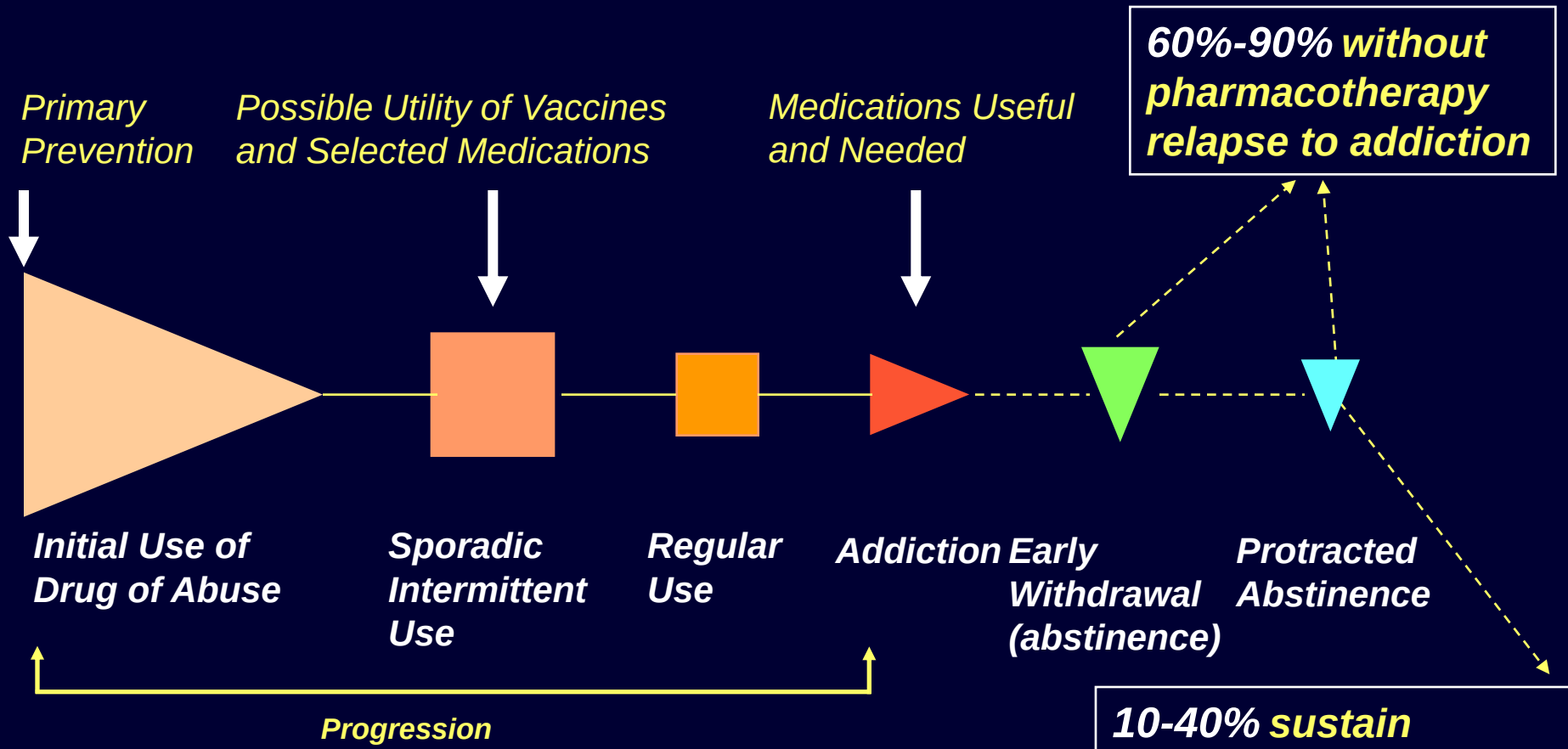
Current Status of Mu Opioid Receptor Directed Treatments for Opioid Addiction and a New Target for Novel Treatments of Cocaine Addiction and Adjunctive Treatment of Other Addictions

Mary Jeanne Kreek, M.D.
Patrick E. and Beatrice M. Haggerty Professor
Head of Laboratory
The Laboratory of the Biology of Addictive Diseases
The Rockefeller University
Senior Physician,
The Rockefeller University Hospital

October 1, 2015
Biarritz, France

Funded primarily by NIH-NIDA (P50-05130), The Adelson Medical Research Foundation, NIH-NCRR (RUH – Dr B. Coller)

Natural History of Drug and Alcohol Abuse and Addictions



ADDICTION: ***Compulsive drug seeking behavior and drug self-administration, without regard to negative consequences to self or others (adapted from WHO).***

Adapted from Kreek et al., Nature Reviews Drug Discovery, 1:710, 2002; 2013

Methadone Maintenance Treatment for Opiate (Heroin) Addiction – 2015

Number of patients currently in treatment: **~ 1.3 million worldwide**

- **USA: ~ 330,000**
- **Europe: ~ 600,000**
- **Rest of world: ~400,000**

Efficacy in "good" methadone treatment programs using adequate doses (80 to 150mg/d):

Voluntary retention in treatment (1 year or more)	50 – 80%
Continuing use of illicit heroin	5 – 20%

Actions of methadone treatment:

- **Prevents withdrawal symptoms and "drug hunger"**
- **Blocks euphoric effects of short-acting narcotics**
- **Allows normalization of disrupted physiology**

Mechanism of action: **Long-acting medication (24h half-life for racemate in humans) provides steady levels of opioid at specific receptor sites.**

- **methadone found to be a full mu opioid receptor agonist which internalizes like endorphins (beta-endorphin and enkephalins)**
- **methadone also has modest NMDA receptor complex antagonism**

Kreek, 1972; 1973; 2015

Status of Methadone, Buprenorphine, and Extended Release Naltrexone Treatments in the United States – 2013 (SAMHSA, 2015)

Methadone Maintenance Treatment	
Facilities	1,282
Patients	330,308
Buprenorphine Maintenance Treatment	
Facilities	3,113
Patients	48,148
Extended Release Naltrexone Treatment	
Facilities	1,718
Patients	3,781

Source: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. National Survey of Substance Abuse Treatment Services (N-SSATS), 2003-2014
Communication from: Cathie E. Alderks, PhD, Federal Project Officer, Behavioral Health Services Information System, Center for Behavioral Health Statistics and Quality, SAMHSA, 2015

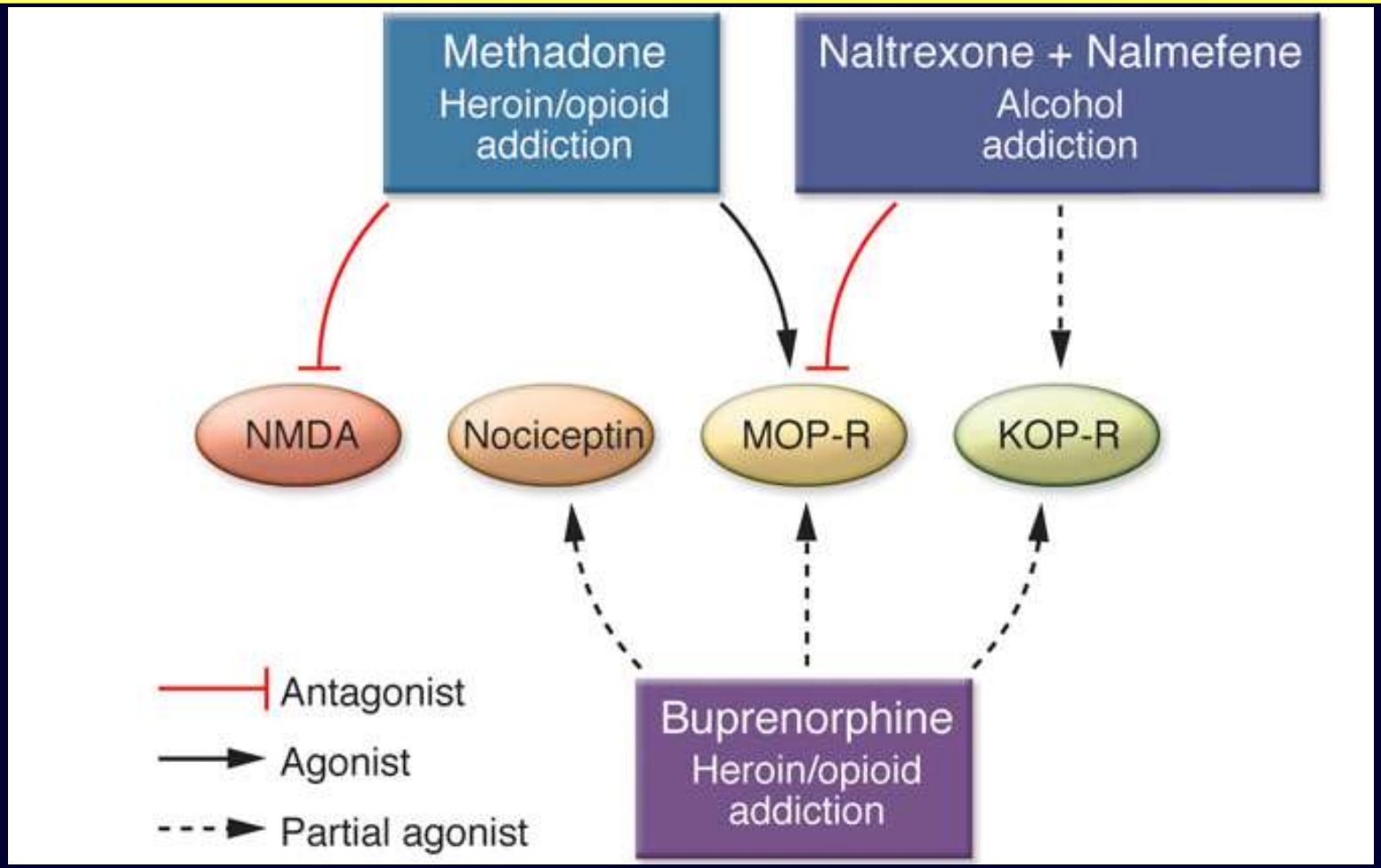
Numbers of Methadone Maintenance Clinics and Patients in Selected Countries in Southeast Asia (2014)

