Granulocyte-colony Stimulating Factor Alters the Proteomic Landscape of the Nucleus Accumbens

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What is the role of inflammation in mental illness?

**Meta-analysis of Cytokines in Depression**

Dysregulation of cytokines or other markers of immune function are seen in many psychiatric illnesses:
- Autism Spectrum Disorder
- PTSD
- Bipolar Disorder
- Alzheimer’s
- Others

How does this affect disease progression, and can it be harnessed as a possible therapeutic strategy?

**Meta-analysis of Cytokines in Schizophrenia and Treatment**

(Miller et al. Biol Psychiatry 2011)
Multiplex Analysis of Serum Cytokines After Cocaine

Experimenter-administered
Cocaine 20 mg/kg/inj 24h
Saline 24h
Blood collection

Experimenter-administered
Cocaine 20 mg/kg/inj 24h
Saline 24h
Blood collection

Fold Change over Saline

M-CSF
VEGF
GM-CSF
IL-6
KC
IL-7
G-CSF
IL-13
MCP-1
TNFα
IL-12p70
IL-12p40
MIP-1b
RANTES
IL-9
IL-5
Eotaxin
IL-15
MIG
IP-10
LIX
MIP-1a
MIP-2
IL-1α

G-CSF - 7 Days Cocaine

Sensitization
Self-Administered

G-CSF (pg/ml)

Intake (mg/kg/day)

r = 0.77
p = 0.03*

r = 0.81
p = 0.008**
Effect of G-CSF on behavioral response to cocaine – Conditioned Place Preference

Day 1
Day 2
Day 3
Day 4

- Testing
- Saline
- Cocaine

Preference (Coc-Sal)

3.75mg/kg
7.5mg/kg
15mg/kg

G-CSF or PBS

PBS

G-CSF

**

*
Effect of G-CSF on behavioral response to cocaine – Conditioned Place Preference

CPP with i.p. antibody

- α-G-CSF antibody or IgG
- Day 1: Testing
- Day 2: Saline
- Day 3: Saline
- Day 4: Cocaine

CPP with antibody in NAc

- α-G-CSF antibody
- Osmotic Minipump
- NAc
- Day 1: Implantation
- Day 2: Recovery
- Day 3: Testing
- Day 4: Saline

Bar charts showing CPP scores:

- CPP with i.p. antibody:
  - IgG: 400
  - α-G-CSF: 200

- CPP with antibody in NAc:
  - IgG: 400
  - α-G-CSF: -200

** Indicates statistical significance.
Discovery proteomics analysis of G-CSF effects

- G-CSF (50μg/kg)
- Cocaine (7.5mg/kg)

7 days

Nucleus Accumbens

Tissue Lysis & Protein Digestion

DIA Mass Spectrometry

Coc vs Saline

GCSF vs Saline

GCSF / Coc vs Saline
Examination of the interaction of G-CSF and Cocaine

G-CSF & Cocaine vs. Cocaine

354 Decreased & 245 Increased
STRING protein-protein interaction analysis

# of edges: 830  
(Predicted: 491) 
$p < 1 \times 10^{-16}$

Synapse (46 proteins): $p = 3.32 \times 10^{-15}$
Presynapse (27 proteins): $p = 2.12 \times 10^{-11}$
Postsynapse (25 proteins): $p = 1.83 \times 10^{-8}$
Western blot validation of proteomic targets

**PSD-95 GluR1**
G-CSF is a potent neuroimmune modulator
- Enhances reward seeking
  - Cocaine & Natural
- Boosts cognitive flexibility
- Enhances DA release and neuronal activation
- Alters synaptic structure

Hypothesis: G-CSF promotes learning & synaptic plasticity.
Future Directions

• Analysis of G-CSF effects on drug extinction and seeking tasks
  • Correlation of proteomic changes with behavioral response
    • (This is partially done but not shown for lack of time)

• Detailed proteomic characterization of synaptic fractions
  • Isolated synaptosomes/PSDs
  • Biotinylated cell-surface markers

• Investigation of cell-specific effects of G-CSF ± Cocaine
  • Microglia / MSNs

• Circuit manipulation and imaging to determine pathways affecting G-CSF behavioral response
Thank You!

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