Update on memory editing methods

2004-2011

2004

In 2004, Science magazine mentioned four new companies—Sention, Cortex Pharmaceuticals, Memory Pharmaceuticals, and Helicon Therapeutics. All four went on to come up against developmental hurdles and severe financial upheavals in trying to market memory-boosting drugs that enhanced long-term potentiation. None of it happened.

In 2004, war veterans in the US alone received benefits payments for PTSD totaling $4.3 billion. Clearly, there’s lots of interest in finding comparatively inexpensive pharmaceutical methods of easing or preventing the emotional distress associated with bad memories. Progress has been varied, as we'll see...

2006

Proteomics -PKMzeta & ZIP

Molecular neuroscience has gained prominence in the quest for a more precise understanding of the biological schematic of memory storage.

There has been good progress in identifying molecules that maintain long-term memory. Way back in In a 1999 paper in the journal Nature Neuroscience, two of the most prominent researchers in brain science, Dr. Jeff W. Lichtman and Joshua R. Sanes of Harvard, listed 117 molecules that were somehow involved when one cell creates a lasting connection with a neighbor, a process known as "long-term potentiation (LTP)."

One of the substances on their list was called PKMzeta. The first molecular mechanism for large-scale long-term memory storage in the brain was recently identified as the persistent action of protein kinase Mzeta (PKMzeta).

The sensorimotor cortex has a role in procedural learning. Previous studies suggested that this learning is subserved by long-term potentiation (LTP), which is in turn maintained by the persistently active kinase, protein kinase Mzeta (PKMζ).

PKMzeta controls storage of complex, high-quality memories that provide detailed information about an agent’s location, concerns and behavior, but does not control the ability to process or express this information [6].

Consolidated memories can be induced to re-enter states of transient instability following reactivation, from which they must again stabilize in order to persist, and this process can also be interfered with chemically.

Pastalkova et al. report the disruption of new and established long-term memories with an inhibitor to protein kinase M zeta (PKMζ) in a recent article in Science[5].

PKMζ is the catalytic subunit of protein kinase C zeta (PKCζ). The researchers blocked its constitutive activity with a synthetic zeta-substrate inhibitory peptide (ZIP) that mimics the regulatory subunit of PKCζ

ZIP inhibits long-term potentiation (LTP) in hippocampal slice cultures. ZIP also reversed LTP in vivo. Twenty-two hours after high-frequency stimulation to the perforant path, ZIP injection into the dentate gyrus blocked LTP in hippocampal regions more than 2 mm from the injection site.

ZIP also disrupted long-term memories. In the active place avoidance test, both memory acquisition and recall depend on the hippocampus. Control rats avoided a pre-memorized shock zone, but rats treated with ZIP before testing did not. However, rats treated with a scrambled ZIP peptide or the kinase inhibitor staurosporine avoided the shock zone similarly to control rats.

ZIP did not affect memory acquisition. Following long-term memory testing, the researchers retrained the rats with shocks for one session and then immediately tested the rats without shocks. Like control rats, ZIP-treated rats avoided the shock zone.

The researchers reasoned that if ZIP disrupted memory storage, then its effect would be permanent, but if ZIP disrupted memory retrieval, then its effect would be temporary.

It can be very hard to tell whether a memory exists unconsciously but cannot be accessed, has been erased, or was never made permanent in the first place. If gene transcription is involved then memory retrieval could be permanently blocked just as original consolidation could be blocked.

So, one week after training and control or ZIP injection, the researchers tested rats in a single training session. Control-treated rats still avoided the shock zone, but ZIP-treated rats did not.

Immunocytochemical analysis failed to detect biotinylated ZIP in the hippocampus, suggesting that ZIP-induced memory disruption persisted despite metabolism of the drug.

Subsequent training reinstated the memory for at least 24 hours. These data therefore suggest that PKMζ is necessary for memory storage, not retrieval.

Thirty days after training, control rats still avoided the shock zone, but rats treated with ZIP two hours before testing did not. Therefore, PKMζ activity in the hippocampus is important in the maintenance of established spatial memories.

These data suggest that PKMζ inhibitors may prove useful in treating problems such as post-traumatic stress disorder and PKMζ activators in treating problems such as retrograde amnesia.

2006

Zinc, Ifenprodil, Ro25-6981, NVP-AAM077 (selective NMDA subtype receptor antagonists)

Zinc has complex effects on NMDA receptors (NMDARs) and may be an endogenous modulator of synaptic plasticity. [32]

Researchers observed that low micromolar concentrations of zinc depress NMDAR synaptic responses by 40–50% and inhibit long-term depression (LTD) but not long-term potentiation (LTP). A combination of zinc plus ifenprodil, an inhibitor of NR1/NR2B receptors, produced no greater inhibition of synaptic NMDARs than either agent alone, suggesting overlapping effects on NMDARs.

Similar to low micromolar zinc, ifenprodil inhibited LTD but not LTP.

NR2B selective antagonists ifenprodil or Ro25-6981 impaired 48-h auditory fear memory (AFM) induced by five but not one CS-US pairing protocol, while similar treatment with the NR2A antagonist NVP-AAM077 disrupted memory for both protocols.

Consistently, genetic over-expression of NR2B C-terminal in the amygdala produced a severe deficit in 48-h AFM for five but not one CS-US pairing protocol, whereas over-expression of NR2A C-terminal impaired memory for both protocols.

Furthermore, pre-conditioning infusion of ifenprodil down-regulated the elevated phosphorylation level of extracellular signal-regulated kinase (ERK) induced by five CS-US pairing protocol. Thus, the involvement of the amygdala in AFM acquisition depends on conditioning strength.

These results suggest that LTD induction depends on specific NMDARs with sensitivity to low micromolar zinc and ifenprodil, but LTP is less dependent on specific NMDAR subtypes.

Because high-affinity sites of NR2A are likely occupied by ambient zinc, the researchers also examined effects of extracellular zinc chelators. Zinc chelation blocked LTP but had no effect on LTD. This LTP inhibition was overcome by APV and NVP-AAM077 but not ifenprodil, suggesting that zinc chelation unmasks tonic NR1/NR2A activation that negatively modulates LTP.

2006/2007

Propranolol (inderal)

Blood pressure medication Propranolol; a beta blocker, has been used as a potential treatment for anxiety disorders and PTSD [7].

Propranolol doesn't actually erase memory; it reduces the weighting on reconsolidation.

