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

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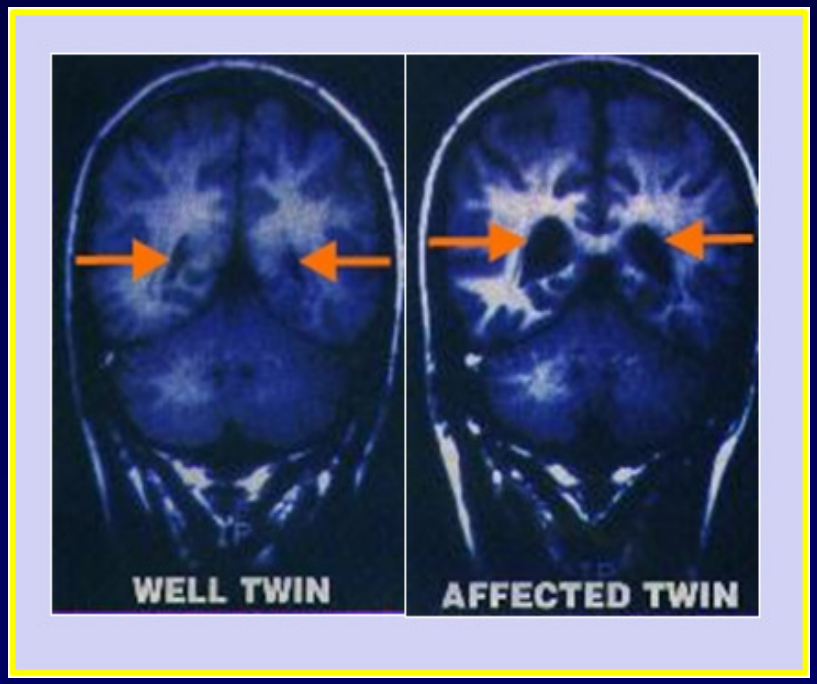
Neurodegeneration in Mental Illnesses

- Schizophrenia
- Bipolar disorders
- Substance use disorders (alcohol)
- Anxiety disorders?
- Personality disorders?

Neuronal degeneration in schizophrenia

Schizophrenia and bipolar disorders

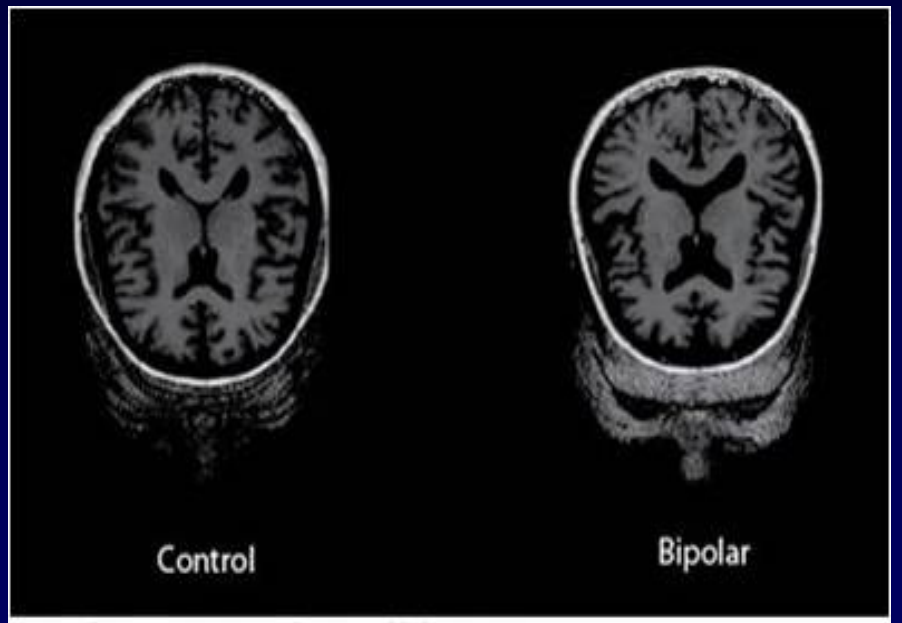
- **Decreased grey & white matter and lateral ventricular dilatation**
  (Largen et al., 1984; De Peri l et al., 2012)



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.)



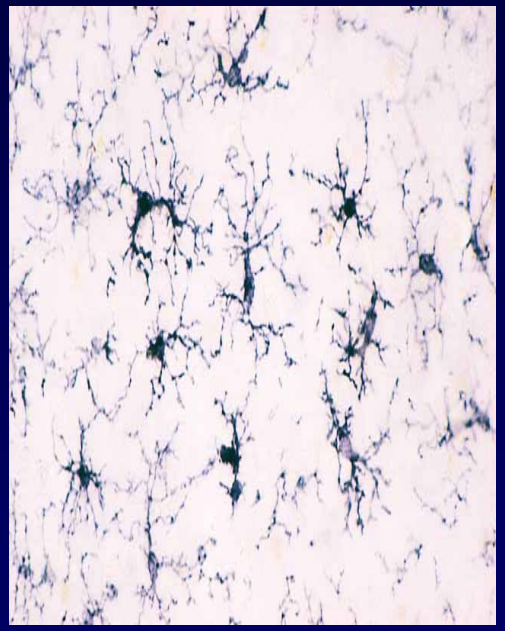
Neuronal degeneration in Substance Abuse

Both MRI's are of middle-aged women

Inflammation and neurodegeneration

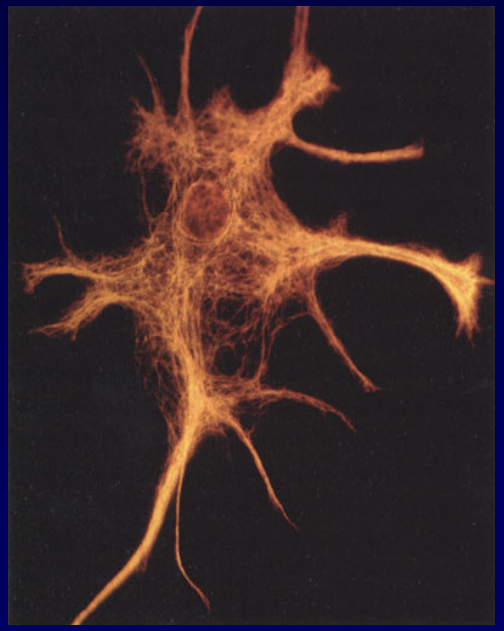
Glial cells :
Key roles in disease and prime targets for therapy

Microglia



Target for
anti-inflammation

Astroglia



Source for
neurotrophin production

Role of microglia in toxin-induced progressive neurotoxicity

(Working Model)

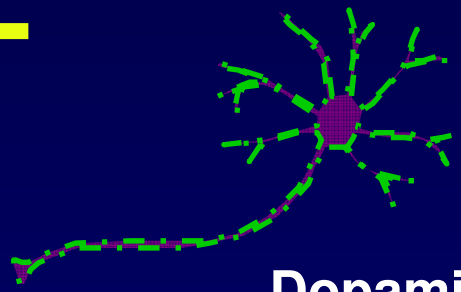
LPS
(Extra Neurotoxin)

MPTP
(Intra Neurotoxin)

