Hyperalgesia and Hyperkatifeia

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4-21-21

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Relative Scope of the Problem: Opioids versus Alcohol

Opioids	
Misuse*	**11,401,000**
% of population	**4.2**
OUD	**2,110,000**
% of population	**0.8**
ED visits	**408,079** Primary reason
	1,461,770 All opioid-related
Deaths	**47,600** Total overdoses
	17,029 Prescription opioids
	28,400 Fentanyl and similar
	15,482 Heroin

Opioid + alcohol overdose deaths
7,270 (15% of all opioid overdose deaths involved alcohol in 2017)

Alcohol	
Use	**178,736,000**
% of population	**65.7**
AUD	**14,500,000**
% of population	**5.3**
ED visits	**1,714,757** Primary reason
	4,936,690 All alcohol-related
Deaths	**~88,000** Total deaths
	49,544 Acute – overdose, injury
	38,880 Chronic – liver, cancer

*Any past year heroin use or prescription opioid use other than as prescribed

Sources: NSDUH, 2017 people aged 12+; Nationwide Emergency Department Sample, 2016; CDC Overdose Death Data, 2017; CDC Alcohol Related Death Inventory, 2006-2010; White et al, 2018

Courtesy of Dr. Aaron White, NIAAA

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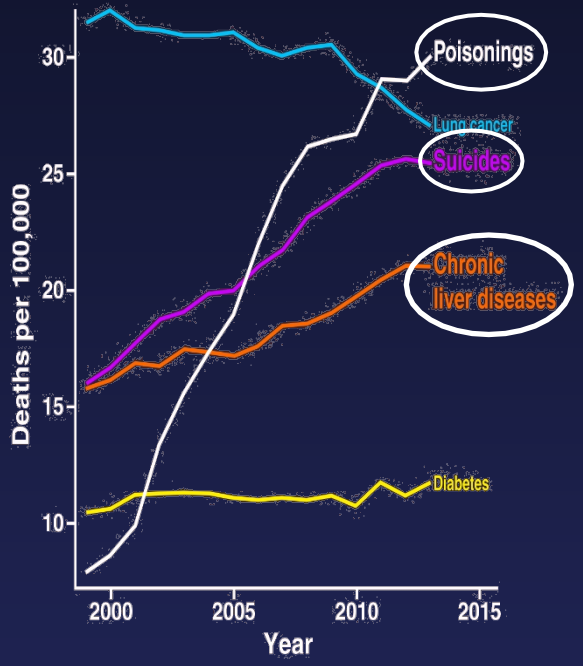
Mortality, Drugs, and Deaths of Despair in the United States

- Morbiditiy and mortality, termed "Deaths of Despair," have been increasing in midlife in the U.S. from 1999 to 2013 (Case and Deaton, 2015)
- These patterns of increased mortality have also been observed across many racial/ethnic groups and age groups (Woolf et al., 2018)
- Drugs and alcohol play a prominent role in "deaths of despair"
- Alcohol contributes to:
  - 15-20% of all drug overdoses
  - 26% of suicides
  - 50% of liver disease deaths
- "Deaths of despair" are contributing to the decreasing life expectancy in the U.S. observed since 2014 (Woolf et al., 2019)

Mortality by cause among White non-Hispanics (age 45-54)



Case and Deaton, 2015

Case A, Deaton A: Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. Proc Natl Acad Sci USA 2015;112:15078-15083

Woolf SH, Schoomaker H: Life expectancy and mortality rates in the United States, 1959–2017. JAMA 2019;322:1996-2016

Outline of Talk

1. **Definitions and Conceptual Framework:** Hyperalgesia, Hyperkatifeia, Opponent Process, Negative Reinforcement

2. **Evidence for Opioid Hyperalgesia:** Preclinical and Human studies

3. **Neurobiological Basis of Hyperalgesia**: Within- and between-system neuroadaptations

4. **Evidence for Opioid Hyperkatifeia:** Preclinical and Human Studies

5. **Neurobiological Basis of Hyperkatifeia**: Within- and between-system neuroadaptations

6. **Convergence of Brain Pain and Negative Emotion Neurocircuits:** Implications for the role of addiction in "deaths of despair" and the effects of the COVID-19 pandemic.

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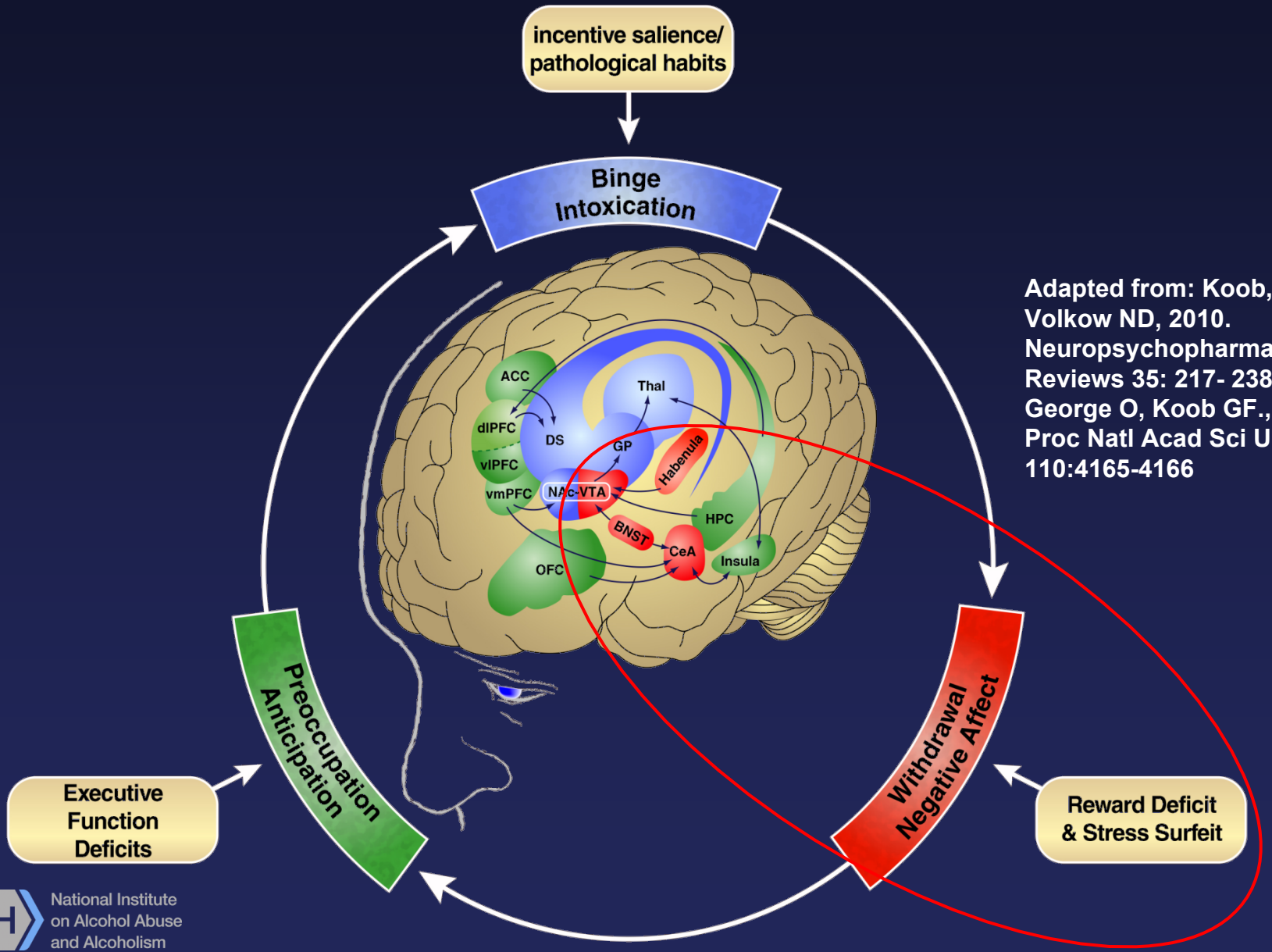
Definitions and Symptoms of Opioid Tolerance, Withdrawal, Opioid Use Disorder, Opioid-induced Hyperalgesia, and Opioid-induced Hyperkatifeia

Condition	*Definition*	*Symptoms*
Tolerance	A decreased analgesic response to a stable dose of opioid	Reappearance of pain with the same intensity as prior to treatment
Withdrawal	A physiological reaction to the abrupt discontinuation of an opioid or following the administration of an opioid antagonist after recent opioid use	Dysphoric mood, gastrointestinal disturbances, muscle aches, lacrimation or rhinorrhea, pupillary dilation, sweating, piloerection, yawning, fever, insomnia
*Opioid use disorder**	A pervasive and problematic pattern of opioid use occurring within a 12-month period, despite negative consequences	Recurrent use resulting in physical and interpersonal deficits, tolerance, withdrawal, drug craving and seeking, changes in mood and personality
Opioid-induced hyperalgesia	A state of diffuse increased pain sensitivity to a stimulus of stable intensity, independent of disease progression	Significant worsening of original pain; diffuse pain that is independent of original pain and worsens with upward dose titration
*Opioid-induced Hyperkatifeia**	Defined as the increased intensity of negative emotional/motivational symptoms and signs observed during withdrawal from abused drugs	

Definitions adapted from The National Council on Alcoholism and Drug Dependence, Inc., The National Institute on Drug Abuse, The Neurobiology of Drug Addiction, and the DSM-5
**Formally opioid abuse and opioid dependence (DSM-4)*

From: Arout CA, Edens E, Petrakis IL, Sofuoglu M. CNS Drugs 2015;29:465-486. Shurman et al. Pain Med 2010;11:1092-1098

Conceptual Framework for Neurobiological Bases Driving Substance Use Disorders



Adapted from: Koob, GF and Volkow ND, 2010. Neuropsychopharmacology Reviews 35: 217- 238; George O, Koob GF., 2013 Proc Natl Acad Sci USA, 110:4165-4166

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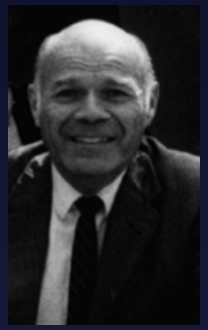
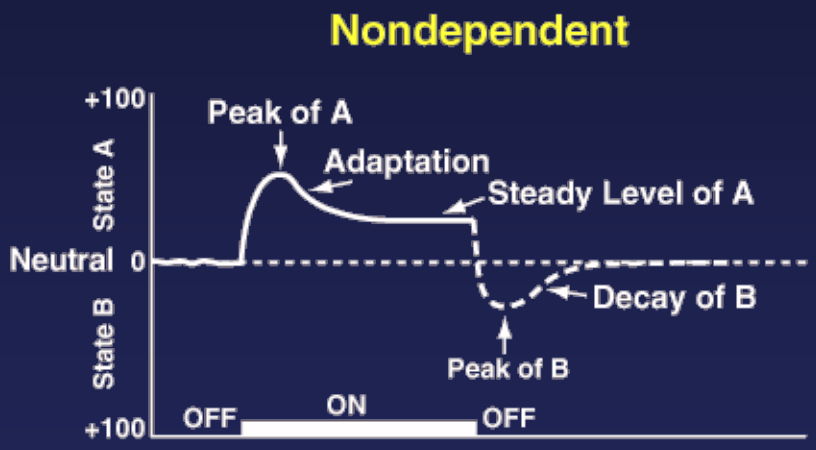
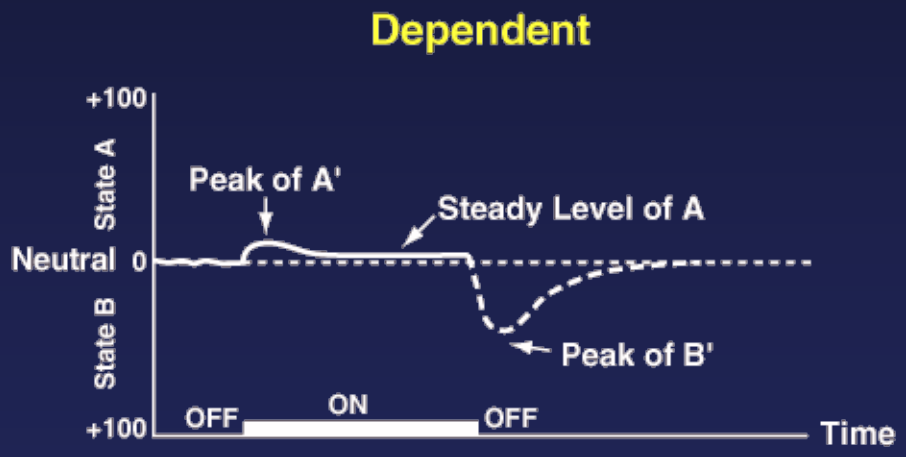
Standard Pattern of Affective Dynamics Produced by Novel and Repeated Unconditioned Stimulus

(Opponent Process or "What Goes Up Must Come Down")



Dr. Richard Solomon





From: Solomon RL. American Psychologist, 1980, 35:691-712.

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Positive and Negative Reinforcement - Definitions

Positive Reinforcement — defined as the process by which presentation of a stimulus (drug) increases the probability of a response (nondependent drug-taking paradigms).

Negative Reinforcement — defined as the process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking)

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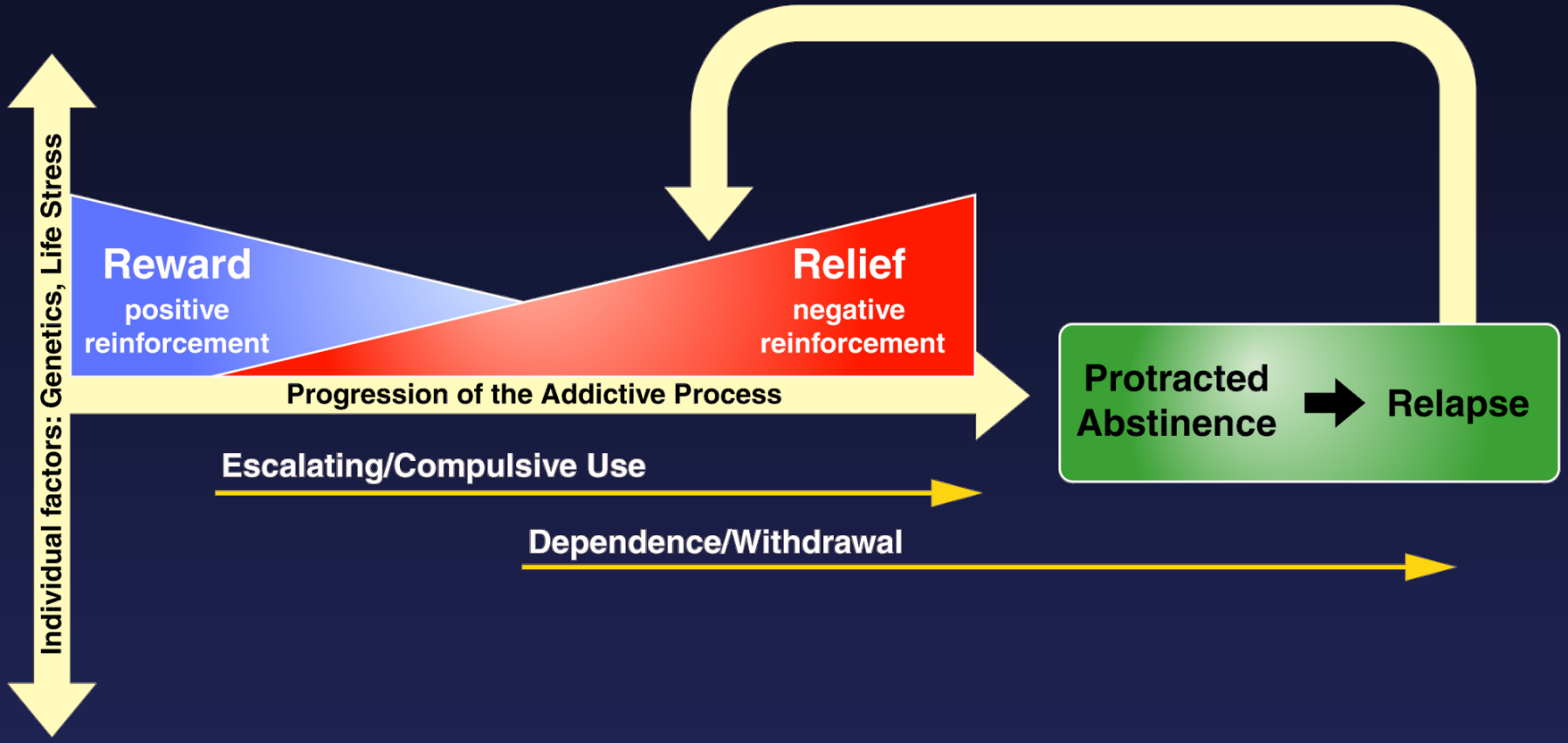
Etiology of Addiction

