Neurotransmitters of Synaptic Plasticity, Learning and Memory in the Perirhinal Cortex

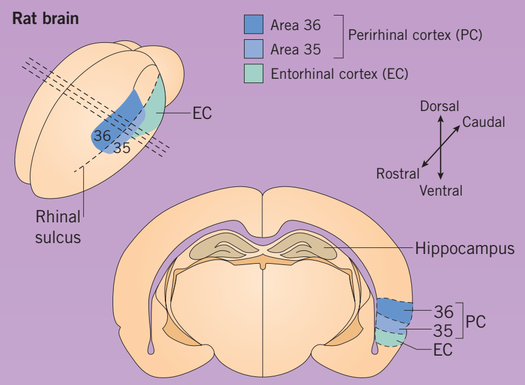
E. Clea Warburton and Zafar I. Bashir
School of Physiology and Pharmacology, University of Bristol, BS8 1TD, UK. Email: E.C.Warburton@bristol.ac.uk; Z.I.Bashir@bristol.ac.uk

Recognition memory enables us to make judgments about whether or not we have encountered a particular stimulus before. Recognition memories are readily acquired during a single encounter and are essential to normal life. Deficits in recognition memory are a major symptom of the classical amnesic syndrome and early Alzheimer's disease. Many of the same neurotransmitter receptors and intracellular signaling cascades that give rise to synaptic plasticity (i.e. long-term depression) in the perirhinal cortex are also required for perirhinal cortex-dependent recognition memory.

In Vivo Mechanisms of Recognition Memory

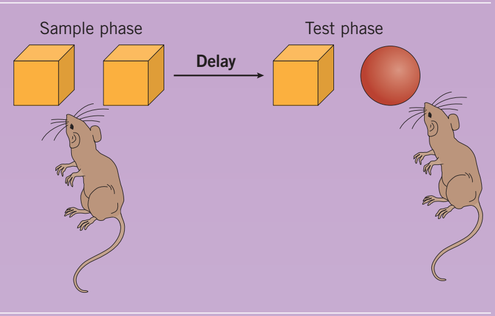
Perirhinal Cortex

The perirhinal cortex is contained within the medial temporal lobe and it is thought to play an integral role in recognition memory, as well as perception and object association. Studies have shown that up to 25% of perirhinal cortex neurons show a reduction in their response to a visual stimulus when it is presented for a second or subsequent time. Neuronal modeling and experimental evidence have suggested that this reduction in synaptic strength provides the neural mechanism by which the familiarity of an object may be encoded within the perirhinal cortex. The role of the perirhinal cortex in memory, and the links between recognition memory and synaptic plasticity, have been demonstrated by way of pharmacological infusion studies (see below). The following experimental data are from rodent models.



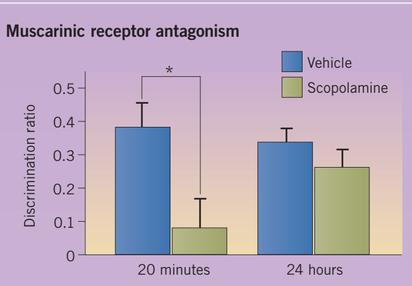
Recognition Memory

Recognition memory may be tested in rodents using single trial object memory tasks. Rodents are allowed to explore an object for a certain length of time in the sample phase, and in a subsequent test phase, the animals are presented with the familiar object and a novel object. In the test phase normal rodents preferentially explore the novel object, thus exhibiting familiarity discrimination; this indicates that their recognition memory for the familiar object is intact. These spontaneous object recognition memory tasks do not require reinforcement or lengthy training periods, and as such, closely parallel tasks that measure human recognition memory.