Activation

Reactive Microgliosis

Microglia

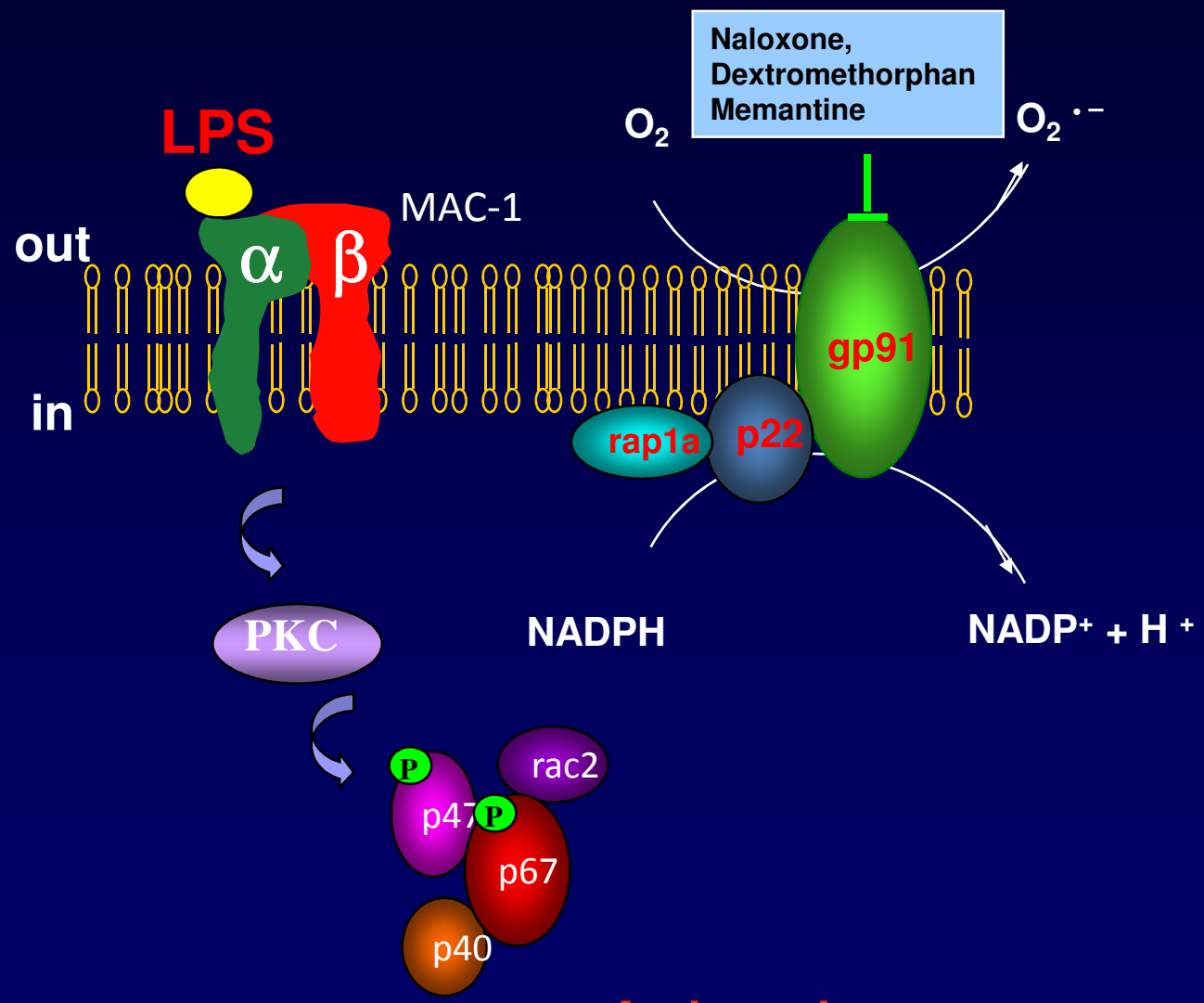


(Self-propelling)

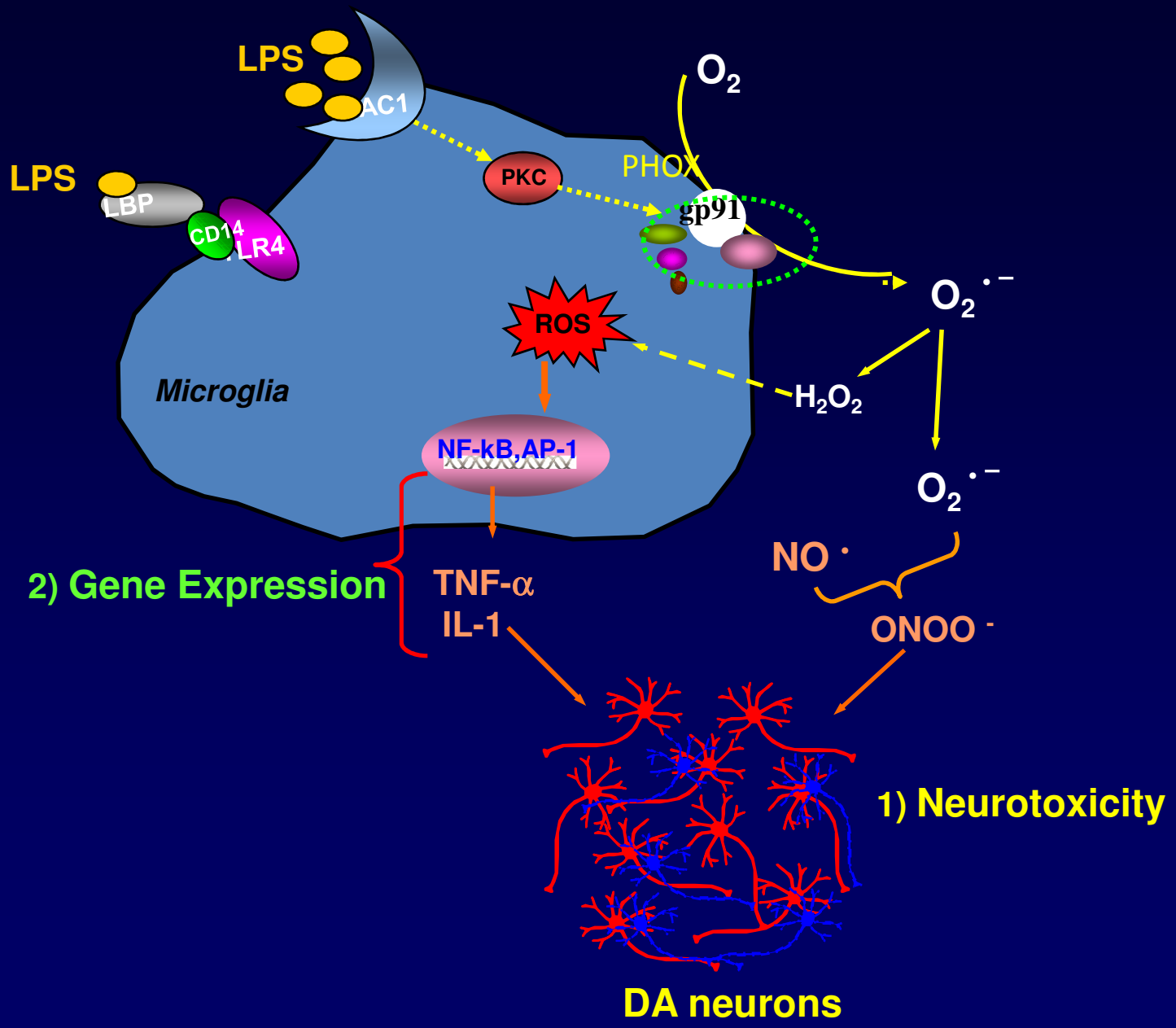
Pro-inflammatory Factors
(ROS, NO., TNFa, IL-1, PGs)