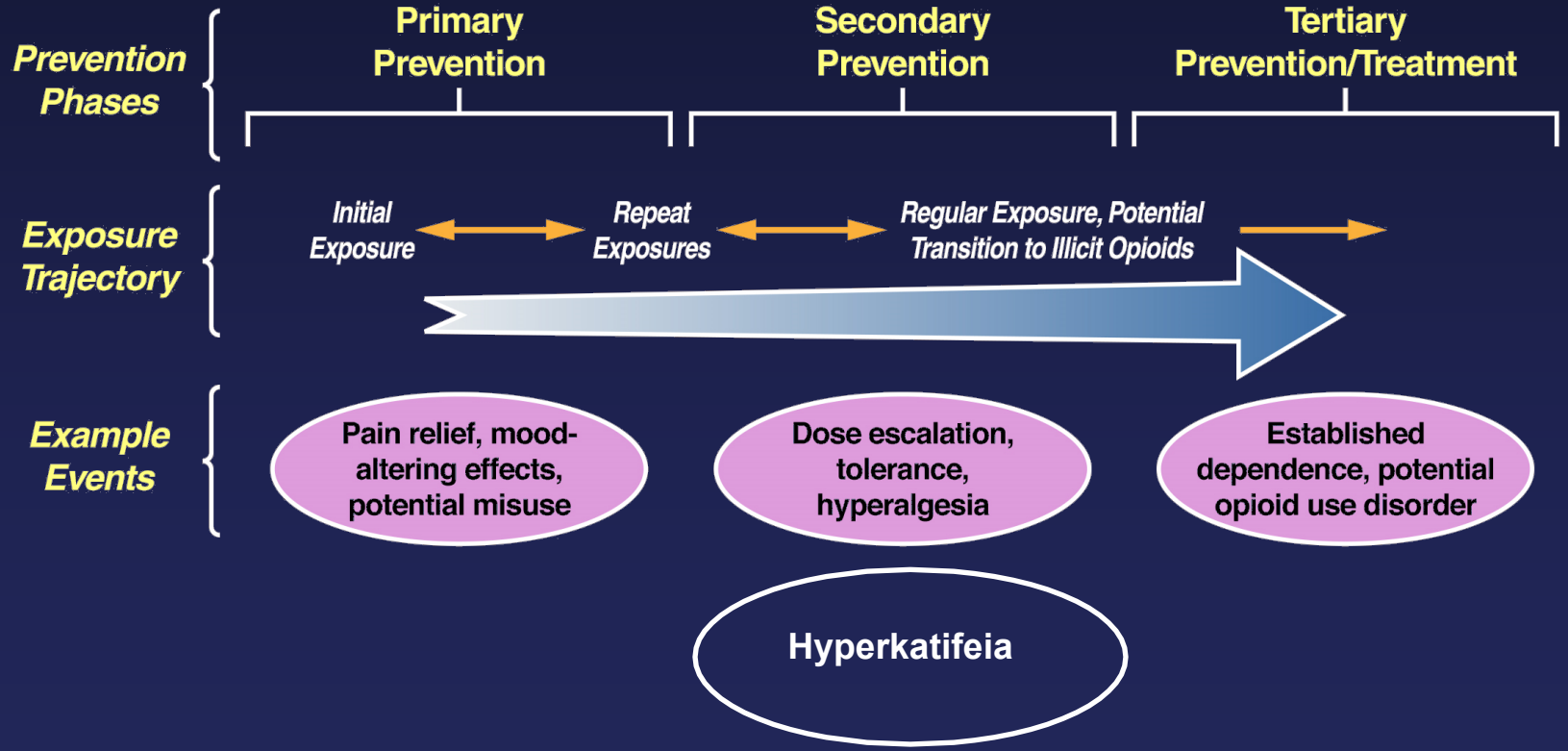


Loss of Control /Compulsivity Derives from:

1. Development of incentive salience and pathological habits for drugs
2. Development of reward deficits and sensitization of stress neurocircuits
3. Compromised executive function

A theoretical framework and modern nomenclature for characterizing therapeutic opioid exposure and the degree to which it contributes iatrogenically to adverse outcomes.

Opioid Exposure and Primary, Secondary, & Tertiary Prevention/Treatment of Long-term Use & Other Related Adverse Outcomes



From: Beauchamp GA, Nelson LS, Perrone J, Lyons MS. Am J Drug Alcohol Abuse 2020;46:671-683.

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Opioid- induced Hyperalgesia

1. Opioid-induced hyperalgesia (OIH) can be defined as a state of nociceptive sensitization caused by exposure to opioids.

2. The condition is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain could actually become more sensitive to certain painful stimuli.

3. OIH can exacerbate a preexisting painful condition and therefore will increase pain intensity above preexisting pain levels.

4. OIH typically produces diffuse pain, less defined in quality, which extends to other areas of distribution from preexisting pain.

5. OIH appears to be a distinct, definable, and characteristic phenomenon that could explain loss of opioid efficacy in some patients.

Gupta S. J Rational Pharmacother Res 2018;4:22-30; Lee M, Silverrman S, Hansen H, Patel V, Manchikanti L. Pain Physician 2011;14:145-161.

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An Early (1965) Report of Hyperalgesia in Individuals with a History of Opioid Addiction

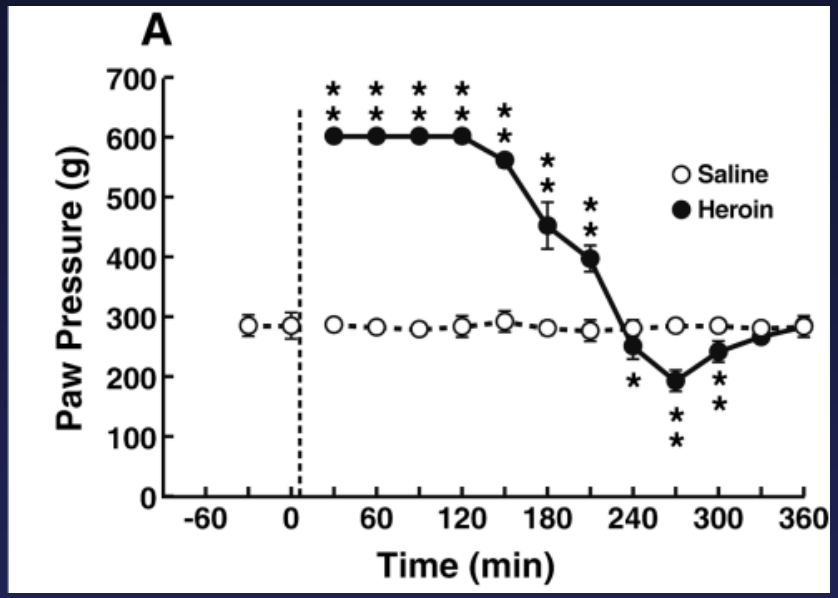
Decrease in pain tolerance times (in minutes) in the cold-pressor test

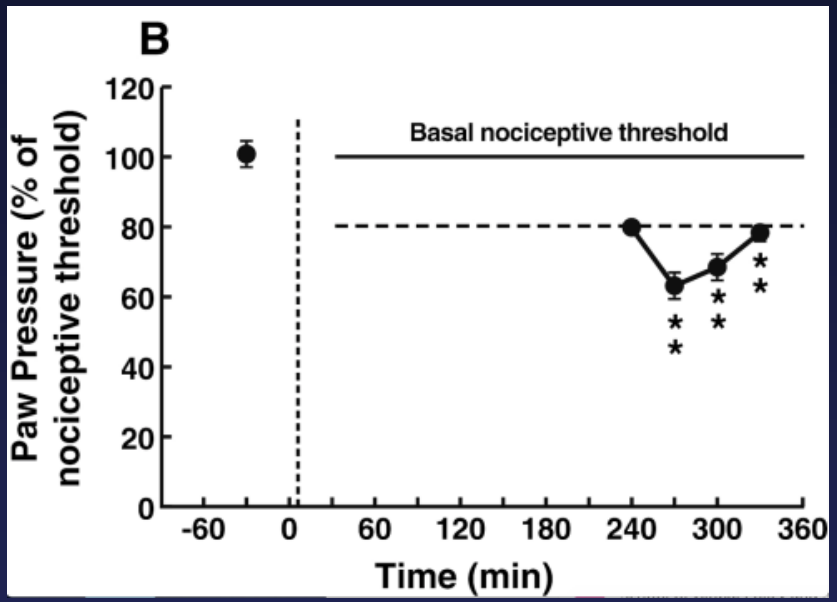
	Group					
	Addicts		Non-addicts		t	p
	M	σ	M	σ		
CPT score (in min.)	1.22	1.28	6.74	5.08	5.16	< 0.001

Subjects were 24 formerly addicted women in the Kingston Penitentiary for women and 24 non-addicted women in the same institution

From: Martin JE, Inglis J. Br J Social Clin Psychol 1965;4:224-229.

Effect of a Single Injection of Heroin on Paw Pressure-induced Vocalization in Rats

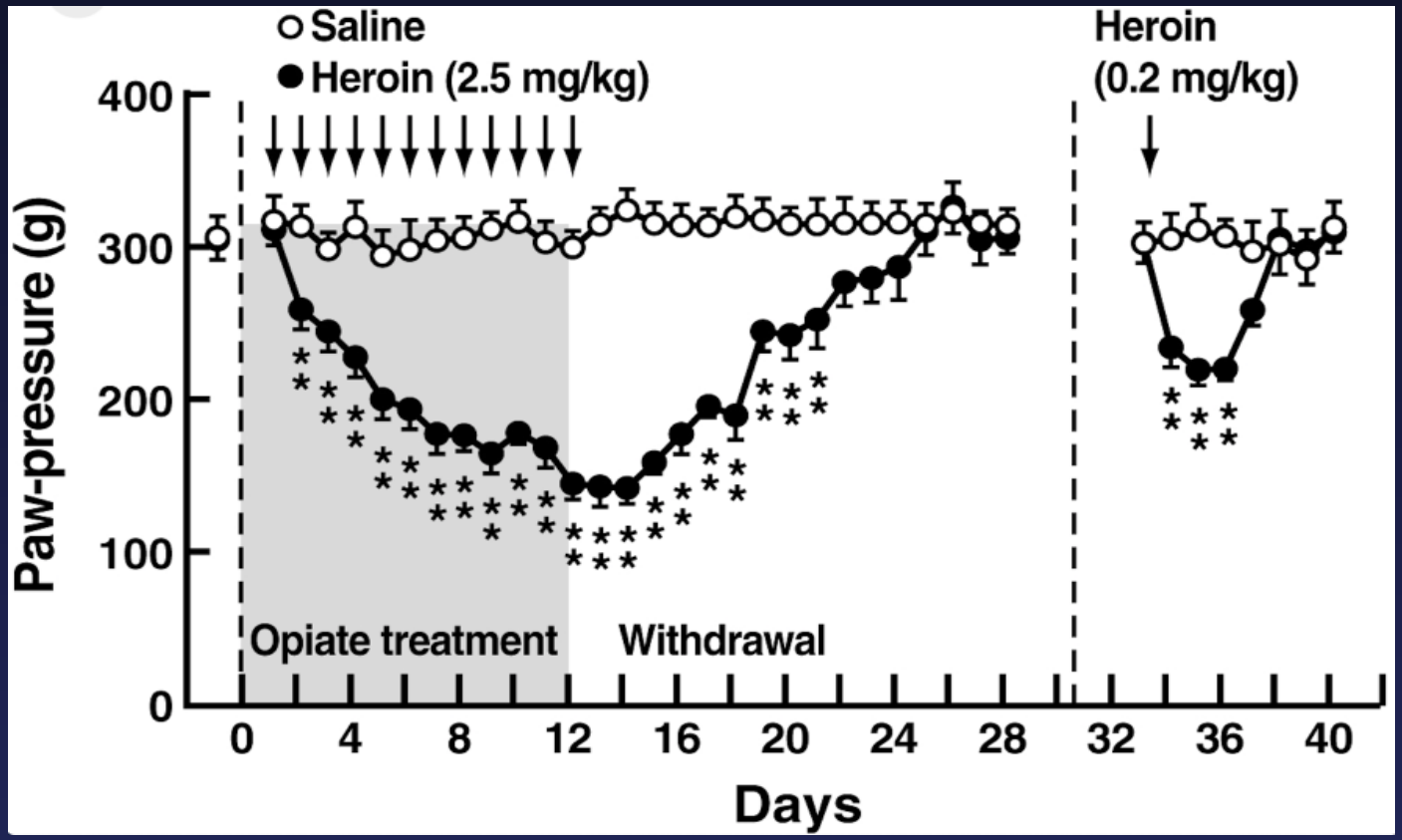




Single injection of heroin (2.5 mg/kg, s.c.) lowered pain thresholds

From: Laulin JP, Larcher A, Celerier E, Le Moal M, Simonnet G. Eur J Pharmacol 1998;10:782-785.

Delayed Effects of 12 Heroin Injections on Basal Nociceptive Threshold in Rats

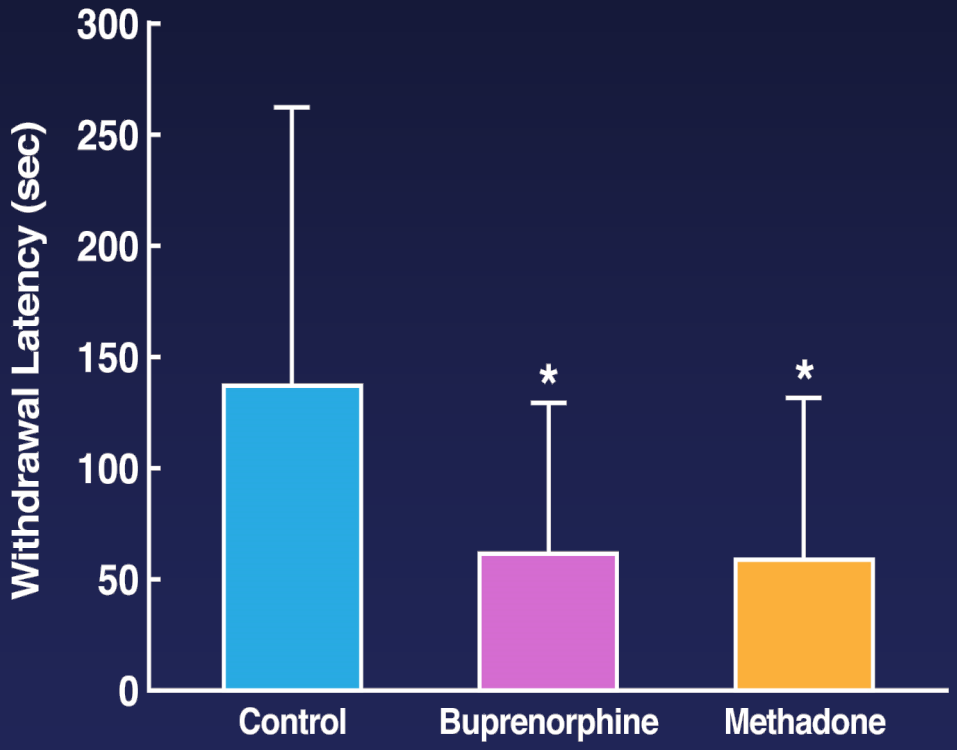


Daily injection of heroin for 12 days produced a delayed effect on pain threshold, manifested by sign hyperalgesia and pain sensitization even after the basal threshold returned to normal

From: Celerier E, Laulin J-P, Corcuff JB, Le Moal M, Simonnet G. J Neurosci 2001;21:4074-4080.

