Methadone and Beyond:
Medication and its Role in Treating Addiction

Mary Jeanne Kreek, M.D.
The Laboratory of the Biology of Addictive Diseases
The Rockefeller University

Blending Clinical Practice and Research:
Forging Partnerships to Enhance
Drug Addiction Treatment

Grand Hyatt Hotel
New York City
March 15, 2002

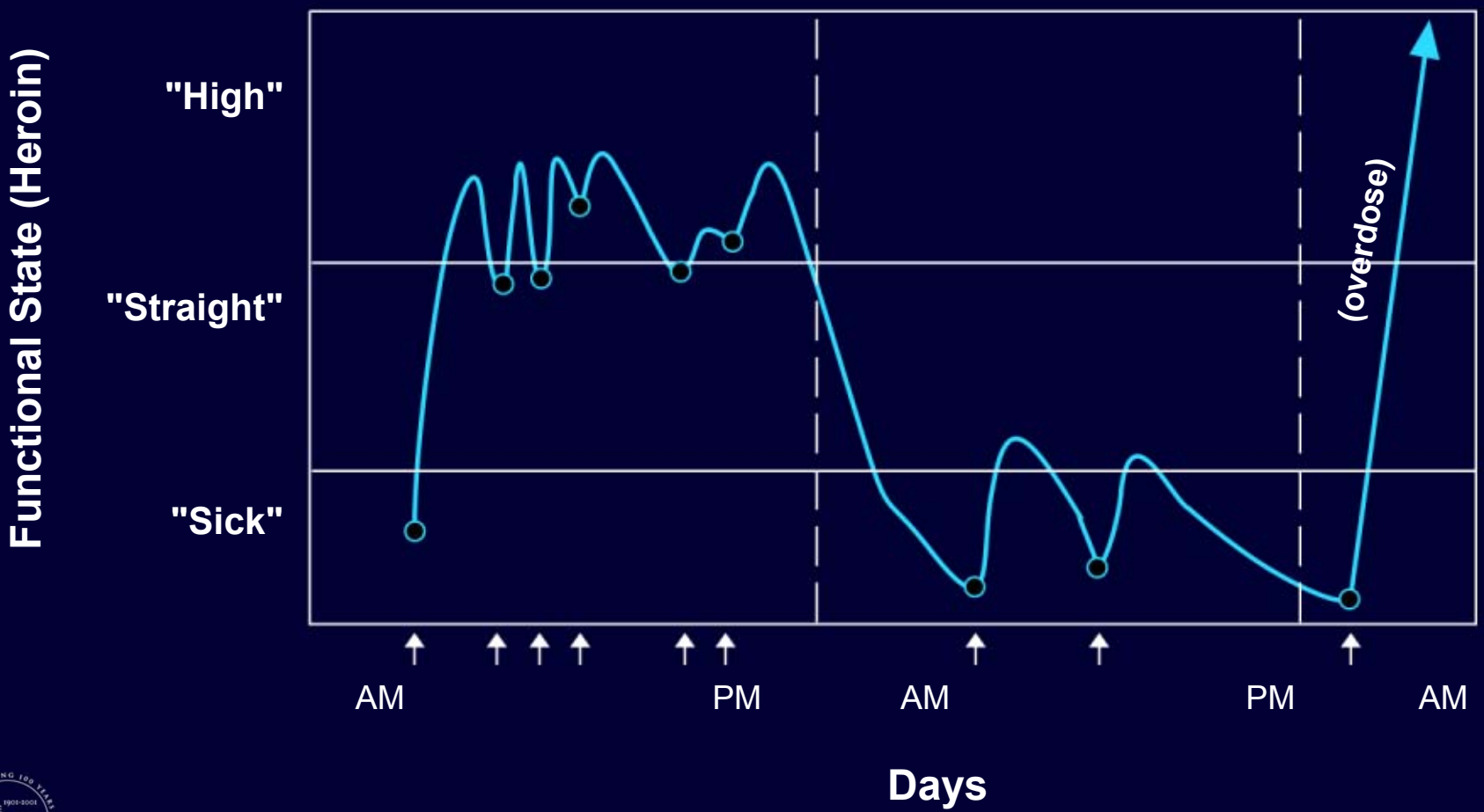
work supported primarily by NIH-NIDA and also by NIH-NCRR and NY State OASAS

Hypothesis (1963–1964)

Heroin (opiate) addiction is a disease – a "metabolic disease" – of the brain with resultant behaviors of "drug hunger" and drug self-administration, despite negative consequences to self and others. Heroin addiction is not simply a criminal behavior or due alone to antisocial personality or some other personality disorder.

Dole, Nyswander and Kreek, 1966

Impact of Short-Acting Heroin As Used on a Chronic Basis in Humans - 1964 Study



Dole, Nyswander and Kreek, 1966

Goals and Rationale for Specific Pharmacotherapy for an Addiction

1. Prevent withdrawal symptoms
2. Reduce drug craving
3. Normalize any physiological functions disrupted by drug use
4. Target treatment agent to specific site of action, receptor, or physiological system affected or deranged by drug of abuse

Kreek, 1978; 1991; 1992; 2001

Characteristics of an Effective Pharmacotherapeutic Agent for Treatment of an Addictive Disease

- Orally effective
- Slow onset of action
- Long duration of action
- Slow offset of action