Dopaminergic
Neuronal
Damage

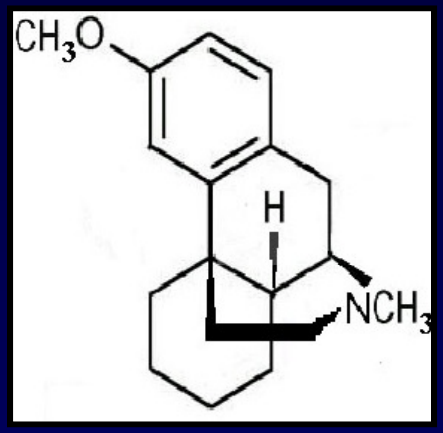
NADPH oxidase (PHOX)



Dual Functions of Superoxide Radicals

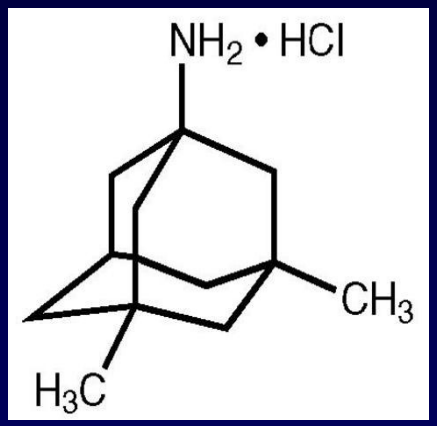


Dextromethorphan (DM)



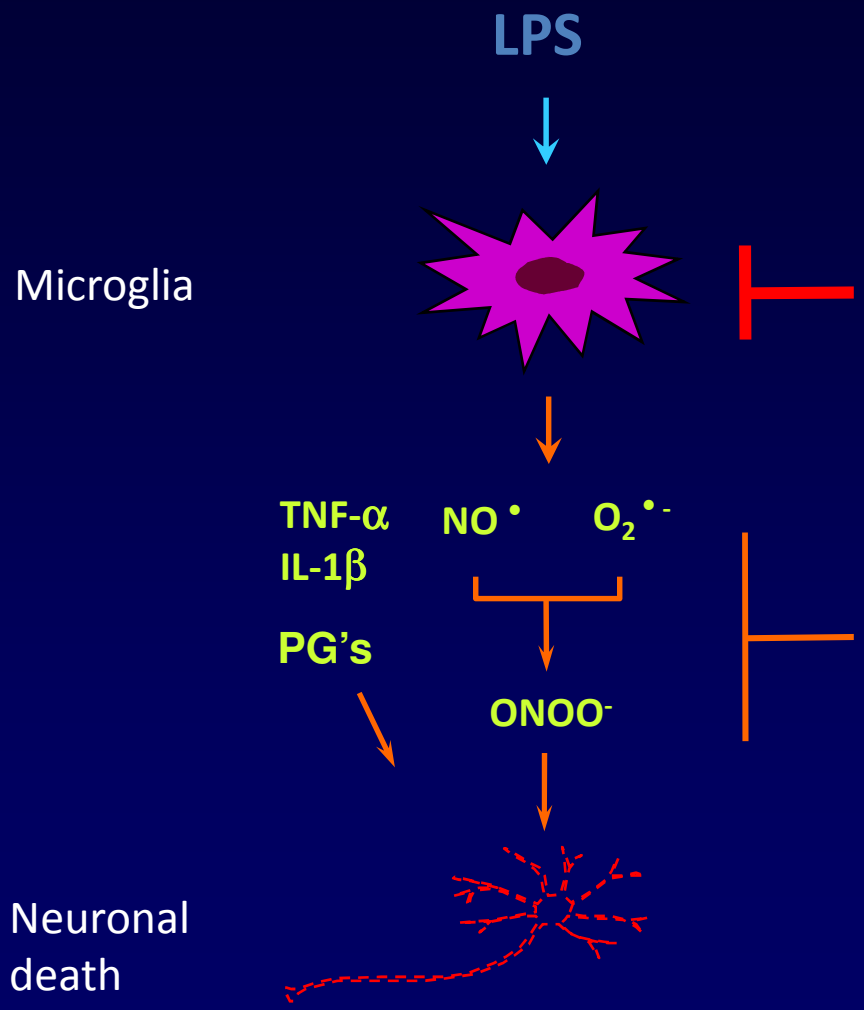
- Non-competitive NMDA receptor inhibitor in large dose for anti-cough effect
- Neuroprotective effects in vitro and in vivo at low dose

Memantine



- Non-competitive NMDA receptor inhibitor in large dosage
- Alzheimer's disease (20 mg/day)
- Neuroprotective effects in vitro and in vivo at low dosage

Novel anti-inflammatory therapy



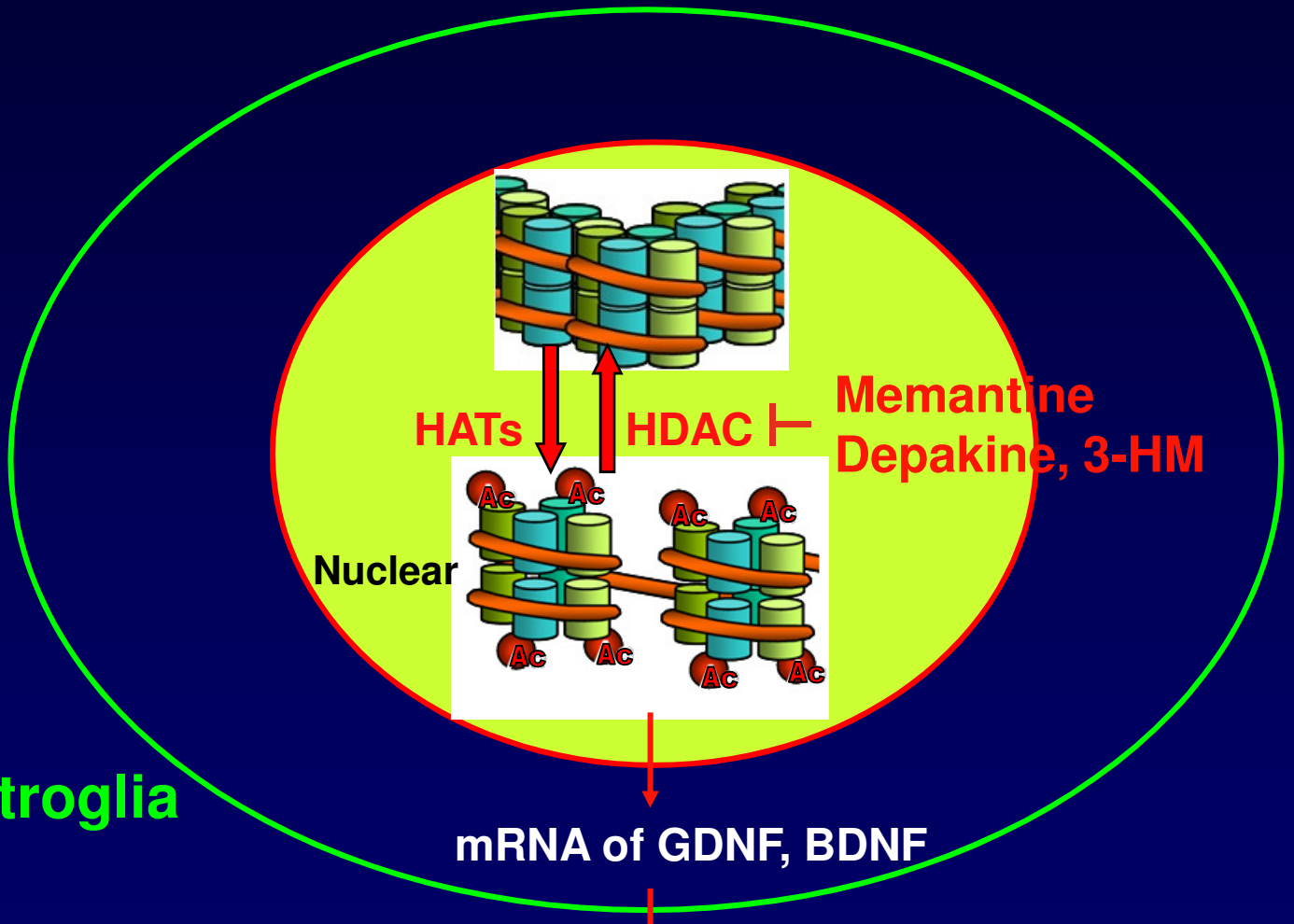
***Novel Strategy*: Modulation of microglial activity**