Country	Number of Methadone Clinics	Number of Patients in MMT
Mainland China	767 clinics 29 Mobile Vans	184,000
Hong Kong SAR	20 clinics	7,100
Macao SAR	2 clinics	182
Taiwan	137 clinics	9,082
TOTAL	926 clinics 29 mobile vans	200,364

Methadone Treatment & Pain Management Conference
Macao SAR, China, April 19, 2015

Organized by:
Vong Yim Mui, *Deputy Director, Social Welfare Bureau, Government of Macao SAR*
Hon Wai, *Head of Department of Prevention and Treatment for Drug Dependence, Social Welfare Bureau, Government of Macao SAR*

Targets of Currently Approved Treatments for Addictive Disorders



Kreek et al, Journal of Clinical Investigation, 12: 3387, 2012

Development of an Addiction: Neurobiology

- Drugs alter normal brain networks and chemicals
- "Rewarding" or "pleasurable" effects of drugs (the so-called "reinforcing effects") involve:
  - Dopamine
  - Endorphins (acting at Mu Opioid Receptors)
- "Countermodulatory" response to reward involves:
  - Dynorphins (acting at Kappa Opioid Receptors)

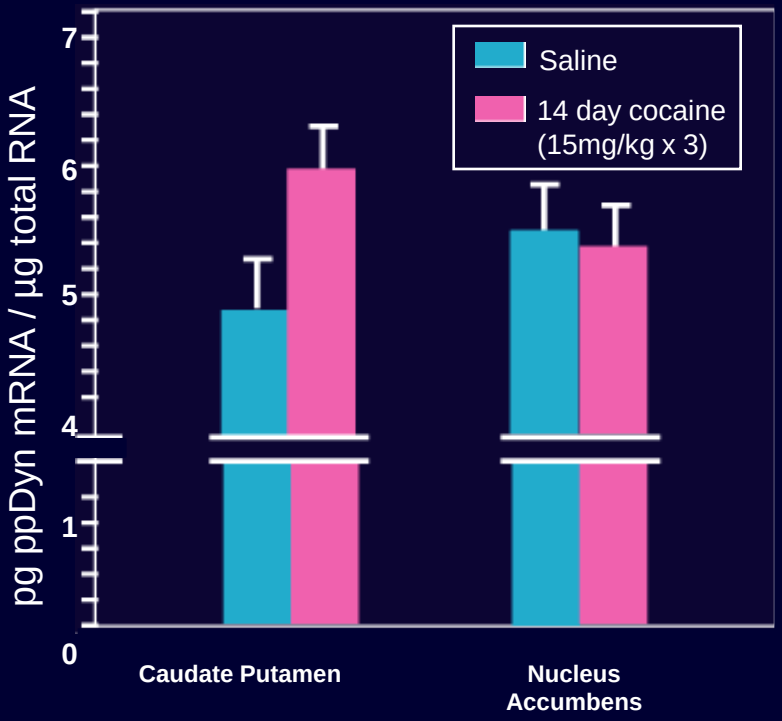
REWARD — MU OPIOID RECEPTOR-ENDORPHIN SYSTEM:
Mu Opioid Receptor Knock-Out Mice

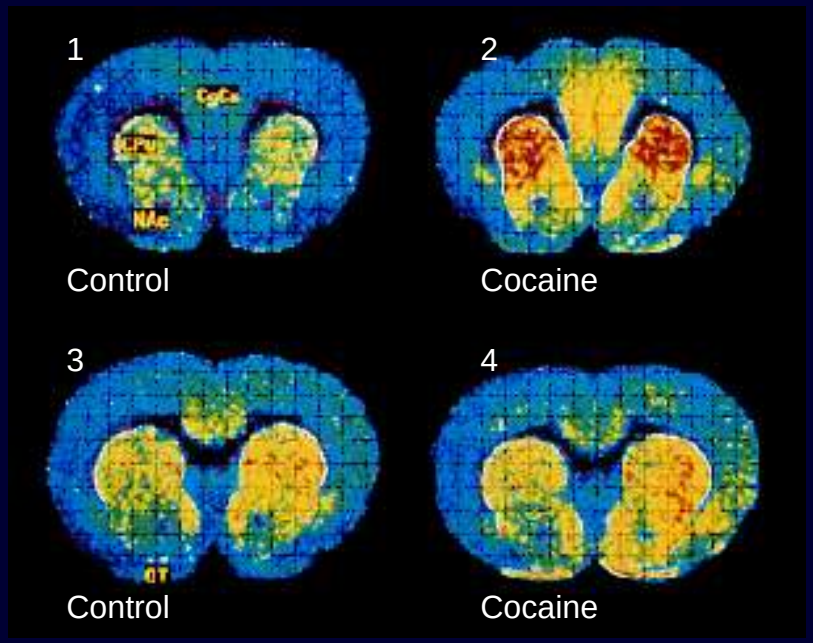
- No morphine or other mu agonist analgesia
- No heroin or morphine self-administration
- No heroin or morphine induced conditioned place preference
- Attenuated self-administration of cocaine
- Attenuated self-administration of alcohol

[Different knock-out constructs and multiple research groups, including Kieffer, Uhl, Yu, Pintar, Loh, with, e.g., Maldonado, Pasternak, Hoellt, Roberts]

Reviewed in Kreek et al., Nature Reviews Drug Discovery, 1:710-726, 2002; 2010

COUNTERMODULATION – KAPPA OPIOID RECEPTOR-DYNORPHIN SYSTEM: Cocaine Increases Kappa Opioid Receptor Density in Rat, But Kappa Opioid Receptor Directed "Dynorphins" Also Increase

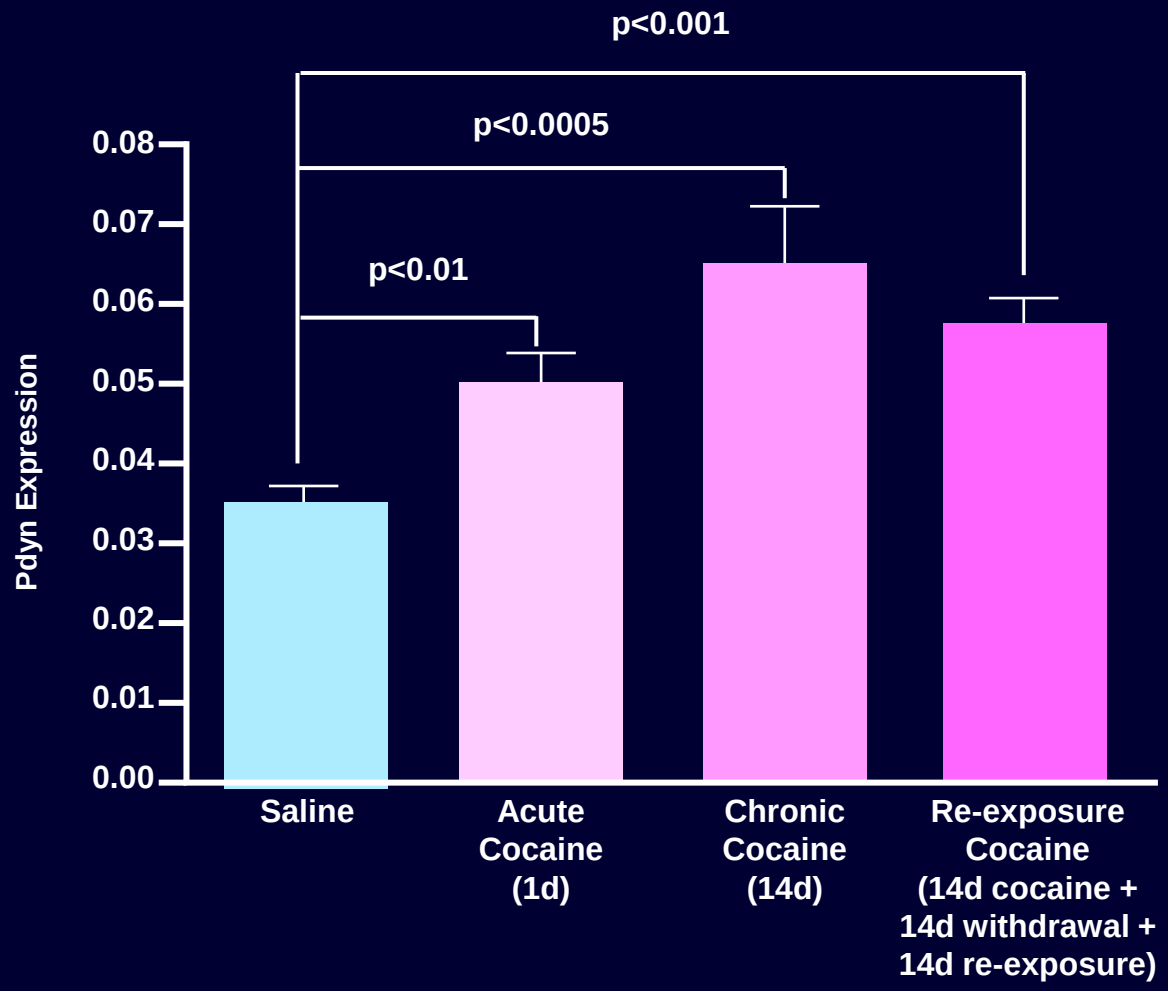




Dynorphin Acting at the Kappa Opioid Receptor Lowers Dopamine Levels and Prevents Surge After Cocaine

