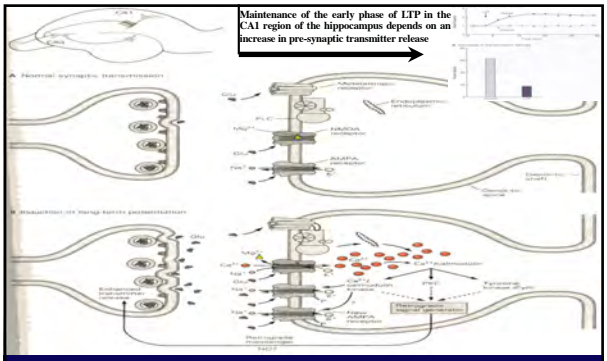


Features of LTP at the CA3-CA1 synapse of the hippocampus. A single pyramidal cell is shown receiving weak and strong synaptic input. Example for *'Associativity'*.

---> Cooperativity, Associativity, Input Specificity ('Cells that fire together, wire together')
--> see Hebb's postulate); specificity: only LTP in the pathways that receive tetanic stimulatio

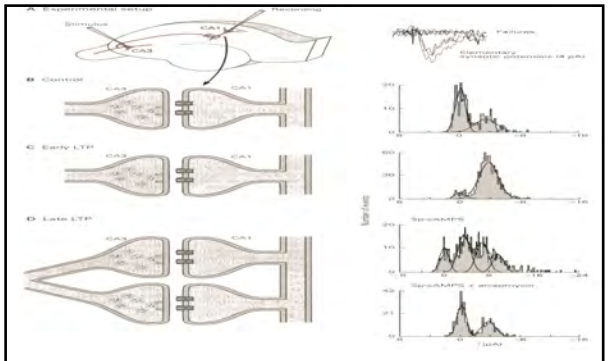


LTP (increase in EPSP) of the mossy fiber pathway to the CA3 region of the hippocampus
Two independent pathways activate the CA3 pyramidal cell: the commissural pathway from the CA3 regio of the contralateral hippocampus and the ipsilateral mossy fiber pathway.
Post-synaptic second messenger block used in CA3 neuron: Ca^{2+} and NMDA-R-blocker; LTP in Moss fiber pathway is not affected and therefore pre-synaptically (thus, *non-associative*) induced and NMDA-R independent. (VGCC-dependent). LTP in Commissural pathway is NMDA-R-dependent and thus post synaptic-dependent.
LTP in Schaffer collateral and Perforant pathways require *'cooperativity'* (activation of several afferen axons together) and *'associativity'* (paired tetanic stimulation; pre- and post-synaptic activity).

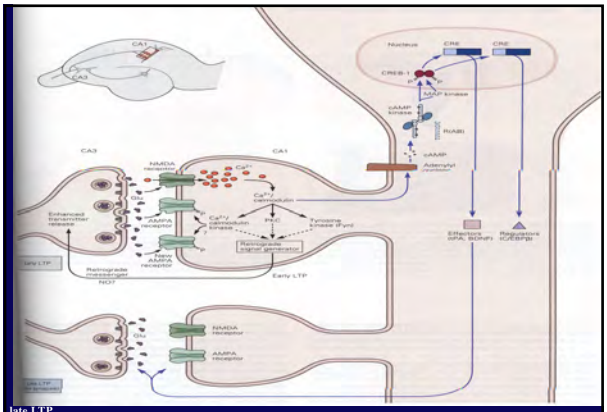


Model for the induction of the early phase of LTP

A high frequency tetanus activates non-NMDA-receptor channels which in turn results in depolarization of post-synapse and takes the Mg^{2+}-block away ---> activation of NMDA-R ---> Ca^{2+}-influx ---> activation of CaMkinaseII, PKC, Fyn, (NO?).
Expression/maintenance of LTP due to events in pre-synaptic neuron: The release of glutamate is enhanced and the probability of transmitter release increases greatly during LTP.