- **Morphinans : Naloxone, D-Morphine Dextromethorphan**
- **Dynorphins, Enkephalin, PACAP**
- **Memantine**

***Conventional Regimen*:**

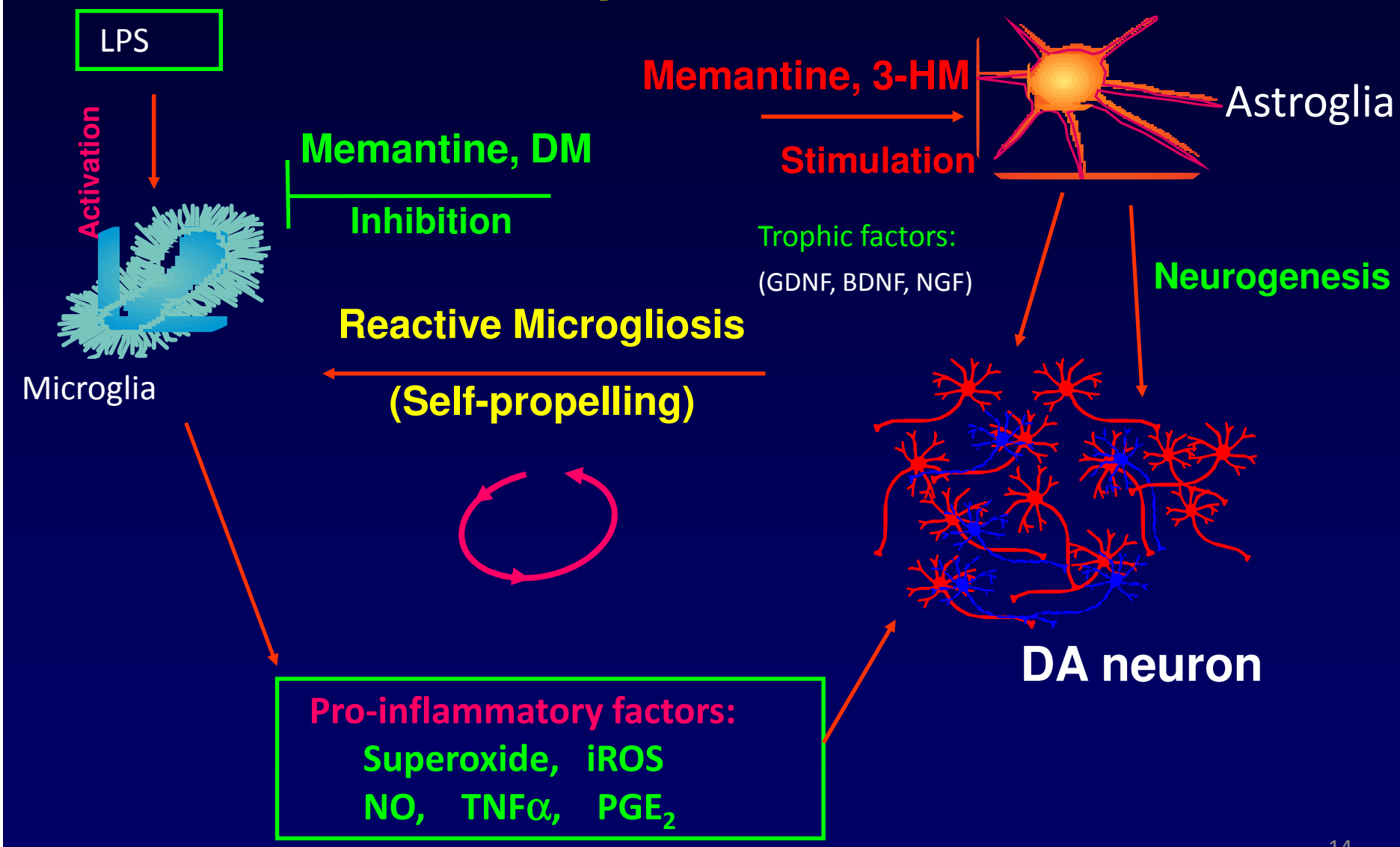
- **Aspirin, COX 2 inhibitors (PG)**
- **Anti-oxidants (Free radicals)**
- **Antibodies (TNF-α, IL-1)**
- **Receptor antagonists (TNF-α)**
- **Cortisone (toxic for long-term use)**

Mechanism underlying Memantine induced increase in expression of neurotrophic factors in astroglia



Chen et al., 2009

Therapy for neurodegenerative diseases and neuroprotective effect



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)

