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9.914 Special Topics: Genetics, Neurobiology, and Pathophysiology of Psychiatric Disorders
Fall 2008

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Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants

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Depression

- Since 1960, depression has been diagnosed as “major depression” based on symptomatic criteria set forth in the Diagnostic and Statistical Manual (DSMIV)
- Depression is not based on objective diagnostic tests, but rather on highly variable set of symptoms

Table 1. Diagnostic Criteria for Major Depression

Depressed mood
Irritability
Low self esteem
Feelings of hopelessness, worthlessness, and guilt
Decreased ability to concentrate and think
Decreased or increased appetite
Weight loss or weight gain
Insomnia or hypersomnia
Low energy, fatigue, or increased agitation
Decreased interest in pleasurable stimuli (e.g.,
sex, food, social interactions)
Recurrent thoughts of death and suicide

A diagnosis of major depression is made when a certain number of the above symptoms are reported for longer than a 2 week period of time, and when the symptoms disrupt normal social and occupational functioning (see DSMIV, 2000).

Neural circuitry of depression

The **hippocampus** and the **prefrontal cortex** were the main focus for a while in depression.

Recent research has focused on other subcortical structures: **nucleus accumbens, amygdala and the hypothalamus.**

Monoaminergic (NEergic/5-HTergic) neurons are particularly important in establishing the neural circuitry in depression

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Depression - treatment

- The treatment of depression was revolutionized 50 years ago, when two classes of agents were discovered: the tricyclic antidepressants (TCA) and the monoamine oxidase inhibitors (MAOI)
- The original TCA agents (imipramine) arose from antihistamine research; MAOI arose from antitubercular drugs
- More recently, led to the discovery of serotonin-selective reuptake inhibitors (SSRI) and norepinephrine-selective inhibitors.

Antidepressants - mechanisms of action

- MAOIs block monoamine oxidase (MAO), so it inhibits 5-HT and norepinephrine metabolism
- TCAs block reuptake pumps for 5-HT and/or norepinephrine; they cannot be reshuttled back into the synaptic neuron; they alter the sensitivity of some 5-HT and norepinephrine receptors
- SSRIs block reuptake pump for 5-HT, 5-HT cannot be reshuttled back in the synaptic neuron

TCA action

SSRI + MAOI - action

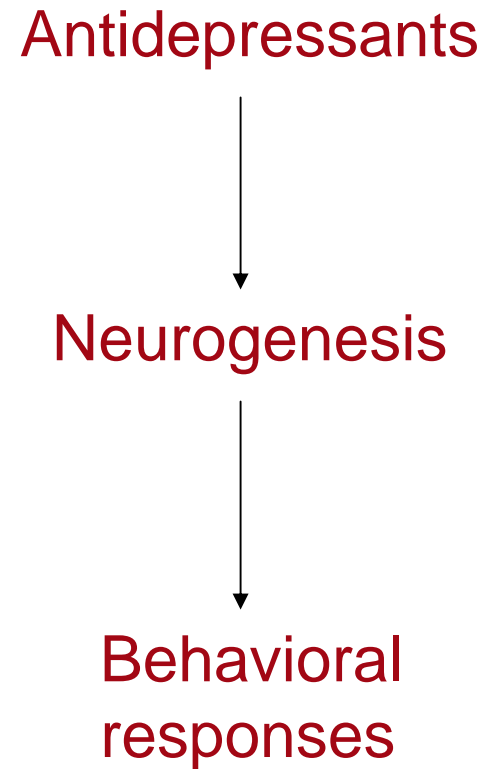
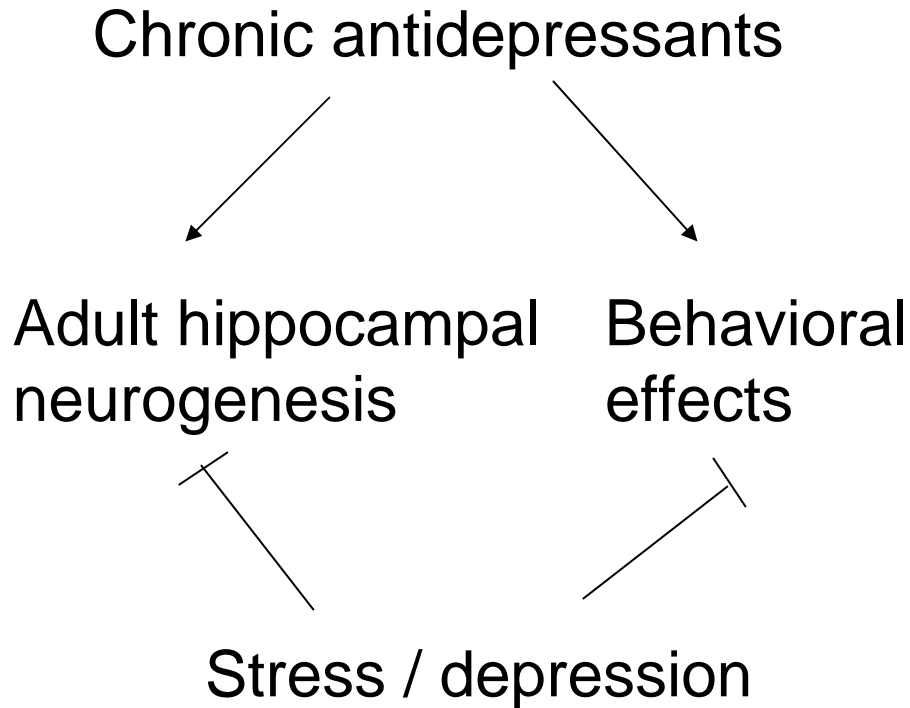
SSRIs