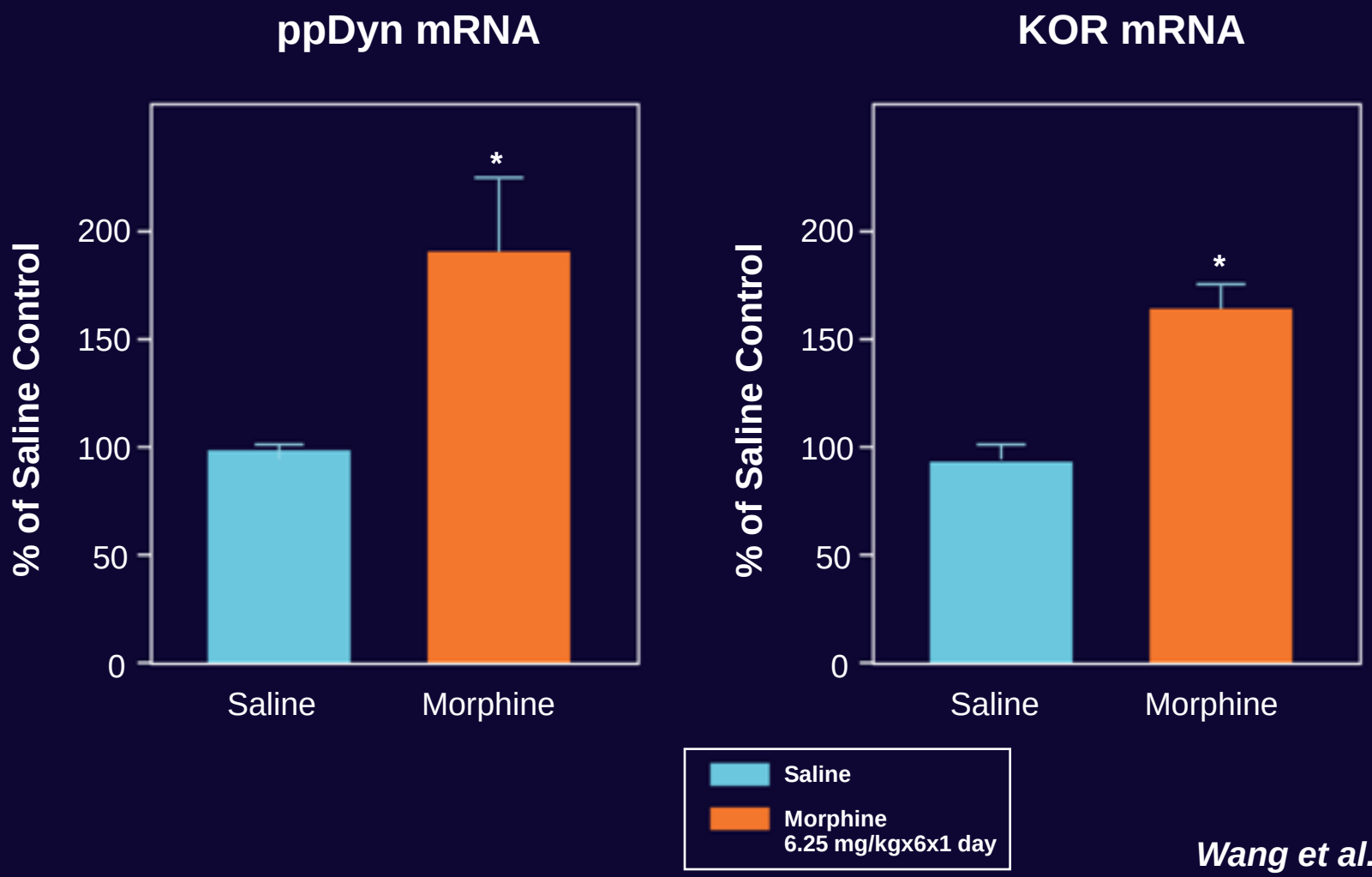
Spangler, Ho, Zhou, Maggos, Yuferov, and Kreek , Mol. Brain Res., 38:71, 1996;
Unterwald, Rubenfeld, and Kreek , NeuroReport, 5:1613, 1994

Increase in pdyn Receptor Gene mRNA Levels in the Caudate Putamen in Response to Acute Cocaine, Chronic Cocaine, and Re-exposure to Cocaine – "Binge" Pattern Administration in Mice



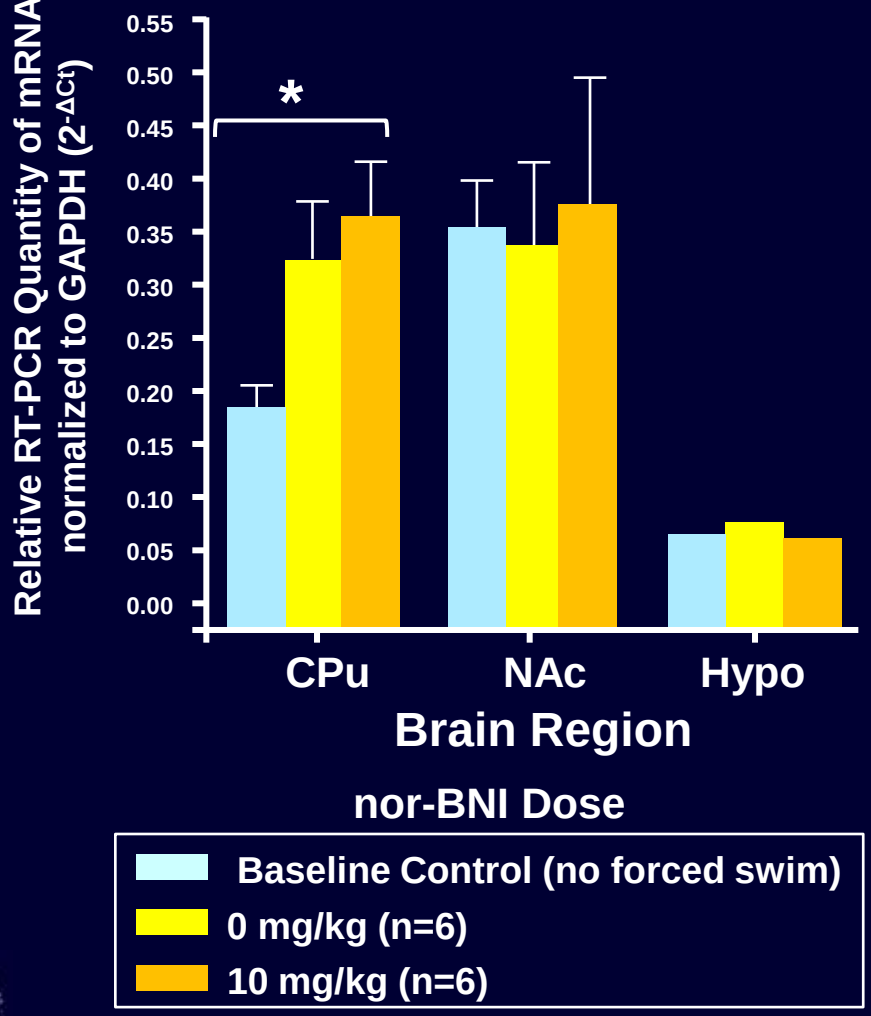
Zhang et al, Neuropharm., 67:259, 2013

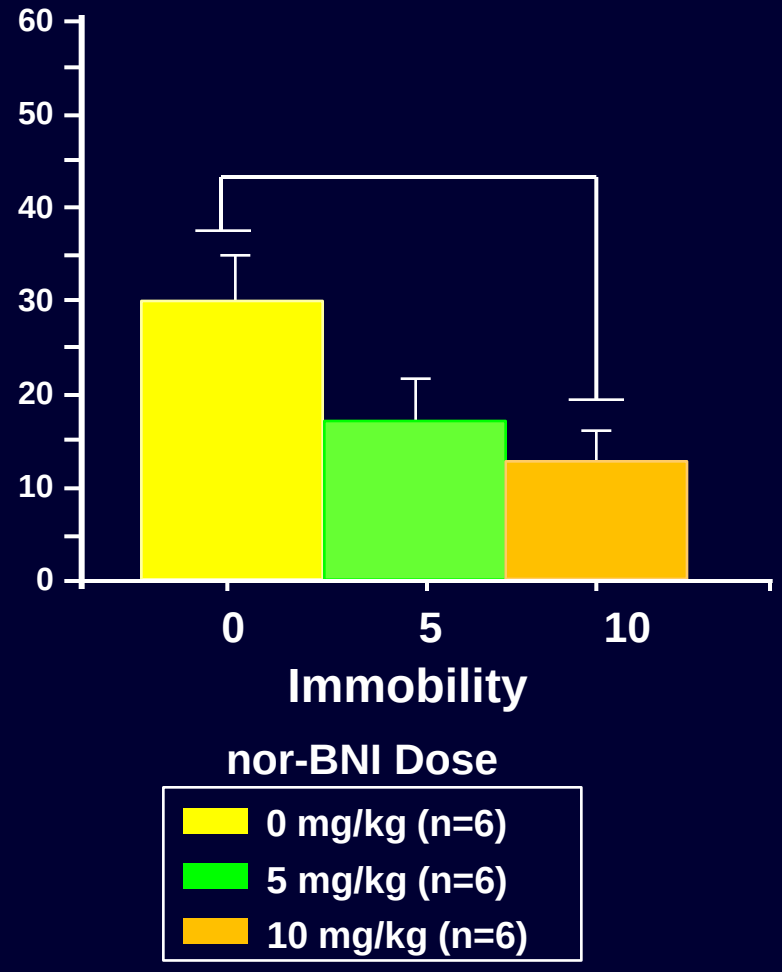
Acute Intermittent Morphine Increases Preprodynorphin and Kappa Opioid Receptor mRNA Levels in the Rat Brain



Wang et al., 1999

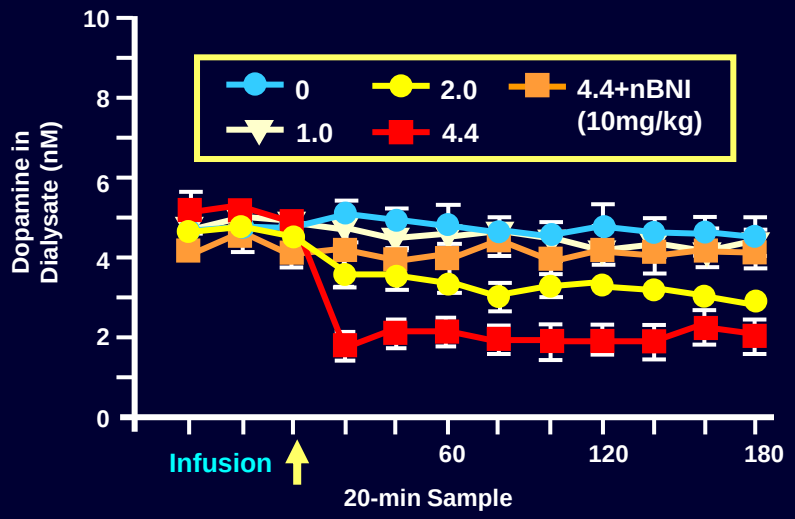
STRESS: Porsolt Forced Swim Test in Rats: Chromatin Alterations in Response to Forced Swimming Underlie Increased Caudate Putamen Prodynorphin Transcription

