Pharmacology and Pharmacokinetics of Alcohol and Opioids (understanding the drugs)

Robert M. Swift, MD, PhD

Professor, Department of Psychiatry
and Human Behavior
Brown University Medical School

Associate Chief of Staff for Research
VA Medical Center Providence, RI

Tufts Health Care Institute's Program on Opioid Risk Management,
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Learning Objectives

- Basic Clinical Pharmacology relevant to opioids and alcohol
- Pharmacology of co-administered alcohol and opioids

Morbidity and Mortality

- Alcohol consumption can be a contributing factor in opioid overdose due to additive or synergistic respiratory depression. (Kramer, 2003; Payte & Zweben, 1998)
- Opiates and alcohol can interact in several ways

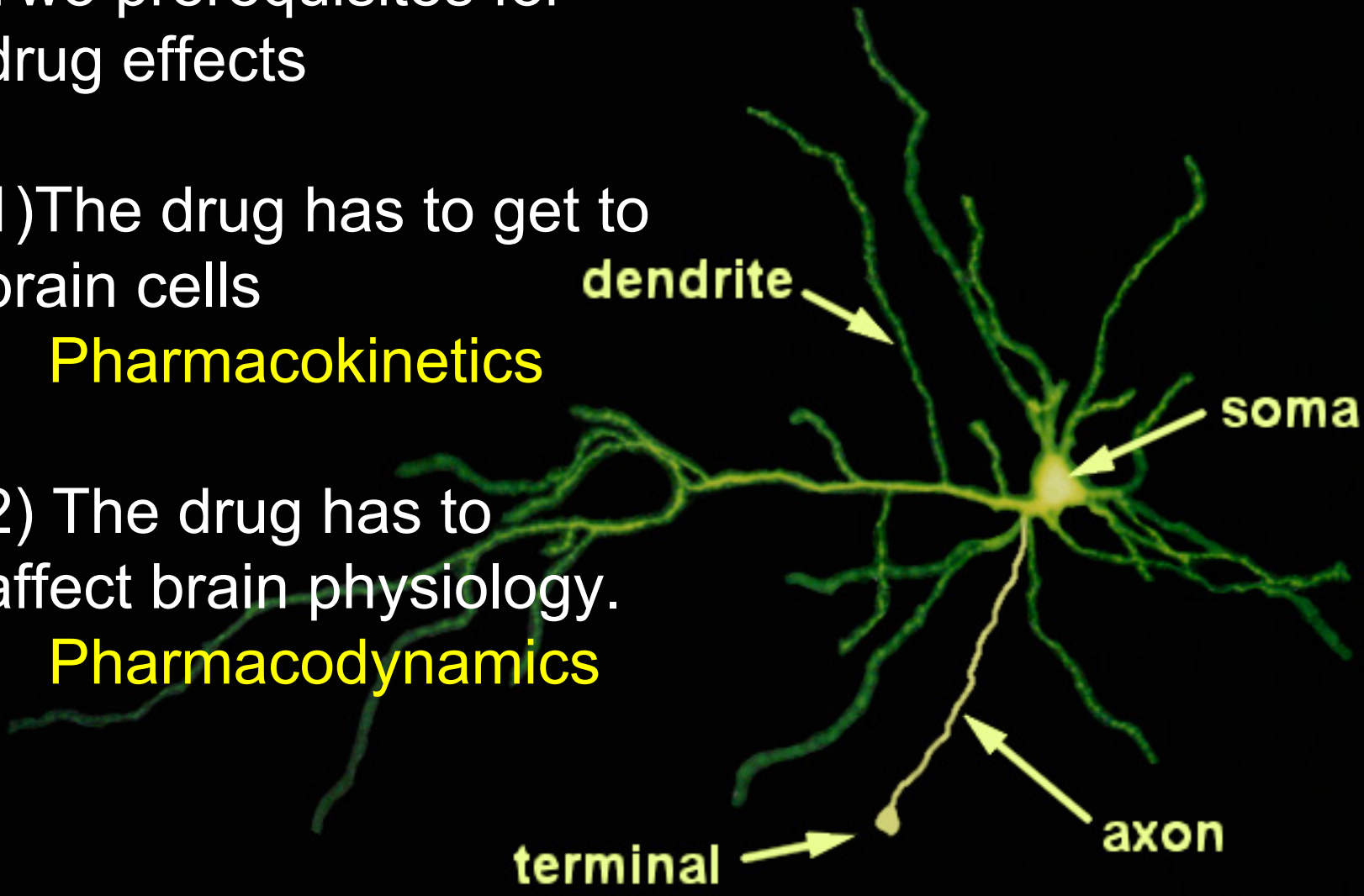
Two prerequisites for drug effects

1)The drug has to get to brain cells

Pharmacokinetics

2) The drug has to affect brain physiology.

