NEW IDEAS FOR THE DESIGN OF EFFECTIVE ANTIDEPRESSANT TREATMENTS

Fritz Henn PhD, MD
Remission Rates for Depression Treatments

- Placebo: 30%
- Effective Psychotherapy: 85%
- Standard antidepressants: 65%
- Severe Depression ECT: 85%

2% population, about 6,200,000 million, of which 15% resistant to all treatments, (over 900,000 per year), relapses are the RULE.
Molecular Signals in Depression

A history of research into the etiology of depression

Stress → CRH

CRH → CREB

CREB → CREB-P

CREB-P → GR

GR → Neutrophins (BDNF)

Neutrophins (BDNF) → Synapses

Synapses → Cells

Cells → µ opioids

µ opioids → Sub. P

Sub. P → NPY

NPY

Stress
Major Depression in USA

**12-month Prevalence:**
6.7% of US adult population

**Severe:**
30.4% of these cases (e.g., 2.0% of US adult population) are classified as “severe”
Cognitive Model of Depression (A.T. Beck)

EVENT

COGNITIVE APPRAISAL DISTORTED

BEHAVIOR (Maladaptive)

BEHAVIORAL INCLINATION (helpless, hopeless)

EMOTION (Depressed, anxious)
Learned Helplessness (LeH)

NAIVE RATS

CONTROL

EXECUTIVE

YOKED

NOT HELPLESS

NOT HELPLESS

NOT HELPLESS

HELPLESS
PFC senses controllability and inhibits stress sequelae

Control

Stress

mPFCv

GLU

GABA

5HT

Cingulum

HIP

AMG

DRN

Modified from Amat et al., Nature Neuroscience 2005
Selective Breeding

20% non helpless

15% helpless

25% non helpless

25% helpless
Learned Helpless Animal

Cytochrome Oxidase Stain
note the Habenula

Non Learned helpless Animal
Metabolic pattern of activity

Helpless

Difference

Resilient
We conditioned monkeys using a Pavlovian procedure with two distinct contexts: one in which rewards were available and another in which punishments were feared.

We found that the population of lateral habenula neurons was most strongly excited by a conditioned stimulus associated with the most unpleasant event in each context: the absence of the reward or the presence of the punishment.
PFC senses controllability and inhibits stress sequelae

Modified from Amat et al., Nature Neuroscience 2005
The Result

The Anatomy of Melancholia
Activation of the Habenula during Tryptophan Challenge
Morris et al Neuroimage 1999
A) Graph showing normalized slope over time with DBS pulses marked as 'first pulse' and 'second pulse'.

B) 

a) Learned Helplessness Test: 
hfDBS to the LHb, mHb or LD

- LHb hfDBS
- mHb hfDBS
- LD hfDBS

Number of lever presses successfully turning off shock within 20 sec.

Baseline, hDBS (150 µA), hDBS (300 µA)

b) Bregma placements: -3.48 mm, -3.72 mm, -4.96 mm

Probe Placement Nissl Stain:

- LHb
- mHb
- LD
Case Report DBS targeting the habenula

- Middle aged woman 25+ yr history of rapidly remitting depression responsive only to ECT over the last 4 years. Very severe suicidal episodes required immediate hospitalization.

- June 2008, Ham D 44 remission from last ECT only 6 days.

- Offer deep brain stimulation with option of the habenular target.

- After 6 weeks, Ham D 22 medication not effective, stimulator increased to maximum inhibition, PET scan showed habenular inhibition

- Follow up at 6 months HamD 3, no cognitive deficits had never felt as well, no manic symptoms, good sleep appetite and concentration.
Figure 1: Electrophysiological and neurochemical properties of a single neuron in the lateral habenula nucleus (LHb) of an anaesthetised rat. a) Location of juxtacellular-labelled neuron in the LHb. b) Photomicrographs showing neurobiotin (NB) labelled LHb neuron immuno-positive for the glutamate marker, EAAC1 (arrow). Scale bar = 10 μm. c) Spike train of the illustrated neuron, displaying a tonic irregular firing pattern. d) Mean extracellular spike waveform, demonstrating broad spike width. e) Inter-spike interval histogram (2 ms bins) indicating an irregular firing pattern.
PSD95 Quantification in cLH Rats

Preparation and sectioning of rapidly frozen brains

Immunohistochemistry for PSD95

Widefield imaging in infralimbic, parietal, and frontal cortices

Deconvolution and automated, high-throughput quantification (puncta counts and volume)
Total PSD95 puncta counts in infralimbic, parietal, & frontal cortices
Glutamatergic Synapse: Anatomy, Physiology and Downstream Changes

- Presynaptic terminal
  - Glutamine
  - Glutamate
  - VGLUTs
  - mGluR2/3
- Postsynaptic spine
  - PSD
  - Increase in spine density
  - BDNF activation
  - mTOR activation
  - EAAT1,2
- AMPA
- NMDA
  - NR2B
  - NR2A
- Glia
  - Glutamine
  - Gln Synthetase
  - Glutamate

Learning
Memory
Plasticity
Astrocytic Glutamate Transporter
mRNA levels
GLU/GABA ratios


Integrative model of functional and metabolic markers of severe anhedonia

Requirements for a new type of Antidepressant

1. Remove toxic glutamate, normalize astrocytic cell functions to **restore** synaptic function
2. Decrease stress induced inflammatory response
3. Minimal side effects
Possible approach

- A drug which induces EAAT2, which increases the removal of excess glutamate, reduces synaptic toxicity.
- One chemical class which does this are $K^+(\text{ATPASE})$ inhibitors which also act against inflammatory changes in the CNS – patented this class as anti-depressants; one compound currently FDA approved - DIAZOXIDE.
Induction of EAAT2 via diazoxide may be a new route to effective clinical antidepressants tested in treatment resistant nLH line.
Summary

- Multiple routes alter helpless behavior, these include NE, 5HT, CRH, and less well established Substance P, M\u03b4 opiates, NPY.
- Astrocyte loss of function may be final step in establishing helplessness, it probably involves decreases in glutamate uptake.
- The underlying pathology, overactive glutamate pathways may contribute to activating the L. habenula, which becomes a major locus of control, of midbrain nuclei and hypothalamus.
- (Probably multiple etiologies and many possible defects leading to dysfunction in the common final anatomical pathway)
THANK YOU!

Martine Mirrione, Daniela Schultz – BNL
Mattias Zink, Barbra Vollmeyer, Alex Sartorious ZI
Bi Li CSHL, Robert Malinow UCSD, Gary Lynch, Ron Seese, Bif Bunney UCI