3. Neurotransmitters

Criteria for a Neurotransmitter

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

1. A neurotransmitter must be synthesized by and released from neurons. This means that the presynaptic neuron should contain a transmitter and the appropriate enzymes need to synthesize the neurotransmitter. Synthesis in the axon terminal is not an absolute requirement. For example, peptide transmitters are synthesized in the cell body and transported to distant sites, where they are released.

2. The substance should be released from nerve terminals in a chemically or pharmacologically identifiable form. Thus, one should be able to isolate the transmitter and characterize its structure using biochemical or other techniques.

3. A neurotransmitter should reproduce at the postsynaptic cell the specific events (such as changes in membrane properties) that are seen after stimulation of the presynaptic neuron.

4. The effect of a putative neurotransmitter should be blocked by competitive antagonists of the transmitter in a dose-dependent manner. In addition, treatments that inhibit synthesis of the transmitter candidate should block the effects of presynaptic stimulation.

5. There should be active mechanisms to terminate the action of the putative neurotransmitter (enzymatic or reuptake by neurons cells).

The Process of Chemical Neurotransmission can be Divided into Five Steps

1. Synthesis of the neurotransmitter in the presynaptic neuron
2. Storage of the neurotransmitter and/or its precursor in the presynaptic nerve 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 and thus can be viewed as homeostatically conserved; in contrast, there is no energy-dependent, high-affinity reuptake process for non-classical transmitters.

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

Catecholamine Neurotransmitters: DA, NE & Epi

Catecholamine Neurotransmitters
DA - Dopamine (DAergic)
NE - Norepinephrine (adrenergic - NE = Noradrenaline)
Epi - Epinephrine (Epiergic - Epi = Adrenaline)

Catecholamine synthesis
- Phenylalanine (PHE)
  - Tyrosine (TYR)
  - Dopamine (DA)
  - Norepinephrine (NE)
  - Epinephrine (Epi)

Catecholamine metabolism
- Tyrosine hydroxylase (TH)
- Phenylethanolamine-N-Methyltransferase (PNMT)
- Dopamine-Beta-Hydroylase (DBH)
- Monoamine Oxidase (MAO)
- Comt

Catecholamine receptors
- Dopamine receptors
- Norepinephrine receptors
- Epinephrine receptors

Dopamine

&

NA-system

Phenylalanine
- Dietary
- Phenylethanolamine
- Hydroxylase
- Phenylalanine-hydroxylase

Dopamine
does not cross BBB
(DBH)
5-HT-system

5-HT: 1% in brain; in the blood (in platelets) and induces contractions of smooth muscle organs; high concentration in intestinal mucosa where it causes contraction of intestinal smooth muscle.

5-HT-5-hydroxytryptamine

Serotonin

similar to LSD

MAO - monoamine oxidase

inhibited by reserpine

LSD

Tryptophan

Trp hydroxylase

Serotonergic neuron

5-HT metabolized to melatonin (in pineal gland)

Trp can be converted to quinolinic and kynurenic acid (kynurenine shunt)

agonist and antagonist, respectively, of NMDA receptors

requires BH4/Fe2+

blocked by cocaine

5-HT:

1% in brain;

In the blood (in platelets) and induces contractions of smooth muscle organs;

high concentration in intestinal mucosa where it causes contraction of intestinal smooth muscle.

GABA-system

GABA-γ-aminobutyric acid

GABA - inhibitory neurotransmitter

Ubiquitous in the CNS

Cl- channel, leads to hyperpolarization, increase of threshold for action potential formation

(GABA-T at mitochondria but GAD in cytoplasm)

(VAAT also for glycine, thus, called vesicular inhibitory amino acid transporter, 10 transmembrane)

At least 3 different types exist, expressed on different (non-GABAergic) neurons

Glutamate transporter (GLT)

Leukotrienes in the CNS

Ubiquitous in the CNS

vasoactive intestinal polypeptide (VIP) and ATP

neuropeptide Y (NPY)

cholecystokinin (CCK)

GABAergic synapse

GABA-T synthesized by vesicular GABA transporter (GAT)

Pharmacological receptors (GABA)

Alcohol (GABAergic neurons)
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 (negative feedback inhibition).