Cold-pressor Withdrawal Latency in Long-acting Opioid-maintained Former Opioid Addicts vs. Matched Controls

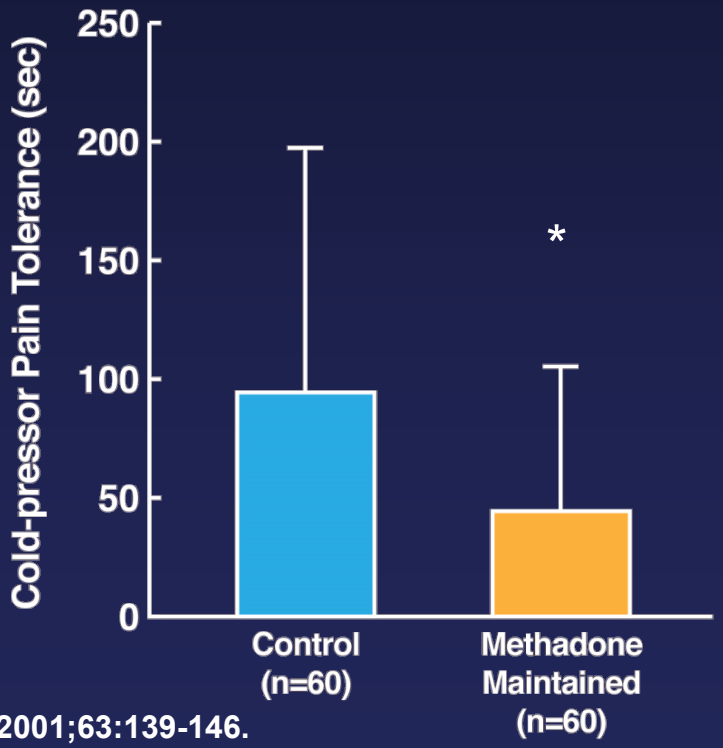
Former opioid addicts receiving MM or BM treatment at a single drug treatment clinic showed diminished pain tolerance



From: Compton P, Charuvastra VC, Ling W. Drug Alcohol Depend 2001;63:139-146.

Cold-pressor Pain Tolerance of Methadone-maintainance vs. Control Individuals

MM individuals were significantly less tolerant of CP pain than control subjects

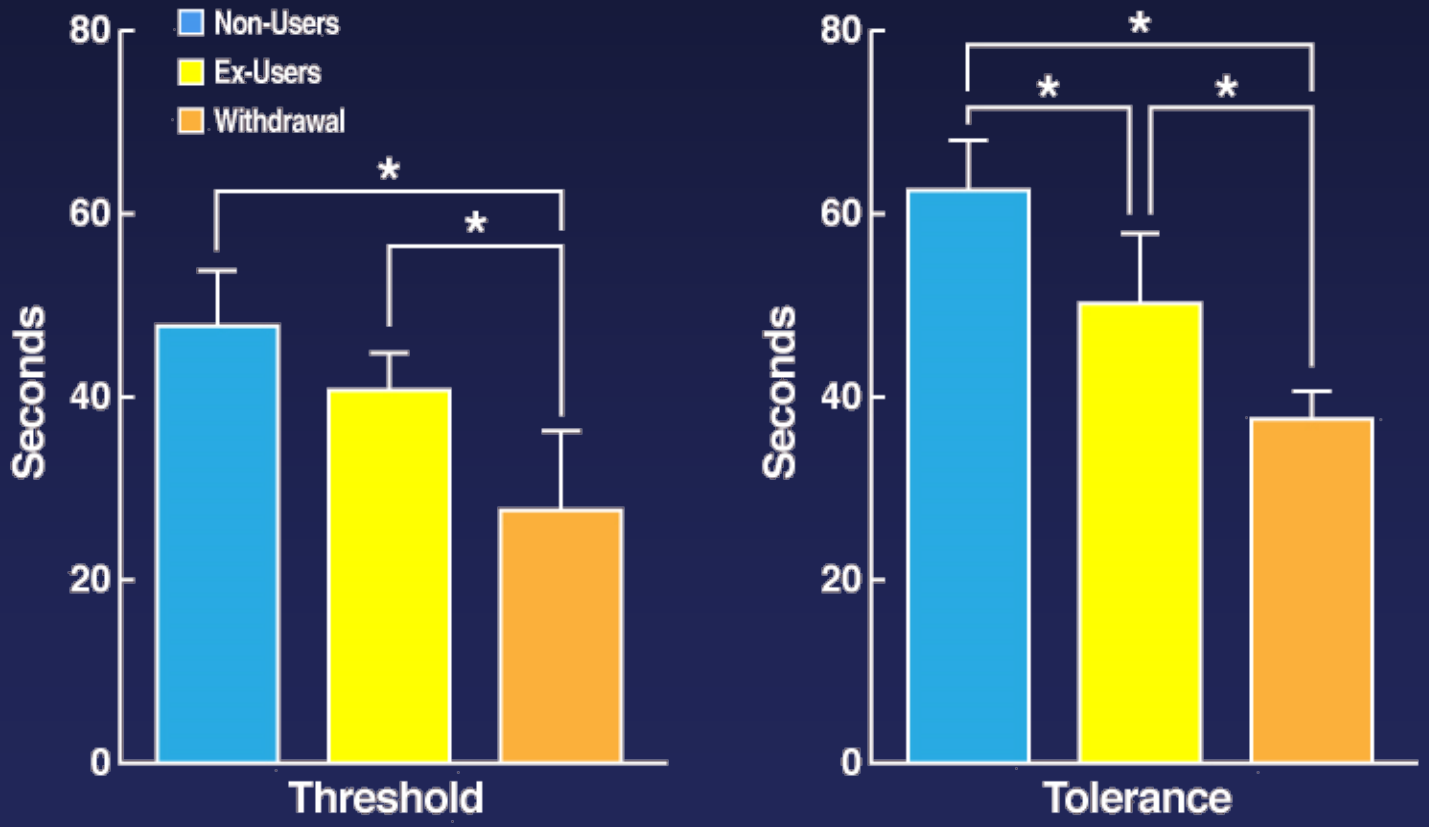


From: Compton P, Charuvastra VC, Kintaudi K, Ling W. J Pain Symptom Management 2000;20:237-245.

Opioid Withdrawal-induced Hyperalgesia in Heroin-dependent Individuals

Effects of Drug History on Ischemic Pain Threshold and Tolerance

The submaximal Tourniquet procedure was used to induce ischemic pain-standard blood pressure cuff. Acute withdrawal: 24-72 h after last heroin dose; Ex-users group: mean length of opioid abstinence was 30 months



From: Carcoba LM, Contreras AE, Cepeda-Benito A, Meagher MW. J Addict Dis 2011;30:258-270.

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Early Conceptualization of Motivational Withdrawal: Within-System vs. Between-System Neuroadaptations

- **Within-System Neuroadaptation—** defined as the process by which the primary cellular response element to the drug would itself adapt to neutralize the drug's effects; persistence of the opposing effects after the drug disappears would produce the adapatation.

- **Between-System Neuroadaptation—** defined as a process by which a different cellular system and separable molecular apparatus would be triggered by the changes in the primary drug response neurons and would produce the adaptation.

From: Koob GF, Bloom FE. Science 1988;242:715-723.

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Within-System and Between-System Neuroadaptations Mediating Hyperalgesia

Within-System Neuroadaptations

- Glutamate (preclinical and clinical)
- GABA (preclinical and clinical)
- Protein kinase C (preclinical)

Between-System Neuroadaptations

- Corticotropin-releasing factor (preclinical)
- Dynorphin/κ-opioid receptor system (preclinical)
- Norepinephrine (preclinical and clinical)
- Neuroimmune system (preclinical and clinical)

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Clinical Pharmacological Studies Investigating Opioid-induced Hyperalgesia

Medication	Mechanism	Citation	Population	Design	Assessment	Main findings
Dextromethorphan	NMDAR antagonism	Compton et al. 2008 [203]	MM patients *N* = 40 Aged 18–55 years	Randomized, double-blind, placebo-controlled	CPT + ES	Had no effect on OIH; noted sex differences in pre-methadone CPT tolerance: DEX worsened female CPT
Gabapentin	Actions at GABA-B receptors, GLT-1, noradrenergic receptors, and α2δ Ca^{2+} channels	Compton et al. 2010 [23]	MM patients *N* = 26 Aged 18–55 years	Randomized, double-blind, placebo-controlled	CPT	Decreased hyperalgesia
Ketamine	NMDAR antagonism	Angst et al. 2003 [88]	Opioid naïve healthy volunteers receiving remifentanil *N* = 10 Aged 20–35 years	Randomized, double-blind, crossover, placebo-controlled	HP + ES	Abolished extension of hyperalgesic skin area seen after remifentanil
		Hang et al. 2011 [166]	Laparoscopic cholecystectomy patients receiving remifentanil *N* = 54 Aged 18+ years	Randomized, placebo-controlled	VAS	Effective in preventing postoperative remifentanil-induced hyperalgesia
		Hong et al. 2011	Laparoscopic gynecologic surgical patients receiving remifentanil *N* = 40 Age range not specified	Randomized, double-blind, placebo-controlled	VAS	Reduced postoperative hyperalgesia and morphine consumption
		Joly et al. 2005 [46]	Abdominal surgery patients receiving remifentanil *N* = 75 Age range not specified	Randomized, double-blind, placebo-controlled	von Frey + PPT	Effective in preventing postoperative remifentanil-induced hyperalgesia; reduced postoperative morphine consumption
		Koppert et al. 2003 [64]	Healthy volunteers receiving remifentanil *N* = 13 Aged 20–40 years	Randomized, double-blind, crossover, placebo-controlled	ES	Enhanced remifentanil analgesia; abolished hyperalgesia
		Luginbühl et al. 2003 [62]	Healthy volunteers receiving remifentanil *N* = 14 Age range not specified	Randomized, double-blind, crossover, placebo-controlled	ES + PPT	Did not prevent remifentanil-induced hyperalgesia on PPT; increased analgesia on ES
		Yalcin et al. 2012 [54]	Abdominal hysterectomy patients receiving remifentanil *N* = 90 Aged 35–70 years	Randomized, placebo-controlled	PPT	Effective in preventing postoperative remifentanil-induced hyperalgesia and reducing postoperative morphine consumption

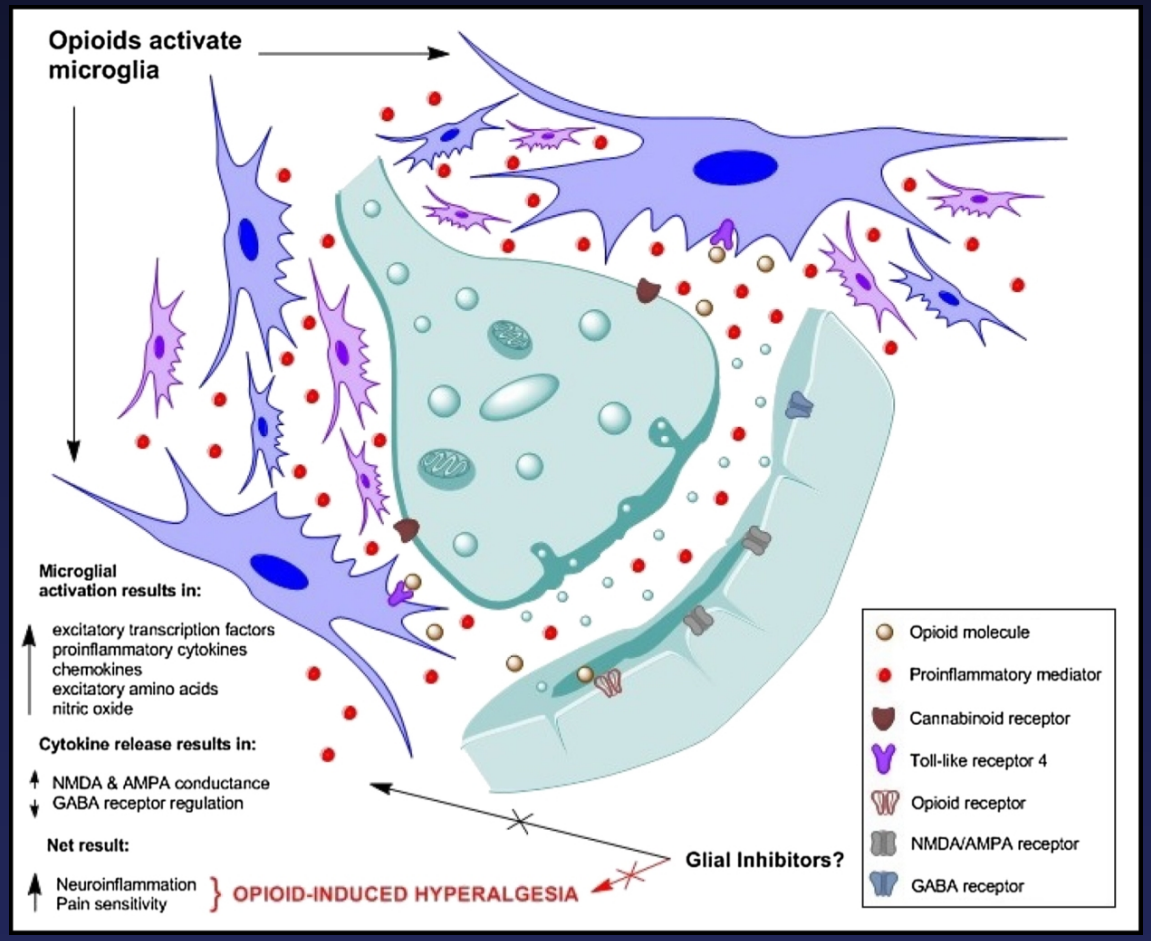
From: Arout CA, Edens E, Petrakis IL, Sofuoglu M, CNS Drugs (2015) 29:465–486.

Clinical Pharmacological Studies Investigating Opioid-induced Hyperalgesia (continued)

Ketamine + pregabalin	NMDAR antagonism; actions at α2δ Ca^{2+}channels	Martinez et al. 2014 [49]	Hip arthroplasty patients receiving sufentanil *N* = 142 Aged 18–80 years	Randomized, double-blind, placebo-controlled	VAS	Ketamine alone reduced the area of postoperative secondary hyperalgesia; each drug alone and the combination reduced postoperative morphine consumption; neither drug alone or the combination reduced postoperative pain intensity
Parecoxib	COX inhibition	Tröster et al. 2006 [167]	Healthy volunteers receiving remifentanil *N* = 15 Aged 20–45 years	Randomized, double-blind, crossover, placebo-controlled	ES	Enhanced remifentanil analgesia and prevented postinfusion remifentanil-induced hyperalgesia
		Lenz et al. 2011 [48]	Healthy volunteers receiving remifentanil *N* = 16 Aged 21–50 years	Randomized, double-blind, crossover, placebo-controlled	ES + CPT	Reduced the area of pinprick hyperalgesia, but not CPT pain
Pregabalin	Actions at α2δ Ca^{2+}channels	Lee et al. 2013 [55]	Laparoendoscopic urologic surgery patients receiving remifentanil *N* = 90 Aged 20–65 years	Randomized, double-blind, placebo-controlled	VAS	A single preoperative dose of pregabalin decreased hyperalgesia
Propranolol	Adrenergic antagonism	Chu et al. 2012 [47]	Healthy volunteers receiving remifentanil *N* = 10 Aged 18–32 years	Randomized, double-blind, crossover, placebo-controlled	ES + HP	Reduced magnitude of ES hyperalgesia; HP hyperalgesia was not evident

From: Arout CA, Edens E, Petrakis IL, Sofuoglu M, CNS Drugs (2015) 29:465–486.

Neuroimmune Mechanisms of Opioid-induced Hyperalgesia



From: Arout CA, Edens E, Petrakis IL, Sofuoglu M. CNS Drugs 2015;29:465-486.

