New approaches to antidepressant drug discovery: beyond monoamines
Olivier Berton & Eric J. Nestler
Nature Reviews Neuroscience 7, 137-151 (February 2006)

Human circuitry of depression

peptidergic = endorphins, enkephalins, etc

Copyright © 2006 Nature Publishing Group
Nature Reviews Neuroscience

Biological Psychology No. 6, Figure 4.3

neurocircuitry

Glutamatergic
GABAergic
Dopaminergic
Peptidergic

Human circuitry of depression

Copyright © 2006 Nature Publishing Group
Nature Reviews Neuroscience

neurocircuitry

Glutamatergic
GABAergic
Dopaminergic
Peptidergic

Hippocampus

Mesolimbic pathway: ventral tegmental area (VTA) to nucleus accumbens, cortex (including the insula), and hippocampus

Mesostriatal pathway: substantia nigra to striatum (caudate and putamen)
New approaches to antidepressant drug discovery: beyond monoamines
Olivier Berton & Eric J. Nestler
Nature Reviews Neuroscience 7, 137-151 (February 2006)

Human circuitry of depression

Note that serotonin systems are not considered primary, although SSRI’s are effective ADs – possibly via secondary effects on other systems

(peptidergic = endorphins, enkephalins, etc) Copyright © 2006 Nature Publishing Group
Nature Reviews Neuroscience

Figure 3: Brain circuitry implicated in resilience to depression and anxiety disorders.
From Neuroscience of resilience
Scott J. Russo, James M. Marshang, Ming-Yu Fan, Deng & Nestler & Eric J. Nestler

Rodent circuitry of “depression”

NA nuclues accumbens, mPFC medial prefrontal cortex, CP caudate putamen, VTA ventral tegmenal area, DMT dorsal medial thalamus, SC/IC superior/inferior colliculus, VP ventral pallidum, SN substantia nigra, ARC arcuate nucleus, LH lateral hypothalamus, LC locus coeruleus

Glutamate=red, GABA=purple, Peptidergic=black, dopamine=blue
Genetic Mouse Models of Depression

Christopher Barkus

A good rodent model of depression would feature many of the depressive-like behaviours detailed below, as well as possibly some of the associated physiological changes commonly seen in depressed individuals, such as altered EEG sleep architecture. When the depressive-like phenotype detected in a mutant mouse model can also be reversed by clinically effective antidepressants, this adds to the validity of the model.

To avoid suggesting we can measure mood per se in rodents, the term “behavioural despair” is often applied to tests sensitive to antidepressant treatment. The two most commonly used tests for behavioural despair in mice are the forced swim test and the tail suspension test.

Are you:
- Feeling sad or guilty often
- Not enjoying daily activities
- Eating or sleeping more, or less
- Feeling irritable or tired
- Having trouble with concentration or memory
- Thinking about suicide

**Forced Swimming**
(also called “behavioral despair” test)
Plexiglass Cylinder

Tail suspension
Other tests:

Anhedonia: sucrose preference, social interaction

Anxiety: Plus maze, thigmotaxis in open field

Circadian and sleep disruptions
• Mouse models (from Barkus chapter)
  
  – Low expressing variant of gene for 5HT transporter/5HT KO mice
  – A2a adrenoreceptor (NE) KO mice
  – Noradrenaline (NE) transporter KO mice
  – CRF models (corticotropin releasing factor from hypothalamus)
  – BDNF models
Higher cortisol (stress) levels in depressed individuals.

In normal controls, dexamethasone (a synthetic cortisol-like glucocorticoid) leads to feedback inhibition of cortisol.

In depressed patients, dexamethasone seems less able to produce feedback inhibition of cortisol (a faulty H-P-A system?)
Depressed patients spend little/no time in deep (stage 3/4) sleep (could reflect the fact that cortisol levels normally fall during the night and rise just before we wake up, but may remain elevated in depressed patients). Elevated REM?