Similar to the use of alpha-2 agents, the idea behind propranolol is to normalize the hyperactive noradrenegic/cortisol levels in PTSD.

When taken while remembering traumatic things, it prevents the rush of norepinephrine and cortisol that normally occurs in those suffering from PTSD (Post Traumatic Stress Disorder). This reduces the strength of the emotion/sentiment response/reaction during reconsolidation.

Repeating this process eventually retrains the brain so that traumatic events can be recalled without invoking much emotion. Often, wrong weighting in the first place is what makes a memory too traumatic. Excessive norepinephrine (and the associated signal transduction activity) is thought to result in a trauma-induced enhancement of memory encoding for the harrowing event [8] and cortisol levels so high that its endogenous production crashes and then plummets (after which trauma victims have very low cortisol and very high norepinephrine; a recipe for either bipolar disorder or PTSD.)

There doesn't seem to be any loss of event memory associated with using Propranolol. One can still remember all the details of a trauma, but no longer suffers from the crippling sentiments that used to come with the recollections.

Animal models of anxiety conditioning have been used to assess possible pharmacological treatments targeting the amygdala, a critical region for memory weighting [8]. These treatments aim to reduce memory weighting on consolidation and reconsolidation (reactivating a memory by retrieving it). Propranolol, injected either systemically or directly into LA (lateral amygdala) lastingly impaired memory weighting. Postreactivation propranolol also significantly weakened fear responses measured 48 h later.

Findings indicate that propranolol disrupts reconsolidation of a memory up to 2 months after training. Therefore, even well-consolidated old fear memories undergo reconsolidation and may be disrupted by means of pharmacological manipulation.

At this point, there don't seem to be any side effects. Inderal has also been used by musicians and other performers to combat stage fright.

2007

More on propranolol for PTSD: According to , propranolol can dull the emotional pain associated with the memory of an event when taken within six hours after the event occurs. Researchers are now (2007) conducting larger studies with propranolol to test these preliminary results and to explore whether propranolol can safely be used to ease traumatic memories from the more distant past [9].

While we already have lots of other drugs that affect the formation of new memories once you start taking the drug (common in certain forms of anesthesia, for example), there still isn't much that can be done to affect memories that have already formed. So it's possible that propranolol could fill an important niche if it lives up to early promise.

It is unclear whether propranolol can dampen factual associations with memories (the PDR lists short-term memory loss as a side effect of the drug).

There is more evidence that it erases the emotional connection to memories. Part of what affixes weighting to our memory is the emotional significance, and this emotional significance is overexpressed biologically through anxiety hormones, particularly cortisol, epinephrine and norepinephrine.

Propranolol is one of the beta blockers that enters brain tissue (many do not) and it is likely that it has its effects not only within the brain but also through attenuation of the rest of the anxiety hormone axes by its peripheral actions.

There was a "60 Minutes" (TV program) on this drug about a year ago. They featured several trauma victims, some of whom have been reliving very painful memories for decades. But, after taking the drug they were no longer bothered by these memories.

For example, a woman who retained memories of a violent rape. Understandably, this caused her to have severe intimacy issues. But after the drug, she was a completely different person and was able to live life as if the tragedy never occurred. Again, the memories themselves didn't fade. Rather, it was the pain associated with the memories that did.

2007

More proteomics: CDK5

Hippocampal cyclin-dependent kinase 5 regulates the loss of fearful associations.

Some memories can decrease and even disappear through a process called extinction, but the mechanisms that are involved are complex. Researchers now find that a molecular pathway in the hippocampus that involves cyclin-dependent kinase 5 (Cdk5) regulates the extinction of contextual fear in mice [10].

The authors found that infusing a Cdk5 inhibitor into the hippocampus facilitated extinction if it was given up to 1 hour after traumatic events (giving it before had no effect), indicating that Cdk5 is involved in the consolidation of the new experience to long-term memory.

Next, the authors increased Cdk5 activity by using transgenic mice in which forebrain expression of the Cdk5 activator p35 was switched on after fear conditioning. They found that increasing Cdk5 activity abolished extinction, whereas switching p35 off returned Cdk5 activity to baseline and re-instated extinction.

So what happens to Cdk5 when extinction takes place? In the complex 3D jigsaw puzzle that is proteomics, causes and effects are rarely clear cut. Findings suggest that, during extinction, decreased Rac-1 activity in hippocampal cells causes a redistribution of Cdk5 and p35 to the

cytosol, which then results in sequestering of p35 from PAK-1. This activates PAK-1 which then, through its involvement in the remodelling of synaptic circuits, facilitates extinction.

This study provided a molecular mechanism for the regulation of anxiety extinction. It opens up new avenues for the development of drugs that will target this pathway and which may be used to extinguish specific memories[11].

MEK inhibitors

For a more selective approach, wiping single memories has been explored further[4].
"A single, specific memory has been wiped from the brains of rats, leaving other recollections intact", we were told. They were using MEK inhibitor U0126.

When reactivated, memories enter a labile, protein synthesis–dependent state, the process referred to as reconsolidation. Fearful memory retrieval produces a synaptic potentiation in the lateral amygdala that is selective to the reactivated memory, and that disruption of reconsolidation is correlated with a reduction of synaptic potentiation in the lateral amygdala.

Thus, both retrieval and reconsolidation alter memories via synaptic plasticity at selectively targeted synapses.

In experiments on this (and others like it), rats were treated with the MEK inhibitor UO126 (which inhibits the kinase activity of MAPKinase Kinase, or 'MEK' (aka MKK or MAP2K).

MEK Inhibitor U0126 is a chemically synthesized organic compound that inhibits the kinase activity of MAP kinase kinase, MEK.

U0126 Inhibits both active and inactive MEK [1],[2]. Downstream inhibition of ERK 1 and ERK 2 mediated responses.

U0126 is not exactly approved for human use [3].

The study adds to our understanding of how memories are made and altered in the brain. It has been shown already that the reconsolidation process can be interrupted with drugs. But this explores how specific this interference was: could the transfer of one specific memory be meddled with without affecting others? [12]

To find out, they trained rats to fear two different musical tones, by playing them at the same time as giving the rats an electric shock. Then, they gave half the rats U0126, which is known to cause limited amnesia, and reminded all the animals, half of which were still under the influence of the drug, of one of their anxious memories by replaying just one of the tones.

When they tested the rats with both tones a day later, untreated animals were still fearful of both sounds, as if they expected a shock. But those treated with the drug were no longer afraid of the tone they had been reminded of under treatment. The process of re-arousing the rats' memory of being shocked with the one tone while they were drugged had wiped out that memory completely, while leaving their memory of the second tone intact.

