Anti-Inflammation and neuroprotective drugs benefit the treatment of heroin dependent patients

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Neurodegeneration in Mental Illnesses

- Schizophrenia
- Bipolar disorders
- Substance use disorders (alcohol)
- Anxiety disorders?
- Personality disorders?
Neuronal degeneration in schizophrenia

Schizophrenia and bipolar disorders

- Decreased grey & white matter and lateral ventricular dilatation

(Largent et al., 1984; De Peri I et al., 2012)
Neuronal degeneration in Bipolar Disorder

- Diffused gray and white matter loss, enlarged ventricles & mild prefrontal volume loss. (Wilde, et al., 1985)

- 17% larger lateral ventricles and 2.5 times in deep white matter hyperintensities. (Kempton, M.J., et al., 2008.)
Neuronal degeneration in Substance Abuse

Both MRI's are of middle-aged women
Inflammation and neurodegeneration
Glial cells:
Key roles in disease and prime targets for therapy

Microglia
Target for anti-inflammation

Astroglia
Source for neurotrophin production
Role of microglia in toxin-induced progressive neurotoxicity

(Working Model)

LPS
(Extra Neurotoxin)

MPTP
(Intra Neurotoxin)

Microglia

Activation

Reactive Microgliosis

(Self-propelling)

Pro-inflammatory Factors
(ROS, NO., TNFα, IL-1, PGs)

Dopaminergic Neuronal Damage
NADPH oxidase (PHOX)

Naloxone, Dextromethorphan, Memantine

Activated

Resting

NADPH

NADP+ + H+

LPS

MAC-1

α

β

 gp91

p22

rap1a

p40

p47

p67

p40

PKC

O2

O2 −

in

out
Dual Functions of Superoxide Radicals

1) Neurotoxicity

2) Gene Expression

Microglia

LPS

LBP

CD14

LR4

AC1

PKC

PHOX

gp91

O2

O2•–

H2O2

O2•–

NO•

ONOO–

TNF-α

IL-1

DA neurons

NF-κB, AP-1

Gene Expression

Neurotoxicity
<table>
<thead>
<tr>
<th><strong>Dextromethorphan (DM)</strong></th>
<th><strong>Memantine</strong></th>
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</thead>
<tbody>
<tr>
<td><img src="image" alt="DM structure" /></td>
<td><img src="image" alt="Memantine structure" /></td>
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<tr>
<td>• Non-competitive NMDA receptor inhibitor in large dose for anti-cough effect</td>
<td>• Non-competitive NMDA receptor inhibitor in large dosage</td>
</tr>
<tr>
<td>• Neuroprotective effects in vitro and in vivo at low dose</td>
<td>• Alzheimer's disease (20 mg/day)</td>
</tr>
<tr>
<td></td>
<td>• Neuroprotective effects in vitro and in vivo at low dosage</td>
</tr>
</tbody>
</table>
Novel anti-inflammatory therapy

LPS

Microglia

Novel Strategy: Modulation of microglial activity
- Morphinans: Naloxone, D-Morphine, Dextromethorphan
- Dynorphins, Enkephalin, PACAP
- Memantine

Conventional Regimen:
- Aspirin, COX 2 inhibitors (PG)
- Anti-oxidants (Free radicals)
- Antibodies (TNF-α, IL-1)
- Receptor antagonists (TNF-α)
- Cortisone (toxic for long-term use)
Mechanism underlying Memantine induced increase in expression of neurotrophic factors in astroglia

HATs → HDAC

Nuclear

Memantine
Depakine, 3-HM

Astroglia

mRNA of GDNF, BDNF

GDNF, BDNF

Chen et al., 2009
Therapy for neurodegenerative diseases and neuroprotective effect

- **LPS**
  - Activation
  - Memantine, DM
    - Inhibition
  - Reactive Microgliosis
    - (Self-propelling)

- **Memantine, 3-HM**
  - Stimulation
  - Trophic factors: (GDNF, BDNF, NGF)

- **Astroglia**

- **Pro-inflammatory factors:**
  - Superoxide, iROS
  - NO, TNFα, PGE₂

- **DA neuron**

- **Neurogenesis**
Hypotheses & Experimental Protocol
in Addition

• Neuro-inflammation worsen progress and neurodegeneration

• Neurondegeneration causing the etiology and progress of mental illness
Treatment of Neurodegeneration disease