Other considerations to interpreting mouse model data:

- Sex
- Environment
- Employment of task parameters (e.g., duration of pre-swim)
- Background strain (e.g., C57 that can climb up tail makes poor background strain for tail suspension task)
**The Flinders Sensitive Line Rat Model of Depression—25 Years and Still Producing**

David H. Overstreet and Gregory Wagner

The Flinders sensitive line (FSL) rat has been purported to be a genetic animal model of depression because of several features that resemble human depressives, including elevated rapid eye movement (REM) sleep and an exaggerated swim test immobility that can be reduced by chronic antidepressant treatments. Previous reviews

It must be emphasized that we had no intention of creating an animal model of depression. The original intent of our work was to create a strain of rat that was resistant to the anticholinesterase agent, diisopropyl fluorophosphate (DFP). The mechanisms underlying this resistance were to be compared with those previously established for rats that became tolerant to DFP following chronic treatment (Russell et al., 1982; Russell and Overstreet, 1987). However, the selective breeding program did not result in a resistant strain of rat; instead, a strain of rat that became progressively more sensitive to DFP was established, with the other strain, sometimes called the Flinders resistant line (FRL), resembling control Sprague-Dawley (SD) rats (Overstreet et al., 1979b).
Note that all drugs show efficacy only after chronic treatment (14 days+) in the FSL model. Also, the FSL model does not show the anhedonia aspect of depression models.

**Possible anti-depressants (AD)**

<table>
<thead>
<tr>
<th>Drug (mg/kg)</th>
<th>Dose</th>
<th>Drug Class</th>
<th>Change in Swimming</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td>5</td>
<td>Tertiary</td>
<td>Significant increase</td>
<td>Paczkowski and Overstreet, 1998</td>
</tr>
<tr>
<td>Desipramine</td>
<td>5</td>
<td>Tertiary</td>
<td>Significant increase</td>
<td>Schiller et al., 1992</td>
</tr>
<tr>
<td>Desipramine</td>
<td>5</td>
<td>Tertiary</td>
<td>Significant increase</td>
<td>Zangen et al., 2001</td>
</tr>
<tr>
<td>Sertraline</td>
<td>5.7</td>
<td>SSRI</td>
<td>Significant increase</td>
<td>Paczkowski and Overstreet, 1998</td>
</tr>
<tr>
<td>Imipramine</td>
<td>15</td>
<td>Tertiary</td>
<td>Significant increase</td>
<td>Schiller et al., 1992</td>
</tr>
<tr>
<td>DPPr</td>
<td>1</td>
<td>Anticholinesterase</td>
<td>No Change</td>
<td>Overstreet and Grobel, 2004</td>
</tr>
<tr>
<td>SSR125-43</td>
<td>2, 30</td>
<td>CRF1 agonist</td>
<td>Significant increase</td>
<td>Overstreet et al., 2006</td>
</tr>
<tr>
<td>SSR2561A</td>
<td>1, 3</td>
<td>5HT receptor antagonist</td>
<td>Significant increase</td>
<td>Overstreet et al., 2006</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>0.3</td>
<td>Analog of MIF</td>
<td>Significant increase</td>
<td>Overstreet et al., 2004</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>2</td>
<td>Stimulant</td>
<td>No change</td>
<td>Overstreet et al., 1996</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>2</td>
<td>Anticholinergic agent</td>
<td>No change</td>
<td>Overstreet et al., 1996</td>
</tr>
<tr>
<td>SSRI494-16</td>
<td>10, 30</td>
<td>VIB antagonist</td>
<td>Significant increase</td>
<td>Overstreet and Grodel, 2005</td>
</tr>
<tr>
<td>CP664.586</td>
<td>10 x 2</td>
<td>CRF1 agonist</td>
<td>Significant increase</td>
<td>Overstreet et al., 2006</td>
</tr>
<tr>
<td>Citalopram</td>
<td>5, 10</td>
<td>SSRI</td>
<td>Significant increase</td>
<td>Overstreet et al., 2004</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1, 10</td>
<td>SSRI</td>
<td>Significant increase</td>
<td>Overstreet et al., 2010</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>7.5</td>
<td>SSRI</td>
<td>Significant increase</td>
<td>Mark et al., 2011</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>7.5</td>
<td>SSRI</td>
<td>Significant increase</td>
<td>Zangen et al., 2001</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>1, 10</td>
<td>GABA antagonist</td>
<td>Significant increase</td>
<td>Mark et al., 2011</td>
</tr>
<tr>
<td>LuAA33810</td>
<td>3, 10</td>
<td>NPY YB antagonist</td>
<td>Significant increase</td>
<td>Walker et al., 2009</td>
</tr>
<tr>
<td>S 2694</td>
<td>1, 20</td>
<td>Melatonin agonist</td>
<td>Significant increase</td>
<td>Overstreet et al., 1998</td>
</tr>
<tr>
<td>S 26928</td>
<td>1, 10</td>
<td>Melatonin agonist</td>
<td>Significant increase</td>
<td>Overstreet et al., 1998</td>
</tr>
<tr>
<td>Inositol</td>
<td>1200</td>
<td>Precursor to inositol</td>
<td>Significant increase</td>
<td>Einat et al., 2002</td>
</tr>
<tr>
<td>Nicotine</td>
<td>0.4</td>
<td>Nicotine agonist</td>
<td>Significant increase</td>
<td>Trimble et al., 1996</td>
</tr>
<tr>
<td>NGF</td>
<td></td>
<td>Many</td>
<td>Trichotrophic factor</td>
<td>Overstreet et al., 2010</td>
</tr>
</tbody>
</table>