The same research team also confirms the idea that the baso-lateral amygdala is central to this process - communication between neurons in this part of the brain usually increases when the anxious memory forms, but it decreases in the treated rats. This shows that the memory is actually deleted, rather than simply breaking the link between the memory and an anxious reaction.

The finding also demonstrates that the amygdala makes distinctions among the anxious memories it holds and helps retrieve.

2008

More research on memory formation

Many scientists are now focusing on later stages of memory formation. In humans, as time passes and memory is defragged and moved to permanent locations, the hippocampus is no longer needed to sustain a recollection, which instead becomes embedded in associated areas distributed across the neocortex.

Studies of amnesia patients with brain damage in the past have conflicted over whether lesions in the hippocampus wipe out recent memories but spare old ones – or completely empty the memory banks.

A careful analysis of eight amnesia patients helped clarify the issue[13]. If damage is only within the hippocampus, patients had trouble recalling events from the past five years or so, but older memories survived. With bigger lesions stretching into nearby brain areas, the amnesia extended back 30 to 50 years – yet early childhood memories could still be accessed. This supports the understanding that the hippocampus and adjacent structures are not lasting repositories of long term memory but does not show whether memories are being wiped, or masked by prevention of recall.

Furthermore, if the damage reaches into the lateral temporal lobes, then even the oldest autobiographical memories cannot be recalled, suggesting this area of N3 is essential to either the permanent storing or recall of memories.

Guanfacine

On another front in 2008, neurobiologists started unraveling the molecular underpinnings of working memory, the mental clipboard that makes it possible to retain a phone number long enough to dial it.

Working memory depends on a network of cells, housed in the brain's prefrontal cortex (N6), that all trigger each other to fire persistently to hold onto that number. Recent research has shown that molecules called HCN channels control whether this neural network is functioning. The channels are like tiny gates in a neuron's cell membrane that let charged molecules flow through.

When the channels are open, they weaken the ability of a neuron to receive information from other cells, and thus disconnect the circuit. But various drugs that shut down the HCN channels enhanced the network's activity. One such drug, a blood-pressure medication called guanfacine, improved the performance of rats as they used working memory to navigate a maze.

The researchers are now (2008) working with a pharmaceutical firm to develop the drug for treating attention deficit hyperactivity disorder [1]. It's possible that a working memory augmenter could be available for NH.

Rohypnol et al

Date rape drugs block the first stage of memory.(In other words, the event is never registered or weighted to begin with.) It's no use taking it before an expected traumatic event though, unless you want to sleep through the entire thing and wake up with a hangover.

Versed (midazolam) and propofol (aka "Milk of Amnesia").

In some places these drugs are now (2008) given by paramedics & ER docs to trauma victims almost in every case. The specific purpose is to induce amnesia. As a paramedic said: "I am about to paralyze you and stick a tube down your throat -- you want to remember that?"

Versed induces anterograde amnesia (from the point of injection forward).

Propofol induces retrograde amnesia for several hours. This means the memories of assault victims with sever injuries are nonexistent for the most part. To the extent they think they remember what happened, it is because they have been told by others what happened and integrated this in to there memories.

It may be up to you to refuse these drugs if you are involved in a trauma but wish to keep the memory! But they may be useful for inclusion in hacks focusing on reconsolidation reweighting (with techniques such as co counseling, for example.)

Both these drugs are on sale online.

2008

CBD

The anti-nausea and memory extinction effects of CBD seem to be closely related.

A research group [14] administered CBD to rats and determined that while THC caused sleepiness, CBD increased wakefulness and significantly decreased REM sleep.

The researchers characterized post-traumatic stress disorder, certain phobias and forms of chronic pain as “human situations which are conditioned” and that might be amenable to treatment with CBD. “I know that many patients with PTSD take cannabis, self administered,” one of them said.

They have been trying to interest the Israeli Ministry of Health in testing CBD and THC at various ratios to treat PTSD. One of the research team reviewed research in recent years that has shed light on aspects of CBD’s mechanism of action. Its lipid-solubility enables it to get into places in the brain that conventional neurotransmitters cannot reach. It is a potent anti-oxidative agent.

It turns out to be an antagonist to a recently discovered receptor called GPR-55 to which THC and 2-AG bind as agonists. It blocks the uptake of adenosine, an inhibitory neurotransmitter that may promote sleep. It blocks the formation of various cytokines (signaling compounds not released by nerves or glands) under certain circumstances. It activates the serotonin receptors. No wonder, then, that CBD plays a role in many clinical conditions.

THC predominates in plants bred for psychoactivity (as cannabis plants have been bred for generations ieverywhere). Cannabidiol -CBD- is the predominant cannabinoid in plants typically bred for fiber. There are only trace quantities of CBD in high-THC plants because one form of the same gene codes for THC synthase and the other codes for CBD synthase. Thus growers selecting for high THC content get low CBD.

Growers hoping to develop plants with a high CBD-to-THC ratio have been stymied by lack of access to an analytical test lab. In surreptitious tests, “high grade” buds were reportedly in the range of 15-20% THC and 0.1% CBD.

In many places drug enforcement administrations have placed CBD as illegal, even though CBD has no known adverse effects and doesn’t induce “euphoria.” The worst side effects attributed to marijuana -tachycardia (accelerated heartbeat), panic, confusion, anxiety, even psychosis- are effects of THC that CBD has been shown to mitigate!

By listing CBD as an illegal substance and denying growers the means to develop high-CBD plant strains, various people are 'protecting' the general public from an immunomodulator with anti-inflammatory, anti-convulsant, anti-psychotic, anti-oxidant, and neuro-protective properties. In whose interests could that possibly be?

Our own experiments with CBD so far show that it appears to prevent memory consolidation of events occuring after its ingestion with about the same effectiveness as extreme alcohol consumption, however there are none of the attendant side effects with the exception of not being able to get out of the chair.

If you grow your own, for high CBD harvest later and store in clear containers.

2008

Anandamide modulates sleep and memory in rats. This goes some way to explaining the effects of cannabis on consolidation.

Researchers [15] assessed the effect of the intracerebroventricular administration of anandamide (ANA) as well as its precursor metabolite arachidonic acid (AA), on the sleep–wakefulness cycle, memory formation, locomotor activity and pain perception.