Vit. B6 is necessary for GABA synthesis.

GIRKS = inwardly rectifying K+ channels

Glutamate-system

Sources of Glu:
- From glucose through the "Krebs" cycle
- From Glu, derived from glutamine
- GDP-glucose-activated glutaminase (GAD)

Glutamate release-modulating autoreceptor

Glutamate Receptor Subtypes

Molecular families of glutamate receptors, each of the two main glutamate receptor divisions contains several functional and subtypes of receptors.
NMDA-receptor, binds NMDA, ionotropic (D-Serine)

NMDA (N-methyl-D-aspartate) is the name of a selective agonist that binds to NMDA receptors but not to other glutamatergic 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 glucose 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 distribution

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).

Acetylcholine (ACh)

Important Neurotransmitter in CNS and of e.g.: motorneurons, preganglionic sympathetic neurons, and neurons innervating sweat glands.
Ionotropic metabotropic
NT = neurotensin
NMN = neuromedin-N
No reuptake by membrane transporters
large dense-core vesicles (100 nm)
Classical neurotransmitters are usually in small synaptic vesicles

Peptides as Neurotransmitters

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 after transcription, it is then acted on by peptidases to form the peptide transmitter, thus, peptide transmitters differ from classical transmitters by being synthesized in the soma rather than axon terminal. The active transmitter thus must be transported in vesicles to the nerve terminal. 
Termination of peptide transmitter action differs from that of classic transmitters, being achieved mainly by enzymatic means and diffusion. Peptides: lack of a specific high-affinity active reuptake process and there is much less specificity in the enzymatic inactivation of peptide transmitters. 

Termination (inactivation) of classical transmitters (small molecule that are derived from either amino acids (Glu, GABA) or intermediary metabolism; usually synthesized by the sequential action of key 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 by enzymatic means (ACh), or both mechanism.

One final difference in the inactivation of peptide and classical transmitter is the product. Once classical transmitters are catabolized, the resultant metabolites are inactive at the transmitter receptor. However, certain peptide fragments derived from the enzymatic inactivation of peptide transmitters are biologically active. An example is angiotensin I ---> II (more active than I).

It is therefore sometimes difficult to distinguish between synthetic 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 therefore considered the transmitter, although the actions of certain peptidase may lead to other biologically active fragments after release.

The 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 (VDCs).
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:

- 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 (repolarization) of action potential.
- 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.
- The properties of K+ channels:
  a. The activation of K+ channels proceeds depending on the membrane depolarization.
  b. The K+ channel does not exhibit an inactivation with maintained membrane depolarization, which is in a sharp contrast to the Na+ channel activation.

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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) Hemisynaptic interactions (Splitter 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 actin–cytoskeleton–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

Purinergic System
Adenosine 5'-triphosphate; a purine nucleotide consisting of adenine, ribose and triphosphate:

Adenosine metabolites
Ribose
Inosine
Hypoxanthine
Xanthine
Uric Acid

Life cycle of synaptic vesicles

Unconventional Transmitters
NO and CO

Adenosine 5'-triphosphate; a purine nucleotide consisting of adenine, ribose and triphosphate

Purinergic Receptors
P₁ = Adenosine
P₂ = ATP, UTP
G protein coupled
Ligand-gated channels
G protein coupled

Life cycle of synaptic vesicles

Unconventional Transmitters
NO and CO

Purinergic Receptors
P₁ = Adenosine
P₂ = ATP, UTP
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G protein coupled

Life cycle of synaptic vesicles

Unconventional Transmitters
NO and CO

Purinergic Receptors
P₁ = Adenosine
P₂ = ATP, UTP
G protein coupled
Ligand-gated channels
G protein coupled

Life cycle of synaptic vesicles
Tetanus toxins and the botulinum toxins, proteases that cleave specific SNARE proteins as shown, can block transmitter release.