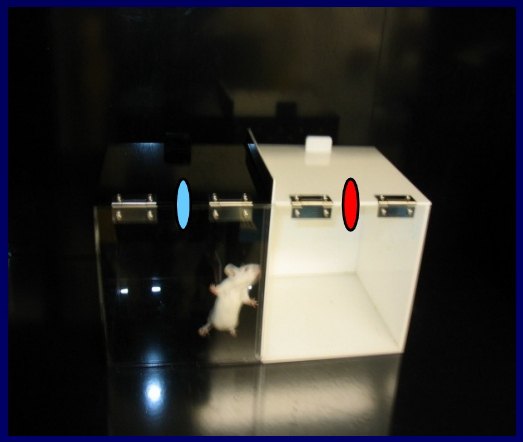
Conditioning

S(Saline)
Black chamber

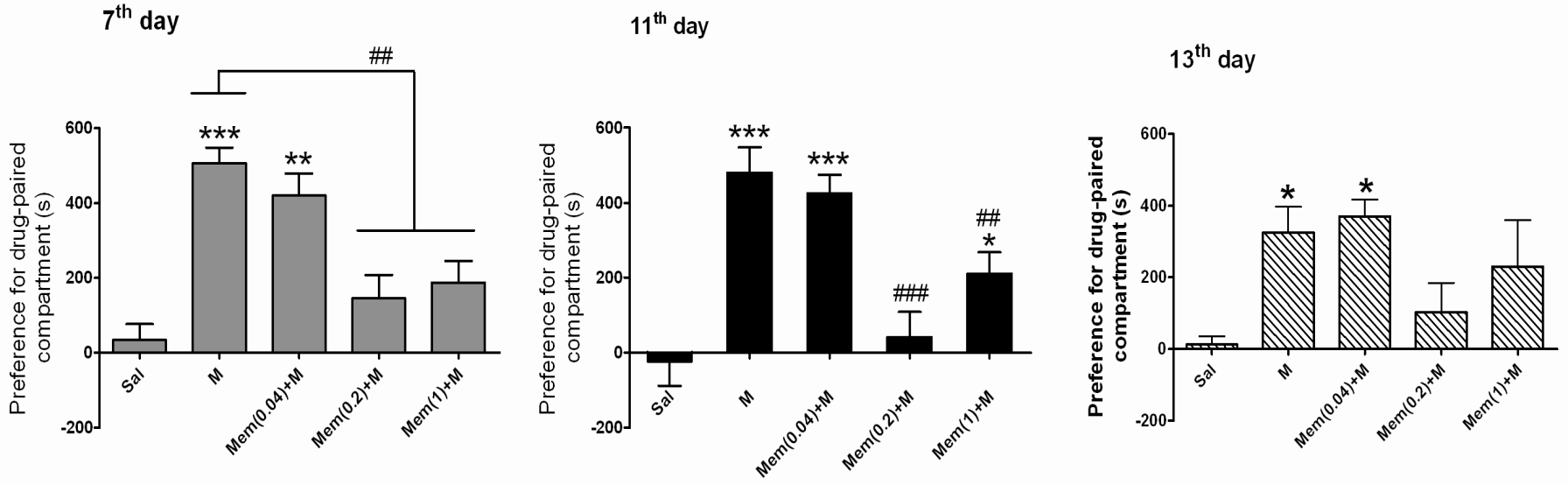
CPP CPP CPP CPP

0 1 2 3 4 5 6 7 8 9 10 11 12 13 days

S + M (Morphine 5mg/kg)
or Mem (Memantine)
+M White chamber



Memantine attenuate chronic morphine induced-CPP in rats

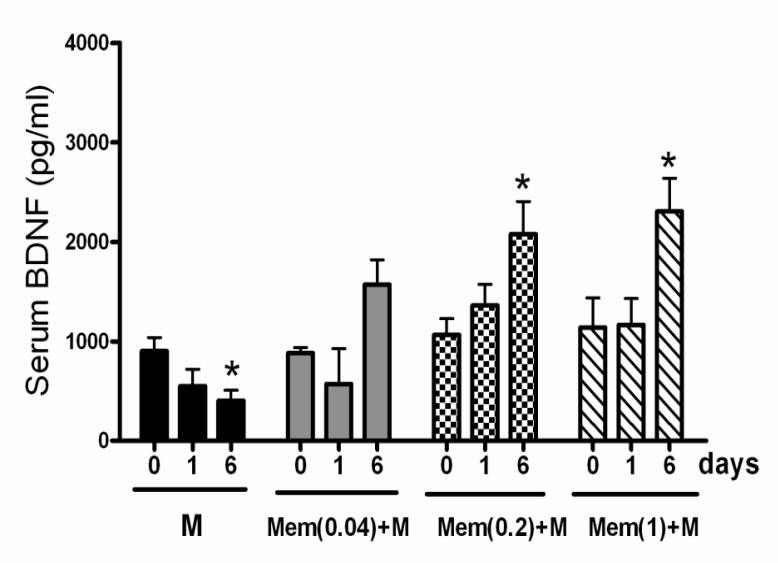


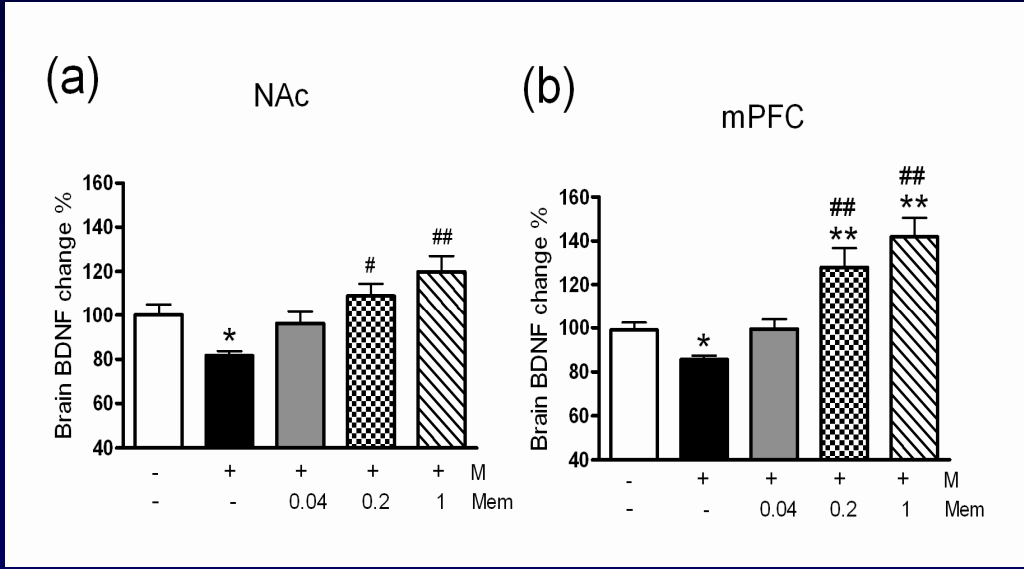
M: Morphine 5mg/kg
Mem: Memantine 0.04-1 mg/kg

