Brain Inhibitory GABAergic Function and Cognitive Deficits: Mechanisms and Therapeutic Targeting

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Disclosures

Co-inventor on a patent application describing compounds and their use for cognitive deficits and mood symptoms in neuropsychiatric disorders

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Symptoms include altered memory, reduced control over emotions, poor decision making and planning, etc. These symptoms are:

- are **prevalent** in depression and other psychiatric disorders
- occur during aging
- associated with increased suicidality across disorders.
- yet, they are **not treated** by current drugs (antidepressants or Ach inhib)
- Antidepressants have no efficacy for cognition

- No drug with novel mechanism of action in psychiatry in last 50-60 yrs
- Need for novel therapeutics based on the pathology of the brain
Over the past 15+ years, multiple large-scale “omics” studies in both the human and rodent brains have led us to consider deficits in the canonical cortical cell microcircuit as a critical component in mood and cognitive symptoms across brain disorders.
Cortical microcircuit (CM)

Excitatory activity is balanced by inhibitory activity, which is orchestrated by distinct GABAergic interneuron (IN) cell types.

CMs are basic units of information processing in brain cortex

Somatostatin (SST)+ dendritic-targeting INs
Parvalbumin (PV)+ perisomatic-targeting INs
Vasoactive intestinal peptide (VIP)+ IN-targeting INs
Excitation-inhibition balance is maintained physiologically at msec level.

Life-long (aging) and pathological changes are maintained by altered patterns of gene expression

Somatostatin (SST)+ dendritic-targeting INs
Parvalbumin (PV)+ perisomatic-targeting INs
Vasoactive intestinal peptide (VIP)+ IN-targeting INs
Reduced Somatostatin (SST) expression in MDD

Meta-analysis across 9 unbiased array studies
Low SST confirmed at RNA and protein levels;  No effects on PV or VIP

Ding et al, Mol Neuropsych. 2014
**SST+ GABAergic microcircuit pathology in depression**

**Human studies:**
- Reduced SST expression in various brain regions in subjects with depression.  

- Reduced SST expression per cell, rather than missing cells.  
  (Seney, 2014, Neurobio.Dx)

- Stress, Aging and Sex moderate SST expression.  

**Mouse studies:**
- Absence of SST replicates behavioral, neuroendocrine and molecular symptoms of depression in mice  
  (Lin, 2014, Mol.Psy.)

- Acute reduction in SST cell function in the frontal cortex affects behavioral emotionality in mice  
  (Soumier, 2014, NPP)
**SST+ GABAergic pathology and cognition**

- **Modeling age-related reduced SST+ GABAergic function increases distractibility**
  

- **Reduced SST+ GABAergic function affects cognition**
  
  - Mice lacking α5-GABAAR display reduced executive functions and autism-like behaviours (Zurek, 2016)
  
  - Reduced PFC SST+ cell function reduces spatial working memory (Abbas et al, 2018)
  
  - Reduced SST+ cell function contributes to memory deficits in mouse models of Alzheimer’s disease (Schmid, 2016)
Reduced SST+ GABAergic cell/function is consistent with reduced GABA levels and function in depression

- Low GABA CSF levels (Gold, 1980; Petty, 1992)
- Low GABA tissue level in OC, FC and ACC (MRS) (Sanacora 1999; Hasler 2005)
- Reduced markers of GABAergic neurons (Rajkowska 2007, Sibille 2008, Klempán 2009, Guilloux 2012, etc)
- Reduced cortical inhibition (Transcranial magnetic stimulation; TMS) (Levinson, 2010)
- Low GABA contributes to increased resting state activity in default-mode network and to rumination (Northoff, 2010)
- Low GABA is associated with anhedonia in adolescent depression (Gabbay 2012)
- Reviewed in Luscher 2011, Fee 2017
Reduced SST+ GABA neuron markers: a replicated pathology in depression and other brain disorders

<table>
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<th>Brain region</th>
<th>Pathological findings</th>
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<td>CSF</td>
<td>Decreased</td>
<td>Dupont et al, 1982</td>
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<td>Temporal cortex</td>
<td>Decreased (immune-reactivity)</td>
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<td>Alzheimer’s disease</td>
<td>CSF</td>
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<td>Bissette et al, 1986; Tamminga et al, 1987</td>
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<td>Candy et al, 1985; Rossor et al, 1980</td>
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<td>Decreased (immune-reactivity)</td>
<td>Candy et al, 1985; Davies &amp; Terry, 1981</td>
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<td>Dournaud et al, 1994</td>
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<td>Parahippocampal cortex</td>
<td>Decreased (neuronal density)</td>
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<td>Dorsolateral prefrontal cortex</td>
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<td>Amygdala</td>
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<tr>
<td></td>
<td>Dorsolateral prefrontal cortex</td>
<td>Decreased (RNA expression / trend level)</td>
<td>Sibille et al, 2011</td>
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Table adapted from Lin & Sibille, *Frontiers in Pharmacology*, 2013.
α5-GABAA receptors mediate the function of SST+ GABA neurons:

- expressed in PyC dendrites in hippocampus and cortex
- mediates SST cell function through dendritic tonic inhibition

Desired pharmacological effect: positive allosteric modulation (α5-PAM)

Hypotheses: (1) Activating α5-GABAA receptors will target the pathology (disease-modifying) and (2) reduce cognitive deficits and mood symptoms.

Fee, Banasr & Sibille; *Biological Psychiatry*, 2017
**α5-GABAA receptor, subunits and benzodiazepines**

**Benzodiazepines (BZD):**
- Anxiolytic, but no pro-cognitive or antidepressant effects,
- Act at several α-GABAA-R, with detrimental side-effects.
- The alpha subunits determine the functional output of BZD-like compounds.

Genetic/pharmacological studies have shown that:
- α1-GABAA-R mediates sedative (and cognitive) effects
- α2-GABAA-R mediates anxiety levels
- α3-GABAA-R has unknown effects
- **α5-GABAA-R:**
  Until recently, unknown effects due to dominant effects at α1/2
  Location restricted to PyC distal dendrites in hippocampus and cortex (and amygdala and v.striatum)
  α5-KO mice display altered cognitive functions

=> Targeting specific α-GABAA-R may uncover novel therapeutic roles for GABA potentiation
Development of novel compounds that activate $\alpha_5$-GABAA-R: $\alpha_5$-positive allosteric modulators ($\alpha_5$-PAM)

Novel $\alpha_5$-PAMs pass the blood brain barrier, activate preferentially $\alpha_5$-GABAA-R, and display safe and promising pharmacological profiles

Prevot et al; Molecular Neuropsychiatry, 2018
α5-PAMs have anxiolytic & antidepressant effects

**Elevated Plus Maze Test**

Forced Swim Test

Prevot et al; *Molecular Neuropsych.*, 2018
α5-PAM and pro-cognitive efficacy in stress models and during Aging

Effect: F=M 15x

Prevot et al; Molecular Neuropsychiatry, 2018
Chronic GL-IL-73 treatment reverses age-related neuronal atrophy

Dendrite Length

Young (3-month) | Old (22-month) | Old + GL-IL-73

Spine counts

Young | Old | Old + Treatment

(2-months; PFC pyramidal neuronal dendritic length and spine density)
Aging and brain disorders impact the SST+ GABAergic components of the cortical microcircuit.

Targeting SST+ GABAergic signaling has potential for:
(1) improving cognitive and mood symptoms across brain disorders and during aging, and
(2) reversing neuronal pathology
αCOG program: New Therapeutic Molecules for Cognition in Depression and During Aging

• Conducting pre-clinical studies for submission to FDA
• If it all lines up well (R & $), begin human trial in 2 years
• First indications: cognitive deficits on the continuum from depression to dementia and Alzheimer’s.
• Target symptoms and underlying pathology
A Conceptual Shift in Brain Disorders:

Moving from categorical definitions...

Causal factors

Alzheimer’s disease.

Parkinson’s disease

Schizophrenia

Bipolar depression

Major Depression

Trmt A

Trmt B

Trmt C

Trmt D

Trmt E
A Conceptual Shift in Brain Disorders:
Moving from categorical definitions...
.... towards a continuous modular perspective

Risk factor A → Trmt A
Risk factor B → Trmt B
Risk factor C → Trmt C
Risk factor D → Trmt G
Risk factor E
Risk factor F
Risk factor G

Alzheimer’s disease
Parkinson’s disease
Schizophrenia
Bipolar depression
Major Depression

Biological evidence-based
Compare to Cardiovascular Disorders:

Moving from categorical definitions...

.... towards a continuous modular perspective
Identified altered SST+ GABA neuron function as a cross-disease endophenotype

Risk factor A
Risk factor B
Risk factor C
Risk factor D
Risk factor E
Risk factor F

Trmt A
Trmt B
Trmt C

α5-PAM
GABA/SST-related pathological endophenotype

Alzheimer’s disease
Parkinson’s disease
Schizophrenia
Bipolar depression
Major Depression

Biological evidence-based
Thank you!!

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