Results indicated that ANA strikingly increases slow-wave sleep (SWS)2 and rapid-eye movement (REM) sleep at the expense of wakefulness (W); while deteriorating memory consolidation.

ANA also increases locomotor activity but does not modify pain perception threshold. In contrast, AA increases W and reduces SWS2, while deteriorating memory consolidation and increasing locomotor activity.

AA has no effect on pain perception. These results suggest that the brain cannabinoid system participates in the modulation of the vigilance states and mnemonic processes. So pigging out on cocoa and joints late at night is not a good idea for memory, but is great if you have insomnia.

2008

NMDA, Dextrophan tartrate & MK-801

Researchers found that Dextrorphan (@22 mg/kg), blocked long- but not short-term memory in a passive avoidance task[16].

This effect was not accompanied by any behavioral alterations that could interfere with passive avoidance performance. The action of dextrorphan was shared by a selective NMDA (N-methyl-D-aspartate) receptor antagonist, MK-801 (5-methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate, 0.1 mg/kg).

The results suggest that dextrorphan affects long-term memory, probably via blockade of NMDA receptors.

I’ve never injected DX straight into my amygdala, so cannot speak from experience here, but it seems that its effect depends on how the anxious reaction is acquired, when the drug is given, where it is administered and how much is given.

Hacking NMDA

The NMDA subclass of glutamate receptor plays an important role in acquisition of emotional memory. Exposure of a lab rat to conditioned anxiety stimuli suppresses vasopressin (VP) release and augments oxytocin (OT) or prolactin (PRL) release from the pituitary.

Experiments have aimed at investigating the effect of administering (peritoneally) various antagonists of NMDA receptors on the emotional memory associated with the suppressive VP and the augmentative OT or PRL responses to conditioned anxiety stimuli[17].

NMDA antagonists injected 30 min before training impair the VP, OT and PRL responses to the testing fear stimuli.

The antagonist injected after training, however, did not block the responses.

In the experiments with non-associatively applied anxiety stimuli, NMDA antagonists did not block the VP, OT or PRL response.

In the experiments with novel environmental stimuli, VP, OT or PRL responses were not impaired.

This selection of results suggest that an activation of NMDA receptors are required to acquire and recall but not to consolidate or retain the emotional weighting associated with VP, OT and PRL responses to conditioned anxiety stimuli.

I think the term ‘conditioned’ is pretty important here –how many humans have their anxiety responses deliberately conditioned? Also, there are BIG differences between experiments done on wild rats and caged rats –so we always have to be careful extrapolating to the human on

such occasions.

We also know that NMDA NR2B and NR2A subtype receptors exhibit difference in electrophysiological and signaling properties. These two subtype receptors have different roles in anxiety memory formation.

Using pharmacological blockade and genetic interference, researchers have found that NR2B is involved in acquisition of auditory anxiety-weighted memory in a conditioning-strength dependent way.

2008

Deep Brain Stimulation (DBS)

May have the potential to enhance existing memory circuits, giving a memory boost to otherwise healthy individuals.

A glimpse of that potential appeared in the Annals of Neurology in January 2008, in a documented case at a Canadian hospital. An obese man sought DBS as a possible treatment to curb his appetite. With the electrodes stimulating his hypothalamus, the man's working memory showed significant improvement and his IQ increased by nine points. [45]

2008

Myosin Vb

To recruit plasticity to help prevent age-related cognitive decline, researchers must first piece together the structural and functional changes behind this basic framework of memory formation. A molecule called myosin Vb may be indispensable to that framework, according to a study published in October 2008. Researchers observed that the myosin molecule in a rodent's hypothalamus facilitated the movement of new receptors, which in turn strengthened synaptic connections. When researchers blocked myosin, it prevented the addition of new receptors. This molecule could represent a new possibility for memory enhancement.[47]

2009

PKMzeta and ZIP again

In a series of studies, one team [18] found that this molecule was present and activated in cells precisely when they were signaled to move into LTP mode by a neighboring neuron.

In fact, the PKMzeta molecules appeared to herd themselves into precisely the connections among brain cells that were strengthened. And they stayed there, indefinitely. PKMzeta looked as if it might be the one that kept the LTP function turned on.

Researchers [19] found that one dose of ZIP even made rats forget a strong disgust they had developed for a taste that had made them sick three months earlier.

The memory erasing results have now been confirmed in many labs around the world, with different drugs that inhibit PKMzeta, and for many different forms of long-term memory.

Interestingly, ZIP does not affect short-term memory, or (once the drug is gone), the formation of new long-term memories in the same brain region.

A big question is, can one augment memory by increasing PKMzeta?

PKMzeta is bound up in the neurofibrillary tangles that are found in the brains of patients with Alzheimer's Disease. This is likely to alter the function of PKMzeta and may contribute to the memory loss characteristic of that disorder.[21]

There are two striking features of the experiments with ZIP that go to the essence of PKMzeta's role in memory:

First, the rapidity with which long-term memories, three month-old in the rats and presumably decades-old in humans, might be erased. This happens almost immediately with the injection of the drug.

Second, is the specificity. Short-term memory, the underlying structure of the brain, and the capacity to form new long-term memories are unaffected.

These two features occur because PKMzeta is an enzyme. (Crash introduction to proteomics: There are two general forms of proteins, structural and enzymatic.)

Mainstream neuroscientists had assumed that hundreds of structural proteins would be involved in the new synapses thought to store long-term memory. And there would be nothing unique to the structural proteins in the memory-storing synapses, as opposed to those synapses formed in development prior to experience.

But enzymes catalyze very specific chemical reactions and can be rapidly inhibited. The

discovery that long-term memories are maintained by the constant action of one such enzyme, and thus memories can be specifically and rapidly erased, was quite a surprise to many.

Enzymes are NHers friends ：)

Zeta Inhibitory Protein (ZIP) diffuses around 1-2 mm from an injection site in the brain, so the region affected is restricted. For more general application, an activity-dependent form of ZIP, i.e., a drug that becomes active only when the neurons are firing intensely, as when a memory is recalled, would be necessary. This might allow a specific, recalled long-term memory to be erased, rather than all long-term memories.

There is a entire subfield of memory research studying the role of what is called “reconsolidation blockade” that aims at essentially the same thing.[20]

How the reconsolidation work with propranolol on trying to reduce the emotional component of post-traumatic stress memories fits in with PKMzeta is actively being explored.

Developing memory enhancers that convert short- into long-term memories by increasing PKMzeta in the brain is also a possibility. This has been done experimentally in the fruit fly [22].