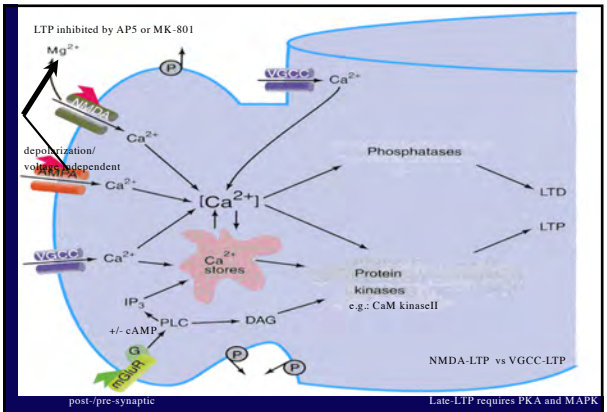


Early and late phases LTP are evident in the synaptic transmissio between a single CA3 cell and a single CA1 cell

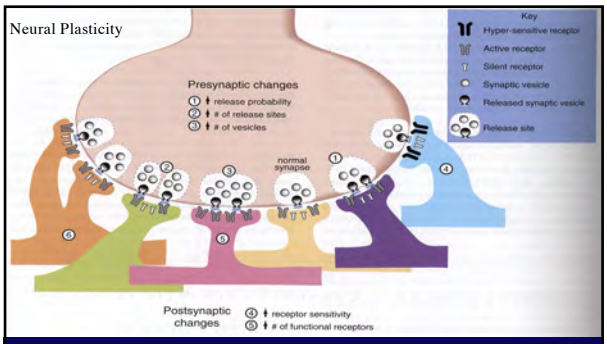


late LTP
(new synapse)

Model for the early and late phase of LTP



Events leading to LTP or LTD



Schematic representation of possible loci for cellular changes involved in the enhancement of synapt efficacy.
1) Increase of transmitter release probability, 2) Increase of number of release sites at the pre-synapt neuron, 3) Increase of numbers of vesicles available for release even the probability does not increa compared to normal or 1). 4) increase in receptor sensitivity at the post-synapse. 5) increase of # functional receptors at the post-synapse. 6) coordinated pre- and postsynaptic morphological chang (growth of new synaptic contacts between the same pair of neurons ---> plasticity).

Neural mechanisms of LTP

- Induction of LTP
  - Activation of NMDA receptors by specific patterns of pre- and post-synaptic activity.
  - Triggering of calcium-dependent second-messenger systems.
- Expression of LTP
  - Trafficking of AMPA receptor proteins to the membrane.
  - ? Activation of intercellular messenger molecules (NO, arachadonic acid)
- Persistence of LTP
  - Translocation of signalling molecules to the cell soma
  - Relevant gene activation and synthesis of mRNAs and 'plasticity-proteins'
  - Distribution of mRNAs and plasticity proteins to synapses to enable stabilisation of the potentiated state.

***LTP expression*: increase number of functional AMPA-R and an increase in transmitter release.**

***early LTP maintenance*: increase of substrate phosphorylation mediated by PKC and CaM kinaseII.**

***late LTP maintenance:* induction of gene expression and protein synthesis.**

taking-home message

- ???

taking-home message

- Memory - Explicit (Semantic & Episodic) and Implicit

taking-home message

- Memory - Explicit (Semantic & Episodic) and Implicit
- both, semantic and episodic knowledge are the result of at least four related but distinct types of processing: *encoding, consolidation, storage, and retrieval*.
- Brain areas involved: esp. Hippocampus / enthorinal cortex / limbic system
- LTP and neural plasticity as important mechanisms

taking-home message:

Neural mechanisms of LTP

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  - Distribution of mRNAs and plasticity proteins to synapses to enable stabilisation of the potentiated state.

taking-home message

One more point

The outcome in late LTP (explicit memory) and long-term sensitization (implicit memory) is the same - strengthen of the synaptic connections: synaptic plasticity (formation of more synapses)