Pain and Addiction: Can we actually see the relationships?

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Behavioral Phenotypes

Stressors

Cross-sensitization to substance use

Dysregulation of HPA axis

↑ striatal DA response to drug
PFC dysregulation

Genetic Variations

Behavioral Phenotypes

Sex Hormones

Continued Drug Use

Uncontrolled Drug Use

Males more vulnerable to addiction

↓ DA to PFC
↓ PFC suppression of Amygdala
↑ Amygdala function
↑ Striatal function

↑ PFC function
↑ Amygdala function

Drug Exposure
**MAO-A**

promoter polymorphism

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**COMT**

val158met polymorphism

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Fig. 1. Means on the composite index of antisocial behavior as a function of MAOA activity and a childhood history of maltreatment (27). MAOA activity is the gene expression level associated with allelic variants of the functional promoter polymorphism, grouped into low and high activity; childhood maltreatment is grouped into 3 categories of increasing severity. The antisocial behavior composite is standardized (z score) to a $M = 0$ and $SD = 1$; group differences are interpretable in SD unit differences (d).

Caspi et al., 2002

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Association of HA2 Scores with COMT Val158 Met Genotype in Two Female Populations

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Mean Tridimensional Personality Questionnaire HA2 scores ($\pm$ standard error) by catechol-O-methyltransferase (COMT) Val158Met genotype for Bethesda women ($n = 75$, $P = 0.087$) and Plains Indian women ($n = 148$, $P = 0.031$).

Caspi et al., 2002

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Enoch et al., 2003
Behavioral Risk Factors for Opiate Analgesic Requirements in Chronic Pain

- Previous or concurrent history of substance abuse
- Elements related to the *characteristics of pain* report:
  - Preoccupation with physical symptoms
  - Subjective lack of treatment efficacy
  - Higher levels of pain and higher variability of pain over time
- Elements related to *emotional functioning* during chronic pain:
  - Depression symptoms
  - Anxiety
  - Psychosocial distress
  - “Pain Catastrophizing” “a negative mental set brought to bear during actual or anticipated painful experience (Sullivan et al., 2004, Pavlin et al 2005)
Behavioral Risk Factors for Opiate Analgesic Requirements in Chronic Pain: Neurobiological Mechanisms?

- Higher levels of pain-associated disability, more negative emotional states:
  - Associated with lower levels of morphine analgesia (Burns and Bruehl 2005; Fillingim et al., 2005; Wasan et al., 2005)
  - Lower endogenous opioid system tone (as evidenced by challenges with the non-selective opioid receptor antagonist naloxone) (Bruehl et al., 2004)

- Role of opiate-induced hyperalgesia?
Mu Opioid Receptor-Mediated Neurotransmission

Distributed in pain regions but also "affective / motivational circuits" - neuronal nuclei involved in the assessment of stimulus salience and cognitive-emotional integration.
µ-Opioid Receptor Quantification with PET

Tracer Transport
(rCBF x Tracer Extraction)

Incorporation to
Specific Binding Sites

1 min 2 min 3 min 5 min 10 min 30 min 70 min

Data Analysis

Generation of Parametric Maps
e.g., Logan Plots (K₁, DVR)

Coregistration with Anatomical MRI

Non-Linear Anatomical Standardization
(ICBM Coordinates)

STATISTICAL PARAMETRIC MAPS OF SIGNIFICANCE
(SPM’99)

Z-VALUE

4 3 2 1
Mu Opioid Neurotransmission

- Experimental evidence (animal models and humans) and transgenic models implicate them in:
  - Endogenous opioid analgesia and effects of opiate analgesics
  - Stress responses and stress-induced analgesia
  - Regulation of affiliative behavior and responses to novelty
  - Regulation of amygdala and nucleus accumbens-mediated responses to salient stimuli, including drugs of abuse
  - Thought to mediate placebo effects during expectation of analgesia