Kreek, 1978; 1991; 1992; 2001

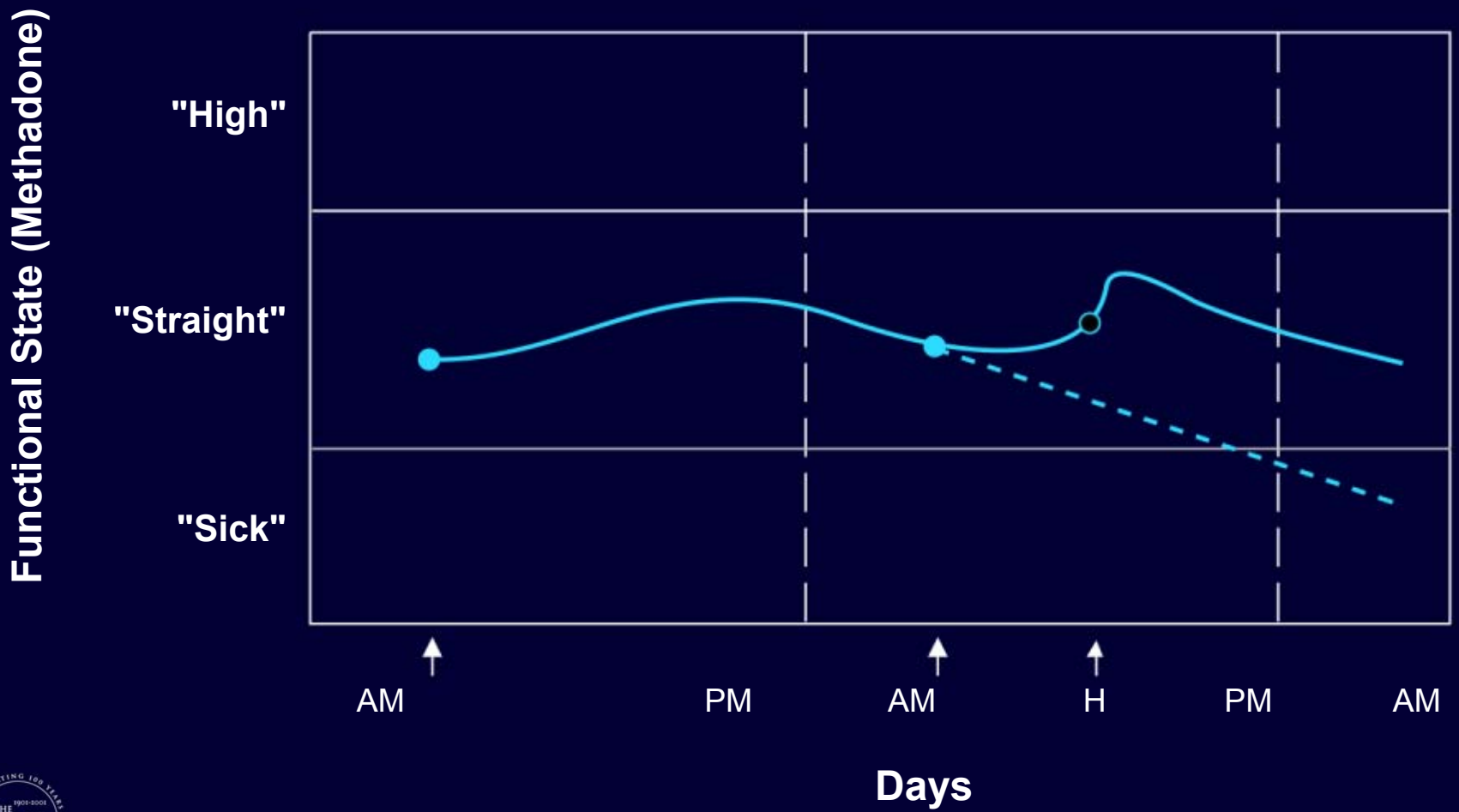
Heroin versus Methadone*

	Heroin	Methadone
Route of administration	intravenous	oral
Onset of action	immediate	30 minutes
Duration of action	3–6 hrs	24–36 hrs
Euphoria	first 1–2 hrs	none
Withdrawal symptoms	after 3–4 hrs	after 24 hrs

** effects of high dosages in tolerant individuals*

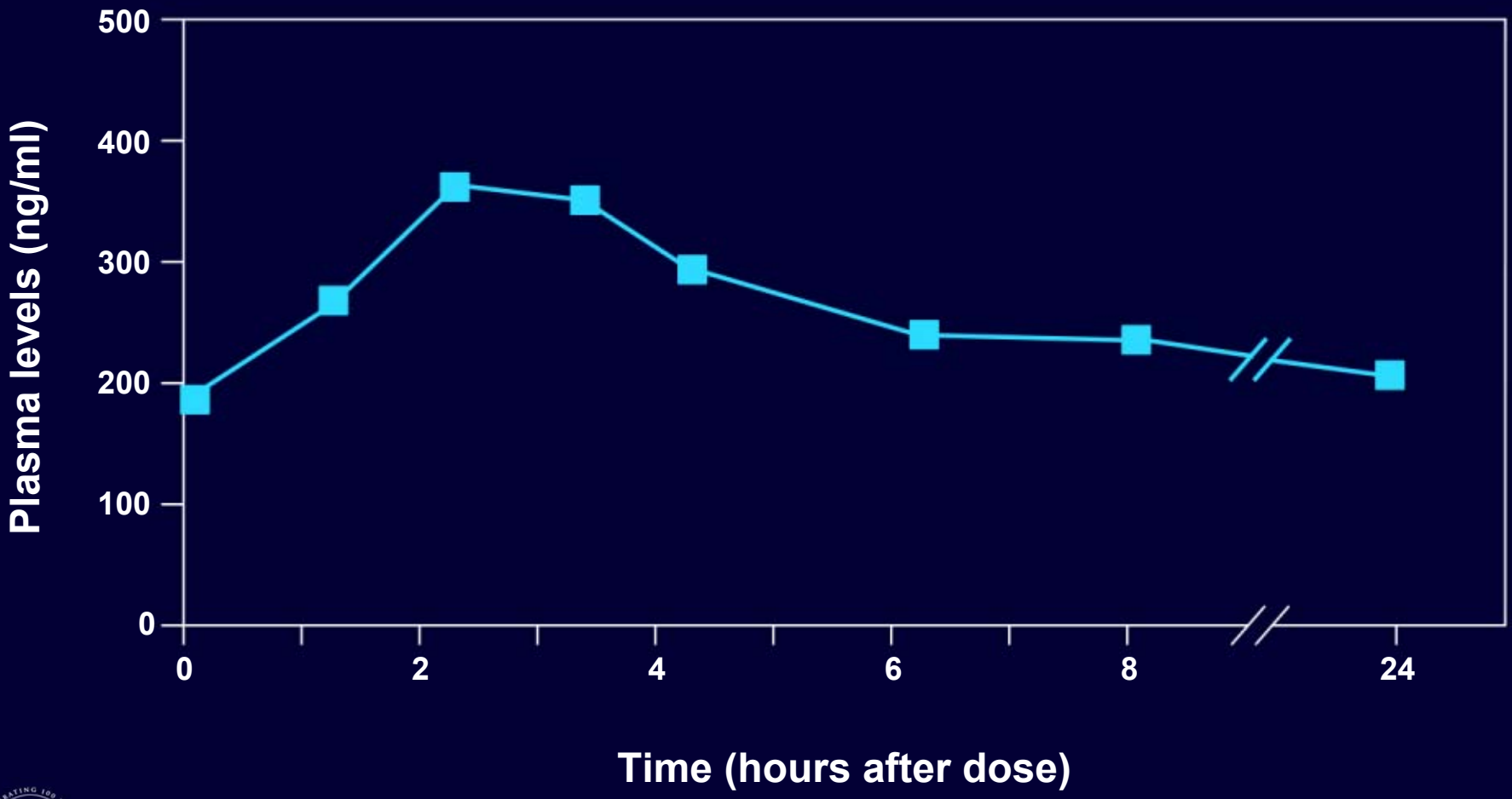
Kreek, 1973; 1976; 1987

Long-Acting Methadone Administered on a Chronic Basis in Humans - 1964 Study



Dole, Nyswander and Kreek, 1966

Plasma Methadone Levels in an Individual Maintained on 100 mg/day



Kreek, MJ, NY State J. Med., 1973

Opioid Agonist Pharmacokinetics: Heroin Versus Methadone

Compound	Systemic Bioavailability After Oral Administration	Apparent Plasma Terminal Half-life ($t_{1/2}$ Beta)	Major Route of Biotrans-formation
Heroin	Limited (<30%)	3 m (30 m for active 6-actyl-morphine metabolite) (4-6 for active morphine metabolite)	Successive deacetylation and morphine glucuronidation
Methadone	Essentially Complete (>70%)	24 h (48 h for active l-enantiomer)	N-demethylation

Kreek et al., 1973; 1976; 1977; 1979; 1982; Inturrisi et al, 1973; 1984

"On-Off" *versus* "Steady-State"

Disruption *versus* Normalization

- **levels of gene expression**
- **receptor mediated events**
- **physiology**
- **behaviors**

Kreek, 1987; 2001

"Blending"– 1969-1973 (to 2002)
Early Formal Linkage Between Academic Centers and Community-Based Treatment Programs

1969 Initiation of special research-based methadone maintenance treatment program for youthful (16 to 21 yo) long-term heroin addicts (more than 3 years of multiple, daily self-administrations of heroin) *(Dole, Nyswander, and Kreek, later joined by Millman and Khuri at the Rockefeller Hospital)*

1971 Relocation of this "Adolescent Development Program" as a community-based treatment facility, with ties to Cornell-New York Hospital and continuing ties to Rockefeller University *(ADP headed by Drs. R. Millman and E. Khuri)*

1973 Creation of a second, separate community-based methadone maintenance treatment facility, the "Adult Clinic", for adult long-term heroin addicts, also with ties both to Cornell-New York Hospital and to the Rockefeller University *(AC headed by Dr. Aaron Wells)*

Kreek, 2002

Methadone Maintenance Treatment for Opiate (Heroin) Addiction

Number of patients in treatment: 179,000

Efficacy in "good" treatment programs using adequate doses:

Voluntary retention in treatment *(1 year or more)* 60 – 80%

Continuing use of illicit heroin 5 – 20%

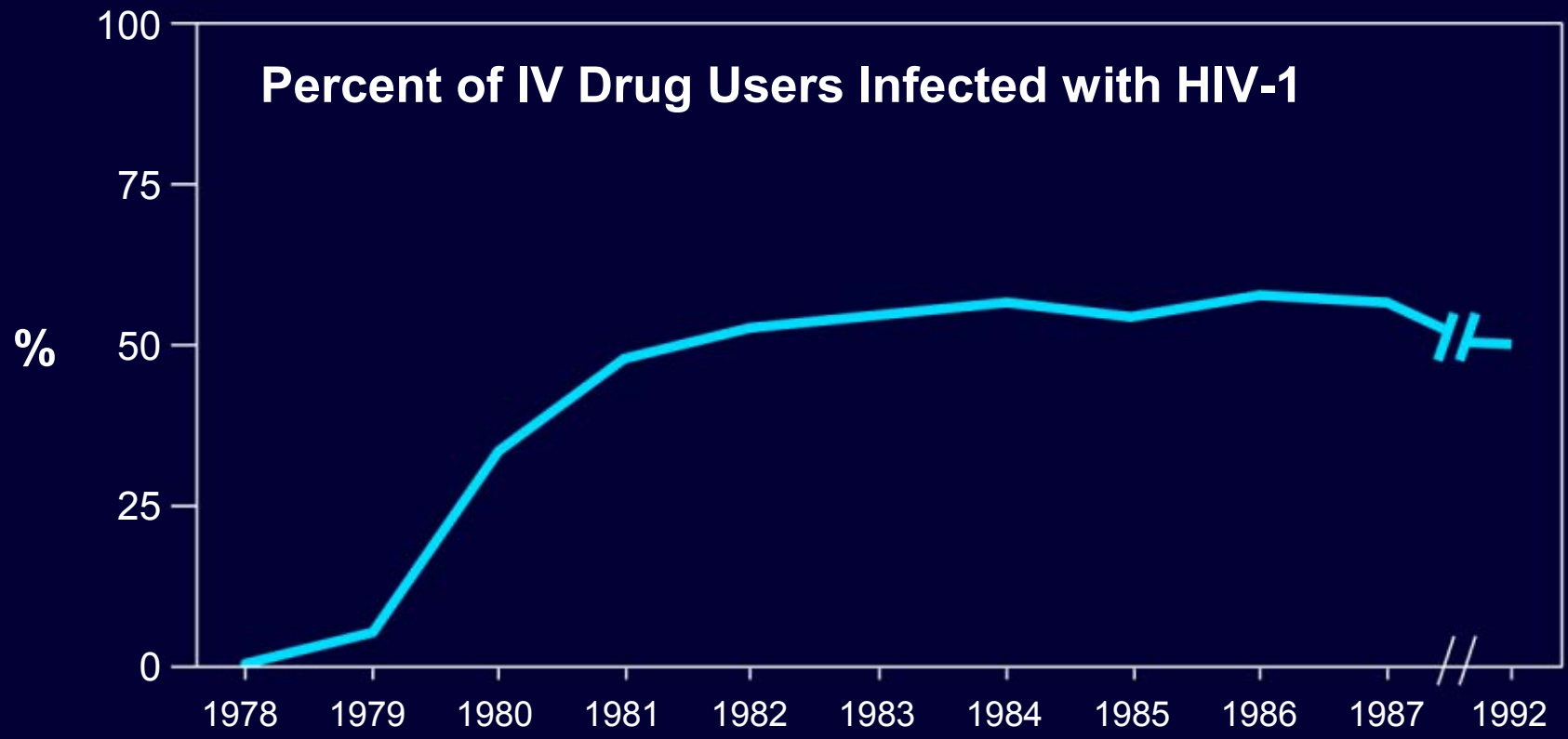
Actions of methadone treatment:

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

Mechanism of action: Long-acting narcotic provides steady levels of opioid at specific mu receptor sites *(methadone found to be a full mu opioid receptor agonist which internalizes like endorphins and which also has modest NMDA receptor complex antagonism)*

Kreek, 1972; 1973; 2001; 2002; Inturrisi et al, in progress; Evans et al; in progress

Identification of HIV-1 Infection and Changing Prevalence in Drug Users New York City: 1978 – 1992; 1983 - 1984 Study



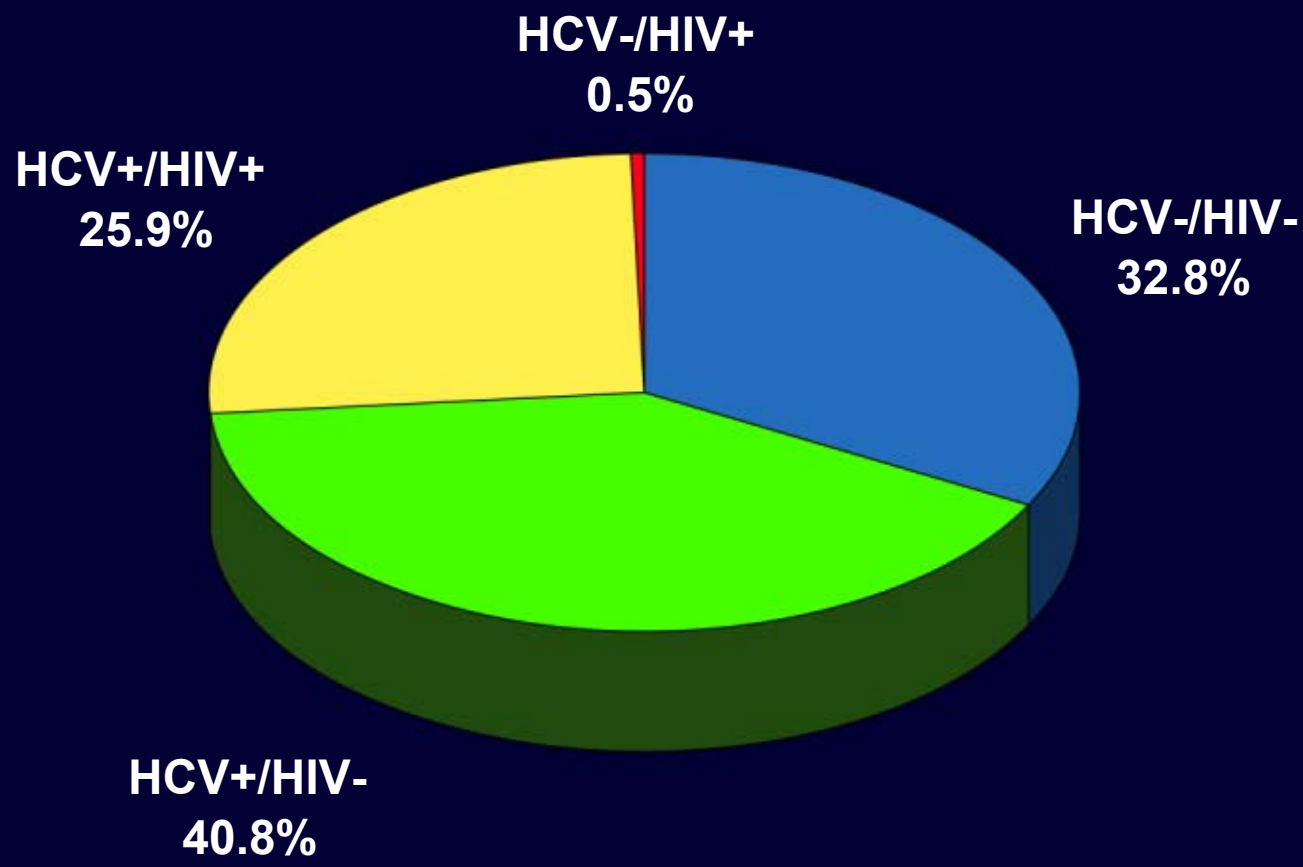
Kreek et al., 1984; Des Jarlais et al., 1984; 1989