*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



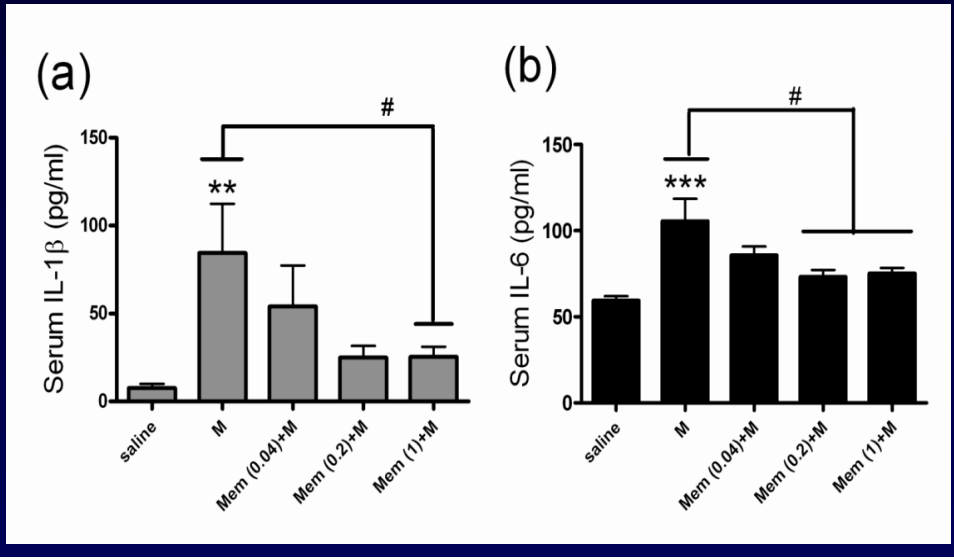


M: Morphine 5mg/kg
Mem: Memantine 0.04-1 mg/kg

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

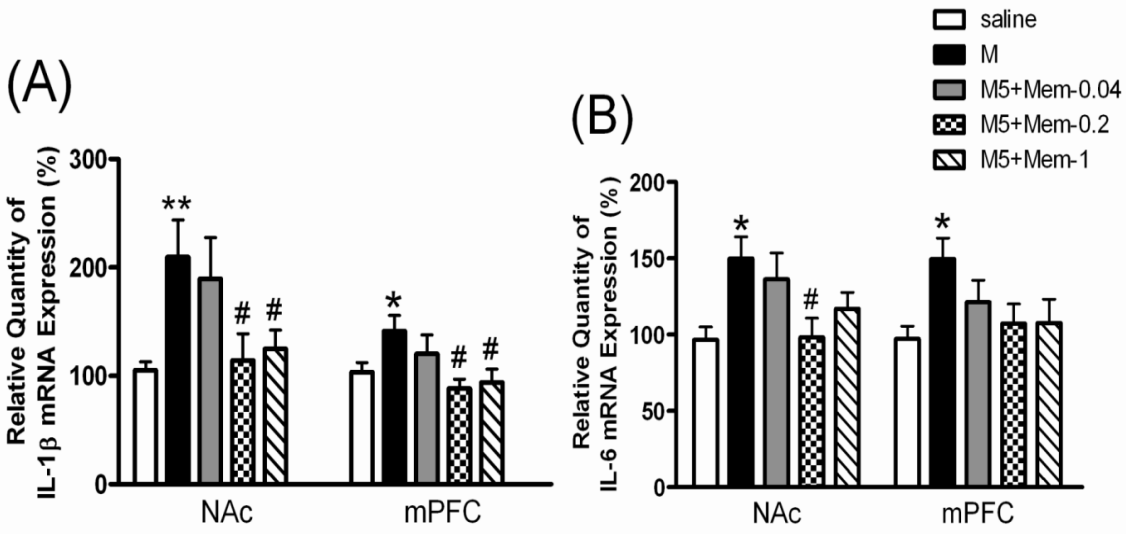
*J. of Neuroimmune Pharm. Dec.*2011

Memantine attenuate 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)

Comments

- 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

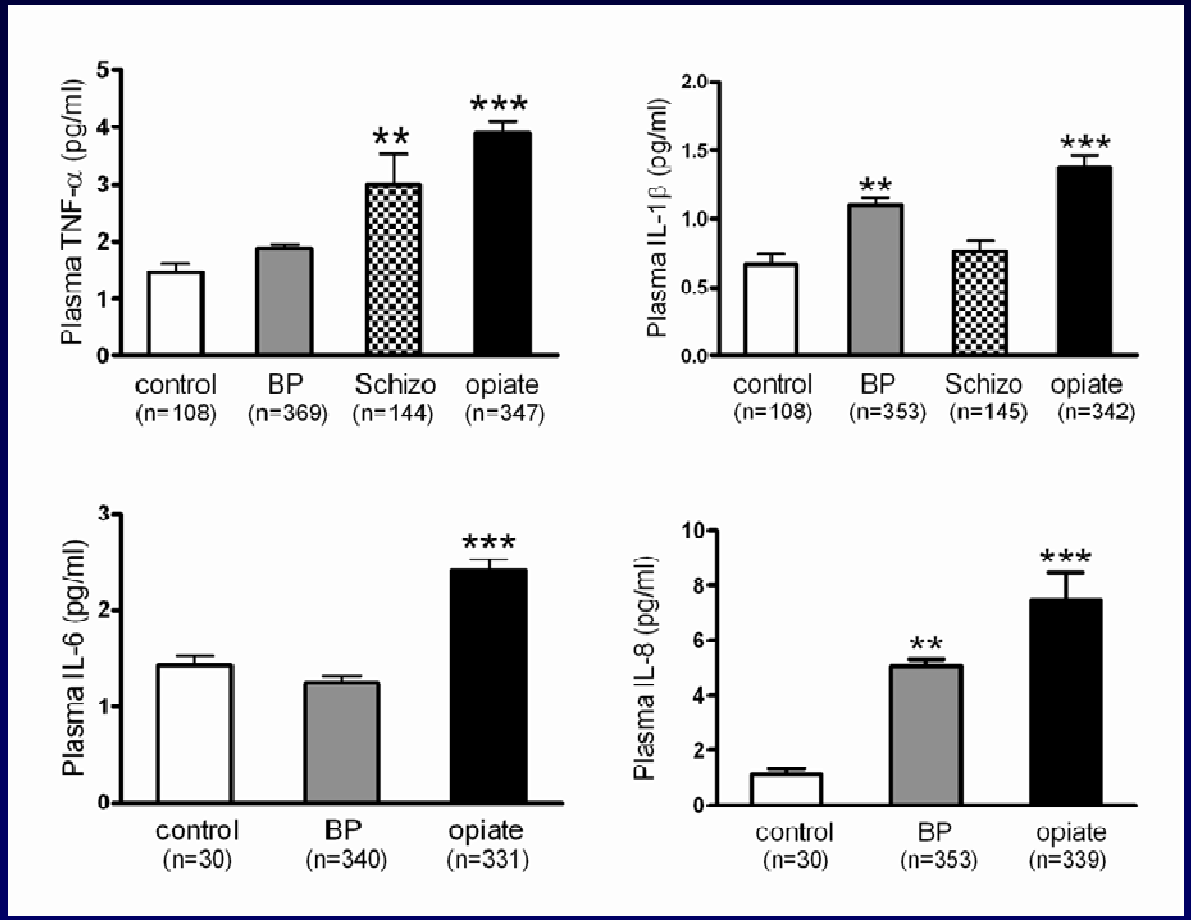
   - DM(60 or 120 mg/day) /placebo

     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)

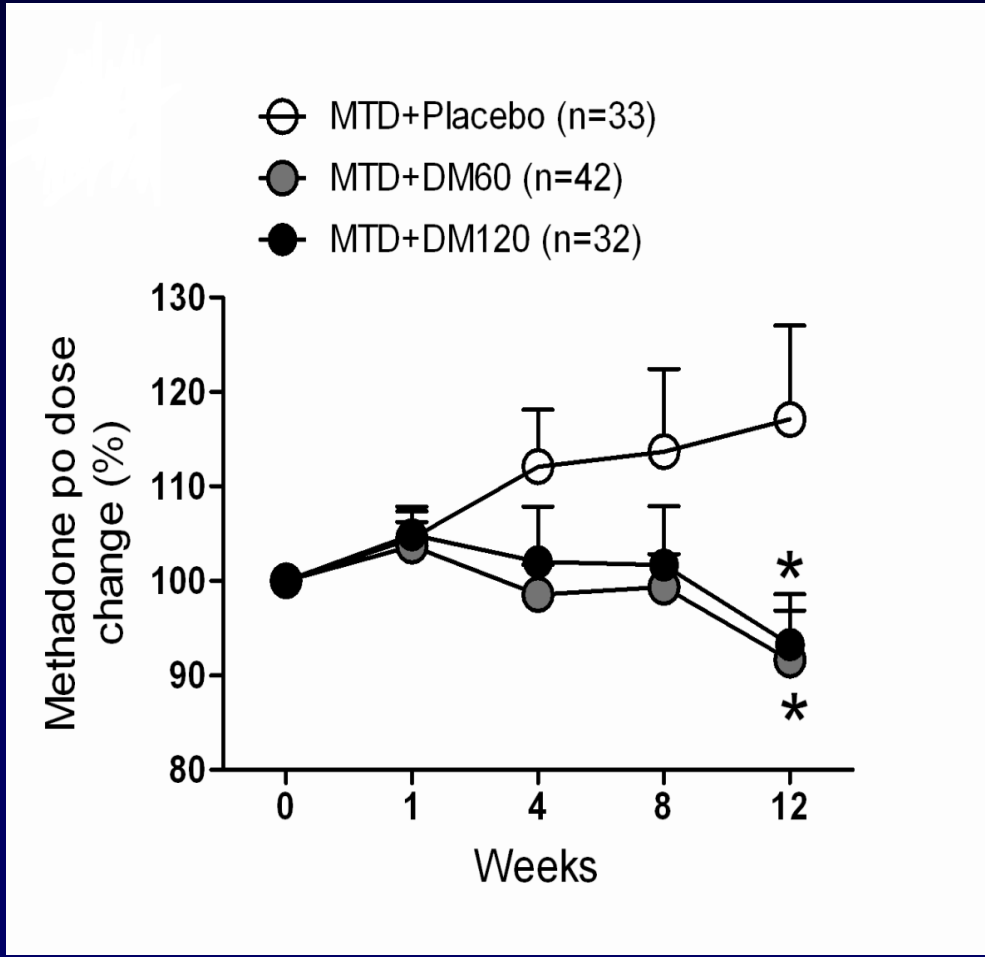
DM for Heroin Addiction with Methadone Maintenance Treatment