- citalopram (Celexa, Cipramil, Dalsan, Recital, Emocal, Sepram, Seropram)
- dapoxetine (no trade name yet; not yet approved by the FDA)
- escitalopram (Lexapro, Cipralext, Esertia)
- **fluoxetine** (Prozac, Fontex, Seromex, Seronil, Sarafem, Fluctin (EUR), Fluox (NZ), Depress (UZB), Lovan (AUS))
- fluvoxamine (Luvox, Fevarin, Faverin, Dumyrox, Favoxil, Movox)
- paroxetine (Paxil, Seroxat, Sereupin, Aropax, Deroxat, Rexetin, Xetanor, Paroxat)
- sertraline (Zoloft, Lustral, Serlain)
- zimelidine (Zelmid, Normud)

Monoaminergic hypothesis of depression

- Most AD's increase levels of monoamine serotonin (5-HT) and/or noradrenaline (NA)
- Biochemical imbalance in the 5-HT/NA system may underlie the pathogenesis of these disorders
- AD's produce a rapid increase in extracellular levels of 5-HT and NA
- Onset of clinical effects usually takes 3-4 weeks; this suggests neurochemical and structural changes in the limbic target areas of monoaminergic projections

□ This paper's hypothesis



Adult neurogenesis

- Production of new neurons in the brain of an adult organism
- SVZ (subventricular zone)
- SGZ (subgranular zone)

- Adult-generated neuronal cells arise from progenitor cells in SGZ
 - migrate into the granule cell layer where they differentiate into granular neurons
 - they integrate into the hippocampal circuitry

NSF test

- NSF - Novelty-Suppressed Feeding test
 - Adapted for 129/Sv mice
 - Mice were subjected to chronic mild stress procedures (5 weeks)
 - Treatment with antidepressants started at the beginning of the third week
 - Mice were subjected to the NSF test after 5 days (acute) and 28 days (chronic) antidepressant treatment

Drugs used

- Fluoxetine: serotonin reuptake inhibitor (SSRI)
- Imipramine: tricyclic antidepressant (TCA)
- Desipramine: tricyclic antidepressant (TCA)

- Haloperidol: antipsychotic drug, used in schizophrenia treatment
- Vehicle: control

Chronic treatment with AD's decreases the latency to feed in the NSF test

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Fig. 1A. and 1B. in Santarelli, Luca et. al. "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants." *Science* 301 (8 Aug 2003): 805-809.

→ None of the drugs produced a change in the **feeding drive** (food consumption) of each mouse after either acute or chronic treatment

Antidepressants -----> Behavioral effects

Fluoxetine chronic treatment increases neurogenesis in the dentate gyrus

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Fig. 2A., 2B., 2C., and 2D. in Santarelli, Luca et. al. "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants." *Science* 301 (8 Aug 2003): 805-809.

Antidepressants -----> Adult neurogenesis

Activation of 5-HT_{1A} is critical for the action of SSRI, but not TCA antidepressants

- KO mice display latency in NSF test
- KO mice are insensitive to chronic fluoxetine, but respond to imipramine
- Fluoxetine increases the number of BrdU + cells in WT, but not in KO mice

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Fig. 3A. And 3C. in Santarelli, Luca et. al. "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants." *Science* 301 (8 Aug 2003): 805-809.