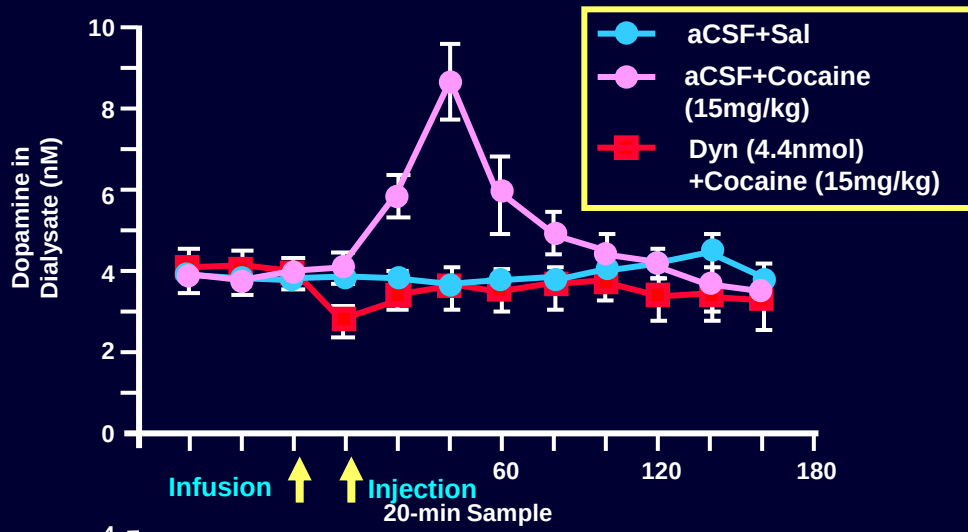


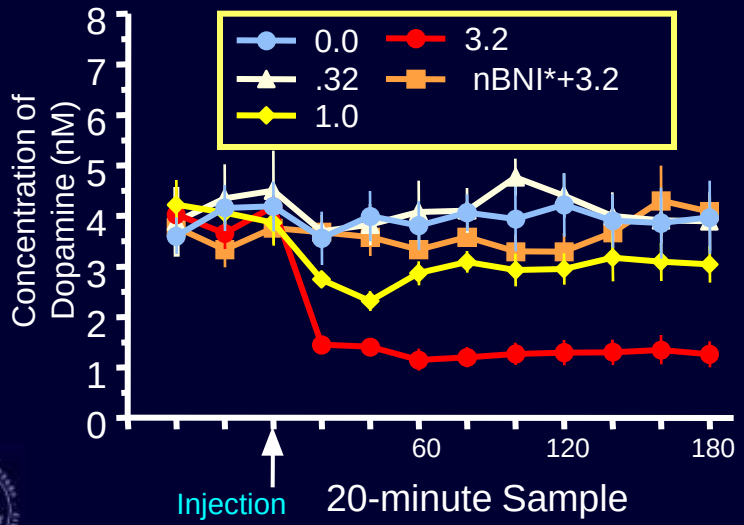


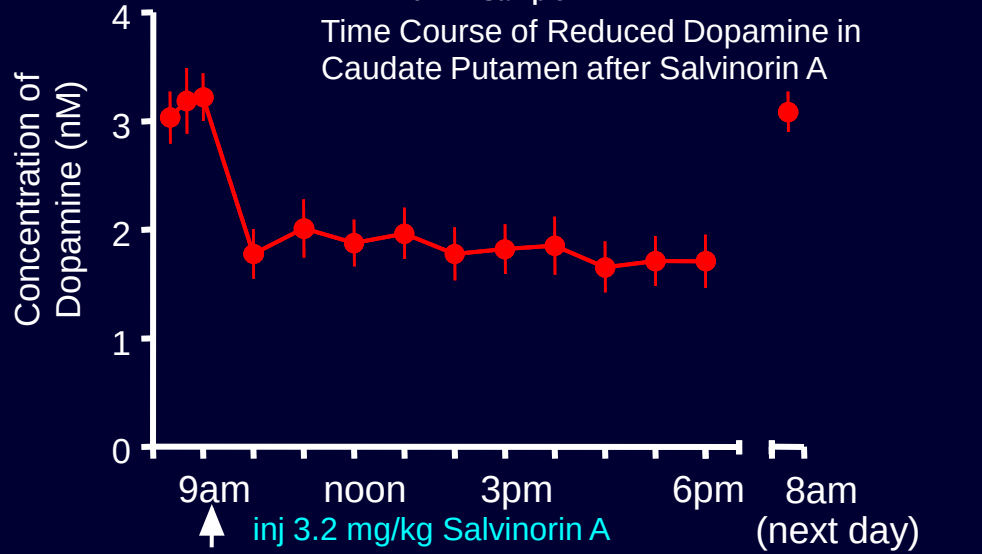
Reed et al., Neuroscience, 220:109-118, 2012

COUNTERMODULATION – KAPPA OPIOID RECEPTOR-DYNORPHIN SYSTEM: Dynorphin A_{1-17} and Salvinorin Lower Basal Dopamine Levels in Mouse Striatum: Effect on Cocaine-Induced Dopamine and Persistence of Effect









Zhang et al, Psychopharm., 172:422, 2004; Zhang et al., Psychopharm., 179:551, 2005; Butelman, JPET 328: 588, 2009

COUNTERMODULATION OF REWARD — KAPPA OPIOID RECEPTOR: Kappa Opioid Receptor Knock-Out Mice

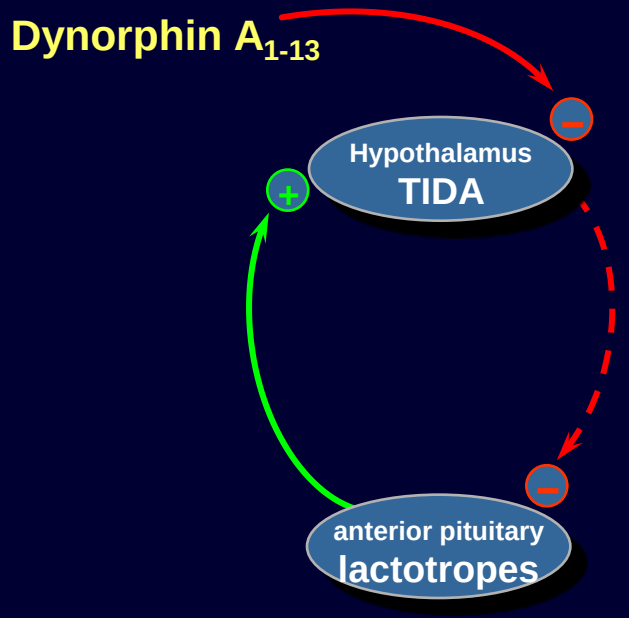
- No response to classic exogenous KOPr agonists (e.g., in analgesia)
- Decreased severity of heroin withdrawal (including physical and emotional signs)
- Increased basal dopamine release
- Increased cocaine-induced dopamine release
- Decreased effect of stress (e.g., on stress-induced potentiation of cocaine reward)
- Decreased THC-induced aversion, and increased THC-induced reward

[Different knock-out constructs and multiple research groups, including Kieffer, Shippenberg, Chavkin, Pintar]

Butelman and Kreek 2015

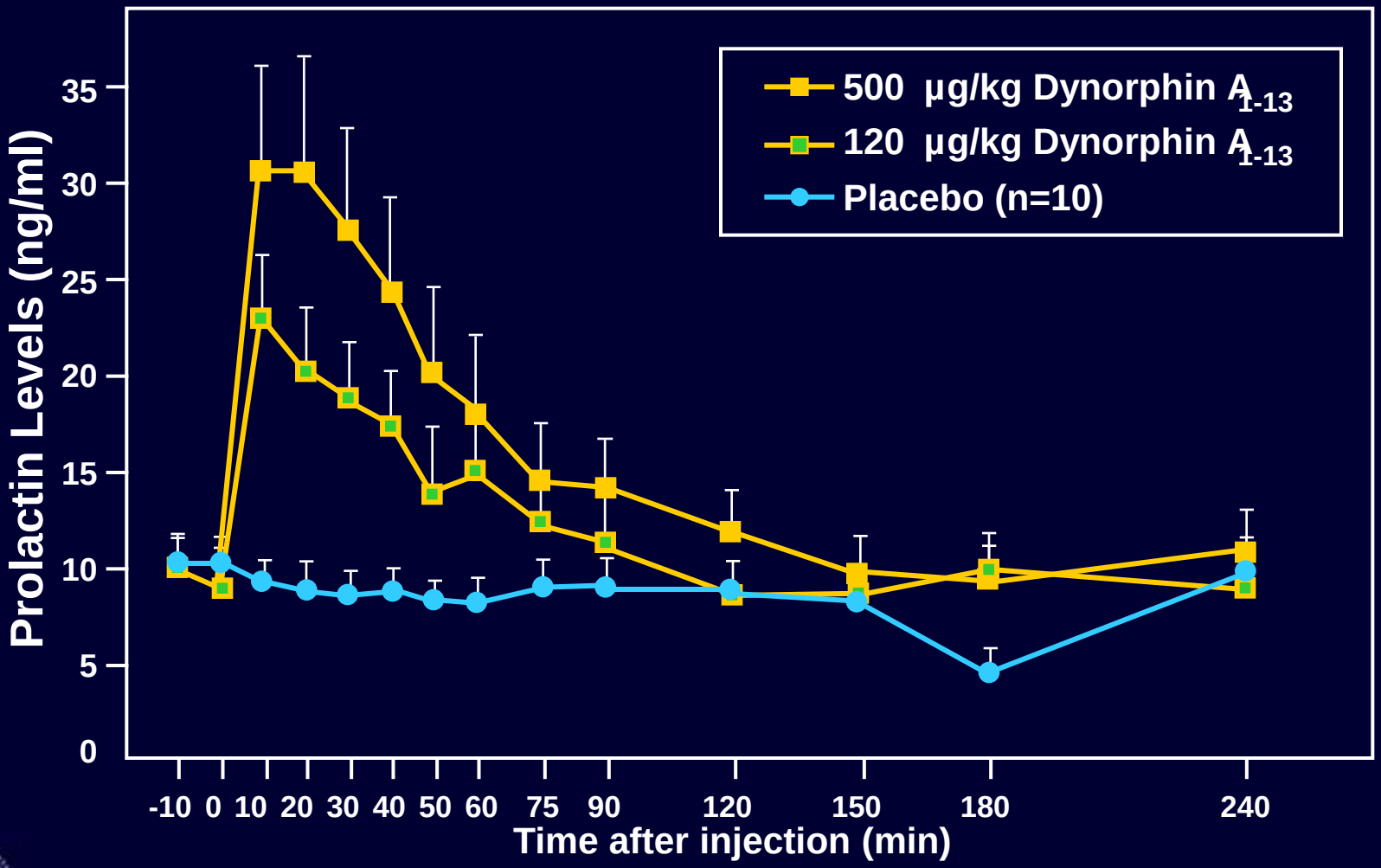
Hypothesis: Dynorphin and the Tuberoinfundibular Dopaminergic System