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

Tricyclics: e.g., imipramine, trade name Tofranil.

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 blocks more, 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.

Drugs:

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Main Effects on Behavior</th>
<th>Main Effects on Synopsis</th>
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<tbody>
<tr>
<td>Amphetamine</td>
<td>Excited, alert, elevated mood, decreased fatigue</td>
<td>Increase release of dopamine and several other neurotransmitters</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Excited, alert, elevated mood, decreased fatigue</td>
<td>Blocks reuptake of dopamine and several other neurotransmitters</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>Increased concentration</td>
<td>Blocks reuptake of dopamine and others, but more gradually than cocaine does</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Motivational effects</td>
<td>Stimulates nicotinic receptor, which among other effects, increases dopamine release in nucleus accumbens</td>
</tr>
<tr>
<td>Opiates</td>
<td>Sedation, withdrawal, overdose potential</td>
<td>Stimulates endorphin receptors</td>
</tr>
<tr>
<td>Cannabinoids (marijuana)</td>
<td>Increased sensory experience, distorted sense of time, decreased pain and nausea</td>
<td>Block negative feedback receptors on presynaptic cells; thereby puts the breaks on release of either glutamate or GABA</td>
</tr>
<tr>
<td>LSD</td>
<td>Distorted sensations</td>
<td>Stimulates serotonin type 2 receptors (5-HT2)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Sedation, decreased arousal</td>
<td>Facilitates GABA, receptor</td>
</tr>
</tbody>
</table>

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 astrocytes
Advanced Neurobiology

Course No: BSE1012
Credits: 3.00
Tuesday: 9:30am – 12:30pm

5. Cognitive Neuroscience: Memory & Learning processes

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**Body:**
Center of Consciousness about our environment
With it we get to know about our surrounding area

**Soul:**
Center of Consciousness about ourselves
With it we get to know about ourselves

**Spirit:**
Center of Consciousness about God
With it we can get in touch with God

---

Cognitive functions controlled by the Trinity of human being

---

**Introduction:** Memory, Dementia & Aging

Structures of the Brain that play a role in memory

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

<table>
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<th>Females</th>
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<td>300</td>
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<tr>
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<td>200</td>
<td>3800</td>
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</table>

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

---

Cognitive Neuroscience ----> Neuropsychology ---->

Memory & Learning

Genes, environment & education ----> behavior

Environment and education: mechanisms: learning and memory

Red

? ?

---

Age group (years)

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</table>

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Aging

Dementia
Alzheimer’s Disease

Alois Alzheimer (1864 – 1915)

Cognitive Neuroscience

First Stainings: The Hippocampus

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

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.
A Taxonomy of Long-term Memory

- **Explicit (declarative)**
  - Factual knowledge of people, places, things, and what these facts mean.
  - Necessitates retrieval of information.

- **Implicit (procedural)**
  - Involved in training reflexive motor or perceptual skills.
  - Necessitates activation of neural pathways.

**Brain Areas involved in Memory & Learning processes**

- Lesion to the Hippocampus
  - 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 reflexive 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 elicit lower conscious awareness or complex cognitive processes, such as comparison and evaluation. The patient needs only to respond to a stimulus or cue, and need not remember anything.
Explicit memory is stored in Association Cortices

can be further classified as

- **episodic** (a memory for events and personal experience)
- **semantic** (a memory for facts)

**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 of which corresponds to a different meaning and can be accessed independently (by visual, verbal or other sensory clues)
  - both, semantic and episodic knowledge are the result of at least four related but distinct types of processing: encoding, consolidation, storage, and retrieval.

  **Encoding:** processes by which newly learned information is attended to and processed when first encountered.

  **Consolidation:** involves gene expression and protein synthesis (and structural changes).

  **Storage:** organize and retain information, mechanism by which memory is retained over time - long-term storage seems to have unlimited capacity. In contrast, short-term working memory is very limited.