**Pitx3 deficient mice as a genetic animal model of co-morbid depressive disorder and parkinsonism**

Kyoung-Shim Kim, Young-Mi Kang, Young Kang, Tae-Shin Park, Hye-Yeon Park, Yoon-Jung Kim, Bae-So Han, Chun-Hyung Kim, Chul-Hee Lee, Paul A. Ardayfo, Pyung-Lim Han, Heng-hyun Jung, Kwang-Soo Kim

**ABSTRACT**

Approximately 40-50% of all patients with Parkinson’s disease (PD) show symptoms and signs of depressive disorders, for which neither pathogenic understanding nor rational treatment are available. Using Pitx3-deficient mice, a model for selective nigrostriatal dopaminergic neurodegeneration, we tested depression-related behaviors and acute stress responses in order to better understand how a nigrostriatal dopaminergic deficit affects the prevalence of depressive disorders in PD patients. Pitx3-deficient mice showed decreased sucrose consumption and preference in the two-bottle free-choice test of anhedonia. Acute restraint stress increased c-fos (known as a neuronal activity marker) expression levels in various brain regions, including the perifornical cortex, striatum, nuclei accumbens, and paraventricular nuclei of the hypothalamus (PVN), in both Pitx3+/+ and −/− mice. However, the stress-induced increases in c-fos levels in the cortex, dorsal striatum, and PVN were significantly greater in Pitx3−/− than +/+ mice, suggesting that signs of depressive disorders in parkinsonism are related to altered stress vulnerability. Based on these results, we propose that Pitx3−/− mice may serve as a useful genetic animal model for co-morbid depressive disorder and parkinsonism.
Normal

ADD

Stimulants

(Increasing levels of D and E)

Paradoxical calming effects of stimulants (increase epinephrine and dopamine) on individuals with ADD/ADHD.
Strengths and limitations of genetic models of ADHD

Raul R. Gainetdinov

Table 1 Summary of observations in DAT mutant models with regard to ADHD-related phenotypes

<table>
<thead>
<tr>
<th>Mutant</th>
<th>DAT expression (%)</th>
<th>Extracellular DA (%)</th>
<th>Locomotor activity</th>
<th>Response to psychostimulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAT-KO</td>
<td>0</td>
<td>500</td>
<td>Extreme hyperactivity</td>
<td>Amphetamines and methylphenidate inhibit hyperactivity</td>
</tr>
<tr>
<td>DAT knockdown</td>
<td>10</td>
<td>200</td>
<td>Moderate hyperactivity</td>
<td>Amphetamines inhibit hyperactivity</td>
</tr>
<tr>
<td>DAT intercross</td>
<td>50</td>
<td>200</td>
<td>Normal</td>
<td>Reduced stimulation after amphetamines</td>
</tr>
<tr>
<td>DAT antisense</td>
<td>60</td>
<td>N.D.</td>
<td>Normal</td>
<td>Reduced stimulation after amphetamines</td>
</tr>
<tr>
<td>Wild type</td>
<td>100</td>
<td>100</td>
<td>Normal</td>
<td>Normal stimulation after amphetamines and methylphenidate</td>
</tr>
<tr>
<td>Transgenic DAT overexpression</td>
<td>150</td>
<td>N.D.</td>
<td>Hypersensitivity in a novel environment</td>
<td>N.D.</td>
</tr>
<tr>
<td>BAC DAT overexpression</td>
<td>300</td>
<td>60</td>
<td>Normal</td>
<td>Markedly enhanced amphetamines stimulation</td>
</tr>
</tbody>
</table>

Detailed description of these mutant models and respective references are presented in the text

N.D. not determined

Reinforcement, Dopamine and Rodent Models in Drug Development for ADHD

Gail Tripp - Jeff Wickers

Attention/vigilance
SCSRT

Locomotion/hyperactivity
Open Field

Impulsivity/
Response inhibition failure
Delay discounting
Glutamate=red, GABA=purple, Peptidergic=black, dopamine=blue