Dynorphin A, by acting directly or indirectly to lower tuberoinfundibular dopaminergic tone, which tonically inhibits prolactin release, causes elevation of serum levels of prolactin in human subjects and non-human primates.



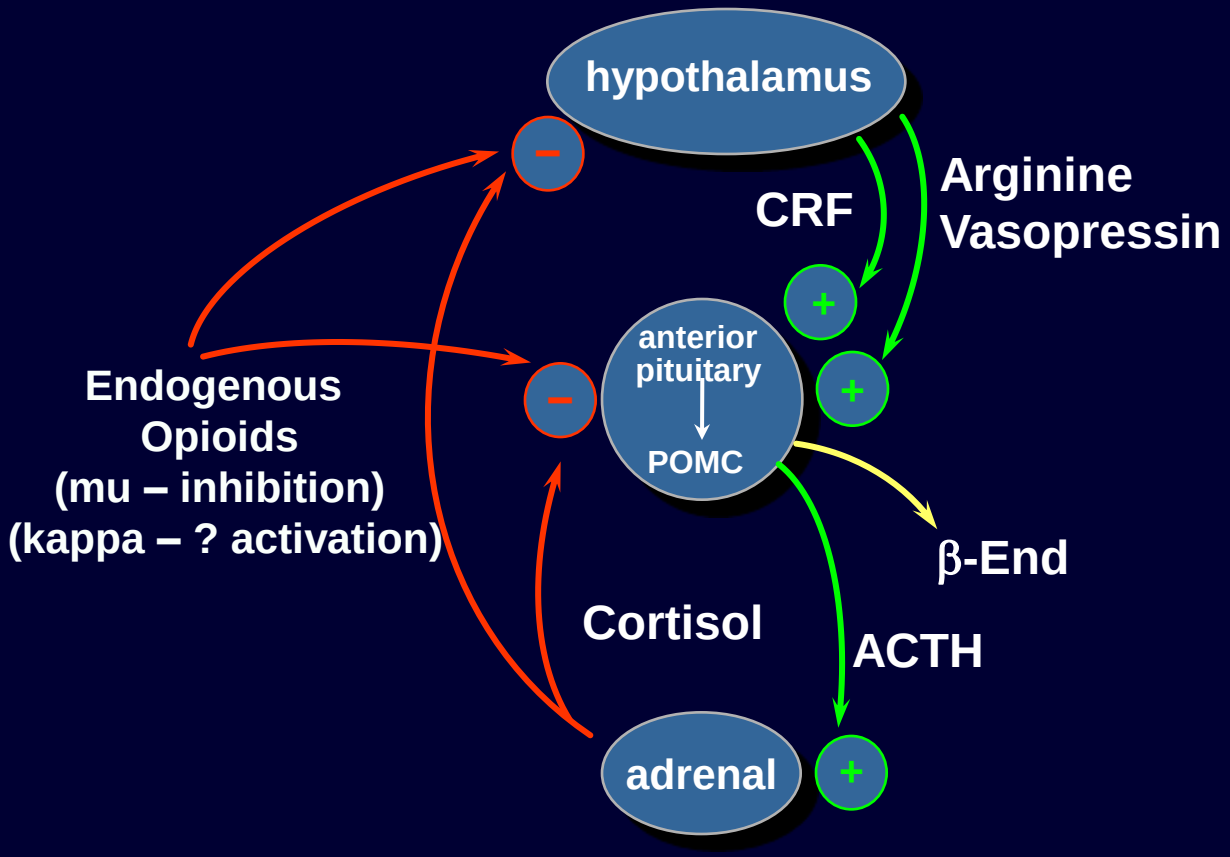
Kreek et al., 1994; 1999; 2013

COUNTERMODULATION – KAPPA OPIOID RECEPTOR-DYNORPHIN SYSTEM: Dose-Response Effects of Dynorphin A_{1-13} on Prolactin Levels (Biomarker) in Normal Volunteers – Prolactin Under Direct Inhibitory Control of Tuberoinfundibular Dopamine



Kreek et al., J. Pharmacol. Exp. Ther., 288:260, 1999

STRESS RESPONSIVITY:
Hypothesis – Atypical Responsivity to Stressors, A Possible Etiology of Addictions – HPA Axis



Atypical responsivity to stress and stressors may, in part, contribute to the persistence of, and relapse to self-administration of drugs of abuse and addictions. Such atypical stress responsivity in some individuals may exist prior to use of addictive drugs on a genetic or acquired basis, and lead to the acquisition of drug addiction.

Kreek, 1972; 1981; 1982; 1984 … 2014

STRESS RESPONSIVITY – Heroin, Cocaine, and Alcohol Profoundly Alter Stress Responsive Hypothalamic-Pituitary-Adrenal (HPA) Axis: Normalization During Methadone Treatment

- Acute effects of opiates
- Chronic effects of short-acting opiates (e.g., heroin addiction)

} Suppression of HPA Axis (decrease levels of HPA hormones)

- Opiate withdrawal effects *
- Opioid antagonist effects
- Cocaine effects *
- Alcohol effects

} Activation of HPA Axis (increase levels of HPA Hormones)

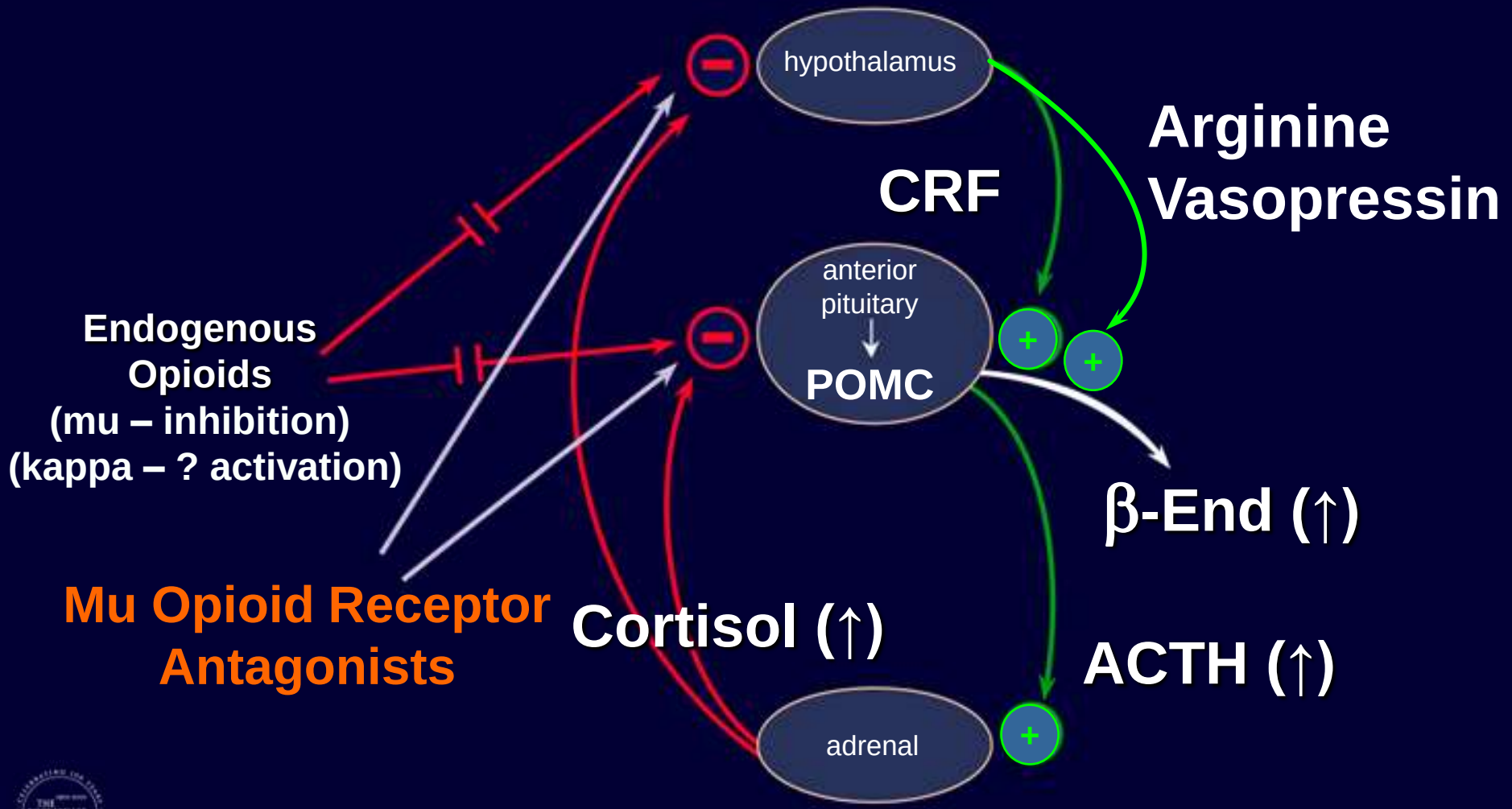
- Chronic effects of long-acting opiate (e.g. methadone in maintenance treatment)

Normalization of HPA Axis

* Our challenge studies have shown that a relative and functional “endorphin deficiency” develops.