Has the research been ongoing long enough to answer the question of permanency? Is the memory erased forever?

Researchers, have done extensive experiments to try to see if, once disrupted by ZIP, a memory ever comes back. They waited weeks, they gave reminders, but the memories haven't so far seemed to return. Remarkably, giving the drug right before or even during the training had no effect on long-term memory formation tested a few days later. The drug has a pure “retrograde” effect.

Experimental result also suggests that the PKMzeta is not made immediately during learning,

but after a few hours, and that the drug itself only lasts a few hours.

2009

Research: Some traumas are bigger than others.

In the same vein as an earlier report that an experimental drug can selectively wipe out stressful memories, researchers have recently found that a gene variant, ADRA2B, increases the vividness of emotional memories.

It has been known for some time that the amygdala is a key brain region for the formation of emotional memories. In humans, previous research has shown [35]that pharmacological manipulation of adrenoceptors affects memory for emotional but not neutral events, a finding consistent with the role of the amygdala in the formation of memories for arousing events. Recent research has shown that a variant of the ADRA2B gene that codes the α2b-adrenergic receptor is linked to individual differences in emotional memory. Moreover, trauma survivors with the ADRA2B deletion variant are more likely to re-experience traumatic events. Following up on these findings, the results reported [36] are the first to tie the deletion variant of the gene to patterns of amygdala activation during the encoding of emotional memories.

Together, the papers [35, 36] break new ground in linking genetic variations in noradrenergic transmission with individual differences in amygdala activation and the enhanced retention of emotional memories.

More proteomics: CREB, alpha-CaM kinase II

Other research demonstrated that the protein CREB can help pinpoint the neurons linked to a particular memory. CREB (CyclicAMP Response Element-Binding) is a cellular transcription factor. It binds to DNA sequences and can increase or decrease transcription of the downstream genes [39]. In both fruit flies and sea slugs, early studies identified CREB's role in converting short-term memories to long-term ones, and had already suggested a basic difference in the molecular mechanisms of short-term versus long-term memories: The latter required new protein synthesis, while the former did not.

Findings with a different protein, alpha-CaM kinase II (CaMKII), demonstrated the chemical's ability to erase both short-term and long-term anxiety memories in a very targeted fashion:

CaMKII is necessary for LTP. When alpha-CaMKII is knocked out in mice, LTP is reduced by 50%. This can be explained by the fact that beta-CaMKII is responsible for approximately 65% of CaMKII activity.[40]

LTP can be completely blocked if CaMKII is modified so that it cannot remain active.

Persistent activation of CaMKII is necessarily for the maintenance of LTP and continues to be involved in the LTP maintenance process even after LTP establishment.

CaMKII is activated by the NMDA-receptor-mediated Calcium elevation that occurs during LTP induction. LTP can be induced by artificially injecting CaMKII. When CaMKII is infused in postsynaptically in the hippocampal slices and intracellular perfusion or viral expression, there is a two- to threefold increase in the response of the synapse to glutamate and other chemical signals. [41]

Administration of certain CaMKII blockers has been shown not only to block LTP but also to reverse it in a time dependent manner.

Back in 2004, researchers had found that anxiety conditioning increased phosphorylated

CaMKII in lateral amygdala synapses and dendritic spines, indicating that fear conditioning could be responsible for regulating and activating the kinase. They also discovered a drug, KN-62 [42] that inhibited CaMKII and prevented acquisition of fear conditioning and LTP.

It is possible with viral vector delivery to inject a specific gene of choice into a particular region of the brain in an already developed animal. A team in 2007 used this method to inject CaMKII into the hippocampus. They found that overexpression of CaMKII resulted in slight enhancement of acquisition of new memories. [43]

CREB served as a marker to help researchers address the long-standing challenge of how to identify the neurons that support a particular memory. Instead of gathering in single areas (as mainstream research expected) the neurons linked to a specific memory tend to be scattered throughout a brain region (every memory is a conglomerate of contributions from a variety of areas.) Remove CREB and anxious memories go with it -either they're wiped, or they remain long-term inaccessible. This is not just removing the emotional weighting of memories; it is removing the actual association of events.

2009

Reconsolidation timing

It had already become clear that each time memory is retrieved, it is susceptible to change (which is called a labile state), and the reconsolidation process can be interrupted (usually pharmacologically).

One researcher's idea was to alter the timing of the extinction process.[24]

In this experiment, the tone to stimulate a fear response was sounded. Then, after an interval,

which made this initial tone presentation stand out, extinction training was applied. The rats treated with this technique showed lower levels of fear induced by the sound itself, but also smaller chances that the original anxious memory would spontaneously resurface.

Having shown earlier that overexpression of alpha-CaM kinase II could delete an established fear memory, another team [44] wanted to know if elevated levels of the protein could derail short-term memory. That was the case when researchers boosted alpha-CaM kinase II activity in mice within ten minutes of engaging the animals in a learning activity—it stunted short-term memory formation. Researchers found that the timing is critical. When the same alpha-CaM kinase II] alteration took place fifteen minutes after the learning activity, it did not result in a disruption of short-term memory.

2009

Stop eating so much crap

Changing your diet to low GI could be a less invasive approach to boosting memory, according to a 2009 study in the Proceedings of the National Academy of Sciences. In Germany, a group of healthy adults ages fifty to eighty demonstrated a 20 percent improvement in verbal memory scores after reducing their calorie intake by 30 percent during a three-month period. [46]

2009/2010

“Non invasive technique”

This abstract out in January sounded extremely promising [23]:

“Recent research on changing fears has examined targeting reconsolidation. During reconsolidation, stored information is rendered labile after being retrieved. Pharmacological manipulations at this stage result in an inability to retrieve the memories at later times, suggesting that they are erased or persistently inhibited. Unfortunately, the use of these pharmacological manipulations in humans can be problematic.

Here we introduce a non-invasive technique to target the reconsolidation of fear memories in humans. We provide evidence that old fear memories can be updated with non-fearful information provided during the reconsolidation window.

As a consequence, fear responses are no longer expressed, an effect that lasted at least a year and was selective only to reactivated memories without affecting others. These findings demonstrate the adaptive role of reconsolidation as a window of opportunity to rewrite emotional memories, and suggest a non-invasive technique that can be used safely in humans to prevent the return of fear.”