Prevalence of HIV-1 (AIDS Virus) Infection in Intravenous Drug Users New York City: 1983 - 1984 Study: Protective Effect of Methadone Maintenance Treatment

50 – 60%	Untreated, street heroin addicts: Positive for HIV-1 antibody
9%	Methadone maintained since<1978 (beginning of AIDS epidemic): less than 10% positive for HIV-1 antibody

Kreek , 1984; Des Jarlais et al., 1984; 1989

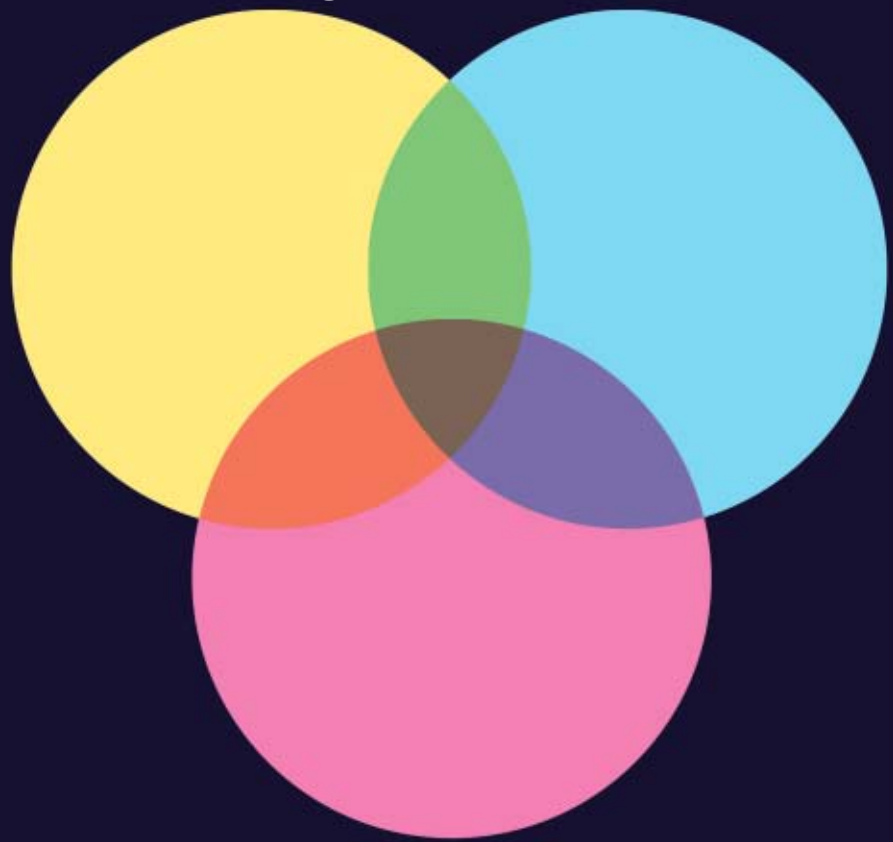
Co-Infection Status - Hepatitis C and HIV-1 in Methadone Maintained Patients



Piccolo, 2001

Factors Contributing to Vulnerability to Develop a Specific Addiction

use of the drug of abuse essential (100%)



genetic (25-40%)

environmental (very high)

drug-induced effects (very high)

Kreek et al., 2000

Primary Site(s) of Major Drugs of Abuse

Heroin	***Depressant***	• Acts primarily on endogenous opioid system • Also affects dopaminergic system
Cocaine	***Stimulant***	• Acts primarily on dopaminergic system, as well as on serotonergic and noradrenergic systems • Also affects opioid system
Alcohol	***Stimulant & Depressant***	• Undefined primary site of action • Affects dopaminergic, serotonergic and opioid systems

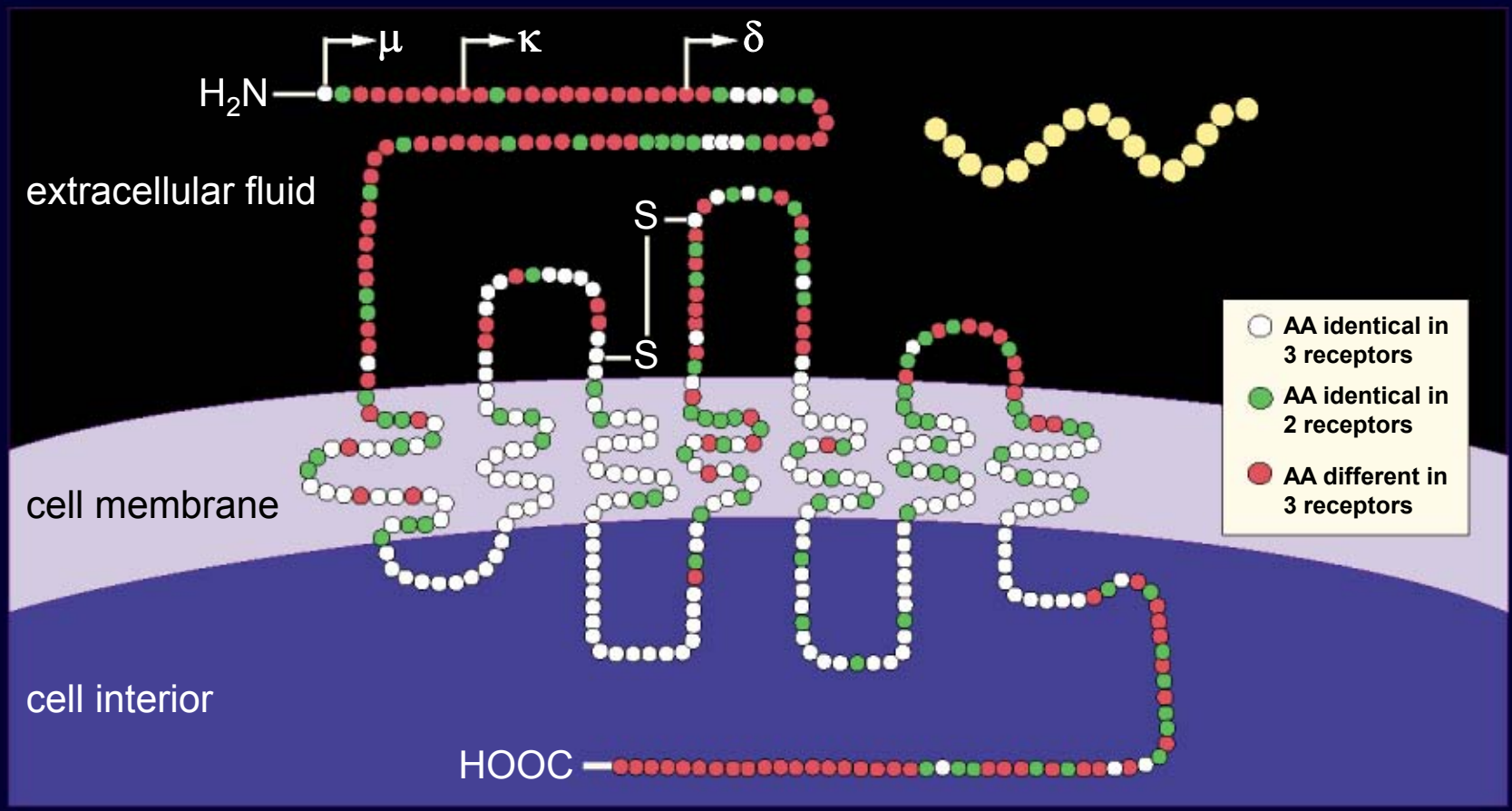
Kreek, 1978, 1987, 2001

Endogenous Opioids and Their Receptors

Opioid Classes	Opioid Receptor Types
Endorphins	Mu
Enkephalins	Delta
Dynorphins	Kappa
Endomorphins (?)	