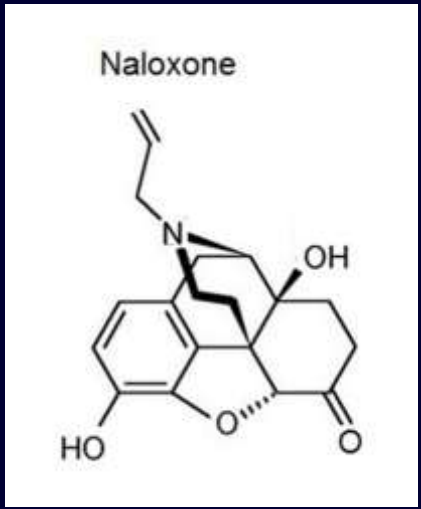
Kreek, 1972; 1973; 1987; 1992 … 2014

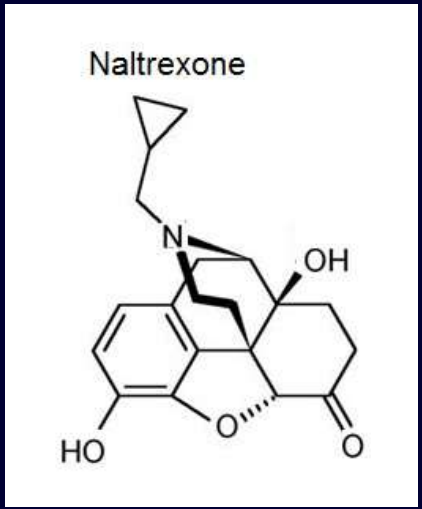
STRESS RESPONSIVITY – Dissecting the Hypothalamic-Pituitary-Adrenal Axis in Humans: Selective Opioid Antagonist Testing

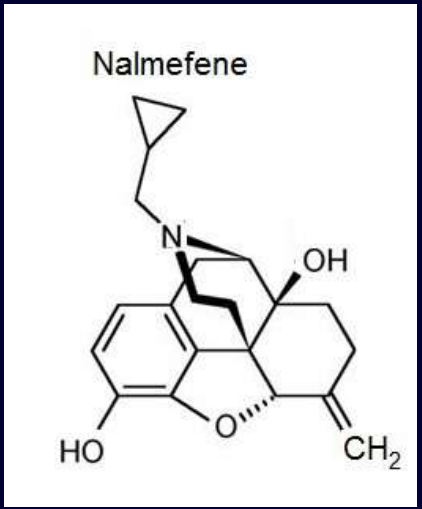


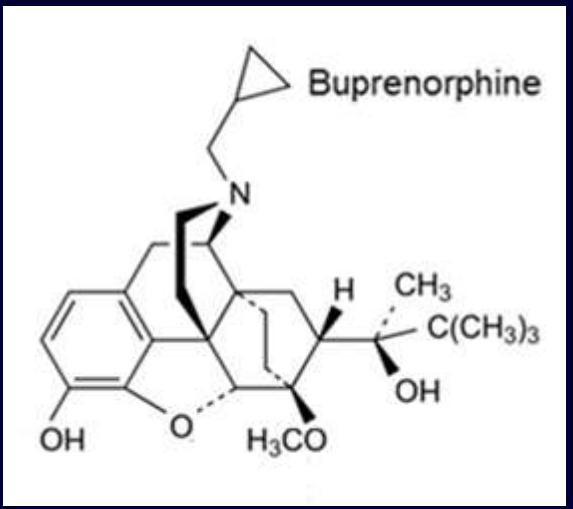
Kreek, 1984; 1998; 2006; 2014

Compounds Approved for Use in Human Therapeutics with KOPr Partial Agonism in Addition to Mu-Opioid Receptor Antagonism or Partial Agonism









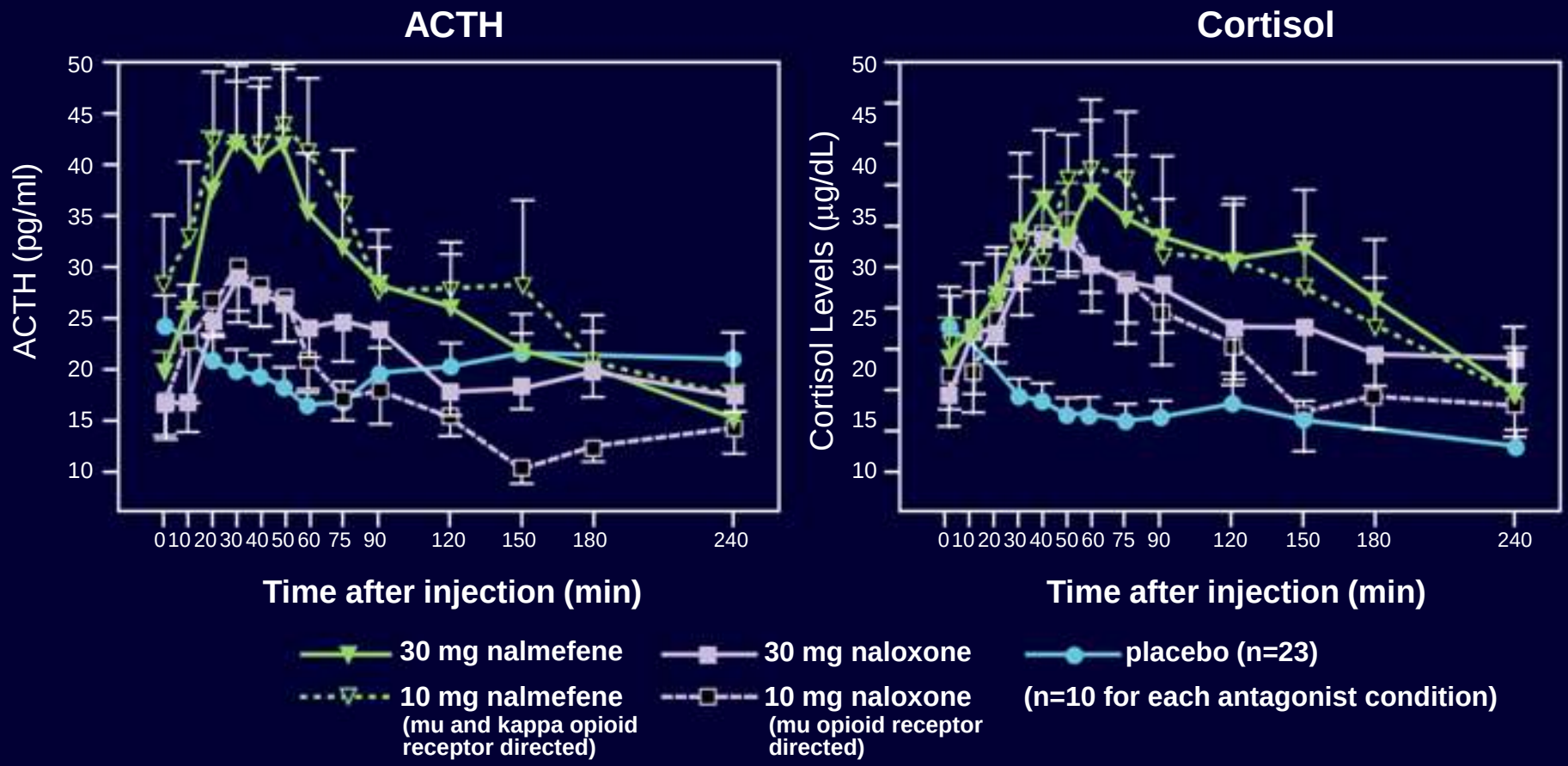
Kreek, Reed, Butelman 2014

Binding Affinity in Cloned Human Receptors

Compound	MOP-r affinity Ki (nM)	KOP-r affinity Ki (nM)	DOP-r affinity Ki (nM)	binding selectivity (MOP-r, KOP-r)
Naltrexone	0.11	0.19	60	MOP-r>KOP-r selectivity
Nalmefene	0.24	0.083	16	KOP-r>MOP-r selectivity
Naloxone	0.66	1.2	120	MOP-r>KOP-r selectivity
Buprenorphine	0.21	0.62	2.1	MOP-r>KOP-r selectivity