  **Retrieval:** Recall and use of stored information. Retrieval involves bringing different kind of information together that are stored separately in different storage sites. It is a constructive process and therefore subject to distortion.

Explicit Memory

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

**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.
Implicit Memory:

- driving a car: learning motor skills
- playing soccer
- learning a language

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. It does not depend directly on conscious processes nor does recall require a conscious search of memory. This type of memory builds up slowly, through repetition over many trials. Examples include:

- Perceptual and motor skills
- Driving a car
- Playing soccer
- Learning a language

Different forms of implicit memory are acquired through different 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: 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.

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.

**Non-Associative Learning**

- Habituation: if the stimulus is neither beneficial nor harmful, the animal learns, after repeated exposure, to ignore it. Postsynaptic (non-) NMDA-receptor sensitivity unchanged – neurotransmitter release reduced = cellular mechanisms mediating the short-term memory for habituation, homosynaptic process. The decrease in synaptic strength is a direct result of activity in the sensory neuron and their central connections in the reflex pathway.

**Cellular mechanisms of non-associative learning**

A tactile stimulus to the siphon elicits the gill withdrawal reflex. Repeated stimuli lead to habituation.

- Sensory neuron (mechanoreceptor), IN = interneuron, MN = motor neuron. (No modulatory / facilitating interneuron (5-HT-release and acting on SN-axon) shown here.)
No synaptic potential in habituated animal in the motor neuron 1 week after training.

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 brief train of shocks to the body wall results in the release of modulatory neurotransmitters, such as 5-HT, from a separate class of interneurons referred to as facilitatory neurons. These facilitatory neurons regulate the properties of the sensory neurons and the strength of their connections with postsynaptic interneurons and motor neurons through a process called heterosynaptic facilitation.

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

Long-Term Sensitization (Implicit Memory)

Simplified scheme of mechanisms in sensory neurons that contribute to long-term sensitization.

CREB2 - repressor; synthesis of ApUch leads to degradation of PKA-regulatory subunit ---> enhanced PKA activity (catalytic subunit) ---> activation of CREB1 ---> gene transcription activation; ApCAM= Aplysia homologue of NCAM (neuronal cell adhesion molecule) is down-regulated ---> regulating process associated with long-term facilitation (neuronal plasticity).

ApTBL=Aplysia tolloid/BMP -like protein, functions as secreted Zn proteases ---> activation of TGF-b --> 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 stimulation.
Long-term sensitization (at least 24 hrs) requires a more extensive training period over an hour or more.

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

The process by which transient short-term memory is converted into a stable long-term memory is called consolidation. Consolidation of long-term implicit memory for simple forms of learning involves gene transcription, new protein synthesis and growth/pruning/habituation of synaptic connections.

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 \(\leftrightarrow\) 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.

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 detectors 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

Long Term Potentiation

LTP is the term used to describe a remarkably long-lasting (hrs - weeks) enhancement of synaptic transmission (persistent increase in synaptic strength as measured by the amplitude of the EPSP in the follower neuron) that occurs at various CNS synapses following a short (conditioning) burst (brief train of stimuli, tetanus) of 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.

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

Three major afferent pathways in the hippocampus

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Three major afferent pathways in the hippocampus

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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

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Three major afferent pathways in the hippocampus
Induction of LTP at the CA3-CA1 synapse of the hippocampus

Two 1s, 100 Hz tetani were delivered with 20s interval. Subsequent test stimuli produce enhanced EPSP that is stable and persists for more than 2 hrs.

LTP at the CA3-CA1 synapse of the hippocampus

Recorded EPSP after induction of 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 stimulation

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

Tetanic stimulation
LTP
LTP
LTP
LTP
LTP
LTP
LTP
LTP

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’.

Early and late phases LTP are evident in the synaptic transmission between a single CA3 cell and a single CA1 cell.
Model for the early and late phase of LTP

Events leading to LTP or LTD

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, arachidonic 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

• 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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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)