- Although vehicle and fluoxetine-treated KO mice show increased latency in the NSF test, they don't display a difference in levels of neurogenesis

Antidepressants -----> Adult neurogenesis ---?--> behavioral effects

5-HT_{1A} receptors are necessary and sufficient to alter NSF behavior and for fluoxetine-induced neurogenesis

- DPAT decreased latency to feed in WT mice, but was ineffective in KO mice
- Activation of 5-HT_{1A} receptor is sufficient to enhance cell proliferation

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Fig. 3B. And 3D. in Santarelli, Luca et. al. "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants." *Science* 301 (8 Aug 2003): 805-809.

X-ray treatment to ablate cell proliferation in SGZ

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Fig. 4 in Santarelli, Luca et. al. "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants." *Science* 301 (8 Aug 2003): 805-809.

- Test whether hippocampal neurogenesis participates in the mechanism of antidepressant drugs
- Use X-ray irradiation to reduce cell proliferation within the SGZ

Irradiation drastically reduced cell proliferation in SGZ, but not in SVZ

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Fig. 4C., 4D. And 4E. in Santarelli, Luca et. al. "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants." *Science* 301 (8 Aug 2003): 805-809.

- Irradiation resulted in 85% reduction in BrdU+ cells in the SGZ
- Number of BrdU+ cells in not affected in SVZ
- Irradiation caused a marked increase in the number of apoptotic cells in SGZ

S,V - sham, vehicle
S,F - sham, fluoxetine
X,V - irradiation, vehicle
X,F - irradiation, fluoxetine



X-ray of hippocampus suppresses behavioral responses to antidepressants

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Fig. 5A. And 5B. in Santarelli, Luca et. al. "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants." *Science* 301 (8 Aug 2003): 805-809.

- AD treatment caused a reduction in latency to feed, but this effect was absent in irradiated mice
- The effect of radiation on AD action is specific to SGZ (SVZ or CRB-neurogenic cerebellar region irradiation does not attenuates response to AD)
- 28-day ablation of neurogenesis in vehicle-treated animals does not produce behavioral deficits

X-ray of hippocampus suppresses behavioral responses to antidepressants

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Fig. 5C. And 5D. in Santarelli, Luca et. al. "Requirement of Hippocampal Neurogenesis for the Behavioral Effects of Antidepressants." *Science* 301 (8 Aug 2003): 805-809.

Another behavioral test:

- **Chronic unpredictable stress (CUS)** --> deterioration of the state of coat and impaired grooming
- Fluoxetine improved the state of the fur/ grooming latency in sham mice, but not in irradiated mice

Antidepressants -----> Adult neurogenesis -----> behavioral effects

Does X-ray affect other brain structures, causing an effect on behavior, or is the behavior specific to a lack of neurogenesis in hippocampus?

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The specific irradiation of the hippocampus alters the behavioral response to antidepressants in NSF/ CUS tests

Conclusions

- Latency to feed in a novel environment is decreased specifically by chronic, not acute treatment with antidepressants (SSRIs or TCAs)
- Antidepressants cause increased neurogenesis in SGZ
- Activation of 5-HT_{1A} receptor is a critical component in the action of SSRIs, but not TCAs
- Disrupting hippocampal neurogenesis with X-irradiation blocks the effects of chronic AD treatment

Antidepressants -----> Adult neurogenesis -----> behavioral effects

Further studies

- Find a good causation, and not correlation experiment to prove that neurogenesis is required for behavioral effects of antidepressants



Antidepressants -----> Adult neurogenesis -----> behavioral effects

What is known now...

- Hen et al (2003): Neurogenesis is required for the effects of imipramine and fluoxetine
- Jiang et al (2005): In rats, the synthetic cannabinoid HU210 has antidepressant-like behavioral effects that depend on neurogenesis
- Airan et al (2007) The fluoxetine induced behavioral effects as assessed in the forced-swim test also requires neurogenesis

BUT...

- Holick et al (2007): In a highly anxious strain of mice (BALB/c) anxiolytic and antidepressant-like behavioral effects of fluoxetine are not blocked by ablation of neurogenesis
- David et al (2007): The anxiolytic and antidepressant-like effects of melatonin-concentrating hormone receptor agonist does not require neurogenesis
- Meshi et al (2006) Beneficial effects of environment enrichment and exercise on learning and anxiety-like behavior can occur independently of increased hippocampal neurogenesis

Current model of antidepressants' action