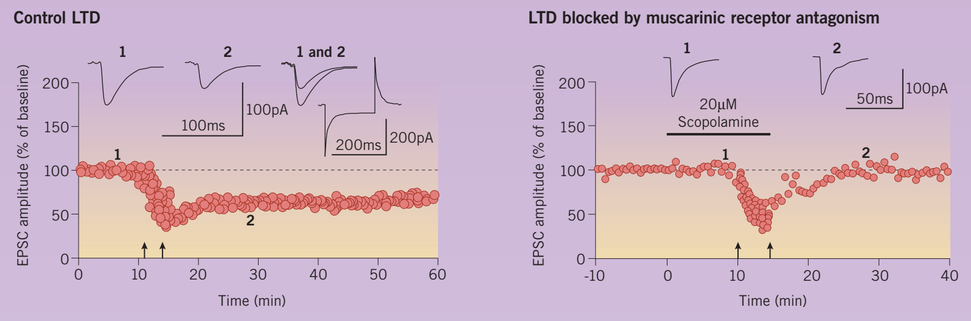
Pharmacological Intervention

Pharmacological intervention may be used to assess the role of different neurotransmitters in recognition memory. Antagonists are delivered directly into the perirhinal cortex of the rodent via indwelling cannulae. As illustrated in the figure, administration of the muscarinic receptor antagonist scopolamine (0.05 ng/µL) impairs recognition memory at a 20 minute, but not 24 hour, delay (*p<0.05). Conversely, administration of the nicotinic agonist MLA impairs memory at a 24 hour, but not 20 minute delay. The discrimination ratio is an index of memory performance, and is calculated as the difference in the amount of time spent exploring the novel and familiar objects as a proportion of total exploration time. This graph has been adapted from Tinsley *et al* (2011).