Kreek, 2001

Human Opioid Receptors μ, δ, and κ



LaForge, Yuferov and Kreek, 2000

Hypothesis — Atypical Responsivity to Stressors: A Possible Etiology of Addictions

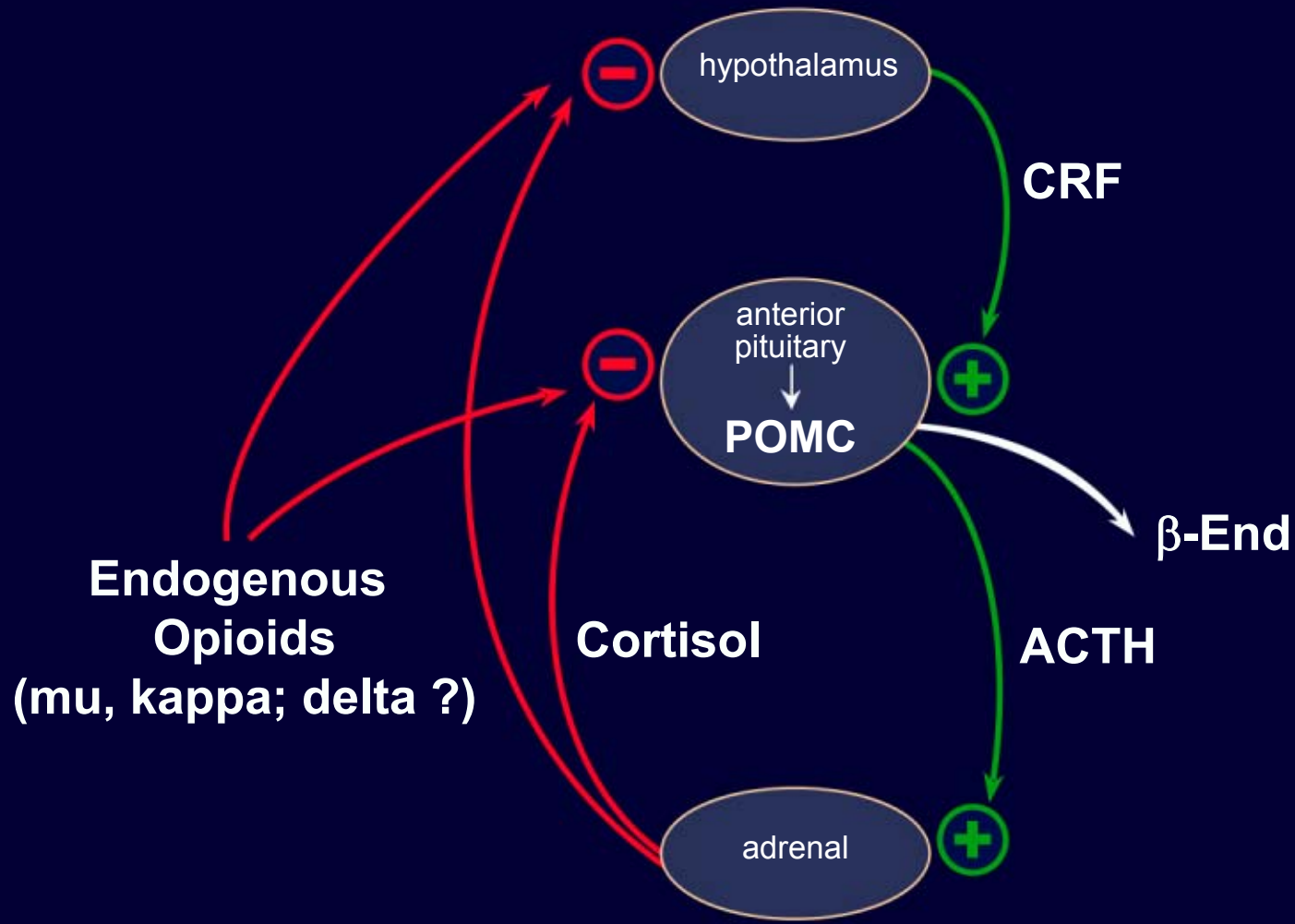
Atypical responsivity to stress and stressors may, in part, contribute to the persistence of, and relapse to self-administration of drugs of abuse and addictions.

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.

Genetic, environmental and direct drug effects may each contribute to this atypical stress responsivity.

Kreek, 1972; 1987; 1992; 2001

Hypothalamic-Pituitary-Adrenal Axis and the Endogenous Opioid System Have Interrelated Roles in the Biology of Addictive Diseases



Kreek et al., 1981; 1982; 1984; 1992; 2001; 2002

Neuroendocrine Effects of Opiates, Cocaine, and Alcohol in Humans: Hormones Involved in Stress Response

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

} Suppression of HPA Axis

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

} Activation of HPA Axis

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

Normalization of HPA Axis

HPA – Hypothalamic-pituitary-adrenal axis (involved in stress response)