Pharmacodynamics



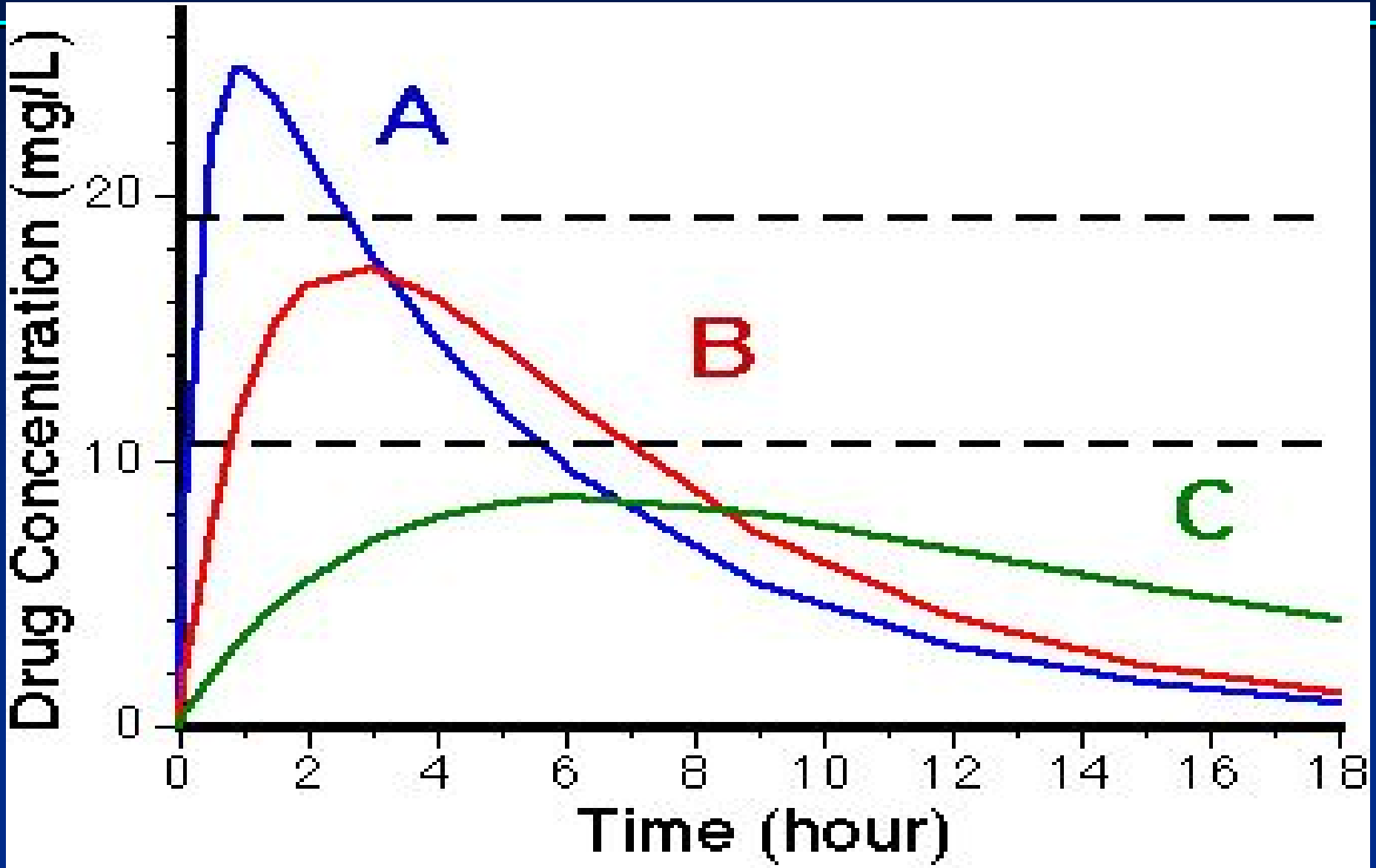
- Pharmacokinetics
  - The processes by which drugs get to their site of action (movement of drugs through the body)
  - Includes absorption, distribution, elimination
- Pharmacodynamics
  - The processes by which drugs exert an effect at their site of action
  - Includes acute and chronic effects on brain receptors