To achieve this, the researchers created a fear memory in the laboratory by showing participants a visual object and pairing it with mild electric shocks -- a process known as classical fear conditioning. Fear conditioning is successful when subjects show a fear response to the object when it is subsequently presented on its own. In order to measure the fear memory, they examined the skin conductance response to the object, an indication of arousal.

Once this fear memory was formed, participants were reminded of the object a day later. This reactivation of the memory was intended to initiate the reconsolidation process. During this process, information that the same object was now "safe" was provided through extinction training. Presenting this new "safe" information during reconsolidation was designed to incorporate it into the initial fear memory. A day later, the participants were tested again to see whether they continued to demonstrate a fear response when presented with the object.

Extinction training on its own led to the reduction of fear, but fear returned when tested at a later time or when following stress. However, the NYU researchers found that if extinction training was conducted during the reconsolidation window, when the memory was temporarily unstable, fear responses did not return. They also showed that rewriting of the fear memory as safe was

specific to the object that was reactivated prior to extinction. Fear memories for other objects returned following extinction, suggesting that the technique is selective rather than having a general effect on memories.

The experiment was conducted over three days: the memory was formed in the first day, rewritten on the second day, and tested for fear on the third day. However, to examine how enduring this effect is, a portion of the participants was tested again about a year later. Even after this period of time, the fear memory did not return in those subjects who had extinction during the reconsolidation window. These results suggest that the old fear memory was changed from its original form and that this change persists over time.

2010

Sleep deprivation

Now knowing that most original consolidation takes place during defragging in sleep, researchers decided to evaluate whether sleep deprivation after exposure to an aversive event might eliminate the associated fear, due to the lack of memory consolidation that would typically occur during sleep.

They evaluated healthy volunteers who were shown video clips of both safe driving and unexpected motor vehicle accidents. Half of the volunteers were then deprived of sleep while the other half received a normal night's sleep.

Later testing sessions revealed that sleep deprivation eliminated the anxiety-associated memories through both anxiety recognition and physiological anxiety reactions.

Sleep deprivation after exposure to a traumatic event, whether intentional or not, may help

prevent wrong weighting on initial consolidation.

One of the researchers said, "New insights into the neurobiology of sleep dependent learning may make it possible for these people to take a medication that disrupts this process while leaving restorative elements of sleep intact."

However, there us no information at this stage regarding whether other, non-anxious memories are affected as well as the targets.

Another team [25] discovered that sleep deprivation in mice undermines the function of a specific molecular mechanism in the hippocampus, the area of the brain responsible for consolidating new memories.

The researchers kept mice awake for five hours. They found increased levels and activity of the enzyme PDE4 and lower levels of the molecule cAMP in these mice. cAMP plays a crucial role in the formation of new connections between brain cells in the hippocampus and the strengthening of old ones. And without these processes we cannot learn.

They then inhibited the activity of the PDE4 enzyme and discovered that this counteracts the effects of sleep deprivation. Lack of sleep leads to an increased PDE4 activity which then blocks the action of cAMP. Consequently fewer connections being formed or strengthened in the hippocampus. This is the first report of researchers 'saving' synaptic plasticity (the ability to develop and strengthen new connections) from the effects of sleep deprivation.

The discovery not only shows how a lack of sleep leads to problems, but also how these problems can be solved. Drugs that stimulate the action of cAMP may make it possible to counteract the effects of sleep deprivation.

2010

PKMzeta and ZIP again again

Whereas the role of PKMζ in animal models of declarative knowledge/memory is established, its effect on procedural knowledge/memory is not well understood.

Researchers [28] showed that PKMζ inhibition, via injection of zeta inhibitory peptide (ZIP) into the rat sensorimotor cortex, disrupts sensorimotor memories for a skilled reaching task even after several weeks of training.

The rate of relearning the task after the memory disruption by ZIP was indistinguishable from the rate of initial learning, suggesting no significant savings after the memory loss.

These results indicate a shared molecular mechanism of storage for declarative and procedural forms of memory.

2010

BDNF again

Once again we hear that researchers have found a way to pharmacologically induce a memory of safety in the brain of rats, mimicking the effect of training.

So what's new?

Rats normally freeze when they hear a tone they have been conditioned to associate with an electric shock. The reaction can be extinguished by repeatedly exposing the rats to the tone with no shock. In this work, administering a protein directly into the brain of rats achieved the same effect as extinction training. The protein, brain-derived neurotrophic factor or BDNF, is one of a class of proteins that support the growth and survival of neurons.

Prior work has shown that extinction training does not erase a previously conditioned fear memory, but creates a new memory associating the tone with safety. The surprising finding here is that the drug substituted for extinction training, suggesting that it induced such a memory.[29] BDNF created a memory of safety in rats that were afraid.

Memory formation involves changes in the connections, or synapses, between neurons, a process known as synaptic plasticity. One brain structure critical for extinction memory in rats is the infralimbic prefrontal cortex (ILC). Drugs that block synaptic plasticity impair the formation of extinction memory when injected into the ILC, causing rats to continue freezing at high levels after extinction training.

BDNF, on the other hand, permits a learning experience to increase the size and strength of synaptic contacts between neurons. Previous work from other groups has implicated BDNF in extinction learning. In this study, after rats were conditioned to fear a tone by pairing it with a footshock, BDNF was infused directly into the ILC. The next day, BDNF-infused rats showed little freezing to the tone, as if they had received extinction training.

Experiments showed that BDNF-induced extinction did not erase the original fear memory. Training to reinstate the tone-shock association was just as effective with the rats receiving BDNF as those without. Also, the effect of BDNF was specific to extinction. It did not reduce general anxiety or change the animals' tendency to move around.

The researchers also found that rats that were naturally deficient in BDNF were more likely to do poorly in extinction trials. These rats were deficient in BDNF in the hippocampus, a brain structure that plays an important role in memory and extinction, and which has connections to the ILC. Failure to extinguish anxious memories is thought to contribute to anxiety disorders,

such as post-traumatic stress disorder (PTSD). People with PTSD have a smaller than normal hippocampus and ILC.

2011

More research

Just one encounter with an aroma can lodge the scent into your memory for years. Researchers have exploited this to gain important insight into memory formation. When the brain encounters an odor, it temporarily saves the data in the hippocampus. But it is the frontal cortex that eventually encodes the memory into long-term storage. Researchers proposed that the hippocampus tags cells in the cortex (decides the eventual location of a memory) at the moment of a memory-generating experience. Breaking communication between the brain regions may interfere with tagging and subsequently handicap long-term memory. For rats, that means forgetting a morsel is tasty and safe. In their study, the team fed cumin-spiced food to a control set of rats and to another group whose frontal cortex had been temporarily cut off from communication with the hippocampus. One week later, the altered rats still enjoyed grub flavored with the spice, as expected. A month out, however, their preference cumin had vanished. This was taken as confirmation that long-term memories cannot form without a link between the hippocampus and the frontal cortex[30] but various other interpretations of this result are possible, as we're sure you'll notice. As far as we know, no such tests have been done on wild type rats either.