Neuroimmune Inhibitors Decrease Opioid-induced Hyperalgesia

Drug name and dose	Chronic opioid name and dose	Species Sex	OIH	Tolerance	Reference
IL-1ra 100 μg it.	Morphine 10 μg it.	Rats Males	Reduced	Reduced	Johnston et al. (2004)
Anti-Cx3cr1 Antibody 10 μg it.	Morphine 10 μg it.	Rats Males	Reduced	Reduced	Johnston et al. (2004)
IL-10 by adenovirus 5 μg it.	Morphine 10 μg it.	Rats Males	Reduced	Reduced	Johnston et al. (2004)
AMD3100 Cxcr4 antagonist 10 mg/kg	Morphine 10 mg/kg	Rats Females	Reduced	Not tested	Wilson et al. (2011)
Minocycline 30–100 mg/kg i.p.	Remifentanyl 240 μg /kg/h i.v.	Rats Males	No effect	No effect	Aguado et al. (2015)
Mac-1 Ab-saporin 20–36 μg it.	Morphine 10 mg/kg sc.	Rats Males	Reduced	No effect	Ferrini et al. (2013)
Bdnf-cKO in microglia	Morphine 10–40 mg/kg sc.	Mice Males	Reduced	No effect	Ferrini et al. (2013)
IL-1ra/sTNFR/anti-IL6 Ab 100 μg/30 μg/0.08 μg it.	Morphine 10 mg/kg sc.	Rats Males*	Reduced	Reduced	Raghavendra et al. (2002)
Propentofyline 1–10 μg it.	Morphine 10 mg/kg sc.	Rats Males	Reduced	Reduced	Raghavendra et al. (2004)
Pentoxifylline 50 mg/kg i.p.	Morphine 10–40 mg/kg sc.	Mice Males#	Reduced	Not tested	Liang et al. (2008)
IL1ra 100 mg/kg i.p. Ibudilast 15 mg/kg i.p.	Morphine 20 mg/kg Codeine 21 mg/kg	Mice Males	Reduced	Not tested	Johnson et al. (2014)
LPS-RS 20 μg it.	Morphine 10 μg it.	Rats Males	Reduced	Reduced	Bai et al. (2014)
IL1ra 100 μg it.	M3G 0.75 μg it.	Rats Males	Reduced	No analgesia	Lewis et al. (2010)
Compound 15 Tlr4 inhibitor	M3G 10 mg/kg i.p.	Rats Females	Reduced	No analgesia	Due et al. (2012)

All studies were performed on naïve animals except in * Raghavendra et al., 2002 where rats underwent spinal nerve transection, and in #Liang et al., 2008 where OIH was followed by hind paw incision.

From: Roeckel LA, Le Coz GM, Gaveriaux-Ruff C, Simonin F. Neuroscience 2016;338:160-182.

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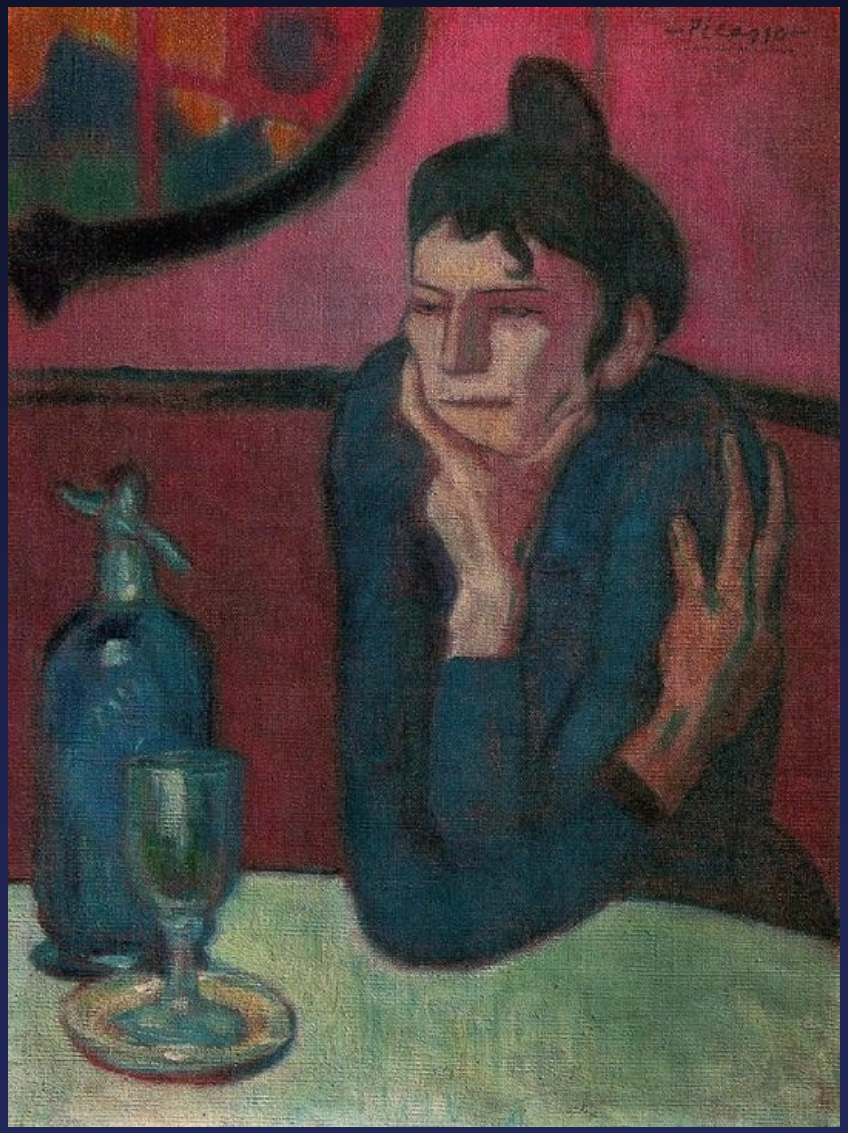
The “Dark” Side of Addiction



"Absinthe Drinker"
Pablo Picasso (1910)

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Opioid-induced Hyperkatifeia

1. Defined as the increased intensity of negative emotional/motivational symptoms and signs observed during withdrawal from abused drugs

2. Derived from the Greek word *katifeia* for dejection, sadness, or negative emotional state

3. "Hyperkatifeia" is hypothesized to represent elements of dysphoria, irritability, alexithymia, or simply symptoms often described as ill at ease, uncomfortable within one's own skin, or simply not hedonically normal, symptoms historically difficult to define.

Shurman, J, Koob, GF, Gutstein, HB. Pain Med 2010;11:1092-1098

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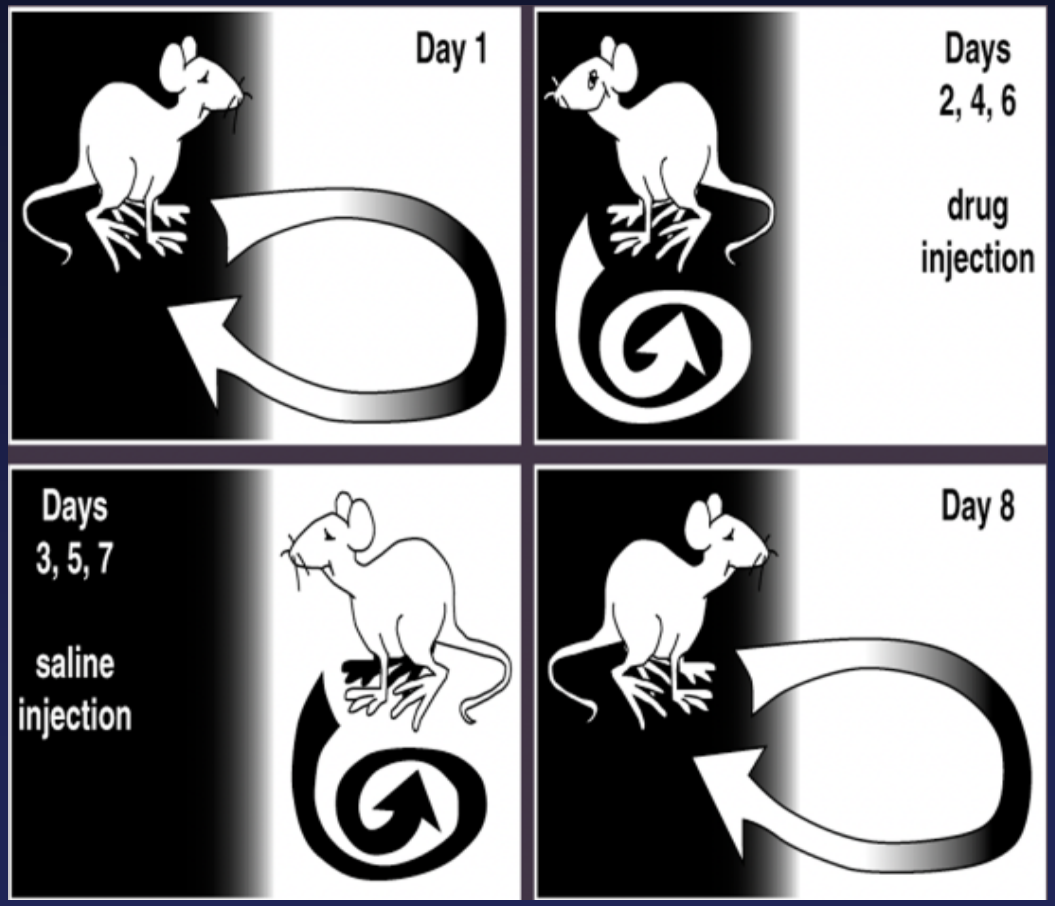
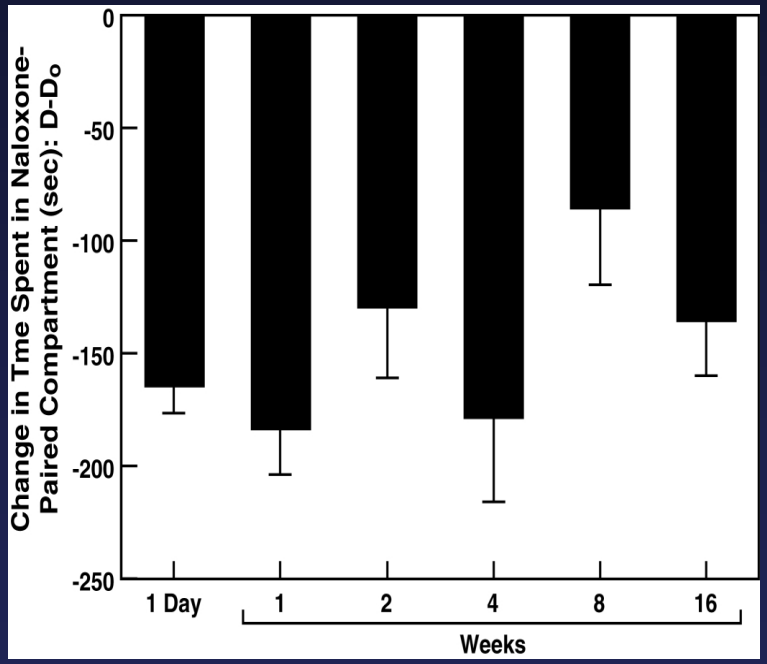
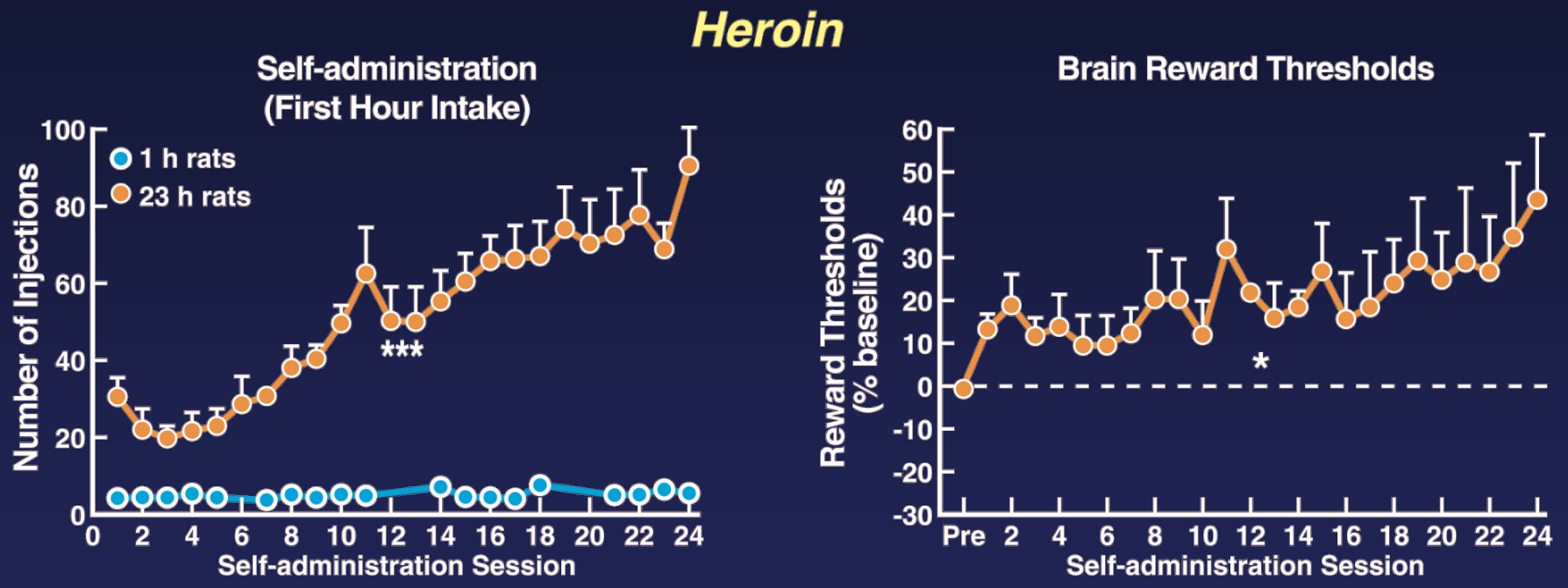
Place Conditioning with Naloxone (15 mg/kg, s.c.) in Morphine-dependent Rats





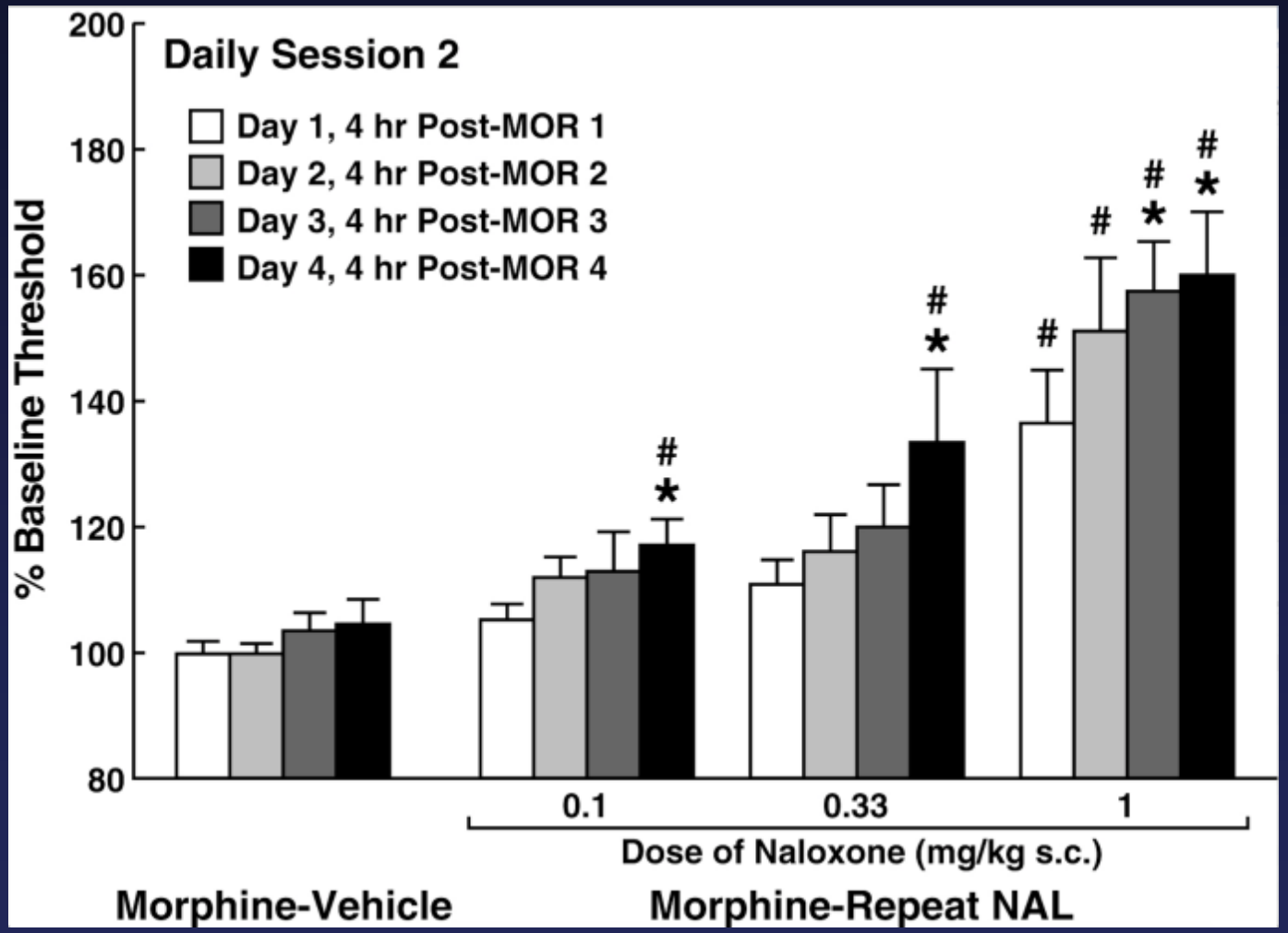
From: Stinus L, Caille S, Koob GF. Psychopharmacology 2000;149:115-120.