Pharmacokinetics: Component Processes

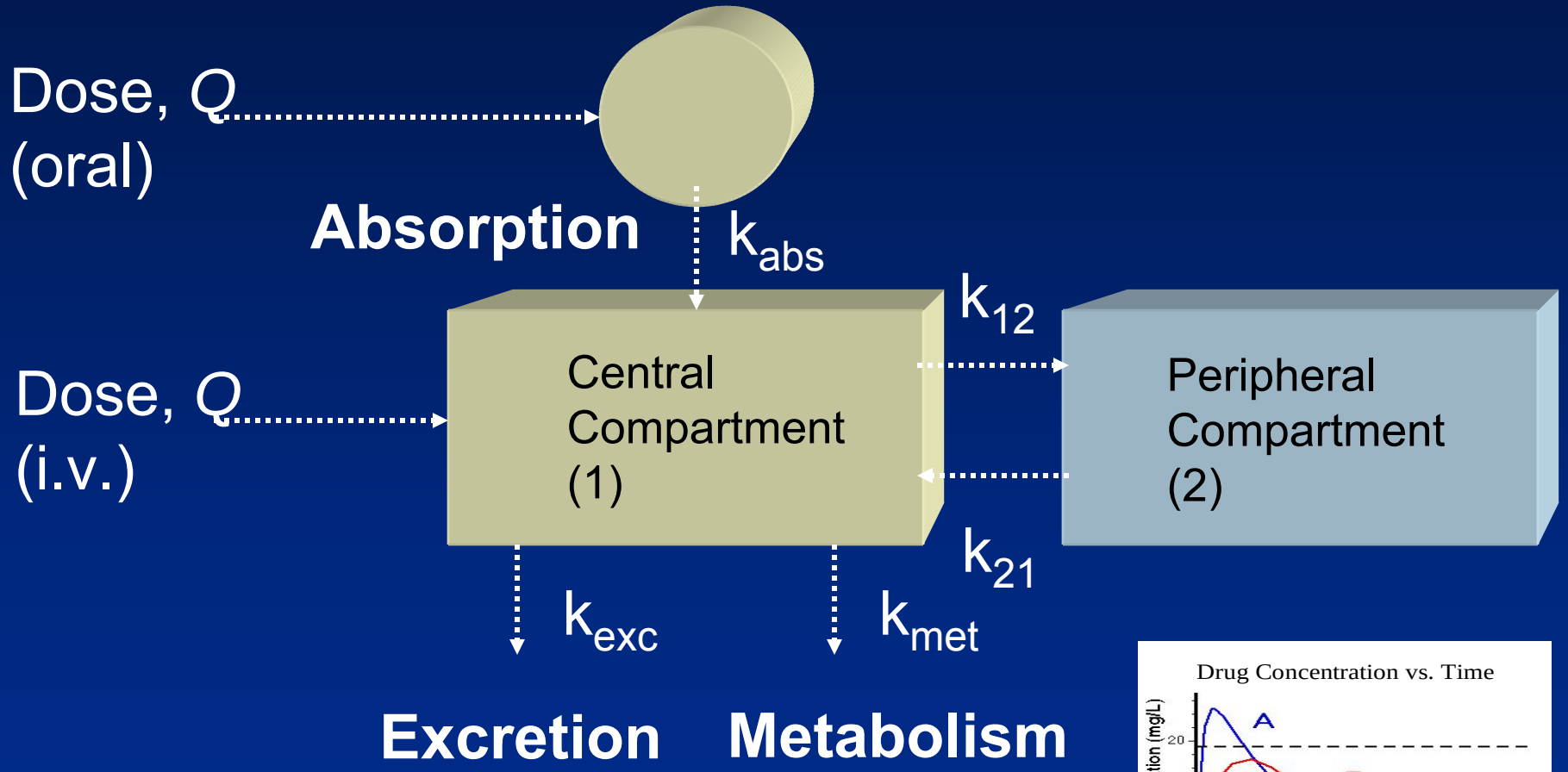
- Liberation (most important for pills)*
- Absorption*
- Distribution
- Metabolism (primarily by the liver)
- Excretion (primarily by the kidneys)

