9.914 Special Topics: Genetics, Neurobiology, and Pathophysiology of Psychiatric Disorders
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Chronic Antidepressant Treatment Increases Neurogenesis in Adult Rat Hippocampus

Malberg, Eisch, Nestler and Duman
Journal of Neuroscience
2000
Depression and Stress

• 2-5% of the U.S. population affected
• 40-50% of the risk is genetic
• But non-genetic factors also contribute such as e.g. stress:
  • Decrease in hippocampal volume associated with depression and stress
    – reduced hippocampal granule cells genesis
    – decreased cell proliferation
    – death of CA3 pyramidal neurons
Depression and Stress

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Does antidepressant treatment influence adult neurogenesis in the hippocampus?
Neurogenesis in the Adult Brain

**Neurogenic Niche:**
Microenvironment that allows differentiation and integration of newborn neurons
(diffusible molecules, influence of neighboring cells or neurons that are connected to these, neurotransmitter levels, synaptic contacts...)

Figure by MIT OpenCourseWare.
Subventricular Zone (SVZ)
Subgranular Zone (SGZ)

Figure by MIT OpenCourseWare.
Chronic Antidepressant Treatment Increases Neurogenesis in Adult Rat Hippocampus

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Bromodeoxyuridine (BrdU)

- Used as thymidine analog
- Incorporates into the DNA during S-phase
- Can be visualized using a BrdU antibody

But keep in mind:
- Does NOT label proliferation but DNA synthesis
  - appropriate controls (for example DNA repair)
- Toxic, mutagenic substance (cell death, alters NA stability, influences cell cycle...)
1) Does chronic antidepressant treatment increase number of BrdU positive cells?

[A] Vehicle ECS
[B] Vehicle ECS + 24 hrs BrdU
[C] ECS + 10 d ECS
[D] ECS + 24 hrs BrdU

GCL, H, SGZ

Tranylcypromine, Fluoxetine

10 d ECS

14-21 d ADT

BrdU

14-21 d ADT

S

4 d

24 hrs

Courtesy of Society for Neuroscience. Used with permission.
1) Does chronic antidepressant treatment increase number of BrdU positive cells?

- ECS: 50% increase
- Chemical antidepressants: 20-40% increase

In general:
- dosage of chemical antidepressants used seems to be relatively high
- Count cells in hilus and SGZ

Is this an effect of chronic treatment or can it also be achieved by acute treatment?
1) Does chronic antidepressant treatment increase number of BrdU positive cells?

- Acute treatment does not affect BrdU-positive cell number
- Long-term treatment leads to a significant increase
- Not seen with non-antidepressant psychotropic drug (haloperidol)
- Consistent with time course for therapeutic action

○ Onset of Fluoxetine 4-6 weeks (dosage dependent?)

![Graph showing BrdU labeled cells per dentate gyrus over time with control, 1D, 5D, 14D, and 28D conditions.](Image)
2) Does chronic treatment increase cell proliferation?

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3) Are the new cells surviving and is treatment influencing survival rate?

- Total number of BrdU labeled cells is decreased both in control and in treated group.
- Treatment does not influence survival.

Do these cells differentiate? Is there an influence on cell fate?
4) What are the cell fates of the newborn cells?

After 4 weeks:
• no clusters

In both control and treated groups:
• 75% neuronal
• 13% non-glial
• 12% not labeled with either marker

→ Antidepressants do not influence differentiation
→ Antidepressants do not influence survival and maturation

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Summary

Chronic antidepressant treatment increases neurogenesis in the dentate gyrus

Treatment:

• increases cell proliferation (increase in BrdU labeled cells)
• does not influence cell survival
• does not influence cell differentiation
Discussion

• Is SGZ neurogenesis necessary for antidepressant function? (Simona)

• Neurogenesis by itself not enough but cells need to be integrated into circuitry (behavioral effect? Simona)

• How do the antidepressants influence neurogenesis? (microenvironment of SVZ but also influence of other brain regions) (Simona)

• Effects are influenced by genetic background of animal

• How does this translate into humans? (reduced volume due to reduced neurogenesis?)

• How does hippocampal neurogenesis contribute to regulation of emotion? (differences between ventral and dorsal hippocampus)