2011

spironolactone & RU486

mineralocorticoid and glucocorticoid receptors

Corticosteroid hormones regulate appraisal and consolidation of information via mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) respectively. How activation of these receptors modulates retrieval of fearful information and the subsequent expression of fear is largely unknown. Researchers tested here whether blockade of MRs or GRs during retrieval also affects subsequent expression of fear memory.[31]

Mice were trained in contextual or tone cue fear conditioning paradigms, by pairing mild foot shocks with a particular context or tone respectively. Twenty-four hours after training, context-conditioned animals were re-exposed to the context for 3 or 30 minutes (day 2); tone-conditioned animals were placed in a different context and re-exposed to one or six tones.

Twenty-four hours later(day 3) and one month later, freezing behavior to the aversive context/tone was scored again.

MR or GR blockade was achieved by giving spironolactone or RU486 subcutaneously one hour before retrieval on day 2.

Spironolactone administered prior to brief context re-exposure reduced freezing behavior during retrieval and 24 hours later, but not one month later. Administration of spironolactone without retrieval of the context or immediately after retrieval on day 2 did not reduce freezing on day 3. Re-exposure to the context for 30 minutes on day 2 significantly reduced freezing on day 3 and one month later, but freezing was not further reduced by spironolactone. Administration of spironolactone prior to tone-cue re-exposure on day 2 did not affect freezing behavior.

Treatment with RU486 prior to re-exposure did not affect context or tone-cue fear memories at any time point.

The researchers concluded that MR blockade prior to retrieval strongly reduces the expression of contextual fear, implying that MRs, rather than GRs, play an important role in retrieval of emotional information and subsequent fear expression.

2011

Gap Junctions, carbenoxolone and mefloquine.

researchers have discovered what may be a completely unexplored drug target for the treatment of anxiety disorders. [26]

Normally, when people or animals experience a frightening event, they learn to fear the place of the event and any signals that were present at the time due to association (cells that fire together wire together). Most neuroscience research has emphasized how this phenomenon occurs through chemical communication among neurotransmitters flowing across synapses -- the space between neurons. However, there are also small, inhibitory neurons in these regions as well, which have direct electrical contact with one another through connecting channels known as "gap junctions."

Neuronal gap junctions form where inhibitory neurons touch one another. They are like an opening between nerve cells, a gap in the membranes separating the cells from one another; they let the electrical activity in one neuron affect the neuron it touches.

Because the gap junctions cause the inhibitory neurons to fire together, they may cause these inhibitory neurons to act as a pacemaker for the excitatory neurons, making them fire at the same time so they are better able to make memories.

The research team used several drugs in rats that block the gap junctions and found that they disrupted critical rhythms in the dorsal hippocampus and prevented anxious spatial memories (for places) from forming. The drugs could block the formation of fear of places when given after the frightening experience.

Rats were injected with two blockers: the general gap junction blocker carbenoxolone and selective blocker mefloquine. Carbenoxolone is used for treating ulcerations and lesions. It has been proven to have negative effects on cognition and serves as a gap junction blocker. Mefloquine is used to prevent malaria and has numerous side effects in humans including anxiety, paranoia, insomnia and seizures, but has serious side effects with long term use.

Neuronal gap junctions may be an unexplored drug target; they hold promise because giving a regular injection of drugs in a cavity near the abdomen worked as effectively as an injection directly into the brain. In addition, the injections worked when given right after the frightening experience.

This research shows how neurons can coordinate their activity, and this coordination is critical for memory formation, implying that we may improve memory formation by facilitating gap junctions when memory is impaired.

2011

More proteomics - protein synthesis inhibitors

It has been well-established that the synthesis of new proteins within neurons is necessary for memory storage. More specifically, this process is important for stabilizing memories because it triggers the production of the new proteins that are required for molecular and synaptic changes during both initial consolidation and reconsolidation.

Using laboratory rats to determine if there were differences between memory consolidation and reconsolidation during protein synthesis, researchers [27] used mild electric shocks paired with an audible tone to generate a specific associative fear memory and, with it, memory consolidation.

They played the audible tone one day later -- a step designed to initiate recall of the earlier fear memory and bring about reconsolidation. During both of these steps, the rats were injected with a drug designed to inhibit the initiation stage of protein synthesis.

Their results showed that the inhibitor could effectively interfere with memory consolidation, but had no impact on memory reconsolidation.

A protein synthesis inhibitor is a substance that stops or slows the growth or proliferation of cells by disrupting the processes that lead directly to the generation of new proteins.

You'll recall that this sort of stuff was going on some time ago (see above) but this time they neglected to say which specific compounds were involved...

2011

More research on Zinc

Zinc as Zn(2+) is an essential ion that is stored in and co-released from glutamatergic synapses and it modulates neurotransmitter receptors involved in long-term potentiation (LTP). However, the mechanism(s) underlying Zn(2+) -induced modulation of LTP remain(s) unclear. This year (2011) research results indicate that Zn(2+) at low concentrations enhances LTP by modulating P2X receptors. Although it is not yet clear which purinergic receptor subtype(s) is responsible for these effects on LTP, the data presented here suggest that P2X(4) but not P2X(7) is involved.[33]

Also discovered: Local blockade of zinc or MAPK in the hippocampus of wild-type mice impairs

contextual discrimination. Mice without the synapse-specific vesicular zinc transporter ZnT3 (ZnT3KO mice) have reduced activation of the Erk1/2 MAPK in hippocampal mossy fiber terminals, disinhibition of zinc-sensitive MAPK tyrosine phosphatase activity, and impaired MAPK signaling during hippocampus-dependent learning. They have complete deficits in contextual discrimination, spatial & working memory.[34]

2011

Metyrapone

Metyrapone has been found in early human trials to reduce recollection of emotional memories in normal volunteers. The volunteers showed significant impairment in ability to retrieve memories with negative emotional content while not impairing memories with neutral content. Researchers found, for instance, that injecting patients with metyrapone while the patient recalls a negative memory, seems to diminish that memory.[37]

The lead author of that research reports: "Metyrapone is a drug that significantly decreases the levels of cortisol, a stress hormone that is involved in memory recall. Manipulating cortisol close to the time of forming new memories can decrease the negative emotions that may be associated with them."