The effects of dextromethorphan on plasma cytokines, methadone dose, and combined use of substances in patients undergoing methadone maintenance therapy

	MTD+Placebo		*p*-value	MTD+DM60		*p*-value	MTD+DM120		*p*-value
	Week 0	Week 12		Week 0	Week 12		Week 0	Week 12	
TNF-α (pg/mL)	4.4 ± 0.5	4.3 ± 0.9	*0.571*	5.0 ± 0.6	3.0 ± 0.4**	*0.0005*	4.0 ± 0.4	2.9 ± 0.3**	*0.0009*
IL-8 (pg/mL)	4.8 ± 0.9	4.3 ± 0.9	*0.145*	7.4 ± 1.1	2.8 ± 0.3*	*0.021*	7.7 ± 1.3	2.92 ± 0.30*	*0.03*
MTD dose (mg)	40.0 ± 4.6	44.8 ± 5.7	*0.349*	47.4 ± 3.2	42.0 ± 2.8	*0.061*	44.1 ± 4.0	41.9 ± 5.3	*0.224*
MTD dose change (%)	100.0 ± 0	117.1±10.0	*0.096*	100.0 ± 0	91.7 ± 5.2*	*0.019*	100.0 ± 0	92.3 ± 5.1*	*0.034*
Urine morphine+	19	18		15	**7**		18	12	
Plasma morphine (pg/mL)	16.5 ± 4.1	39.6 ± 12.0	*0.064*	22.0 ± 7.4	14.6 ± 3.1	*0.236*	24.1 ± 6.7	17.9 ± 4.0	*0.52*
Urine AMPH+	3	0		4	1		2	0	

(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)

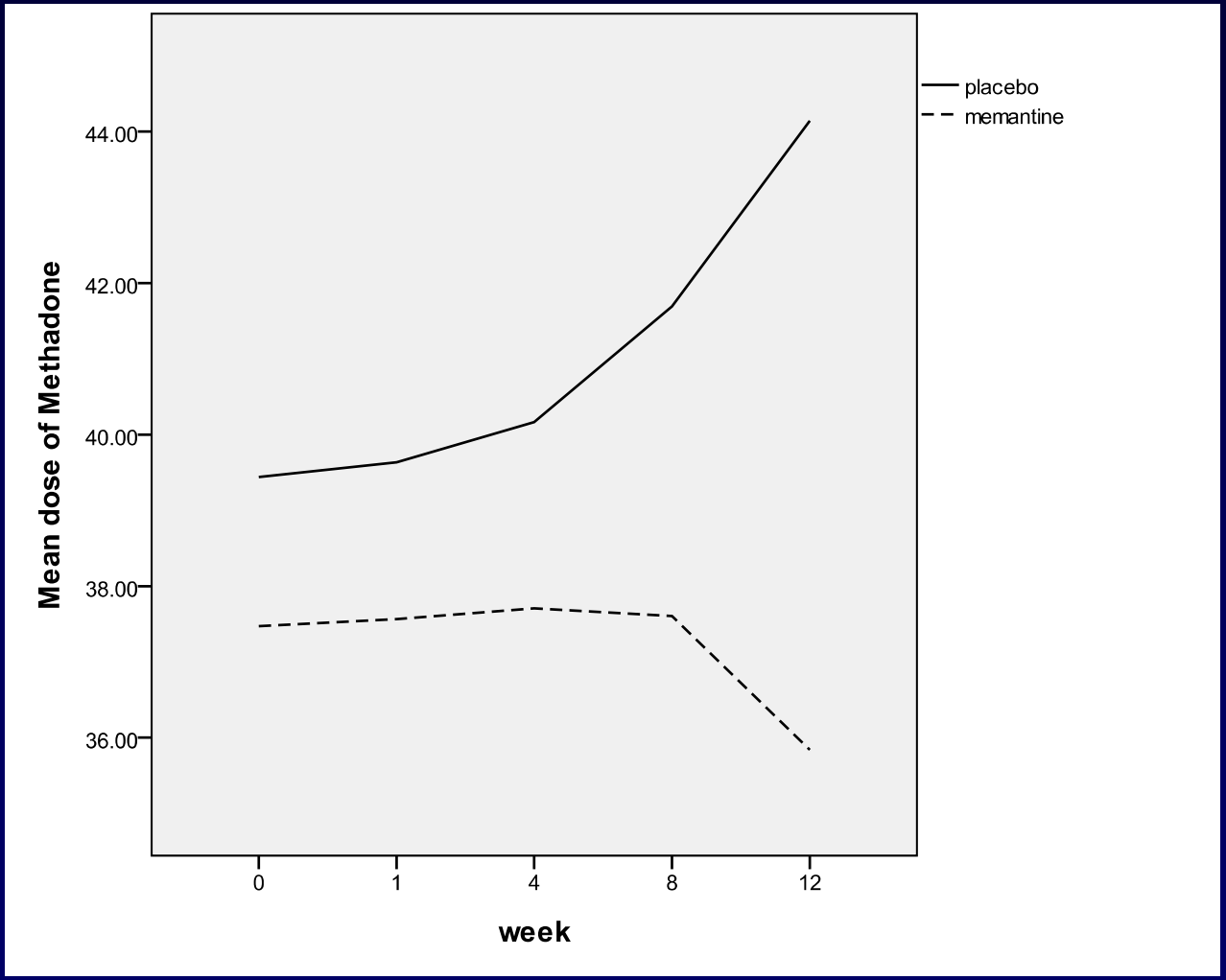
Heroin dependence with methadone treatment taking memantine or placebo