Extended Access to Heroin Produces Compulsive-like Responding and Parallel Increases in Brain Reward Thresholds



From: Kenny PJ, Chen SA, Kitamura O, Markou A, Koob GF. J Neuroscience 2006;26: 5894-5900.

Effects of Acute and Repeated Morphine and Naloxone Administration on Brain Reward Thresholds in Rats

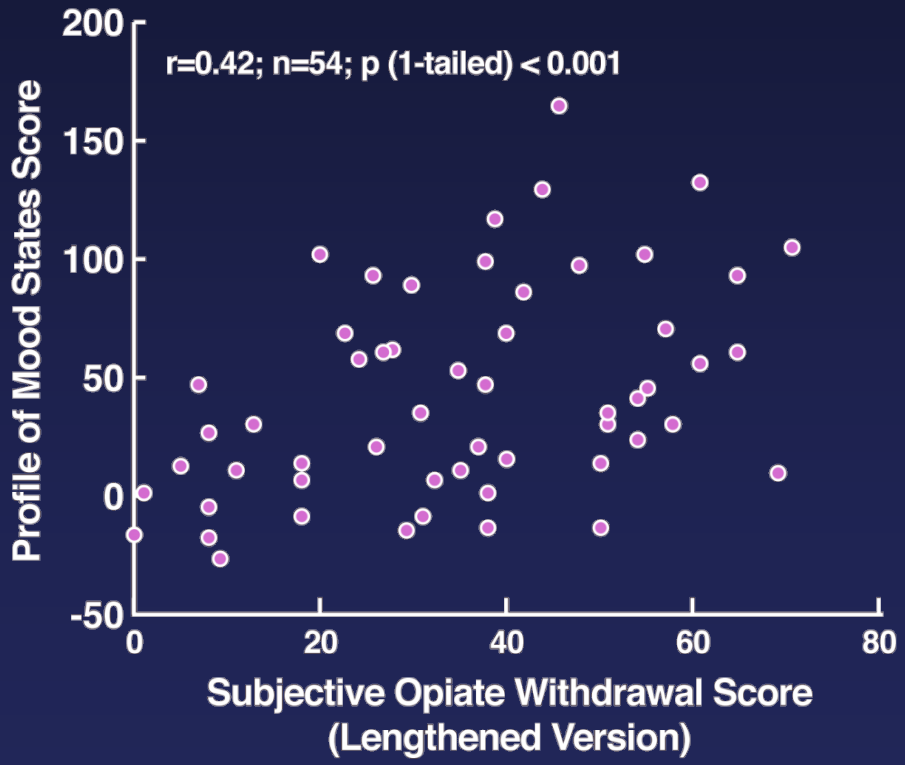


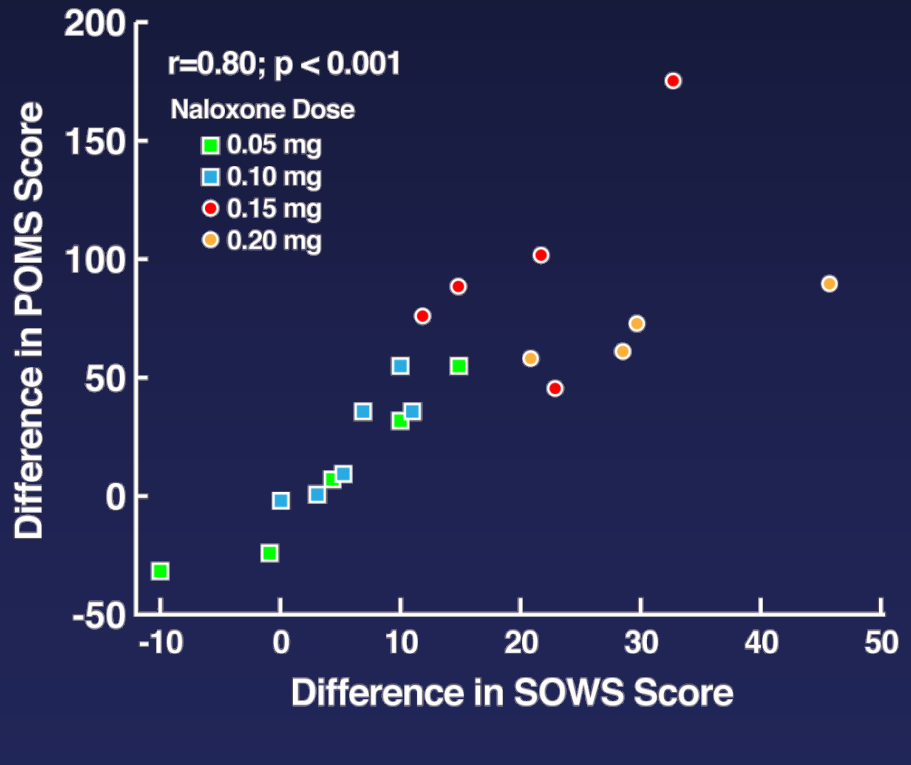
From: Liu J, Schulteis G. Pharmacol Biochem Behav 2004;79:101-108.

The Dysphoria of Heroin Addiction

Correlations of subjective opiate withdrawal scores (SOWS) and dysphoria from the Profile of Mood States Scores (POMS) in spontaneous withdrawal (left) after naloxone infusion (right) in individuals with heroin addiction

Scores during a 1-week period of heroin use prior to application for treatment





From: Handelsman L, Aronson MJ, Ness R, Cochrane KJ, Kanof PD. Am J Drug Alcohol Abuse 1992;18:275-287; Kanof PD, Handelsman L, Aronson MJ, Ness R, Cochrane KJ, Rubinstein KJ. J Pharmacol Exp Ther 1992;260:355-363.

Problems and Concerns Patients Attribute to Opioid Use by Average Daily Dose (weight-adjusted)

	Opioid Morphine Equivalent Daily Dose				
	1-19mg	20-49mg	50-119mg	120+mg	p-value [a]
Psychosocial Problems					
Loss of interest in activities, %	4.9	9.6	8.0	14.6	**0.01**
Trouble concentrating, %	6.5	15.6	17.2	24.0	**0.04**
Feeling slowed down, sluggish, %	14.8	15.7	18.0	25.1	**0.03**
Feeling depressed, anxious, %	4.0	7.8	8.2	15.1	**0.0004**
Interference with work, family social activities, %	10.8	16.9	22.9	32.2	**<.0001**
Hard to think clearly, %	8.6	14.6	17.1	24.2	0.15
Less alert when driving or other activity require vigilance, %	20.8	28.7	35.8	45.4	**0.007**
Control Concerns					
Preoccupied with opioids, %	5.0	10.1	7.2	9.2	0.24
Concern about control over use, %	2.8	4.7	5.4	8.0	0.63
Need higher dose for same effect, %	19.5	24.8	34.6	41.5	**<.0001**
Worry about opioid dependence, %	17.2	30.1	37.4	46.8	**<.0001**
Want to stop or cut-down on opioids, %	33.9	44.5	50.3	51.5	**0.01**
Opioids caused family problems, %	1.7	4.5	7.4	10.7	**0.046**
Family or friends thought might be addicted to opioids, %	5.8	11.0	18.2	24.9	**<.0001**

[a] p-value for opioid dose adjusted for health plan and opioid type.

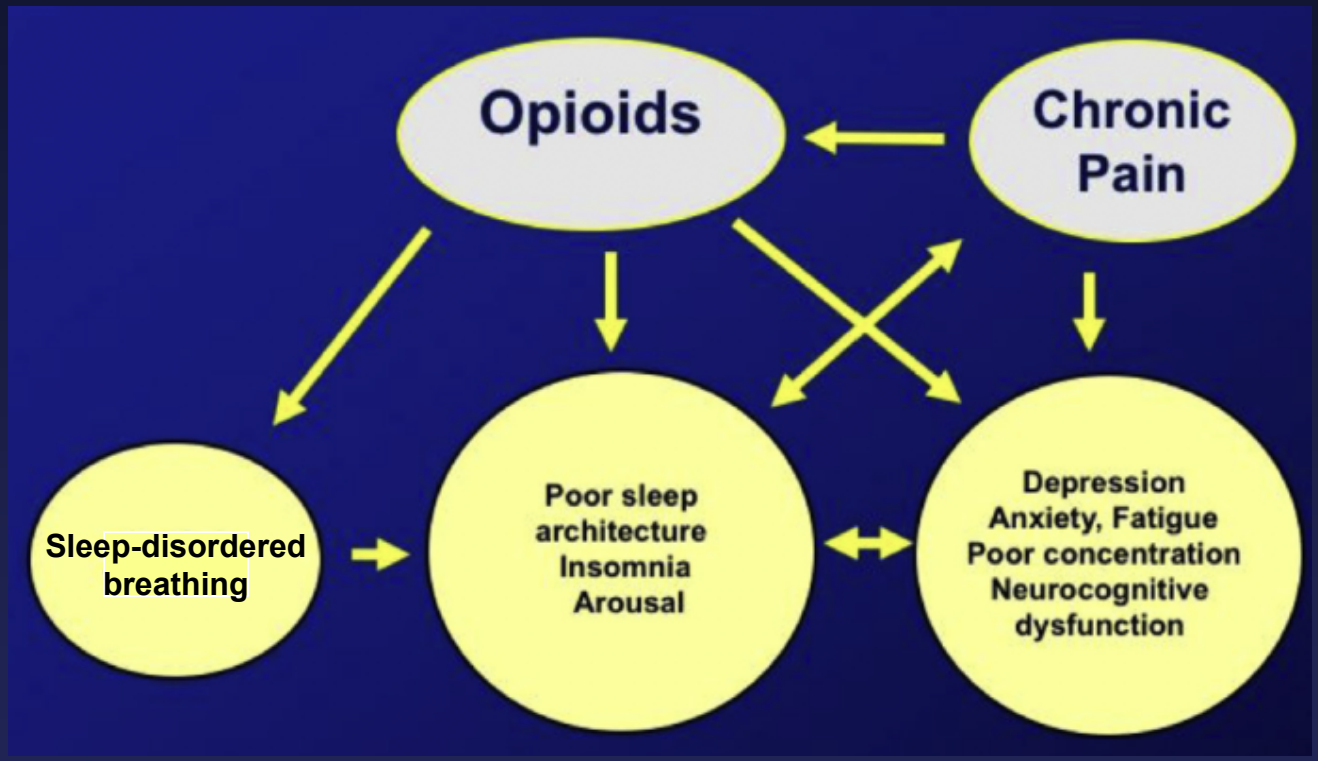
From: Merrill JO, Von Korff M, Banta-Green CJ, Sullivan MD, Saunders KW, Campbell CI, Weisner C. Gen Hosp Psychiatry 2012;34:581-587.

Association between Opioid Misuse with Anxiety and Depression: Longitudinal Studies

- Survey-based longitudinal studies suggest that relations between anxiety and depression and opioid misuse and OUD may be bi-directional in nature (Martins et al., 2009; Martins et al., 2012).
- Some early studies found that anxiety and depressive symptoms preceded the onset of later opioid use problems, suggesting that these symptoms and disorders may be risk factors for opioid use problems (Maddux et al., 1987).
- Several other studies provide evidence that prescription opioid misuse is prospectively related to the onset of anxiety and depressive disorders (e.g., Merrill et al., 2012)
- Prescription opioid use may precede the development of depression (Mackesy-Amiti et al., 2012; Merrill et al., 2012)

From: Rogers AH, Zvolensky MJ, Ditre JW, Buckner JD, Asmundson GJG. Clin Psychol Rev 2021;84:101978.

Biodirectional Relationship Between Opioids, Chronic Pain, and Sleep



From: Cao M, Javaheri S. Sleep Med Clin 2018;13:271-281.

Outline of Talk

1. Definitions and Conceptual Framework: Hyperalgesia, Hyperkatifeia, Opponent Process, Negative Reinforcement

2. Evidence for Opioid Hyperalgesia: Preclinical and Human studies

3. Neurobiological basis of Hyperalgesia: Within and between system neuroadaptations

4. Evidence for Opioid Hyperkatifeia: Preclinical and Human Studies

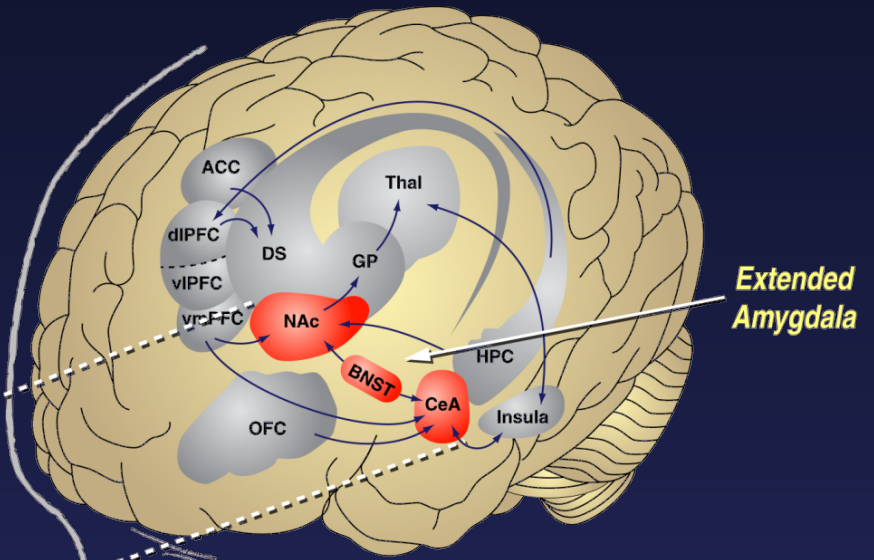
5. Neurobiological Basis of Hyperkatifeia: Within- and between-system neuroadaptations

6. Convergence of Brain Pain and Negative Emotion Neurocircuits: Implications for the role of addiction in the "Deaths of Despair" and the effects of the Covid 19 pandemic.