Unfortunately, it can also cause dizziness, headache, vomiting, nausea, and so on, as well as severe allergic reactions, dehydration, confusion, and adrenal insufficiency.

2011

Still working on PKMzeta

Researchers discover that long-term memory in the marine snail can be erased by inhibiting the activity of protein kinase M (PKM). Next steps include studying the relationship between PKM and the synapses and how the structure of synapses changes when PKM is inhibited.[38]

Todd Sacktor has taken out a patent on PKMzeta, so it's only a matter of time before any product comes out of the mainstream closet and onto the net. If, that is, there is any product. At the beginning of this update we noted how companies intending to produce drugs that could be used for enhancement are having a difficult time, and this is mostly because they are getting bought out by big pharma. Two possibilities remain: either big pharma wants to prevent such developments or (more likely) wants a monopoly.

Other stuff that's been found out

Trauma intervention techniques like EFT and TAT have proved to work very well at reducing the emotions associated with trauma, as do neurofeedback, biofeedback and co counseling. These approaches allow you to retain the memory, but your response to it becomes less of a reaction and more of a healthy response.

The more we know about how long-term memory is induced in the brain and how our memories are maintained in the brain, the more we are going to be able to induce or treat long-term memory loss. The fundamental mechanisms of learning and memory are identical, as far as we can tell.

Where can I find out about/get...?

http://www.chemicalbook.com/ProductIndex_EN.aspx

Party on, dudes :)

Footnotes

1. Recent work (Ramos & Arnsten, 2005; Arnsten & Li, 2007) has shown that alpha-2 receptors are much more prominent post-synaptically, and guanfacine is more selective for those than for pre-synaptic autoreceptors (and is selective to a greater extent than clonidine , another alpha-2 blood pressure med known to produce sedation.

2. Also see the fun MAP Kinase Signal Transduction Animation [google] by Dr. Vic Lemas .

3. Apparently U0126 is in the “early clinical phase” for cancer treatment and is viewed as a “radical approach” to stroke therapy. TMost published studies have been done with cell cultures, with a few in live rodents. The target pathway’s many areas (cell cycle, cytoskeleton, stress response, growth, differentiation, motility, etc) suggests that U0126 could be the mother of all side effect drugs, meaning that it probably won’t be approved for humans. However, the potential for abuse suggests in many cases 'official' approval will only matter so much. It’s ubiquitous in reasearch (lots of labs use it) and pretty inexpensive. People who really want it can get it.

4. Original paper: Doyere V, Debiec J, Monfils MH, Schafe GE, Ledoux JE. (2007). Synapse-specific reconsolidation of distinct fear memories in the lateral amygdala . Nat Neurosci. Mar 11

5. Pastalkova, E. et al. Storage of spatial information by the maintenance mechanism of LTP. Science 313, 1141–1144 (2006).

6. Source: Nature NeuroScience

http://www.brainatl as.com/aba/ 2006/060921/ full/aba1683. Shtml

7. Strawn & Geracioti, 2007

8. Debiec & LeDoux, 2006

9. Strawn & Geracioti 2007

10. Nature Reviews Neuroscience 8, 651 (September 2007)

11. Sananbenesi, F. et al. A hippocampal Cdk5 pathway regulates extinction of contextual fear. Nature Neurosci. 10, 1012–1019 (2007)

12. Joseph LeDoux of the Center for Neural Science at New York University and colleagues

13. Larry Squire, a neuroscientist at the University of California, San Diego and the Veterans Affairs San Diego Medical Center

14. led by Eric Murillo-Rodriguez

15. Eric Murillo-Rodríguez, Manuel Sánchez-Alavez, Luz Navarro,Dolores Martínez-González, Rene Drucker-Colín and Oscar Prospéro-García

16. J Sierocinska, E Nikolaev, W Danysz, L Kaczmarek

17. Neuropharmacology 2008

18. Dr. Todd C. Sacktor, André A. Fenton

19. Yadin Dudai & team at the Weizmann Institute of Science in Israel

20. Karim Nader, Joseph LeDoux, Susan Sara, Cristina Alberini, Yadin Dudai, and others.

21. Source for this section: Online questionnaire with Dr Todd C Sacktor, April 2009

22. Jerry Yin and Eric Drier, when at the Cold Spring Harbor Laboratories, and now at the University of Wisconsin, Madison.

23. “Preventing the return of fear in humans using reconsolidation update mechanisms”, Daniela Schiller, Marie-H. Monfils, Candace M. Raio, David C. Johnson, Joseph E. LeDoux & Elizabeth A. Phelps. Source:
http://www.nature.com/nature/journal/vaop/ncurrent/abs/nature08637.html?lang=en

24. Marie Monfils, an assistant professor of psychology at The University of Texas at Austin

25. Robbert Havekes and colleagues in the 22 October issue of Nature.

26. led by UCLA professor of psychology Michael Fanselow, The research is published Jan. 7 2011 in the journal Science.

27. Eric Klann, Kiriana Cowansage, Joseph LeDoux, and Charles Hoeffer.

28. Erasing Sensorimotor Memories via PKMζ Inhibition, Lee Michael von Kraus, Todd Charlton Sacktor, Joseph Thachil Francis. Source: PLoS One [Open Access] http://www.plosone.org/article/info:doi/10.1371/journal.pone.0011125

29. Dr. Gregory Quirk."Drug substitutes for training in rats, inducing a memory of safety." June 3rd, 2010 in Medicine & Health / Research. www.physorg.com/news194792258.html The work is reported in the June 4 issue of Science.

30. Bruno Bontempi and colleagues from the University of Bordeaux in France

http://discovermagazine.com/2011/jul-aug/28-severed-brain-connection-prevents-rats-remembering-spicy-delicious

31. Blocking Mineralocorticoid Receptors prior to Retrieval Reduces Contextual Fear Memory in Mice Ming Zhou, Merel Kindt, Marian Joëls, Harm J. Krugers

32. http://www.jneurosci.org/content/26/27/7181.full.pdf OR http://www.jneurosci.org/content/26/27/7181.full

33. http://www.bioportfolio.com/resources/pmarticle/146749/Zinc-Enhances-Long-term-Potentiation-Through-P2x-Receptor-Modulation-In-The-Hippocampal.html

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