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

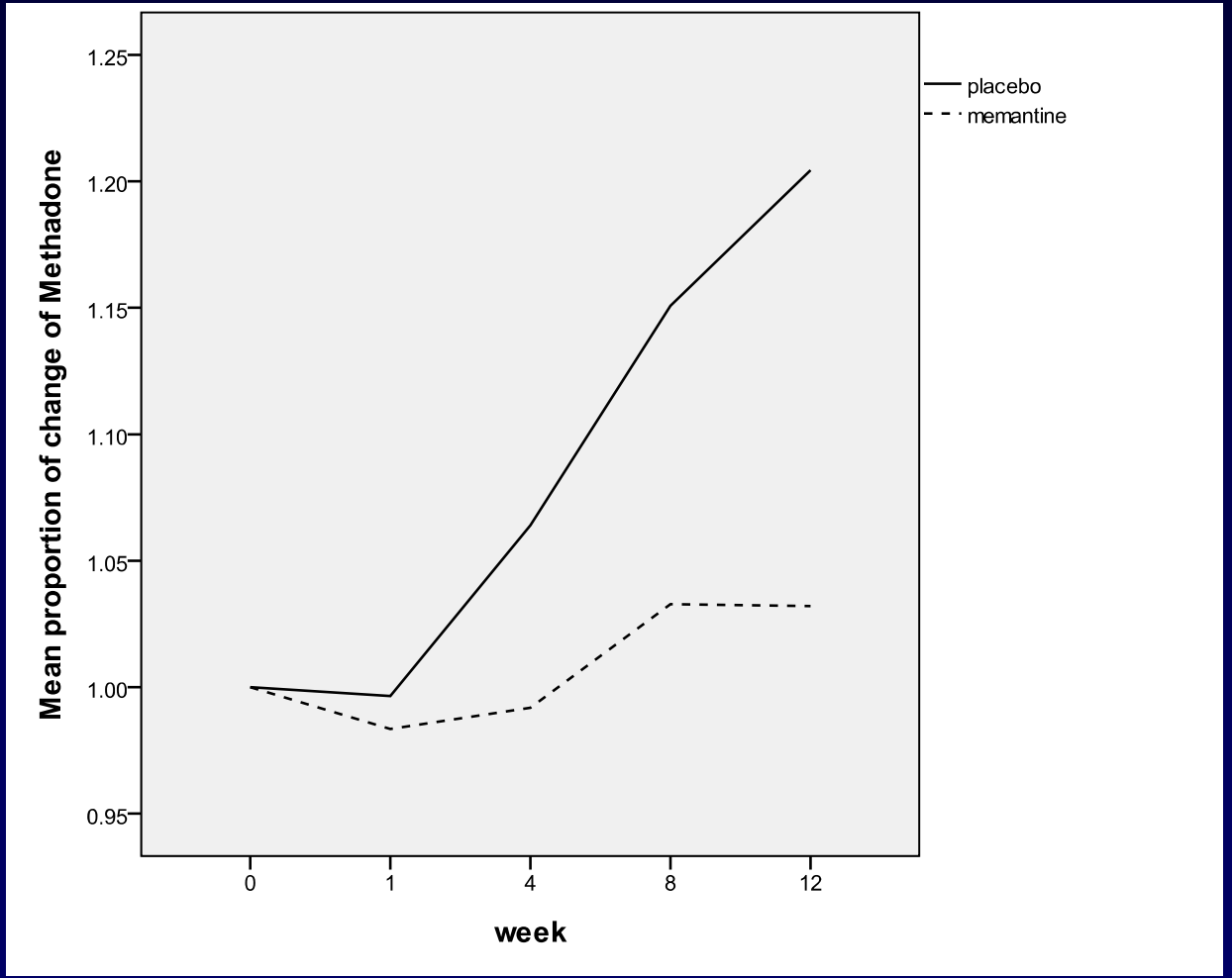
Changes in Methadone dosage and cytokines after memantine or placebo treatment

Parameter	Estimate	SE	t	p-value
Primary Outcome				
Methadone Dose Required	–0.948	0.446	–2.128	0.034*
% of Change from baseline of Methadone Dose Required	–0.031	0.014	–2.242	0.025*
Secondary Outcome				
TNF-α (pg/mL)	–0.035	0.012	–2.924	0.004**
CRP (pg/mL)	–0.017	0.010	–1.630	0.104
IL-6 (pg/mL)	0.003	0.010	0.283	0.777
IL-8 (pg/mL)	–0.016	0.017	–0.921	0.357
TGF-β1 (pg/mL)	0.028	0.012	2.403	0.017*
BDNF	312.75	212.40	1.472	0.142

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



Comments

- 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

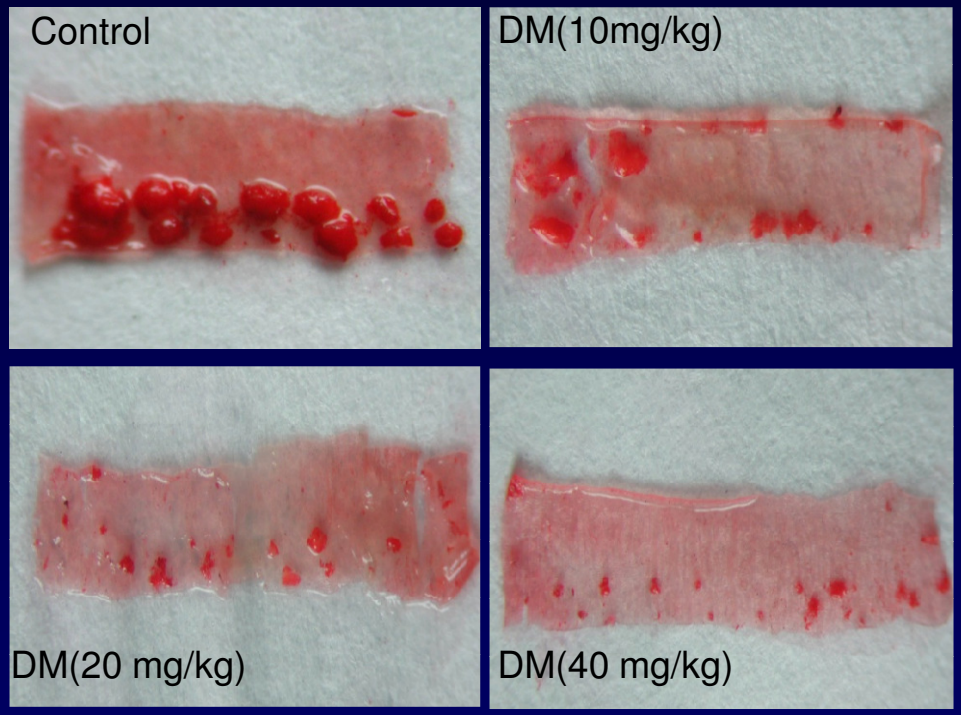
  (Chen et al. 2013)

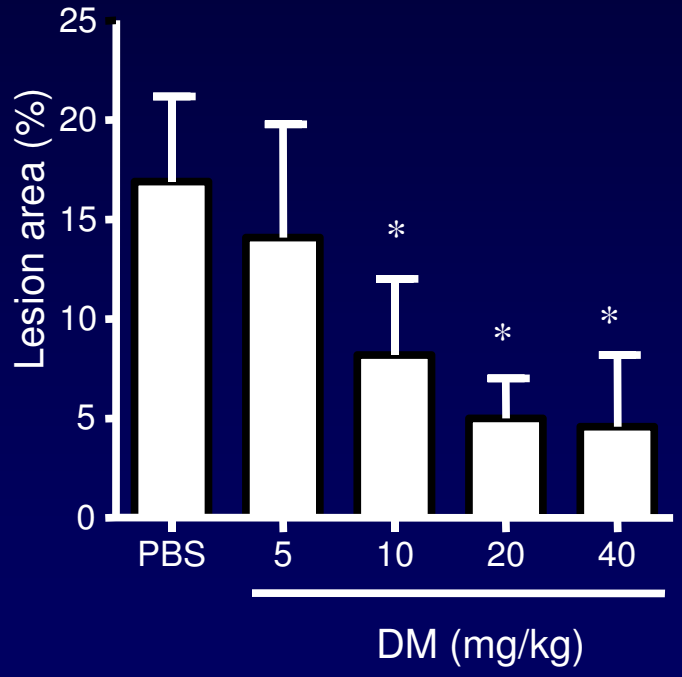
Potential beneficial effects of anti-inflammation-related drugs

- **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

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