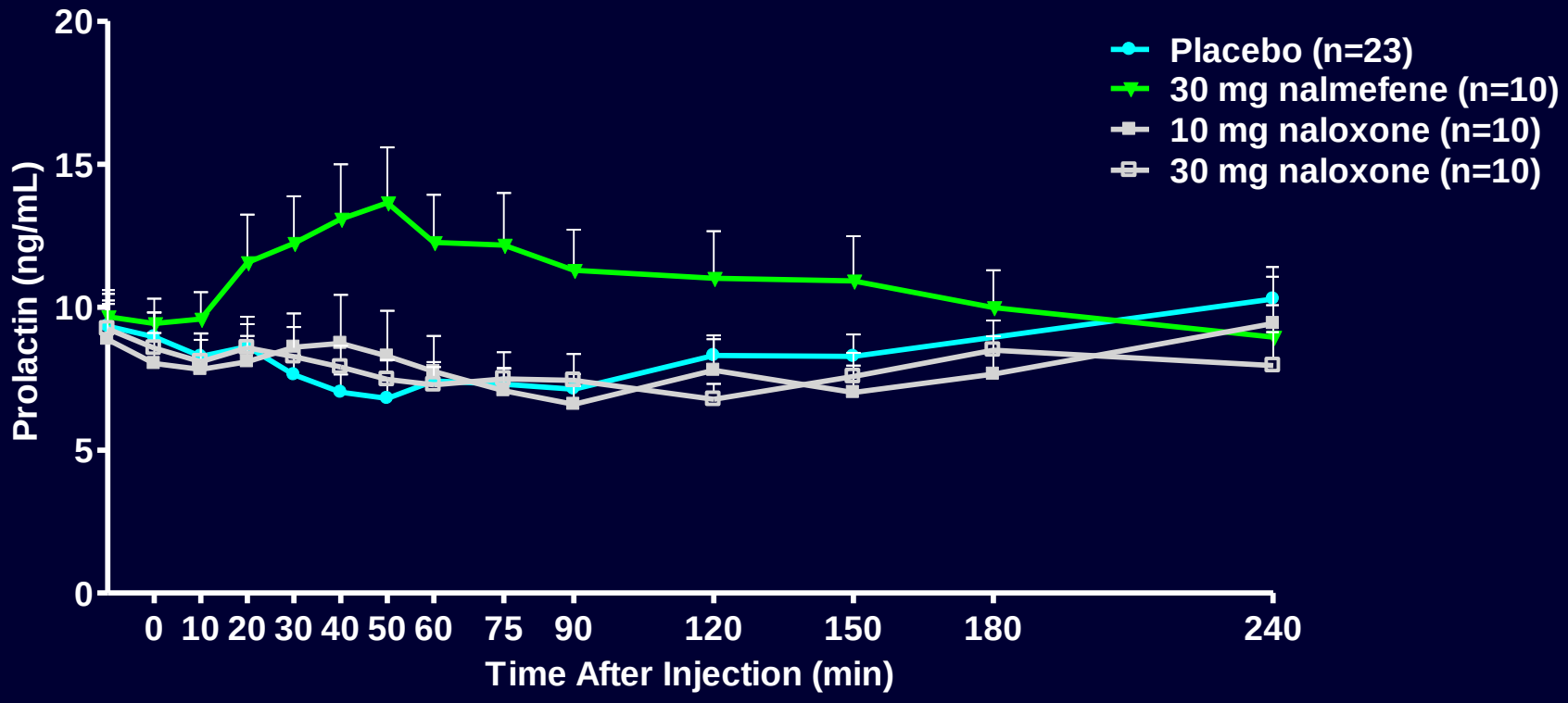
Selected References from the Bidlack Laboratory (to equalize methodology):
Naltrexone and naloxone: Wentland et al., 2009 (Bioorg Med Chem Lett)
Nalmefene: Bart et al., 2005 (Neuropsychopharmacol)
Buprenorphine: Wentland et al., 2009
Kreek, Reed, Butelman 2013.

Nalmefene (mu/kappa Directed) Causes Greater HPA Axis Activation Than Naloxone (mu Directed) in Normal Human Volunteers (n=23)



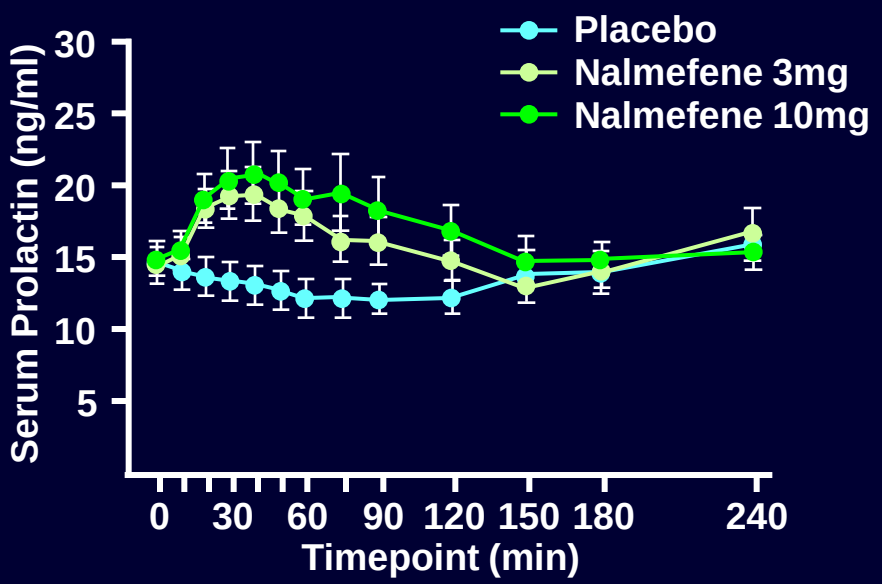
Schluger, Ho, Borg, Porter, Maniar, Gunduz, Perret, King, and Kreek, Alcohol. Clin. Exp. Res., 22,1430, 1998

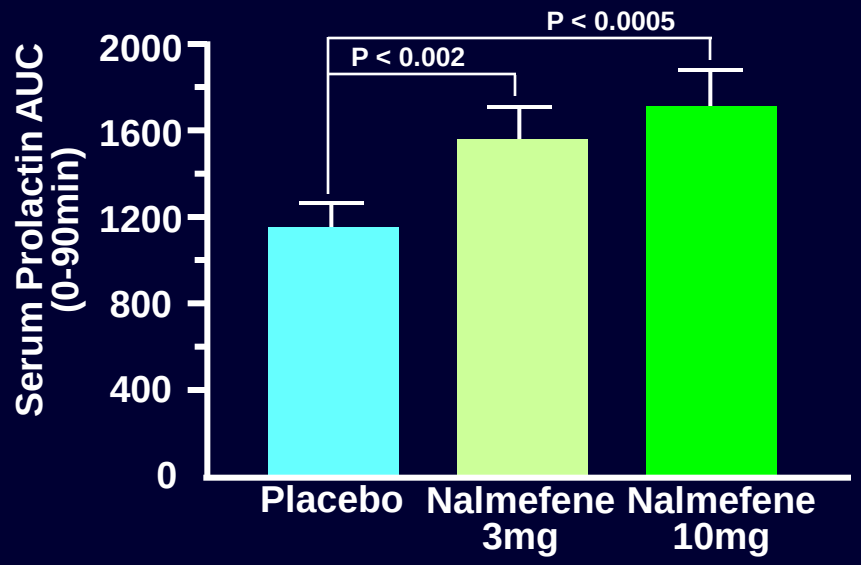
Nalmefene, But Not Naloxone, Causes Modest Increases in Serum Prolactin Levels in Normal Human Male Volunteers: Evidence of Kappa Partial Agonist Activity



Unpublished data from
Schluger, Ho, Borg, Porter, Maniar, Gunduz, Perret, King, and Kreek, Alcohol. Clin. Exp. Res., 22,1430, 1998, 2013

Nalmefene (Mu Antagonist, Kappa Partial Agonist) Effects a Modest Elevation in Serum Prolactin Levels