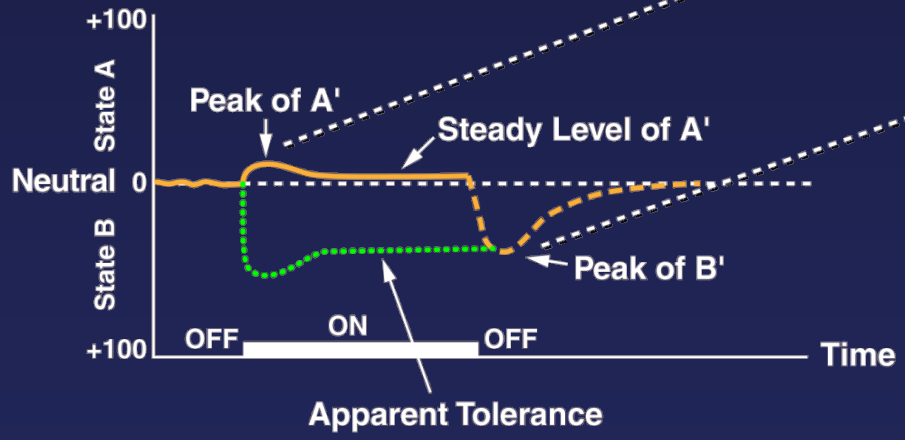
Neurochemical Basis of Opponent Process: Reward Deficit and Stress Surfeit

Within System:
Reward Deficit

↓ Dopamine
↓ Opioid Peptides



After Many Stimulations



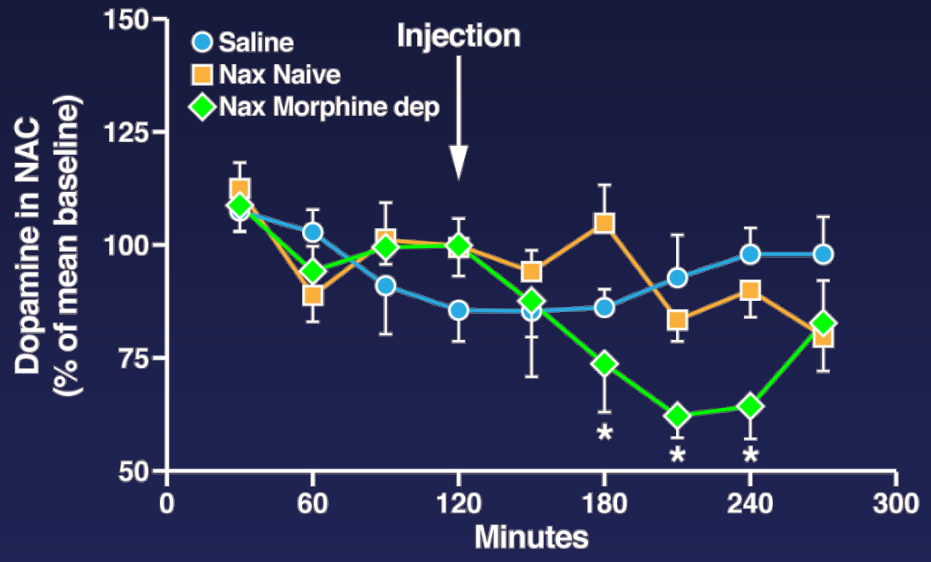
Between System:
Stress Surfeit

↑ CRF
↑ dynorphin
↑ norepinephrine
↑ vasopressin
↑ hypocretin (orexin)
↑ Neuroimmune factors

Adapted from: George O, Koob GF. Proc Natl Acad Sci U S A 2013;110:4165-4166.

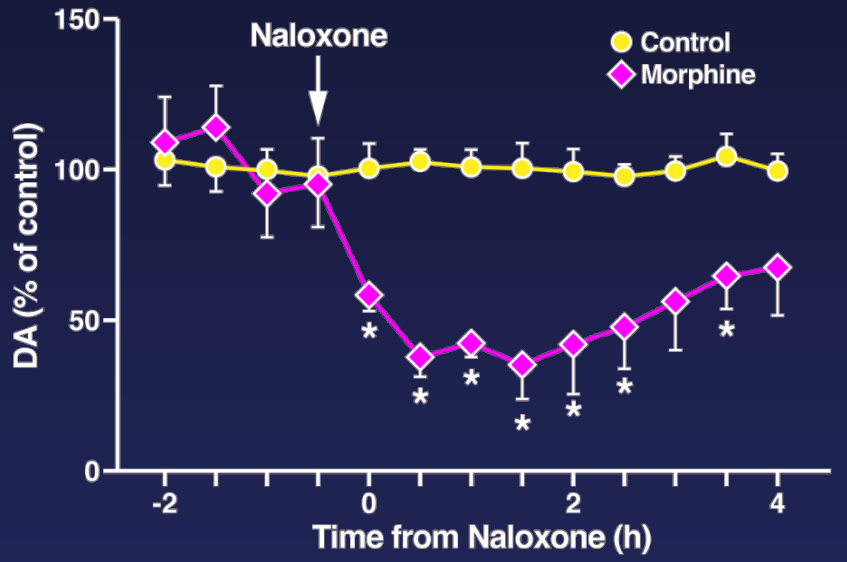
Decreased Dopamine Release in the Nucleus Accumbens Produced by Precipitated Opioid Withdrawal

Morphine 7 daily injections (20 mg/kg, i.p.)
Followed by naloxone (20 mg/kg, i.p.)



Pothos E, Rada P, Mark GP, Hoebel BG. Brain Res 1991;566:348-350.

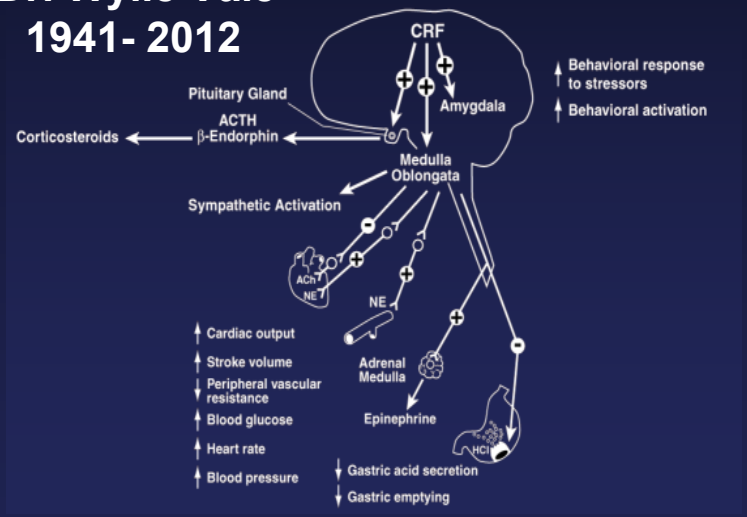
Morphine pellets (75 mg, sc) for 4 days followed by naloxone (2 mg/kg, i.p.)



Rossetti ZL, Hmaidan Y, Gessa GL. Eur J Pharmacol 1992;221:227-234.

Addiction / Corticotropin-Releasing Factor Interactions

Dr. Wylie Vale
1941- 2012



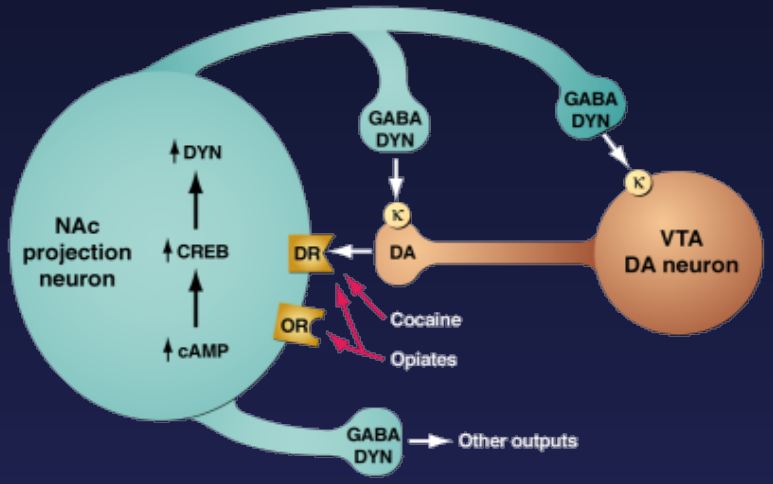
	CRF Antagonist Effects			
Withdrawal-induced changes in extracellular CRF in CeA	Withdrawal-induced anxiety-like or aversive responses	Baseline self-administration or place preference	Dependence-induced increases in self-administration	Stress-induced reinstatement
↑	↓	–	↓	↓

Modified from: Swanson LW, Sawchenko PE, Rivier J, Vale W. Neuroendocrinology 1983;36:165-186.
Koob GF. Neuron 2008;59:11-34.

NIH National Institute on Alcohol Abuse and Alcoholism

Interactions between Addiction and Dynorphin/κ-Opioid System

Dynorphin Control of Mesocorticolimbic Dopamine- Within System



From: Carlezon WA Jr, Nestler EJ, Neve RL. Crit Rev Neurobiol, 2000, 14:47-67; Nestler EJ. Nat Rev Neurosci, 2001, 2:119-128.

Distribution of Prodynorphin in Rat Brain

From: Khachaturian H, Lewis ME, Schafer MKH and Watson SJ, Trends Neurosci, 1985, 8:111-119

κ-Opioid Antagonist Effects

Withdrawal-induced changes in dynorphin peptide and prodynorphin mRNA in NAc	Withdrawal-induced anxiety-like or aversive responses	Baseline self-administration or place preference	Dependence-induced increases in self-administration	Stress-induced reinstatement
↑	↓	↑	↓	↓

Modified from:. Koob GF. Neuron 2008;59:11-34.

Between-System Targets for Hyperkatifeia in the Withdrawal/Negative Affect Stage

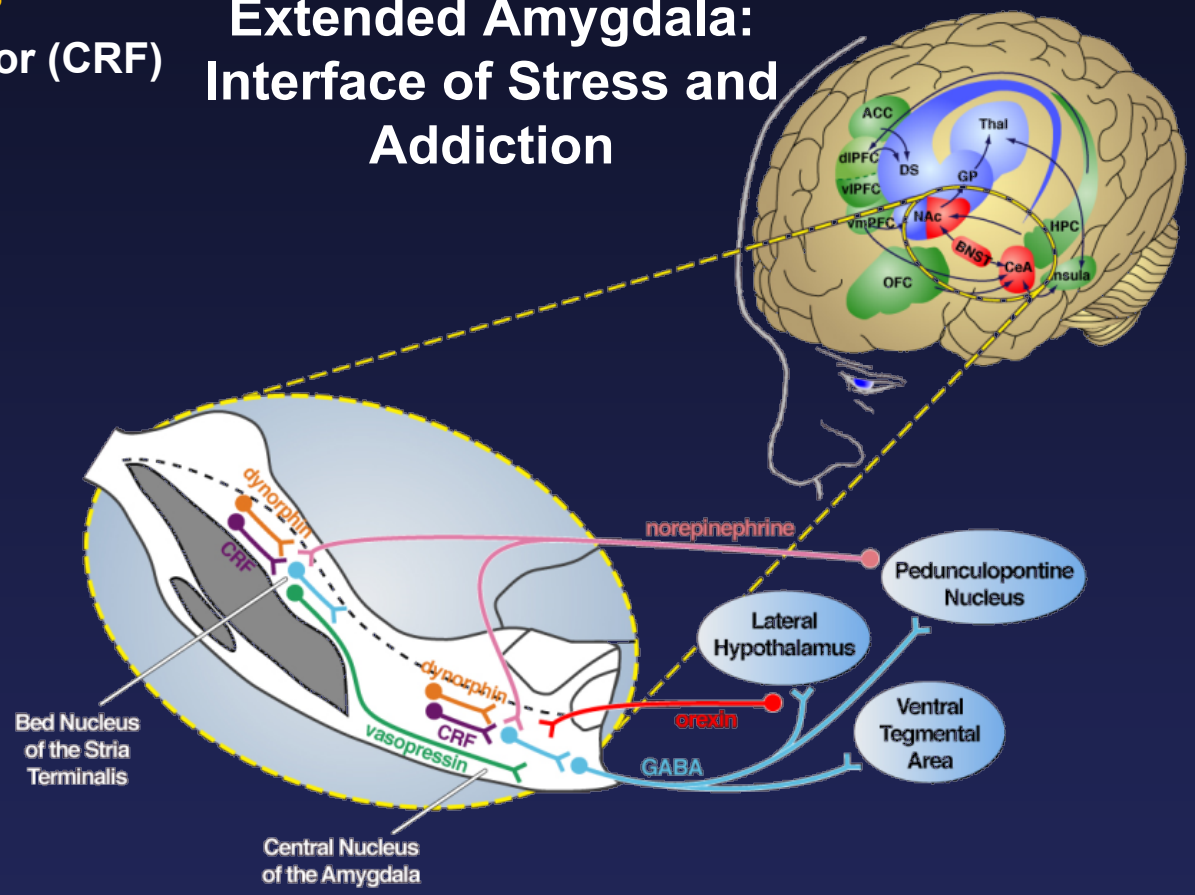
Stress Neurotransmitters

- ↑ Corticotropin-releasing factor (CRF)
- ↑ Norepinephrine
- ↑ Dynorphin
- ↑ Vasopressin
- ↑ Orexin (hypocretin)
- ↑ Substance P
- ↑ Glucocorticoids
- ↑ Neuroimmune factors

Anti-stress neurotransmitters

- ↓ Neuropeptide Y
- ↓ Nociceptin (orphanin FQ)
- ↓ Endocannabinoids
- ↓ Oxytocin

Extended Amygdala: Interface of Stress and Addiction



From: Koob GF. Neuron 2008;59:11-34; George O, Koob GF. Proc Natl Acad Sci U S A 2013;110:4165-4166; Koob GF. Pharmacol Rev 2021;73:163-201.

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6. **Convergence of Brain Pain and Negative Emotion Neurocircuits: Implications for the role of addiction in "Deaths of Despair" and the effects of the COVID-19 pandemic.**

Sally Robin: I was put on opioids for headaches and neck pain, and at first it felt great

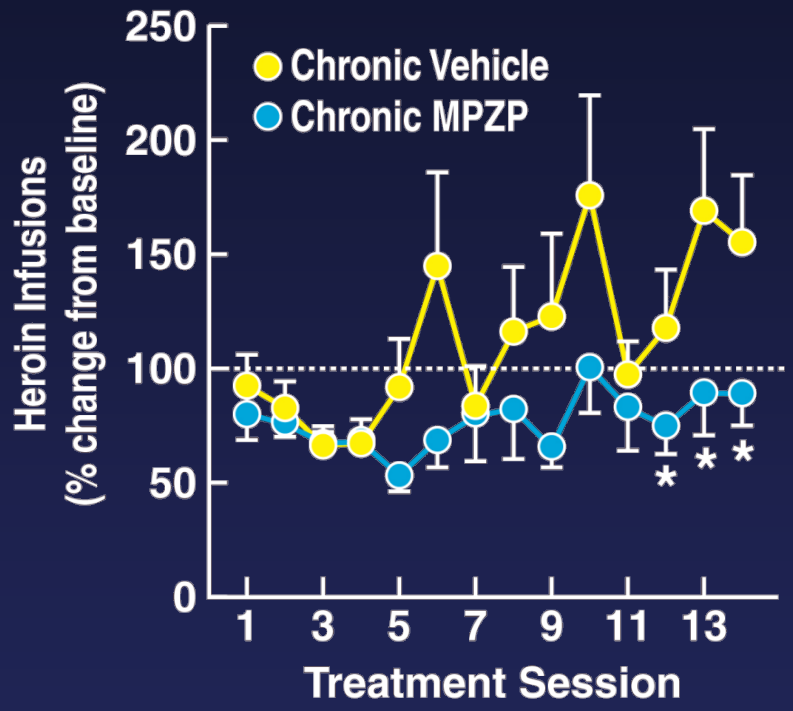
There is a lot of mental illness in my family, and I was physically and sexually abused when I was a child. So I wasn't surprised when I was diagnosed with depression and PTSD in my 30's. I started getting headaches when I was in high school. When I first took opioids, it was as though all my troubles were over. I was in college doing a bachelor's degree, but my headaches interfered so much I took a semester off. After I started using opioids, I was able to go back to school and graduate. I am 52 years old now, and I have been taking opioids ever since school. I know they don't help my pain, but if I try to come off, I feel wretched, and my headaches and neck pain come back with a vengeance.