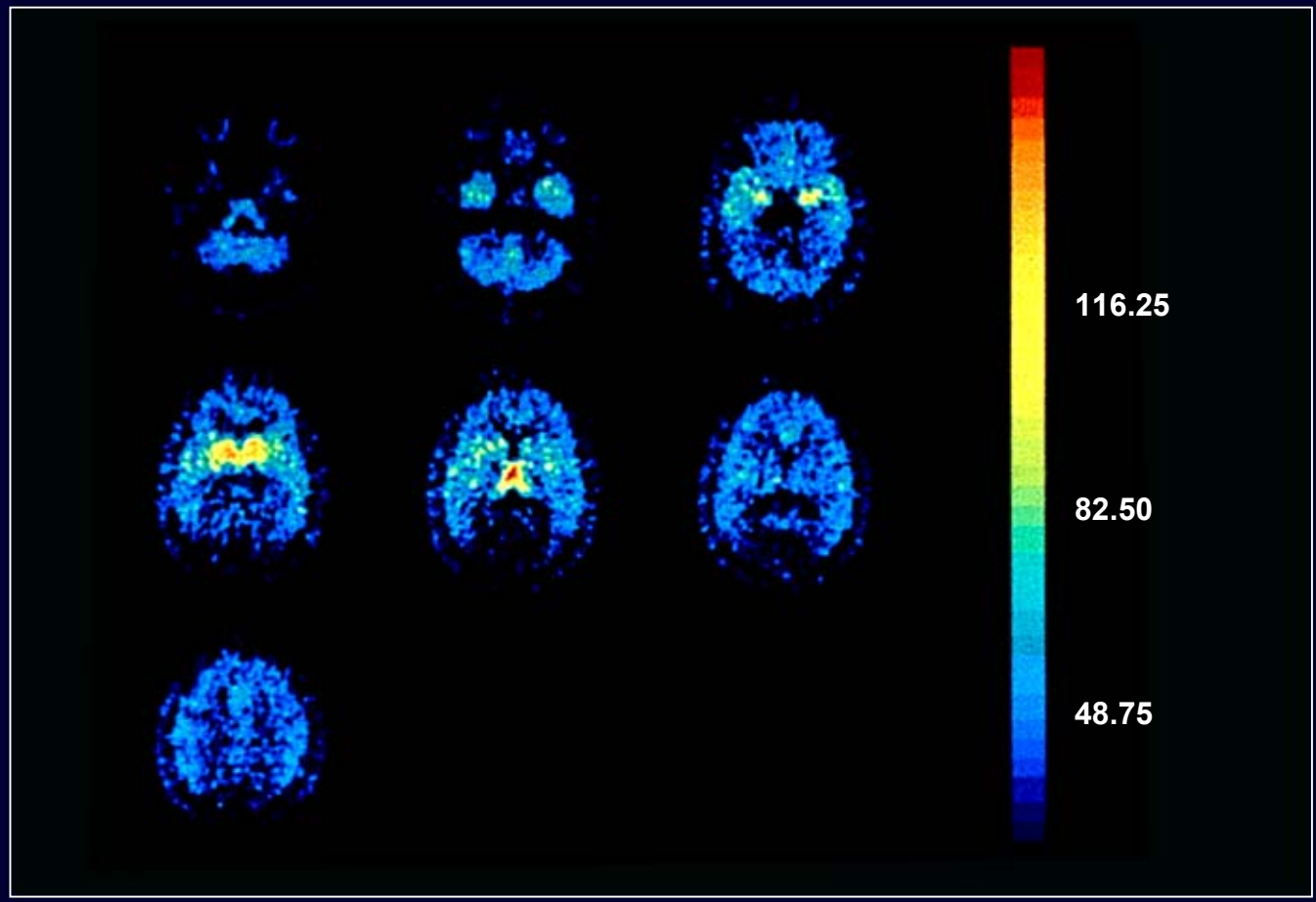
Kreek, 1972; 1973; 1987; 1992; 2001

Metyrapone Testing: a Chemically-Induced "Stress"

- Heroin addicts
  - hyporesponsive
- Methadone maintained former heroin addicts
  - euresponsive
- Drug-free, opioid medication-free former heroin addicts
  - hyperresponsive
- Cocaine addicts- recently abstinent
  - hyperresponsive
- Cocaine addicted, methadone maintained former heroin addicts
  - hyperresponsive

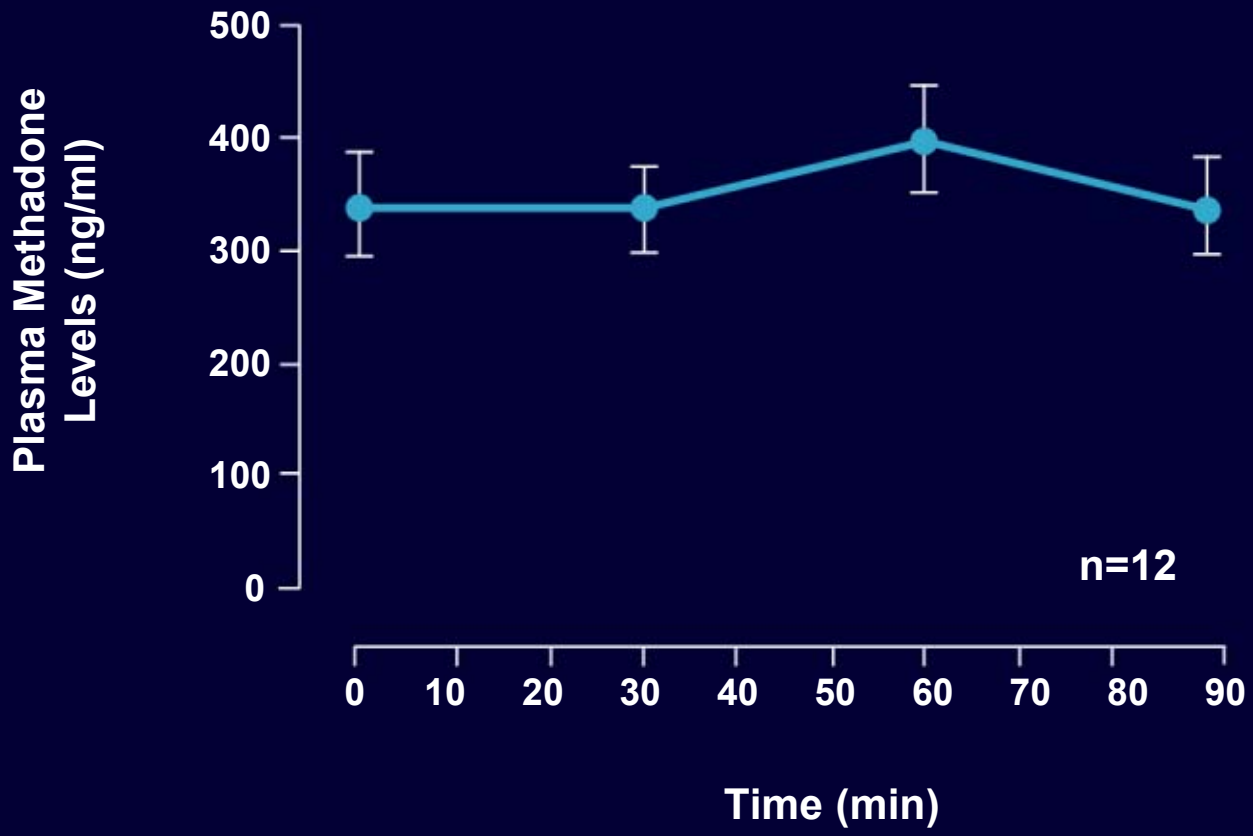
Kreek, 1972; 1973; 1984; 1987; 1992; Kreek et al., 1984; Schluger et al., 2001

[^{18}F] Cyclofoxy (a Selective Opioid Antagonist) Binding in Human Brain: Normal Volunteer PET Study - NIH



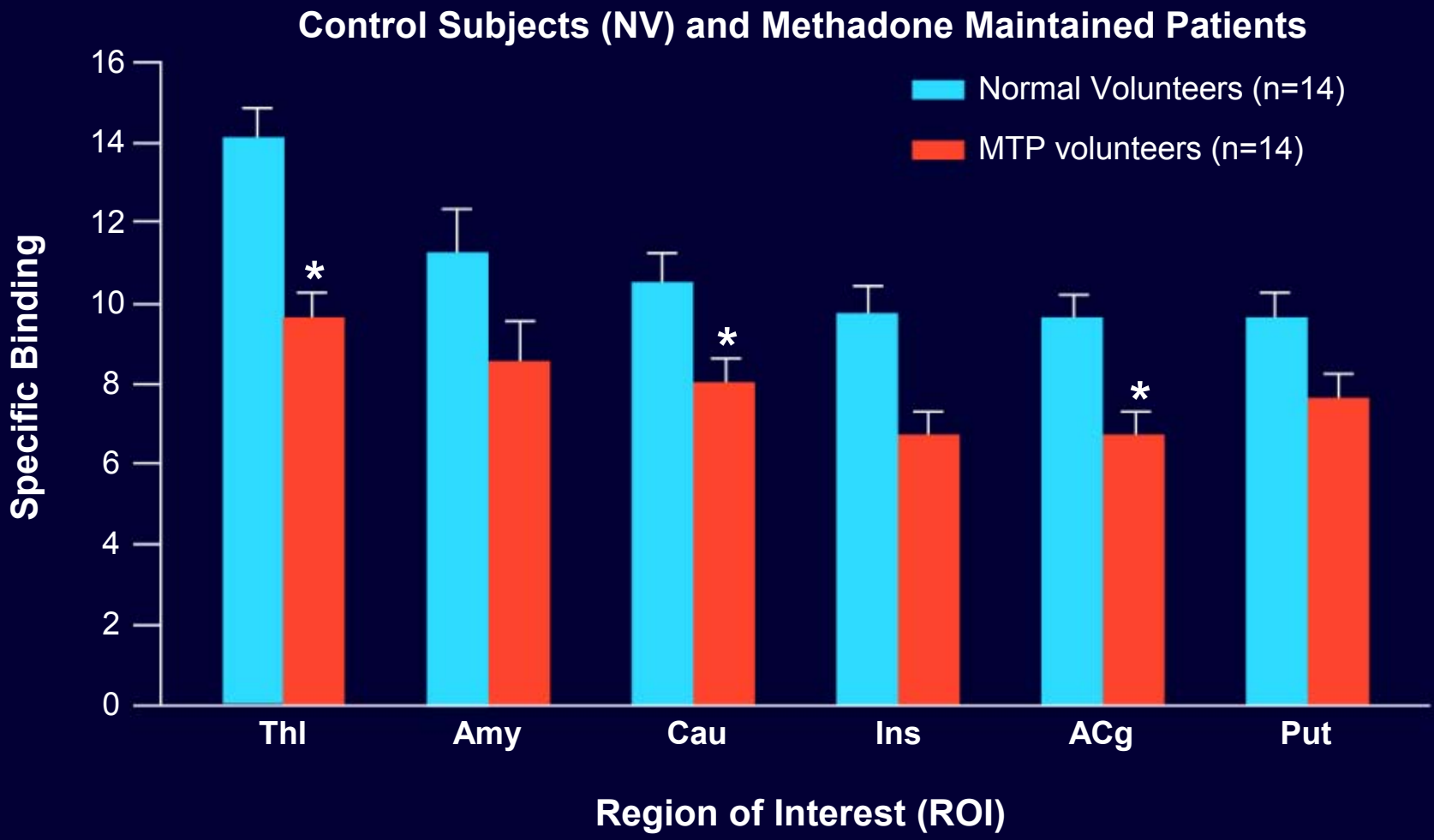
Eckelman, Rice and the NIH PET group, 2000