• Current therapy treatment symptom or slowing or inhibiting the progress

• Development of novel therapy for central and peripheral diseases
Research Aims

• Analysis of plasma cytokine and BDNF levels
  – Cytokine through BBB and correlation of BDNF in central and plasma (Laske, 2006)

• The relationship of plasma cytokine, BDNF levels with heroin dependent

• Memantine and DM development of neuroprotective and neurogenesis therapy
The relationship between inflammation and opioid dependence
Animal data

Morphine addiction behavior model
(Condition Place Preference: CPP)
CPP Test (Condition Place Preference Test)

Conditioning

S (Saline) Black chamber

S + M (Morphine 5mg/kg) or Mem (Memantine) + M White chamber
Memantine attenuate chronic morphine induced-CPP in rats

M: Morphine 5mg/kg
Mem: Memantine 0.04-1 mg/kg

*P<0.05, **p<0.01, ***p<0.001 vs Saline group.
##P<0.01, ### p<0.001 vs Morphine group.

Chen et al., J. of Neuroimmune Pharm. Dec. 2011
Memantine potentiate serum BDNF expression

M: Morphine 5mg/kg
Mem: Memantine 0.04-1 mg/kg

*P<0.05, **p<0.01 vs Saline group.
#P<0.05, ## p<0.01 vs Morphine group.

J. of Neuroimmune Pharm. Dec. 2011
Memantine attenuates chronic morphine-induced serum and brain cytokines expression

*P<0.05, **p<0.01, ***p<0.001 vs Saline group.

#P<0.05 vs Morphine group.

J. of Neuroimmune Pharm. Dec. 2011
## Comments

- Large dose memantine 7.5 – 20mg/kg effective in NMDA receptor

- Low dose memantine (0.2 - 1mg/kg) not effective in NMDA receptor antagonist in rat *(Chen et al. 2012)*

- Low dose memantine (0.2 – 1 mg/kg) inhibition morphine addiction, decreasing cytokines and increasing BDNF in rat.

- Benefit in neuroprotection and neurogenesis *(Chen et al. 2012)*
• Inflammation relative addictive behavior in rat

• Low dose memantine effective inhibition inflammation and addictive behavior

(Chen et al. 2012)
Human Heroin dependence treatment
Method and results

1. Double-blind, Placebo-Controlled, Randomized

2. Heroin dependence with methadone treatment

- DM(60 or 120 mg/day) /placebo
  196 recruited at baseline and 48 DM60mg, 44 DM120mg and 42 placebo left after 12 weeks treatment

- memantine (5mg/day) /placebo
  133 recruited at baseline and 52 memantine and 53 placebo left after 12 weeks treatment
Method and results

1. Double-blind, Placebo-Controlled, Randomized

2. Heroin dependence with methadone treatment

- DM (60 or 120 mg/day) /placebo
  170 recruited at baseline and 42 DM60mg, 32 DM120mg and 33 placebo left after 12 weeks treatment

- Memantine (5mg/day) /placebo
  133 recruited at baseline and 52 memantine and 53 placebo left after 12 weeks treatment
Plasma Cytokine

(Chen et al., 2012)
DM for Heroin Addiction with Methadone Maintenance Treatment
The effects of dextromethorphan on plasma cytokines, methadone dose, and combined use of substances in patients undergoing methadone maintenance therapy