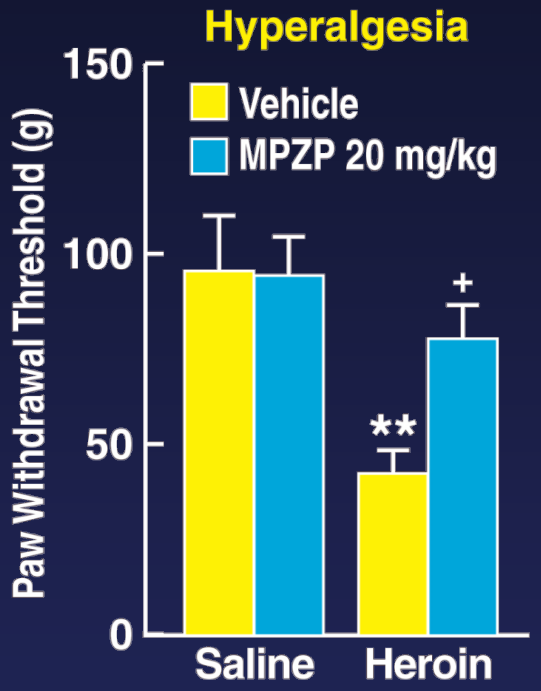
I have never been able to work, and I live with my mother.

Case history provided by Jane Ballantyne M. D.; not real name or photo

CRF_1 Receptor Antagonist MPZP Blocks Development of Heroin Escalation and Withdrawal-induced Hyperalgesia

Dr. Paula Park

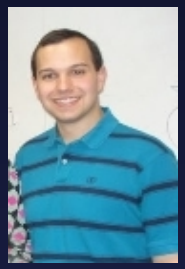




Over 14 treatment sessions, vehicle-treated rats displayed a gradual increase in heroin intake over the entire session that significantly diverged from chronic MPZP-treated rats by the end of training.

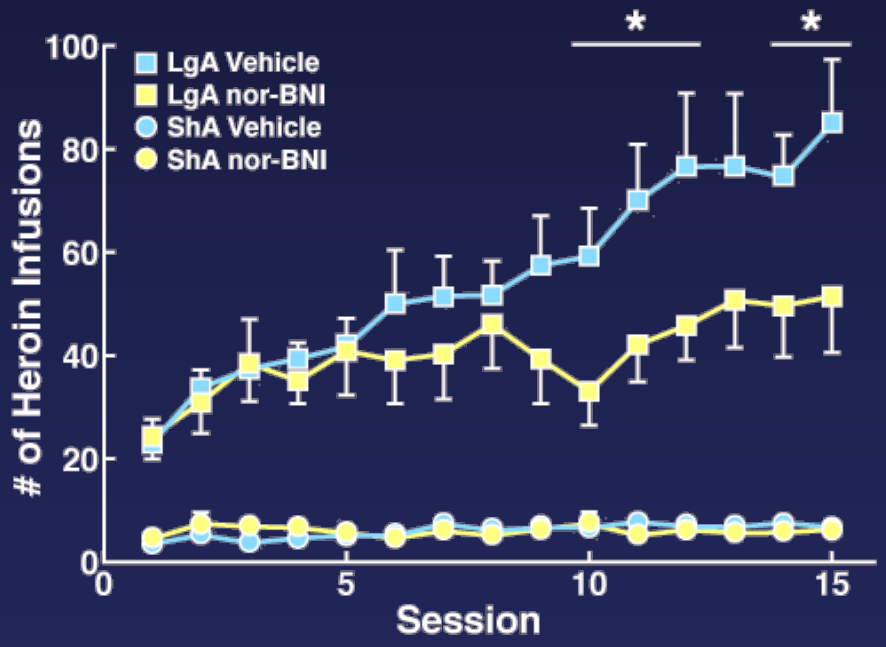
From: Park PE, Schlosburg JE, Vendruscolo LF, Schulteis G, Edwards S, Koob GF. Addict Biol 2015;20:275-284.

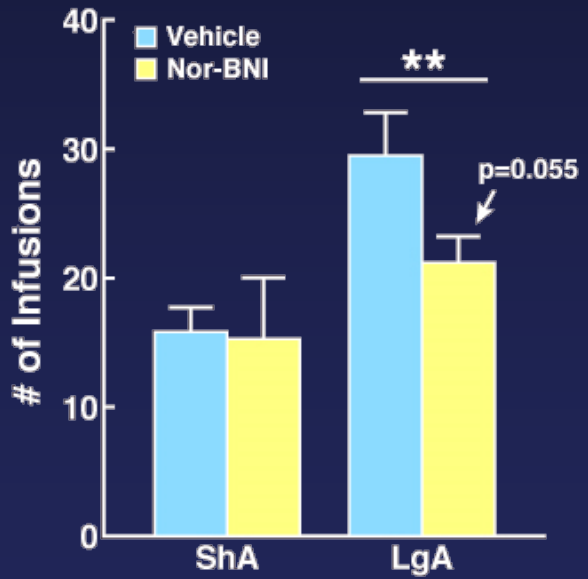
κ-Opioid Receptor Antagonist Nor-BNI Blocks Development of Heroin Escalation and Compulsive Drug Taking



Dr. Joel Schlosburg

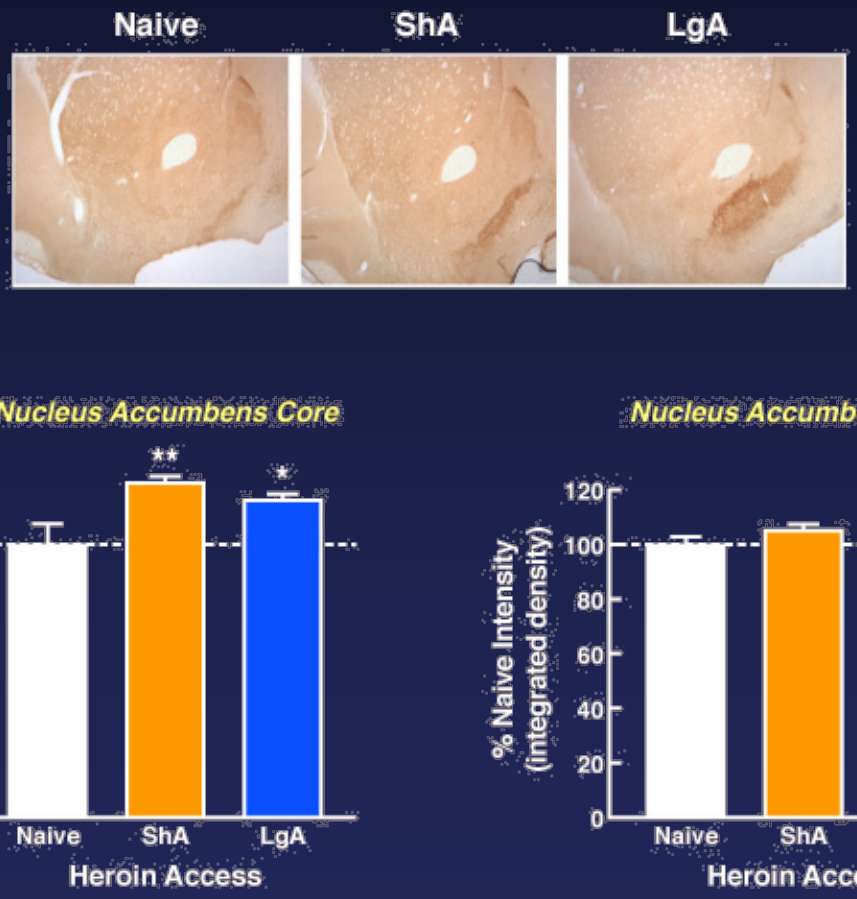
Dr. Timothy Whitfield





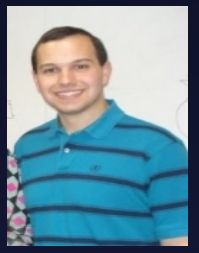
From: Schlosburg JE, Whitfield TW Jr, Park PE, Crawford EF, George O, Vendruscolo LF, Koob GF. J Neurosci 2013;33:19384-19392.

Increases in Immunohistochemical Staining for Prodynorphin in Nucleus Accumbens Shell with Extended Access to Intravenous Heroin

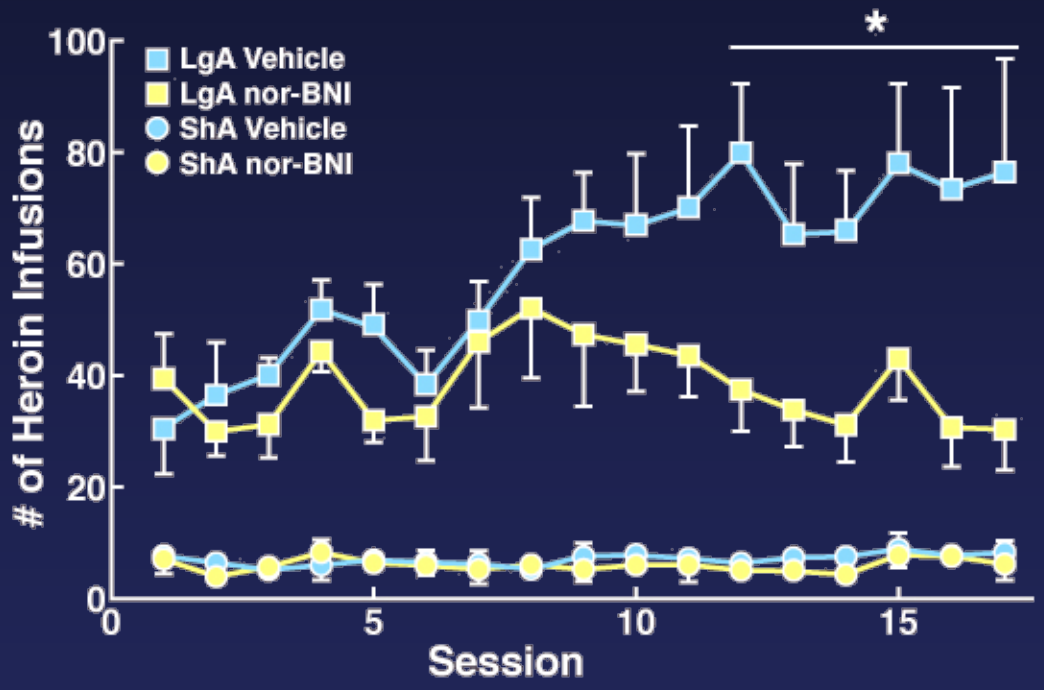


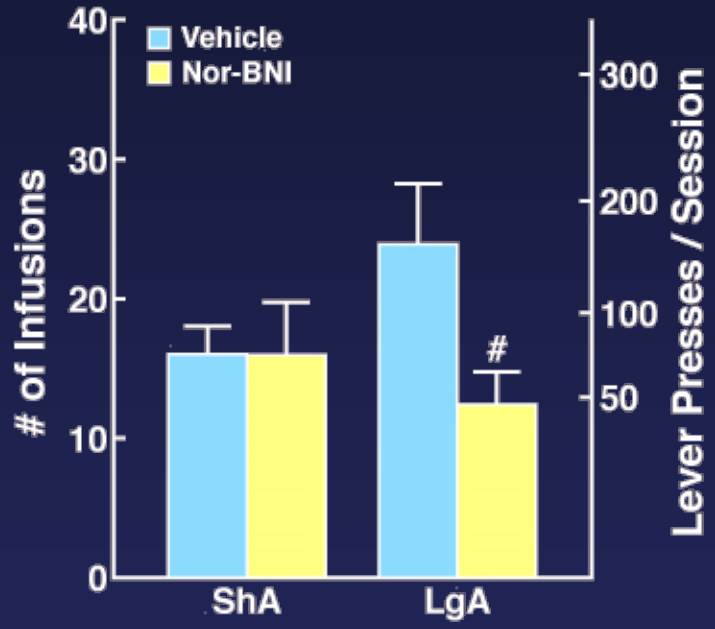
From: Schlosburg JE, Whitfield TW Jr, Park PE, Crawford EF, George O, Vendruscolo LF, Koob GF. J Neurosci 2013;33:19384-19392.

κ-Opioid Receptor Antagonist nor-BNI Injected in Nucleus Accumbens Shell Blocks Development of Heroin Escalation and Compulsive Drug Taking