Plasma Methadone Levels in Long-Term, Methadone-Treatment Patients Sampled Across the 90-min PET Scan Session: 22.5 to 24h After Last Oral Dose of Methadone



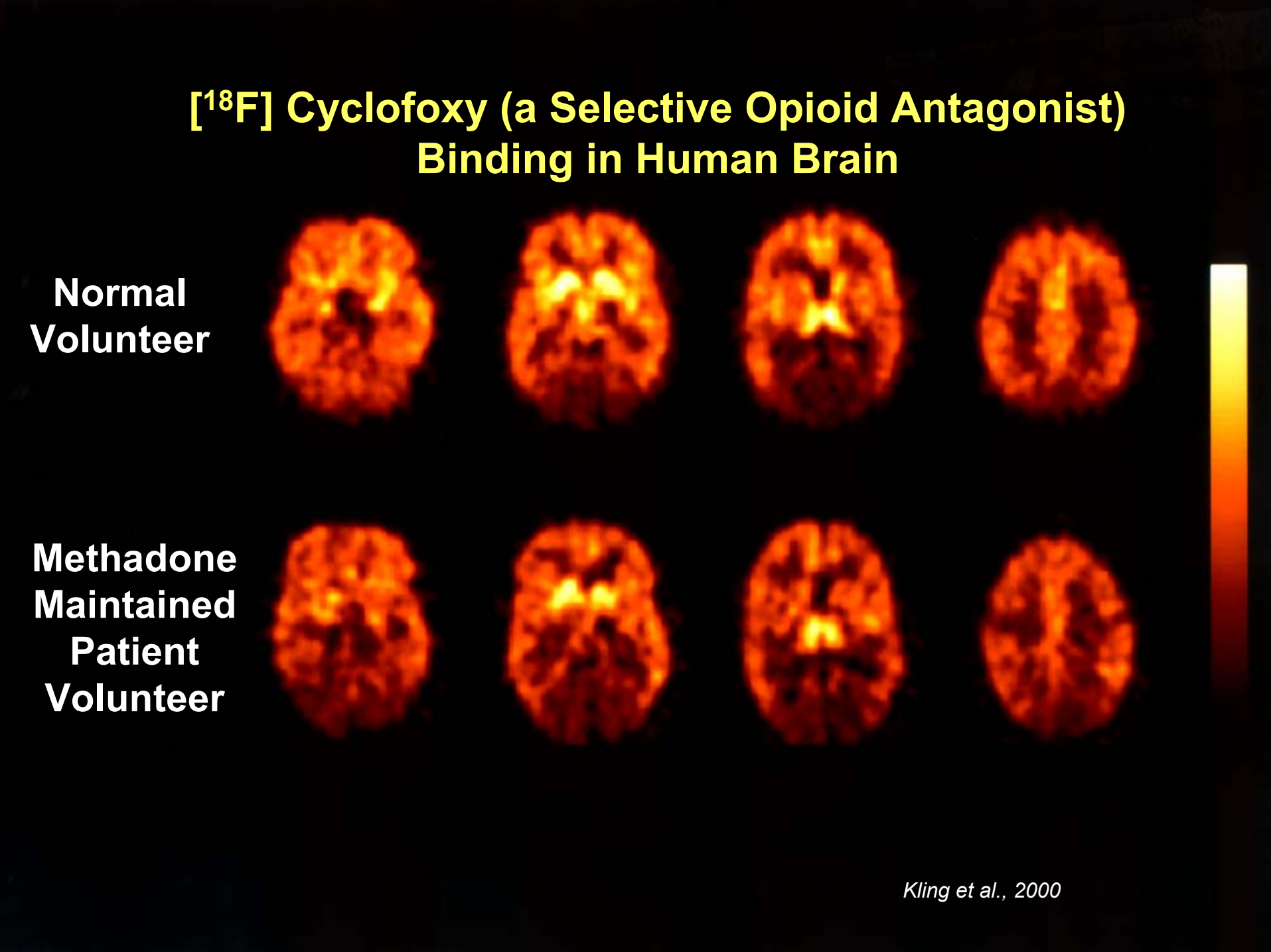
Kling et al., 2000

Selected Regions of Interest for Addictive Disease and Pain Research : PET Imaging Using [^{18}F] Cyclofoxy



Kling et al., 2000

[^{18}F] Cyclofoxy (a Selective Opioid Antagonist) Binding in Human Brain



Kling et al., 2000

Methadone Maintenance Treatment Allows Normalization of Endogenous Opioid-Related Physiological Functions Disrupted During Chronic Heroin Use

Neuroendocrine Function

- **Hypothalamic-Pituitary-Adrenal Axis – Stress Responsivity** levels and circadian rhythm of release of POMC peptides (β Endorphin; ACTH and cortisol)
- **Hypothalamic-Pituitary-Gonadal Axis – Reproductive Biology** levels and pulsatile release of LH and testosterone levels

Immune Function

- **Natural Killer Cell Activity**
- **Absolute Numbers of Cells** — T cells; T cell subset levels; B cells; NK cells
- **Immunoglobin Levels (M and G)**

Kreek, 1972; 1973; 1978; 1987; 1992; 2001; Novick et al., 1989

Hypothesis: Genetic Variability and the Opioid System

Some of the individual genetic variability in susceptibility to the development and persistence of, or relapse to, opiate addiction may be due to polymorphisms of the mu opioid receptor.

Also, individual differences in responses to endogenous opioids ("physiogenetics") or pharmacotherapies ("pharmacogenetics") may be mediated by variant forms of the mu opioid receptor.