- Direction of modulation is typically suppressive of the relevant response (e.g., pain, stress, anxiety, ...)
- Typically activated by stimuli that threatens the homeostasis of the organism (e.g., unpredictable stress, sustained, more rostral pain...
Previous Results

**µ-Opioid System Suppression of Sensory and Affective Qualities of Pain**  
(Zubieta et al., Science 293:311, 2001)

Note the interindividual variations in binding and release

**µ-Opioid Receptor Mediated Antinociception Differs in Men and Women**  
(Zubieta et al., J Neuroscience 22:5100, 2002)

**Sex Differences: Regulation by Estradiol**  
(Smith et al., J Neuroscience 26:5777-5785, 2006)
Parallel HPA and μ-Opioid System Activation

Cortisol Release During Pain (log AUC)

ACTH Release During Pain (log AUC)

Heitzeg et al., 2003
μ-Opioid System Suppression of Sensory and Affective Qualities of a Pain Stressor

• During sustained painful stress, μ-opioid neurotransmission is activated to suppress responses.

• This activation takes place in numerous regions (anterior cingulate, prefrontal cortex, insula, thalamus, ventral basal ganglia, amygdala, PAG).

• Some of these regions are involved in the perception and regulation of sensory aspects of pain (i.e., intensity and localization -thalamus, PAG-).

• ...But also in the regulation of stimulus salience and cognitive-emotional integration -anterior cingulate, insula, nucleus accumbens, ventral pallidum, amygdala-.)
Effects of Drugs of Abuse on DA Neurotransmission
Individually Housed

Socially Housed

Dominant


Subordinate
Basal Ganglia Dopamine and Pain

• In animal models, results equivocal depending on pain model (phasic, acute, or more sustained).

• Typically implicate D2 and not D1 receptors in the nigrostriatal pathway.

• Mesolimbic DA activated by more prolonged pain, not acute pain (pain as a stressor ?).

• Animal model data suggest an antinociceptive effect of dopamine in the ventral basal ganglia (blocked by D2 antagonists).

• In humans, however, D2 antagonists have been used in the treatment of chronic pain with success in RCT’s. Interspecies differences?
Basal Ganglia Dopamine and Pain

- DA D2 receptor concentrations in humans ([\(^{11}\text{C}\)]raclopride and PET) in putamen inversely correlated with cutaneous pain thresholds in healthy subjects and in atypical facial pain (Hagelberg et al., 2002, Pertovaara et al., 2004; Martikainen et al., 2005).

- Reduced \([^{18}\text{F}]\)FDOPA uptake in idiopathic mouth burning syndrome, not in atypical facial pain (Jaaskelainen et al., 2001)

- Increases in putamen D2, but not D1 ([\(^{11}\text{C}\)]NNC-756) receptor concentrations in idiopathic mouth burning syndrome and atypical facial pain (Hagelberg et al., 2003)
Activation of DA D2 Neurotransmission During Sustained Pain: Healthy Controls

Overall Response: Baseline - Pain

Saline Control - Pain

(Baseline - Pain) - (Saline Control - Pain)

Correlations

- MPQ Sensory, $r = 0.67$
- VAS Intensity, $r = 0.72$
- MPQ Sensory, $r = 0.76$
- VAS Intensity, $r = 0.79$
- PANAS negative, $r = 0.53$
- PANAS fear, $r = 0.45$

(Scott et al., J Neuroscience 26:10789-10795, 2006)
Activation of DA D2 Neurotransmission During Sustained Pain: Healthy Controls

(Scott et al., J Neuroscience 26:10789-10795, 2006)
Monoamine- Opioid Interactions

Zubieta et al., Nature Medicine, 1996
COMT Val^{158} Met Polymorphism: Hypothesized Effects

- Reduction in enkephalin mRNA
- Increase in µ-opioid receptor binding
- PFCTX, striatopallidal pathway
- Models: psychostimulant administration, D2 agonists
  - Met^{158} met COMT alleles?
- Increase in enkephalin mRNA
- Reduction in µ-opioid receptor binding
- Models: 6OHDA, D2 antagonists
  - Val^{158} val COMT alleles?
Psychophysiological responses: Correlations with COMT activity