Dr. Joel Schlosburg

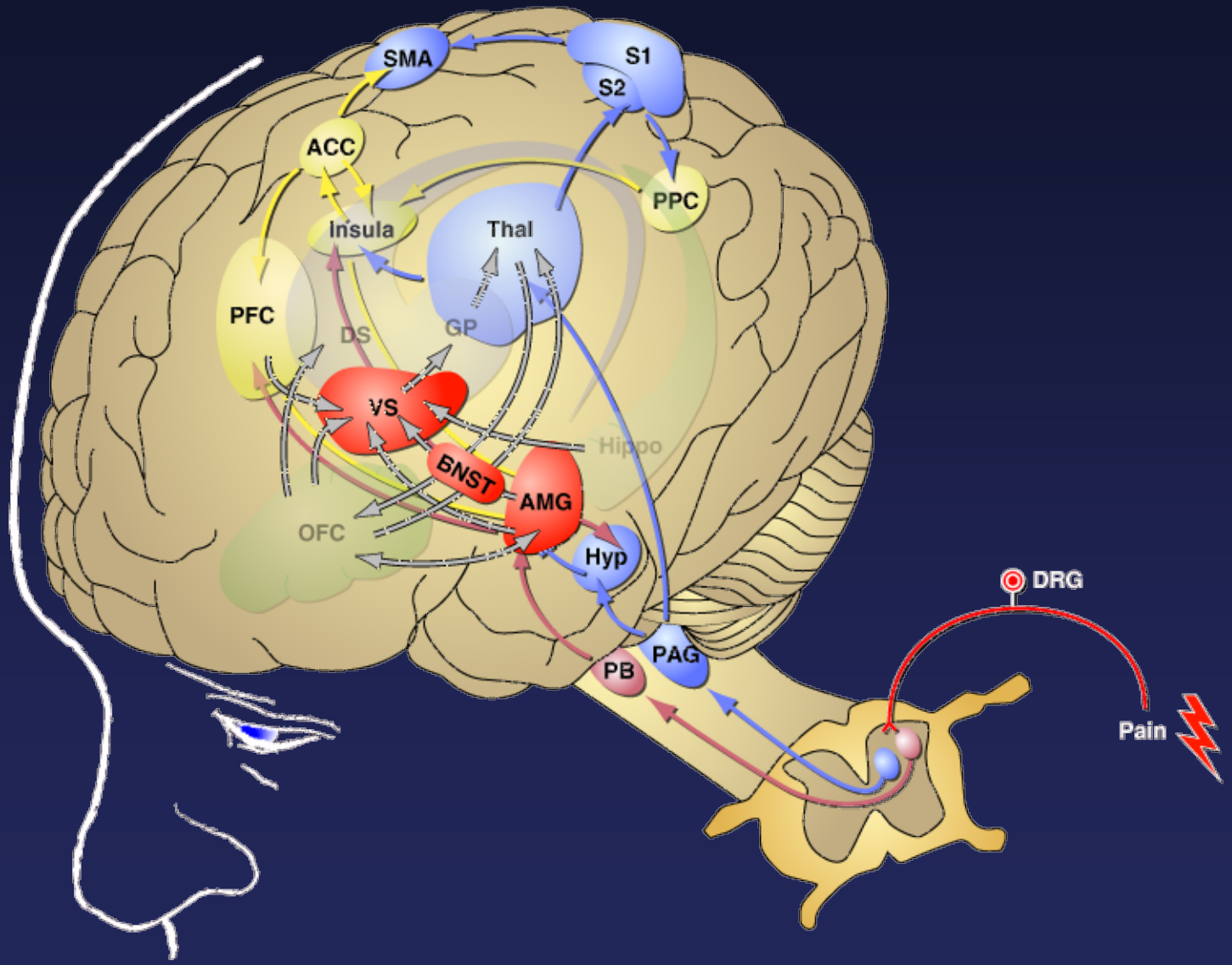




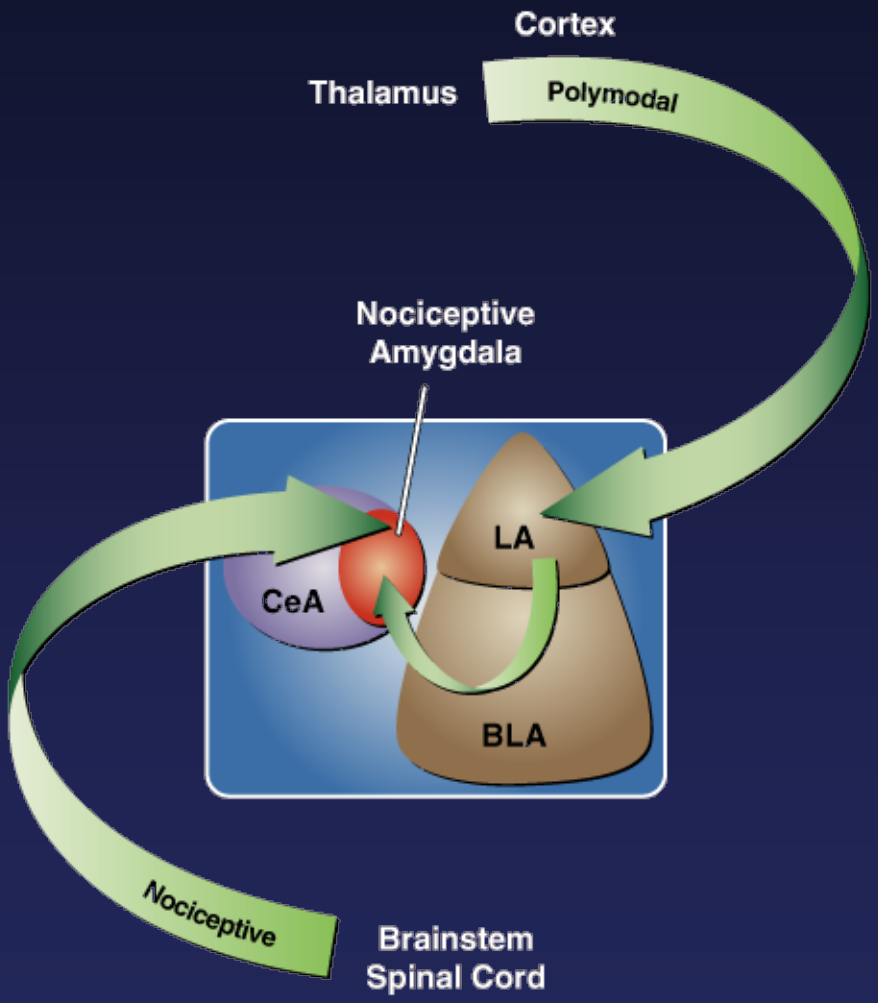
Nor-BNI: 4 μg/side, bilateral in aCSF

From: Schlosburg JE, Whitfield TW Jr, Park PE, Crawford EF, George O, Vendruscolo LF, Koob GF. J Neuroscience 2013;33:19384-19392.

Neurobiological Circuitry of the Overlap of Pain and Addiction

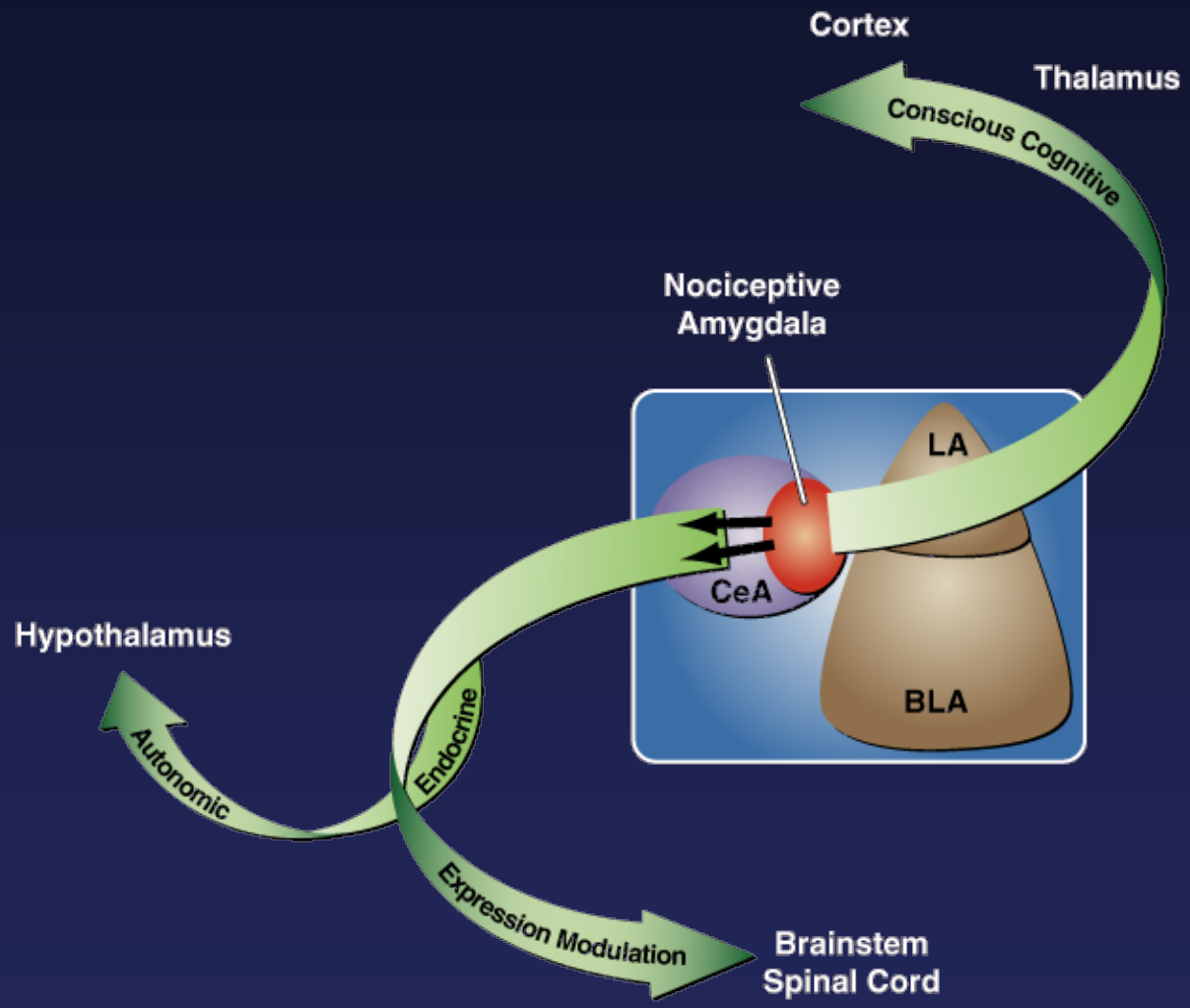


Major Sensory and Nociceptive Inputs to the Amygdala



From: Neugebauer V, Li W, Gird GC, Han JS. Neuroscientist 2004;10:221-234.

Major Pain-related Outputs from the Amygdala



From: Neugebauer V, Li W, Gird GC, Han JS. Neuroscientist 2004;10:221-234.

Allostatic Change in Emotional State Associated with Transition to Drug Addiction

Homeostasis

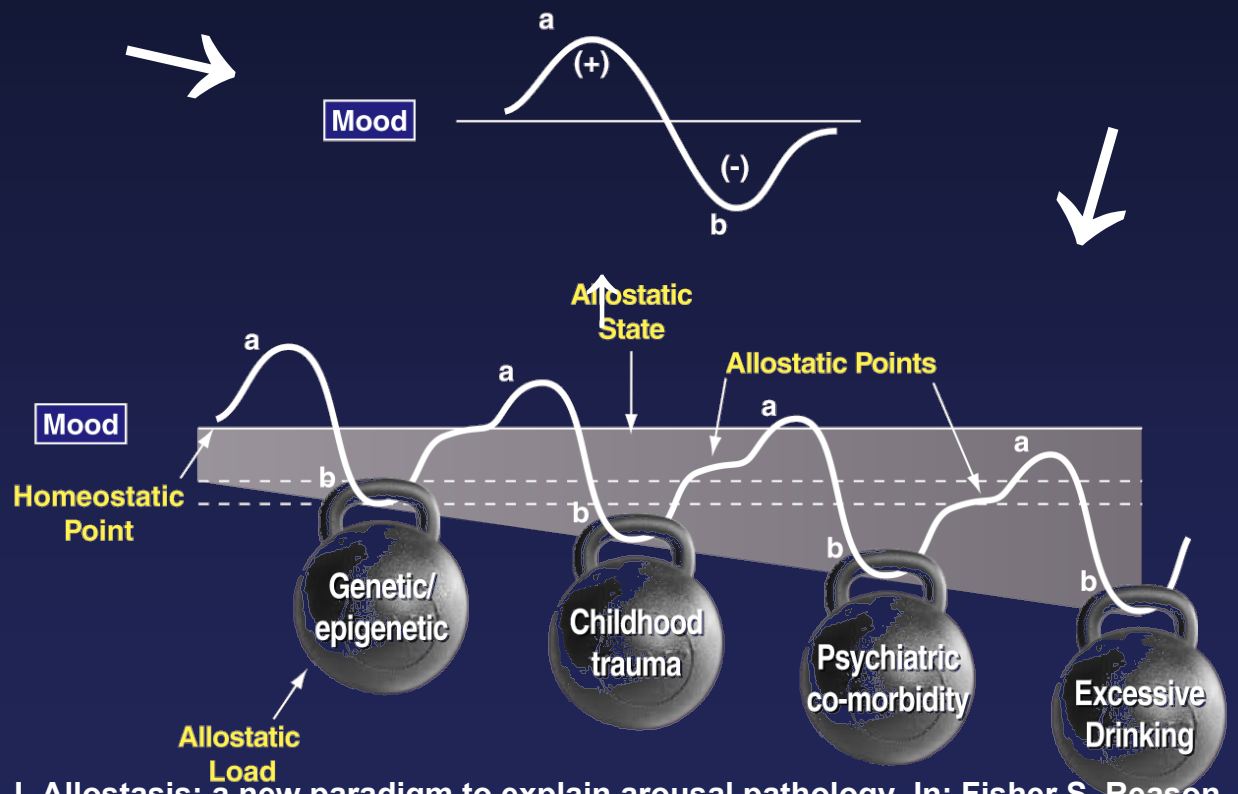
physiologic equilibrium

normal set point

stable

wide dynamic range

no pathology



Allostasis

compensated equilibrium

abnormal set point

inherently unstable

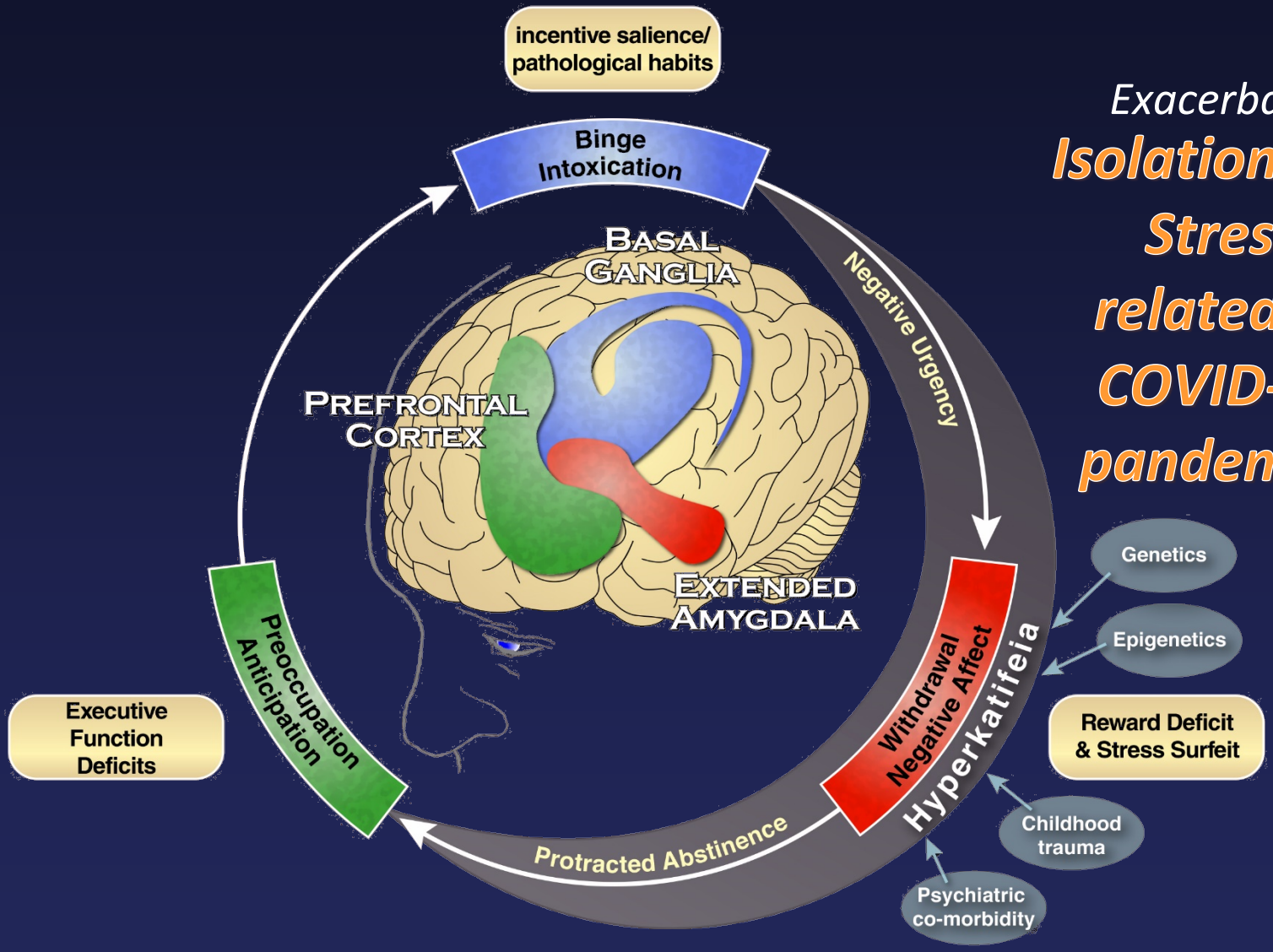
restricted range

leads to pathology

From: Sterling P, Eyer J. Allostasis: a new paradigm to explain arousal pathology. In: Fisher S, Reason J (eds) Handbook of Life Stress, Cognition and Health, John Wiley, New York, 1988, pp. 629-647

Koob GF, Le Moal M. Neuropsychopharmacology 2001;24:97-129.

Addiction as a Coping Response: Hyperkatifeia, Deaths of Despair, and COVID-19



Exacerbated by

Isolation and Stress related to COVID-19 pandemic?

From: Koob GF, Powell P, White A. J Psychiatry 2020;177:1031-1037.

Conclusions

1. **A conceptual framework of neuroadaptation** involving hyperalgesia, hyperkatifeia, opponent process, and negative reinforcement may be a key part of the addiction potential for opioid drugs.

2. **Opioid-induced hyperalgesia** has been observed in animal models following chronic opioids, in opioid-dependent individuals, and in patients treated therapeutically with chronic opioids. Neurobiological mechanisms involve both within- and between-system neuroadaptations.

3. **Opioid-induced hyperkatfeia** has been observed in animal models following chronic opioids, in opioid-dependent individuals, and in patients treated therapeutically with chronic opioids. Neurobiological mechanisms involve both within- and between-system neuroadaptations.

4. **Significant overlap in the engagement of brain circuits mediating negative emotional states (hyperkatifeia) and pain** may be hypothesized to explain the role of alcohol and opioids in "deaths of despair" and the effects of social isolation caused by the COVID-19 pandemic.

NIH National Institute on Alcohol Abuse and Alcoholism

Thank You!

George F. Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health

Senior Investigator
Integrative Neuroscience Research Branch
Intramural Research Program
National Institute on Drug Abuse

National Institute on Alcohol Abuse and Alcoholism