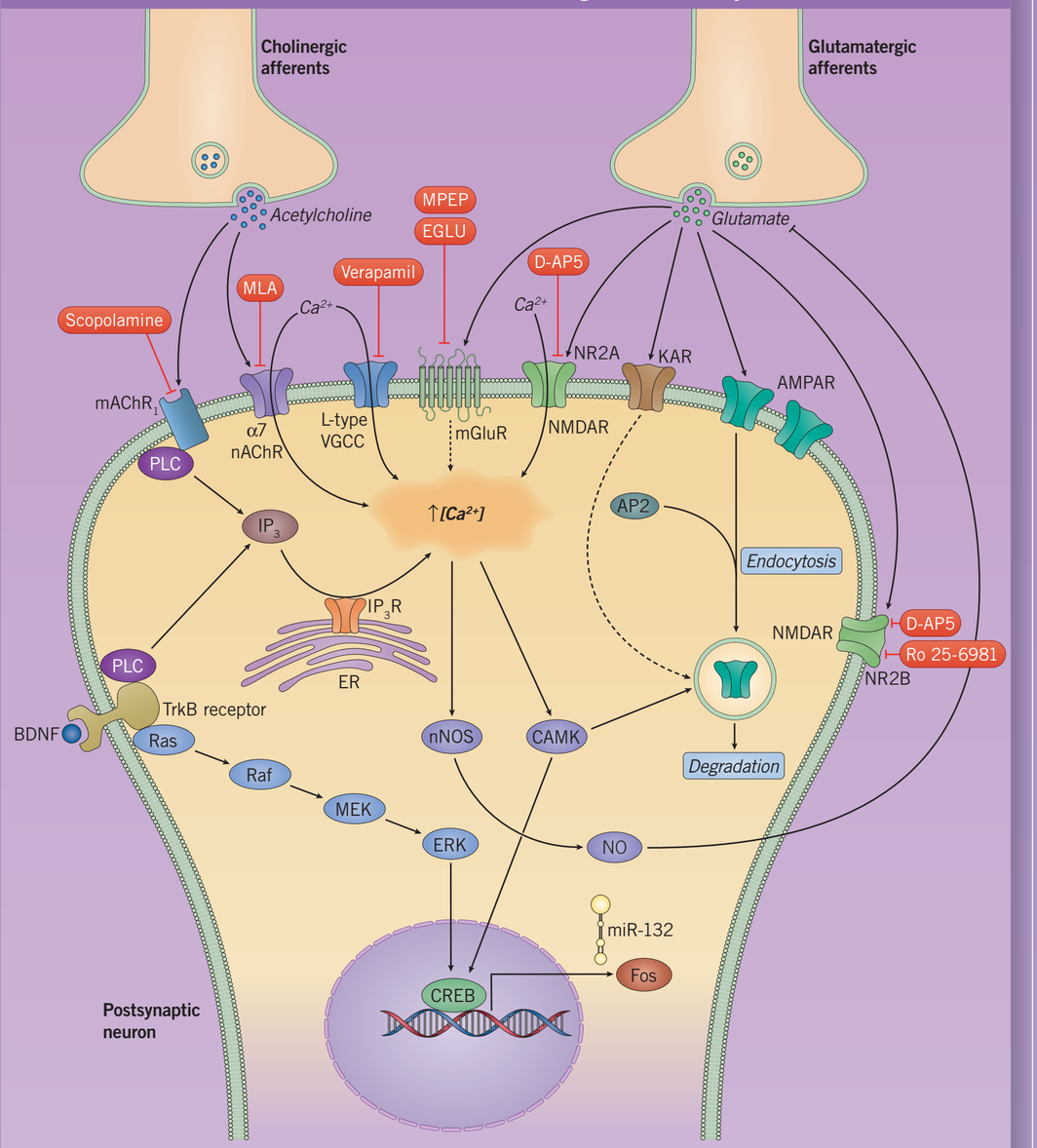


Elucidating the Mechanisms of Long-term Depression

Scopolamine also prevents the induction of long-term depression (LTD) in the perirhinal cortex. Synaptic plasticity is assessed using electrophysiological recordings from slices of perirhinal cortex. Below (left) is a graph showing the amplitude of evoked synaptic responses. LTD is experimentally induced using conditioning stimulation (indicated by two upward arrows). Application of scopolamine (right) prevents this induction; thus, there is thought to be a close relationship between recognition memory and LTD. The traces below are representative EPSCs taken from the time points indicated (1 and 2). These graphs have been adapted from Cho *et al* (2000) and Warburton *et al* (2003).



Cellular Mechanisms of Recognition Memory



Cellular Mechanisms of Long-term Depression and Recognition Memory

Many neurotransmitters and intracellular signaling cascades have been identified to be involved in both LTD and recognition memory; these are illustrated by this schematic. The release of glutamate and acetylcholine from presynaptic afferents activates a range of postsynaptic receptors. Activation of cholinergic receptors (nAChR and mAChR) and glutamate receptors (mGluR, NMDAR, AMPAR) prompts an influx of Ca^{2+} ions, as does the activation of TrkB receptors and L-type VGCC. The resultant increase in intracellular Ca^{2+} concentration prompts the activation of calcium-calmodulin related kinases (CAMKs), resulting in the phosphorylation of both AMPA receptors (leading to endocytosis and LTD), and the transcription factor CREB. CREB is also phosphorylated as a result of a MAPK signaling cascade initiated by BDNF/TrkB. CREB can upregulate the immediate early gene *c-Fos*, and regulates the production of the microRNA miR-132, though the mechanisms by which they sustain LTD are not known. It is thought that the Ca^{2+} increase also activates neuronal nitric oxide synthase (nNOS), resulting in the synthesis of nitric oxide (NO), which in turn inhibits the release of glutamate and constitutes a form of negative feedback. Expression of LTD can be mediated through internalization of synaptic AMPA receptors, a process that is reliant on the interaction between AMPA receptors and the AP2 protein, an adaptor protein involved in clathrin-mediated endocytosis. KAR activation also results in a change in synaptic strength, potentially as a consequence of its involvement in AMPAR endocytosis. Pharmacological inhibition (in red) of cholinergic or glutamatergic receptors has been shown to impair either long- or short-term recognition memory.

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Muscarinic M_1 Receptors	Pirenzepine, Scopolamine, VU 0255035
Calcium Signaling	
CAMK	KN-93, STO-609
IP_3 Receptors	2-APB, (-)-Xestospongin C
L-type Calcium Channels	(±)-Bay K 8644, Diltiazem, Isradipine, Nifedipine, Verapamil
Glutamate Receptors	
AMPA Receptors	CNQX
Kainate Receptors	UBP 302
NMDA Receptors	D-AP5, DL-AP5, Ro 25-6981, TCN 213, TCN 237
mGlu Group I Receptors	ADX 10059, CDPPB, MPEP, VU 0285683
mGlu Group II Receptors	EGLU, LY 341495, Ro 64-5229
Non-selective Glutamate	DNQX, MNI-caged-L-glutamate
MAPK Signaling	
ERK	FR 180204, TCS ERK 11e, XMD8-92
MEK	PD 0325901
Nitric Oxide Signaling	
nNOS	ARL 17477, N^{ω}-Propyl-L-arginine
TrkB Signaling	
TrkB Receptor	7,8-Dihydroxyflavone, ANA 12, BDNF (human), LM 22A4

Glossary

AMPAR	AMPA receptor
BDNF	Brain-derived neurotrophic factor
CAMK	Calcium/calmodulin-dependent kinases
CREB	cAMP response element-binding protein
EC	Entorhinal cortex
EPSC	Excitatory postsynaptic current
ER	Endoplasmic reticulum
ERK	Extracellular signal-regulated kinase
IP3R	Inositol 1,4,5-trisphosphate receptor
KAR	Kainate receptor
LTD	Long-term depression
mAChR	Muscarinic acetylcholine receptor
MAPK	Mitogen-activated protein kinase
mGluR	Metabotropic glutamate receptor
MLA	Methyllycaconitine
nAChR	Nicotinic acetylcholine receptor
NMDAR	NMDA receptor
nNOS	Neuronal nitric oxide synthase
PC	Perirhinal cortex
VGCC	Voltage-gated calcium channel

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