<table>
<thead>
<tr>
<th></th>
<th>MTD+Placebo</th>
<th>p-value</th>
<th>MTD+DM60</th>
<th>p-value</th>
<th>MTD+DM120</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 12</td>
<td>Week 0</td>
<td>Week 12</td>
<td>Week 0</td>
<td>Week 12</td>
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<tr>
<td>TNF-α (pg/mL)</td>
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<td></td>
<td>4.4 ± 0.5</td>
<td>4.3 ± 0.9</td>
<td>5.0 ± 0.6</td>
<td>3.0 ± 0.4</td>
<td>4.0 ± 0.4</td>
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<td>0.57</td>
<td>0.000</td>
<td>0.000</td>
<td>0.019</td>
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<tr>
<td>IL-8 (pg/mL)</td>
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<td></td>
<td>4.8 ± 0.9</td>
<td>4.3 ± 0.9</td>
<td>7.4 ± 1.1</td>
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<td>7.7 ± 1.3</td>
<td>2.92 ± 0.3</td>
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<td>0.14</td>
<td>0.021</td>
<td>0.03</td>
<td>0.019</td>
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<td>MTD dose (mg)</td>
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<tr>
<td></td>
<td>40.0 ± 4.6</td>
<td>4.6</td>
<td>47.4 ± 3.2</td>
<td>2.8</td>
<td>44.1 ± 4.0</td>
<td>2.8</td>
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<td></td>
<td>0.34</td>
<td>0.061</td>
<td>0.224</td>
<td>0.034</td>
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<tr>
<td>MTD dose change (%)</td>
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<tr>
<td></td>
<td>100.0 ± 0.0</td>
<td>0</td>
<td>100.0 ± 0.0</td>
<td>5.2*</td>
<td>100.0 ± 0.0</td>
<td>5.1*</td>
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<td>0.09</td>
<td>0.019</td>
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<tr>
<td>Urine morphine*</td>
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<tr>
<td></td>
<td>19</td>
<td>18</td>
<td>15</td>
<td>7</td>
<td>18</td>
<td>12</td>
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<tr>
<td>Plasma morphine (pg/mL)</td>
<td>16.5 ± 39.6</td>
<td>0.06</td>
<td>22.0 ± 14.6</td>
<td>0.236</td>
<td>24.1 ± 17.9</td>
<td>0.52</td>
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<tr>
<td>Urine AMPH*</td>
<td></td>
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</tbody>
</table>
|                      | 3           | 0       | 4        | 1       | 2         |         | *(Chen et al., 2012)*
Heroin-dependent with methadone (MTD) therapy add on Placebo, dextromethorphan (DM) 60 mg/day (MTD+DM60) or MTD+DM120

(Chen et al., 2012)
Comments

• Low dose DM (60-120mg/day, 1-2mg/kg)
• Plasma level 10–200 ng/ml (28-560 nM)
• No effect in NMDA receptor antagonist
  (IC50: 5–50 μM) (Church et al. 1994)

• Effective in morphine addiction with methadone treatment
  Inhibition of methadone tolerance (one of important factors of addiction)

• Benefit in neuroprotection and decreasing neurodegeneration
  (Chen et al. 2013)
Heroin dependence with methadone treatment taking memantine or placebo

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
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<th>P-value</th>
<th>Endpoint</th>
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<th>P-value</th>
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<tr>
<td></td>
<td>Memantine</td>
<td>Placebo</td>
<td>Memantine</td>
<td>Placebo</td>
<td>Memantine</td>
<td>Placebo</td>
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<tr>
<td>Number (n)</td>
<td>53</td>
<td>75</td>
<td></td>
<td>45</td>
<td>58</td>
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<tr>
<td>Gender (male/female)</td>
<td>43/10</td>
<td>63/12</td>
<td>0.813</td>
<td>40/5</td>
<td>49/9</td>
<td>0.575</td>
</tr>
<tr>
<td>Age, mean (SD), (years)</td>
<td>37.06 ± 6.97</td>
<td>36.93 ± 7.15</td>
<td>0.923</td>
<td>37.91 ± 6.66</td>
<td>37.09 ± 6.94</td>
<td>0.524</td>
</tr>
<tr>
<td>Year of Heroin Use, mean (SD)</td>
<td>8.48 ± 7.10</td>
<td>7.58 ± 6.44</td>
<td>0.465</td>
<td>8.39 ± 7.27</td>
<td>7.35 ± 5.98</td>
<td>0.436</td>
</tr>
<tr>
<td>TNF-α (pg/mL), mean (SD)</td>
<td>3.65 ± 2.67</td>
<td>3.77 ± 3.30</td>
<td>0.824</td>
<td>2.28 ± 1.89</td>
<td>3.84 ± 3.78</td>
<td>0.006</td>
</tr>
<tr>
<td>CRP (ng/mL), mean (SD)</td>
<td>3902 ± 2929</td>
<td>3933 ± 3164</td>
<td>0.956</td>
<td>2518 ± 1951</td>
<td>3130 ± 2339</td>
<td>0.161</td>
</tr>
<tr>
<td>IL-6 (pg/mL), mean (SD)</td>
<td>2.40 ± 2.16</td>
<td>2.49 ± 2.56</td>
<td>0.833</td>
<td>1.81 ± 1.39</td>
<td>2.34 ± 2.67</td>
<td>0.229</td>
</tr>
<tr>
<td>IL-8 (pg/mL), mean (SD)</td>
<td>6.22 ± 9.77</td>
<td>5.01 ± 4.50</td>
<td>0.351</td>
<td>3.50 ± 4.78</td>
<td>2.99 ± 2.85</td>
<td>0.503</td>
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<tr>
<td>TGF-β1 (ng/mL), mean (SD)</td>
<td>23.12 ± 15.69</td>
<td>23.62 ± 15.70</td>
<td>0.860</td>
<td>23.65 ± 12.55</td>
<td>18.00 ± 14.63</td>
<td>0.042</td>
</tr>
<tr>
<td>BDNF (ng/mL), mean (SD)</td>
<td>9.08 ± 6.11</td>
<td>11.35 ± 8.49</td>
<td>0.098</td>
<td>9.00 ± 4.74</td>
<td>8.87 ± 5.91</td>
<td>0.905</td>
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<tr>
<td>Methadone dosage (mg)</td>
<td>34.32 ± 20.00</td>
<td>36.07 ± 22.90</td>
<td>0.655</td>
<td>35.84 ± 22.40</td>
<td>44.14 ± 24.22</td>
<td>0.082</td>
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Changes in Methadone dosage and cytokines after memantine or placebo treatment

