Pharmacological Manipulation of Memory: Facts, Fictions & Ethics

Peter B. Reiner
National Core for Neuroethics

604.827.5836
peter.reiner@ubc.ca

Pharmacological Manipulation of Memory

- Cognitive Enhancers
  - Cholinomimetics
  - Glutamate receptor modulators
    - Ampakines
  - cAMP/CREB modulators
- Therapeutic Forgetting
Memory declines with age

Cholinomimetics

- Loss of basal forebrain cholinergic neurons in aging & Alzheimer’s disease
- Electrolytic, excitotoxic and immunotoxic lesions of basal forebrain produce memory impairments
- Muscarinic antagonists produce memory impairments
Cholinomimetics

- Based on the cholinergic hypothesis, acetylcholinesterase inhibitors were developed for Alzheimer’s disease
- Donepezil (Aricept) approved for Alzheimer’s disease in 1996
- Rivastigmine (Exelon) approved in 2000
- Clinical trials of donepezil in young adults yield mixed results

Cholinomimetics

- The cholinergic hypothesis fomented much basic and clinical research
- Cholinomimetics were originally developed for AD
- Selective nicotinic receptor agonists are now in clinical development for a range of memory disorders
Glutamate receptor modulators

- Glutamate receptors mediate the bulk of excitatory synaptic transmission in the brain
- Abundant evidence suggests that glutamate receptors are involved in synaptic plasticity

Ampakines are the prototypical glutamate receptor modulators

- In 1984, Gary Lynch & Michel Baudry put forth a radical hypothesis suggesting that an increase in the number of glutamate receptors underpinned LTP
- In the early 1990’s Cortex began to develop AMPA receptor modulators called ampakines
Ampakines improve recall of nonsense syllables

Ampakines as cognitive enhancers

- Hypothesis emerged more from hunch than data
- A wealth of data has developed supporting the role of AMPA receptors in synaptic plasticity
- Mechanism of ampakine action remains unclear
Memories are encoded with differing temporal patterns

- LTP can be induced with different patterns
- Late LTP is protein synthesis dependent

Scharf et al., 2002
Fear conditioning is protein synthesis dependent

Nadler et al., 2000

CREB: A molecular target for long-term memory

- Convergent data from Aplysia, Drosophila & rodent brain all suggest that CREB mediates the protein-synthesis sensitive components of long-term changes in synaptic strength
CREB: A molecular target for long-term memory

- The cAMP/CREB cascade has several intervention points
- Phosphodiesterase inhibition is well established

PDE4: A molecular target for long-term memory

- PDE4 is an attractive target
  - cAMP specific
  - widely expressed in brain
What to enhance?

Neuroethics of Cognitive Enhancement

- Coercion
- Distributive Justice
- Authenticity
- Safety
Memories are encoded with differing temporal patterns.

The Reconsolidation Hypothesis

- Memories are imperfectly stable
- Recalling a memory makes it labile
- Reconsolidation integrates memories
Fear Conditioning

Anatomy of the amygdala
β-blockers impair reconsolidation of auditory fear conditioning

Interference with reconsolidation using *timed* extinction


Therapeutic Forgetting

- Reconsolidation as the basis for ongoing memory updating
- Pharmacological & behavioural means of manipulating memories.