<table>
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<tr>
<th>COMT Enzyme Activity</th>
<th>High Val/Val (n = 3)</th>
<th>Intermediate Met/Val (n = 22)</th>
<th>Low Met/Met (n = 4)</th>
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<tr>
<td>Genotype</td>
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<tr>
<td></td>
<td>Age</td>
<td>24.7 ± 2.5</td>
<td>24.5 ± 2.1</td>
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<td>Education</td>
<td>17.3 ± 1.5</td>
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<td>Acute Pain (15 sec) VAS Intensity</td>
<td>50.0 ± 35.0</td>
<td>47.4 ± 28.0</td>
<td>47.5 ± 8.7</td>
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<td>Sustained Pain (0-20 min) VAS</td>
<td>34.2 ± 6.6</td>
<td>37.3 ± 8.8</td>
<td>39.5 ± 7.3</td>
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<td>Average Infusion rate (µl/min) 0-10 min</td>
<td>72.3 ± 78.2</td>
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<td>10-20 min</td>
<td>188.4 ± 60.6</td>
<td>149.7 ± 56.7</td>
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<td>Rating - Stimulus Ratio MPQ Sensory</td>
<td>11.1 ± 5.9</td>
<td>16.2 ± 8.6</td>
<td>25.9 ± 19.4</td>
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<td>0.3 ± 0.5</td>
<td>2.6 ± 2.9</td>
<td>5.1 ± 7.2</td>
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<td>17.8 ± 11.5</td>
<td>25.6 ± 14.0</td>
<td>42.9 ± 37.8</td>
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<td>PANAS Negative Affect (Pain)</td>
<td>2.1 ± 3.6</td>
<td>7.5 ± 8.5</td>
<td>16.0 ± 19.2</td>
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Dysregulation of Opioid Mechanisms in Chronic Pain

- Opioid receptor concentrations reduced in rheumatoid arthritis and trigeminal neuralgia in humans (\([^{11}C]\)diphrenorphine and PET), reversed after 3 to 12 weeks of pain relief (Jones et al., 1994, 1999).

- Similar results in post-stroke pain and one case of pontine infarction (Willoch et al., 1999, 2004)

- Secondary to activation of endogenous opioid neurotransmission, receptor downregulation or both?

- Relationship with clinical pain report?
Dysregulation of Opioid Mechanisms in Chronic Pain: Fibromyalgia

- N = 11 women diagnosed with fibromyalgia
- N = 11 matched controls
- fMRI with thumb pressure
- PET with [¹¹C]carfentanil

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<th>L AMY</th>
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<td>∆BP</td>
<td>25±13</td>
<td>21±15</td>
<td>23±17</td>
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</table>
Dysregulation of Opioid Mechanisms in Chronic Pain: Fibromyalgia

BOLD -fMRI Response to 2kg/cm² pressure

A

Relationship with Clinical Pain

r = -0.76
p < 0.01

B

Correlation AMY µ-ORs and INS BOLD response

r = -0.72
p = 0.01

C

Harris et al., under review
Conclusions

- Two neurochemical systems centrally implicated in the effects of opiates and drugs of abuse, the endogenous opioid/µ-opioid receptor and the dopaminergic/D2 receptor, are also involved in responses to sustained pain in humans.
  - Think of pain as a physical and emotional stressor

- Substantial interindividual variability is observed in the function of these systems at the level of pain report and affective responses to pain.
  - Subject to genetic and gonadal steroid influences

- Evidence of DA D2 and µ-opioid system dysregulation in various forms of chronic pain.
  - Reducing initial risk for opiate abuse in chronic pain patients?
  - Effect of individual variability in chronic pain samples?
  - Implications for opiate and other drug abuse risk not explored.
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