<table>
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<tr>
<th>Parameter</th>
<th>Estimate</th>
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<th>t</th>
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<tbody>
<tr>
<td>Primary Outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Methadone Dose Required</td>
<td>−0.948</td>
<td>0.446</td>
<td>−2.128</td>
<td>0.034*</td>
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<tr>
<td>% of Change from baseline of Methadone Dose Required</td>
<td>−0.031</td>
<td>0.014</td>
<td>−2.242</td>
<td>0.025*</td>
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<tr>
<td>Secondary Outcome</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>TNF-α (pg/mL)</td>
<td>−0.035</td>
<td>0.012</td>
<td>−2.924</td>
<td>0.004**</td>
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<tr>
<td>CRP (pg/mL)</td>
<td>−0.017</td>
<td>0.010</td>
<td>−1.630</td>
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<td>IL-6 (pg/mL)</td>
<td>0.003</td>
<td>0.010</td>
<td>0.283</td>
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<td>IL-8 (pg/mL)</td>
<td>−0.016</td>
<td>0.017</td>
<td>−0.921</td>
<td>0.357</td>
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<tr>
<td>TGF-β1 (pg/mL)</td>
<td>0.028</td>
<td>0.012</td>
<td>2.403</td>
<td>0.017*</td>
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<tr>
<td>BDNF</td>
<td>312.75</td>
<td>212.40</td>
<td>1.472</td>
<td>0.142</td>
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</table>
Change of Methadone dose in memantine and placebo after 12 weeks of treatment
Change of Methadone dose normalized using the baseline (week 0 = 100%) after treatment.
• Low dose memantine (5mg/day)

• Plasma level 10–50 ng/ml (0.05–0.2 μM)

• No effect in NMDA receptor antagonist (IC50: 2–3 μM) (Parsons et al. 1999)

• Effective in morphine addiction with methadone treatment
  Inhibition of methadone dosage & tolerance (important factors of addiction)

• Benefit in neuroprotection and decreasing neurodegeneration (Chen et al. 2013)
Potential beneficial effects of anti-inflammation-related drugs

- **Addiction**
  - Opiate abuse
  - Alcohol abuse
  - Smoking
  - Compulsive eating disorder

- **CNS diseases**
  - Bipolar disorders
  - Depression
  - Schizophrenia
  - Alzheimer’s dis.
  - Brain ischemia
  - Parkinson’s dis.
  - MS
  - Spinal injury

- **Peripheral diseases**
  - Asthma
  - Arthritis
  - Arteriosclerosis
  - Cancer
  - Diabetes
  - Heart attack
  - Hepatitis
  - Inflammatory pain
  - Crohn’s dis.
  - Lupus
  - Sepsis (endotoxemia)
Peripheral effect in animal and human
Dextromethorphan (DM) decreases high lipid diet-induced atherosclerotic lesion formation in apo-E-deficient mice

The lipid-rich atherosclerotic lesions were identified with Oil-Red-O staining.

(Liu et al. 2009)
Conclusions

• Regulating over-inflammation and/or autoimmune effectiveness from central to peripheral

• Treatment symptoms and treatment progress
Acknowledgement

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- Shiou-Lan Chen, PhD.
- Shih-Heng Chen, PhD.
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