LaForge, Yuferov and Kreek, 2000

Human Gene Diversity: Single Nucleotide Polymorphisms (SNPs) in Genes

- SNP — a single nucleotide polymorphism, that is, one nucleotide or base of any base pair that is different from the "usual", "prototypic", (or first identified and recorded base)

- Coding region — that part of a gene which codes for a peptide (protein)

- Allelic Frequency:

<1%	low or rare
1–5%	intermediate
>5%	high or frequent

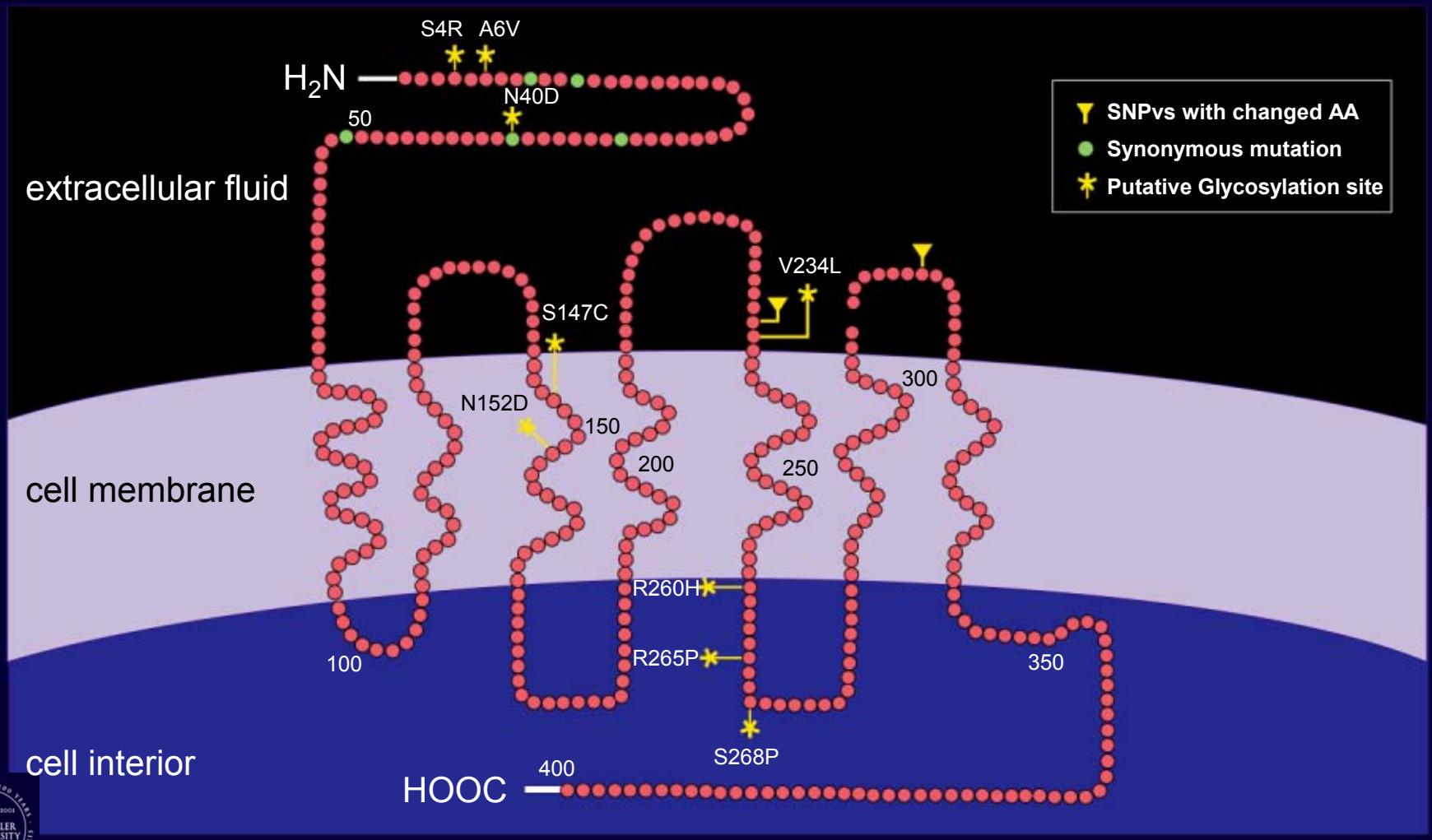
Three Single Nucleotide Polymorphisms in Human Mu Opioid Receptor Gene

Variant (nucleotide position)	Exon location	Protein domain	Corresponding amino acid change	Allele frequency
A118G	1	N-terminus	Asn 4 Asp (N40D)	10.5% (26 heterozygous; 3 homozygous)
C17T	1	N-terminus	Ala 6 Val (A6V)	6.6% (14 heterozygous; 3 homozygous)
G24A	1	N-terminus	Synonymous mutation	2% (6 heterozygous)

** Nucleotide position 1 is first base of the start codon.*

Bond et al., 1998

Human MOR Gene SNPs



Kreek, Yuferov and LaForge, 2000

Mu Opioid Receptor Gene: Evidence of Association or Linkage With Addictions

Alcohol Dependence

- For: Town, et al., 1999
- No Evidence For: Bergen, et al., 1997; Kranzler et al., 1998; Sander et al., 1998; Gelernter et al., 1999; Gscheidel et al., 2000.

Opioid Dependence

- For: Bond et al., 1998; Szeto et al., 2001.
- No Evidence For: Kranzler et al., 1998; Li et al.,2000; Franke et al., 2001.

Mixed Drug Dependence

- For: Berrettini et al., 1997; Hoeho et al., 1997.
- No Evidence for: Kranzler et al., 1998; Gelernter et al., 1999

adapted from K.S. LaForge, 2001

Pharmacotherapies for Specific Addictive Diseases

I. Opiate Addiction (primarily Heroin Addiction)*
   a. Methadone (mu-opioid receptor agonist)
   b. LAAM (mu-opioid receptor agonist)
   c. Buprenorphine + Naloxone (partial mu-opioid receptor agonist + a non-orally bioavailable mu opioid antagonist)
   d. (Naltrexone[mu-opioid receptor antagonist])***

II. Alcoholism**
   a. Naltrexone (mu-plus kappa receptor antagonist)
   b. Nalmefene (mu-plus kappa-opioid receptor antagonist
   c. Acamprosate (NMDA antagonist)

III. Cocaine, Amphetamines and Other Stimulants Addictions
   NONE

IV. Nicotine Addiction **
   a. Nicotine replacement (patch; gum; inhaler; other nicotine delivery systems)
   b. Bupropion

---

* *Effective in >60% of unselected persons (high)*
** *Effective in >30% to 50% of unselected persons (moderate)*
*** *Effective in >15% of unselected persons (low)*

Kreek, 2000

Future of the Role of Medications in Treating Addictions: A Few Major Needs

1) **Broad acceptance of need for and implementation of combined pharmacotherapy** (specific, targeted, safe, and effective) **and counseling and other behavioral treatments** (specific, as well as general, and effective), each in "adequate doses", in the treatment of many long-term drug abusers and addicts, entering into and during chronic recovery.

2) **Reduction (and ultimately eradication) of stigma** against former drug abusers and addicts in various forms and stages of effective treatment and thus recovery, along with **increased resources** (fiscal and manpower) for treatment.

3) **Expansion and enhancement of bidirectional (clinical-laboratory) input and support of research** (neurobiological, molecular, genetic, and behavioral, as well as prevention and treatment research) for future development of improved primary prevention, early intervention, and treatment approaches.

Kreek, 2002

The Laboratory of the Biology of Addictive Diseases
Mary Jeanne Kreek, M.D. – Professor and Head
2002

Laboratory Scientists
Ann Ho
K. Steven LaForge
Eduardo Butelman
Vadim Yuferov
Yan Zhou
Stefan Schlussman
Yong Zhang
Andrew Chen
Dmitri Proudnikov
Brian Reed
Thomas Kroslak

Laboratory Adjunct Scientists
Ellen Unterwald
Vanya Quinones-Jenab
Charles Inturrisi

Clinical Scientists
Gavin Bart
Lisa Borg
Mark Green
Scott Kellogg

Clinical Adjunct Scientists
Paola Piccolo
Joan Culpepper-Morgan
Lawrence Brown
James Kocsis
Elizabeth Khuri
Aaron Wells

Research Nurses
Kathy Bell
Elizabeth Ducat

Administrative Staff
Karen Perry
Susan Russo
Kitt Lavoie

Assistants for Research
Abena Amoah
Jonathan Ball
Wan-Xin Feng
David Fussell
Sara Handy
Lauren Hofmann
Benjamin Seides

Laboratory Worker
Laura Nunez