Role for CCR5 in Plasticity and Memory

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CCL5 and CCR5 were identified in a mouse reverse genetic screen for mutations that enhance memory.
Knockouts of CCL5 and CCR5 enhance long-term memory for contextual conditioning.
Delta32 is a naturally occurring CCR5 null allele
Maraviroc is a well tolerated FDA approved CCR5 antagonist!
Summary

• CCR5 modulates the biochemistry, cellular physiology and neurocircuit biology of memory
• CCR5 modulates memory stability
• CCR5 antagonists could be used as plasticity and cognitive enhancers
• CCR5 inhibition enhances recovery after brain injury
• Human studies suggest that CCR5 has similar function in humans
• CCR5 KOs and knock downs prevent deficits in biochemistry, cellular physiology and memory caused by the GP120 V3 loop peptide
Post-training enhancement in MAPK/CREB signaling, CA1 LTP and hippocampal memory in CCR5 KOs
CCR5 knockout results in normal short-term, but enhanced long-term memory for contextual conditioning.
Jody testing spatial learning in mice
CCR5 knockout results in enhanced spatial memory
CCR5 knockout results in enhanced social memory
Enhanced hippocampal MAPK and CREB activation following contextual conditioning in CCR5 KOs
Enhanced hippocampal CA1 LTP in CCR5 KOs
Adult Hippocampal Manipulations of CCR5
AAV5 shRNA decreases CCR5 expression in the CA fields of the hippocampus
AAV5-CCR5 knock-down in neurons

shRNA-Cont

shRNA-CCR5

eGFP

NeuN

eGFP/NeuN

Iba1

eGFP/Iba1

Merge

DAPI
AAV5-CCR55 knock-down results in enhanced contextual memory
AAV5-CCR5 knock-down results in enhanced spatial memory
Treatment with Maraviroc, an FDA approved CCR5 inhibitor, enhances hippocampal memory
Treatment with a CCR5 antagonist enhances contextual memory.
Treatment with a CCR5 antagonist enhances social memory
Treatment with a CCR5 antagonist enhances social memory in Nf1 mice

**Social recognition test**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Exploration time (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT/Control</td>
<td>Familiar: 40% Novel: 40%</td>
</tr>
<tr>
<td>WT/Maraviroc</td>
<td>Familiar: 40% Novel: 40%</td>
</tr>
<tr>
<td>Nf1/Control</td>
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<tr>
<td>Nf1/Maraviroc</td>
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</tr>
</tbody>
</table>
Beyond the hippocampus:
Enhanced cortical spike-time dependent plasticity and somatosensory plasticity in CCR5 KOs and AAV5 knock-downs
Decreases in CCR5 (AAV5, KO) lead to enhanced somatosensory cortical LTP
Decreases in CCR5 (AAV5, KO) lead to enhanced somatosensory plasticity

With Kevin Fox Laboratory
Beyond the hippocampus:
Enhanced retrosplenial spine turnover and clustering in CCR5 KOs

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2-photon Imaging Through a Cranial Window

Cranial Window

Sparse Thy1-YFP labeling
Behavior + Imaging Paradigm

Day
-3
0

Baseline Phase

Learning Phase
1
2
3
4
5

Image
Spine turnover before learning in retrosplenial cortex is highly correlated with contextual memory: in vivo 2-Photon studies

![Graph showing correlation between Baseline Spine Turnover and Future Contextual Learning]
Enhanced baseline retrosplenial spine turnover in CCR5 KOs: 2-Photon studies
Spine clustering in retrosplenial cortex is increased after learning and is highly correlated with contextual L&M: 2-Photon studies
Enhanced retrosplenial spine clustering following contextual training in CCR5 mutants: 2-Photon studies
Mechanisms of learning and memory affected by CCR5 are highly conserved
Beyond Memory:
Enhanced recovery after brain injury in manipulations that decrease CCR5 function
Enhanced recovery following stroke in mice with AAV5-shRNA for CCR5

With Thomas Carmichael Laboratory
Enhanced recovery following stroke in mice treated with Maraviroc

Grid walking

With Thomas Carmichael Laboratory
CCR5 improves recovery after Traumatic Brain Injury

Shohami’s lab, Jerusalem
Enhanced recovery (spatial learning) following TBI in rats with hippocampal AAV5-shRNA for CCR5

With Esty Shohami Laboratory
Enhanced recovery (spatial learning) following TBI in rats treated with Maraviroc

With Esty Shohami Laboratory
CCR5: Human Stroke Studies
With the Shohami and Bornstein labs
Naturally occurring CCR5 null allele (delta 32)
Tel Aviv Brain Acute Stroke Cohort (TABASCO) Study

- Analyzed: 563
- Non-carriers: 476
- Delta 32 Heterozygotes: 82
- Delta 32 Homozygotes: 5
- Total Delta 32 carriers: 15.5%
Improved cognitive performance one year after stroke in delta 32 carriers
Transgenic over-expression of CCR5 leads to hippocampal memory deficits
CCR55 transgenic over-expression causes deficits in memory for contextual conditioning.
CCR5 transgenic over-expression causes deficits in spatial memory
The V3 loop peptide from GP120, an HIV protein, causes acute memory deficits that are prevented by a CCR5 KO or knock-down
V3 loop peptide causes acute MAPK signaling deficits

Cannulation 2 weeks → Cont or V3 Infusion 30 min → Training 1 or 3 h → Dissect CA1

p-MAPK/t-MAPK

*p*
V3 loop peptide causes acute synaptic plasticity deficits:
V3 loop peptide causes acute synaptic plasticity deficits: rescue by the CCR5 null mutation
CCR5 KO prevents acute contextual memory deficits caused by the V3 loop peptide.
AAV5-CCR5 knock-down prevents acute contextual memory deficits caused by the V3 loop peptide
Summary

• KO, knock-down and pharmacological inhibition of CCR5 result in enhancements in MAPK/CREB signaling, LTP, and memory.
• CCR5 inhibition enhances spine turnover and spine clustering, two phenomena associated with higher rates of learning and memory.
• CCR5 inhibition enhances cortical spike time dependent plasticity, and sensory plasticity
• CCR5 inhibition enhances recovery after brain injury
• CCR5 antagonists could be used as plasticity and cognitive enhancers
• CCR5 KOs and knock downs prevent signaling, LTP and learning deficits caused by the GP120 V3 loop peptide
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