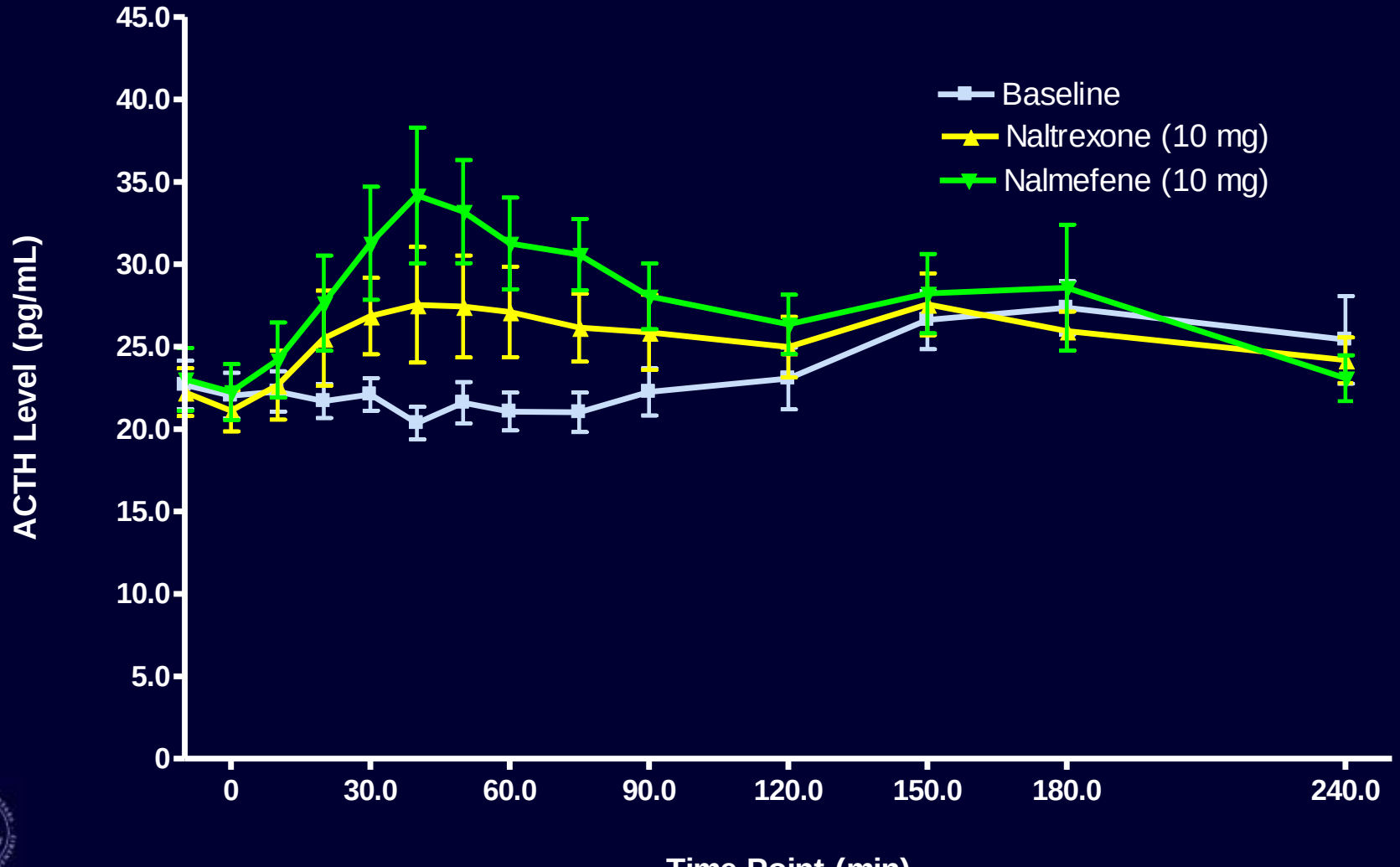




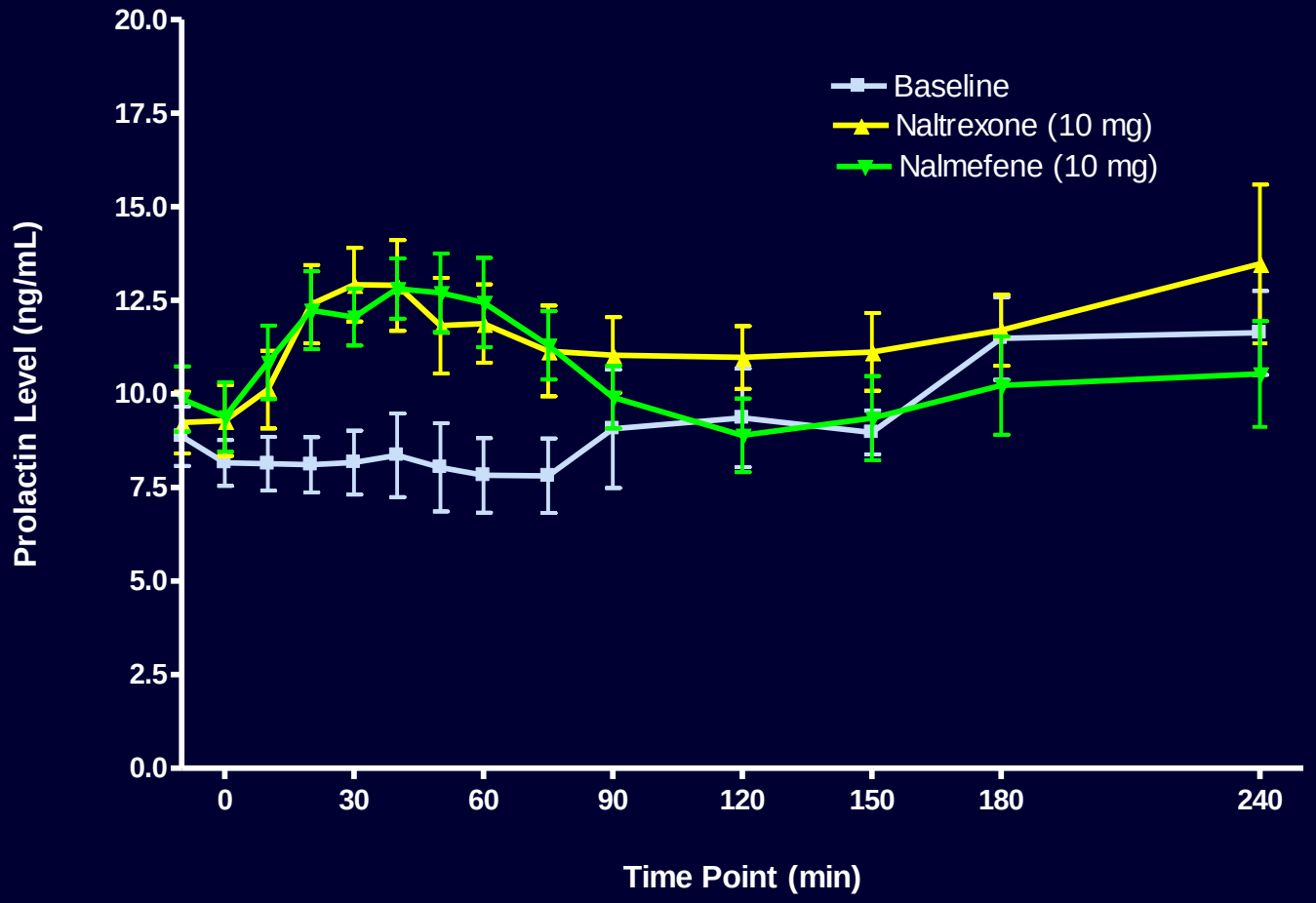
n = 33

Bart et al., Neuropsychopharmacology, 30:417-422, 2005

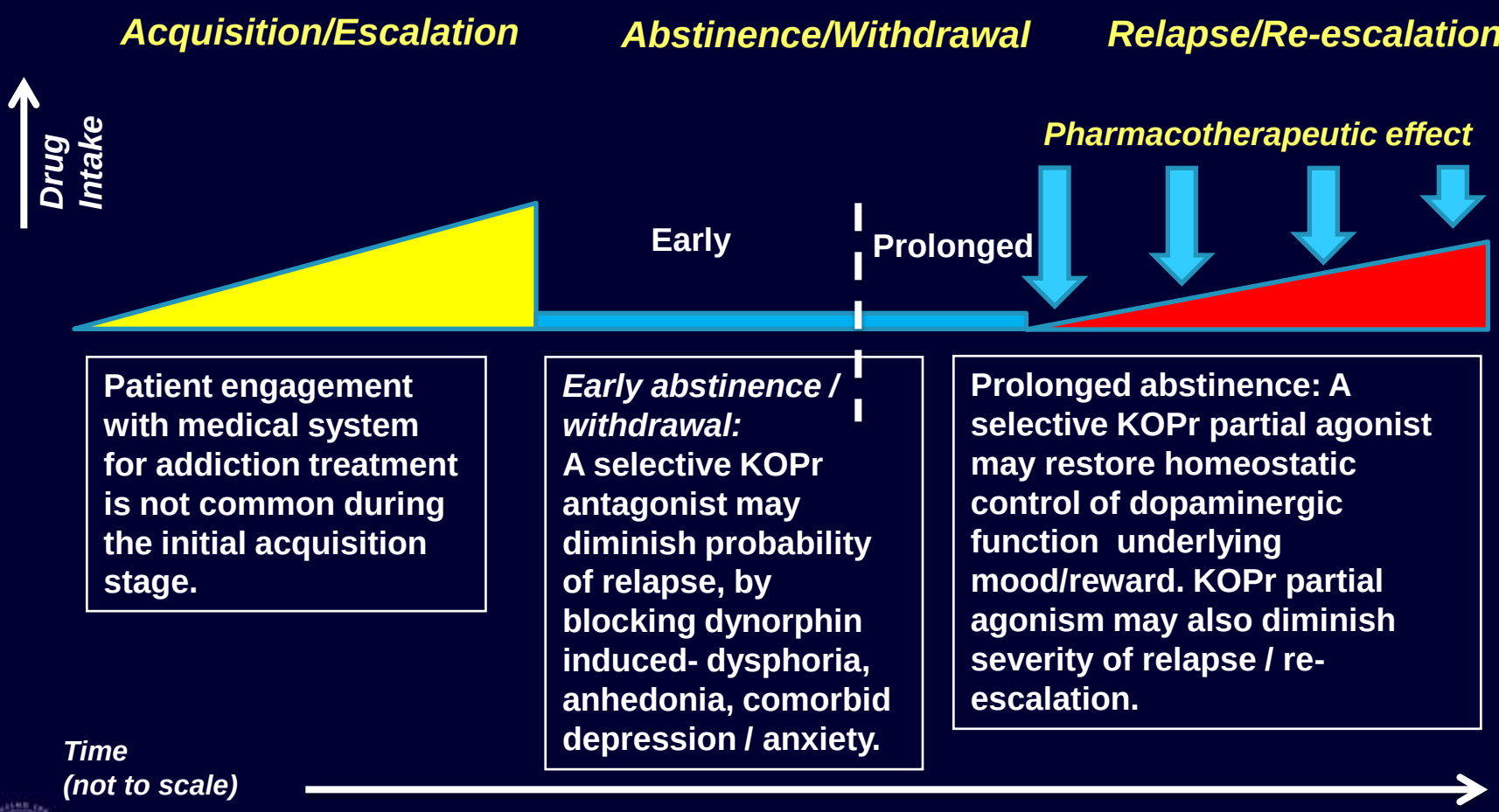
Study in Progress:
ACTH Plasma Levels for Naltrexone and Nalmefene
Normal Volunteers Male & Female (N=15)



Study in Progress: Prolactin Serum Levels for Naltrexone and Nalmefene – Normal Male Volunteers Males (N=10)



Potential pharmacotherapeutic approaches within an addiction-like cycle



Butelman, Yuferov, and Kreek, Trends Neurosci.35:587-596, 2012.

Potential biological targets identified (e.g. KOPr)

- **Need: Compounds selective for this target KOPr (agonist, biased agonist, partial agonist, and antagonist).**
- **Major Clinical Concern with High Efficacy Kappa Agonist: Depressive symptoms; dysphoria; psychotomimesis**
- **Actual Concern of Research Clinician: None. Tolerance develops to psychotomimetic effects. One recent study showed little to no problems when a kappa agonist is given to persons with long term drug abuse or addiction.**

Selective Kappa Opioid Receptor Antagonist "OpraKappa" Study – in progress (September 21, 2014 – present)

Group I; Diagnosis: Normal Healthy Volunteers

- Males
- Females

Group II; Diagnosis: Cocaine Dependent

- Males
- Females

Group III; Diagnosis: Early abstinence from cocaine dependence: 1 week to 6 months

- Males
- Females

Group IV; Diagnosis: Drug free former cocaine dependent: abstinence greater than 6 months

- Males
- Females

To date, 34 subjects studied. No adverse effects.

OpraKappa Study Design: Opioid Receptor Antagonist

Night of Admission:

-Beck Depression Inventory (BDI)

Study Day 1: Baseline Day (no drug administered)

-Neuroendocrine testing

-Beck Depression Inventory (BDI)

-Mood and Drug Effect (VAS) Scales

-Cocaine Craving Scale (CCQ) *Cocaine dept. groups only

Study Days 2 & 5: 10 mg OpraKappa administered

-Neuroendocrine testing

-Beck Depression Inventory (BDI)

-Mood and Drug Effect (VAS) Scales

-Cocaine Craving Scale (CCQ) *Cocaine dept. groups only

Study Days 3 & 4: 10 mg OpraKappa administered

-Beck Depression Inventory (BDI)

-Mood and Drug Effect (VAS) Scales

-Cocaine Craving Scale (CCQ) *Cocaine dept. groups only

Day of Discharge:

-Beck Depression Inventory (BDI)

Kreek in progress, September 2014-present