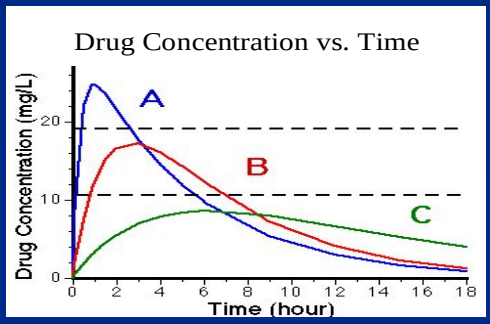
* Bioavailabiity

Opiate Drug Concentration vs. Time

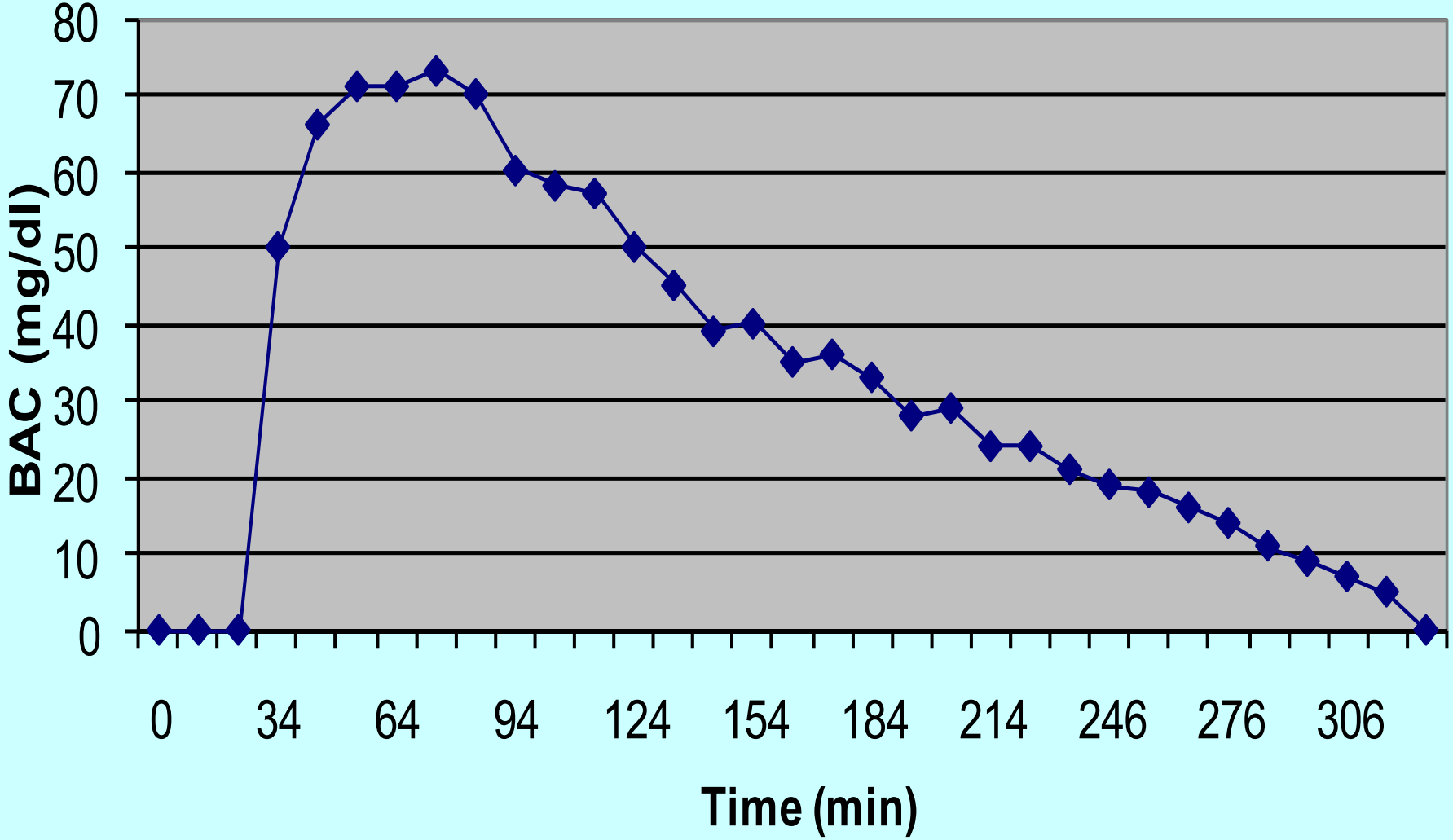


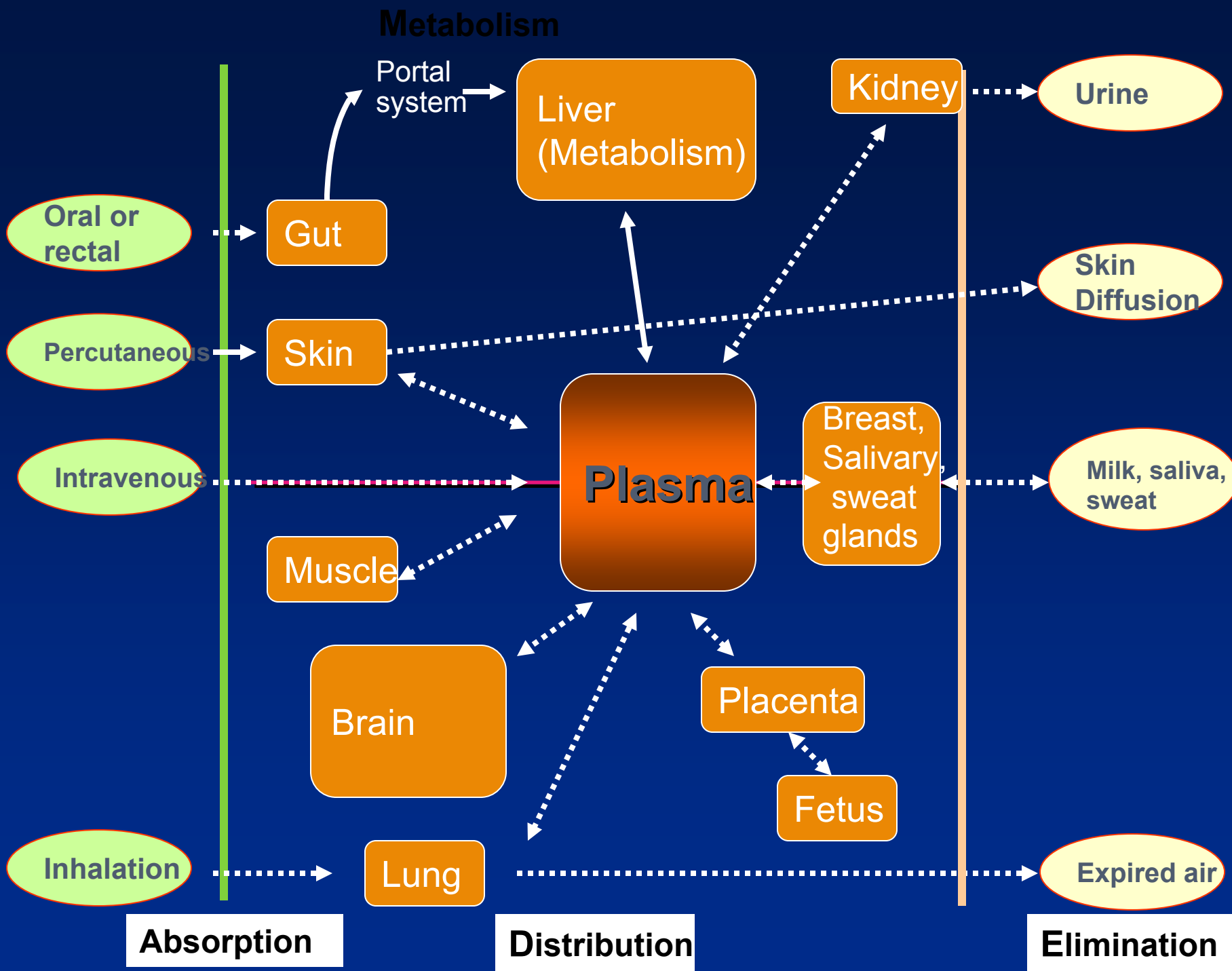
Two-compartment model





Blood Alcohol Concentration vs. Time
Zero-order kinetics




Metabolism
Portal system
Liver (Metabolism)
Kidney
Urine
Oral or rectal
Gut
Skin Diffusion
Percutaneous
Skin
Intravenous
Plasma
Breast, Salivary, sweat glands
Milk, saliva, sweat
Muscle
Brain
Placenta
Fetus
Inhalation
Lung
Expired air
Absorption
Distribution
Elimination

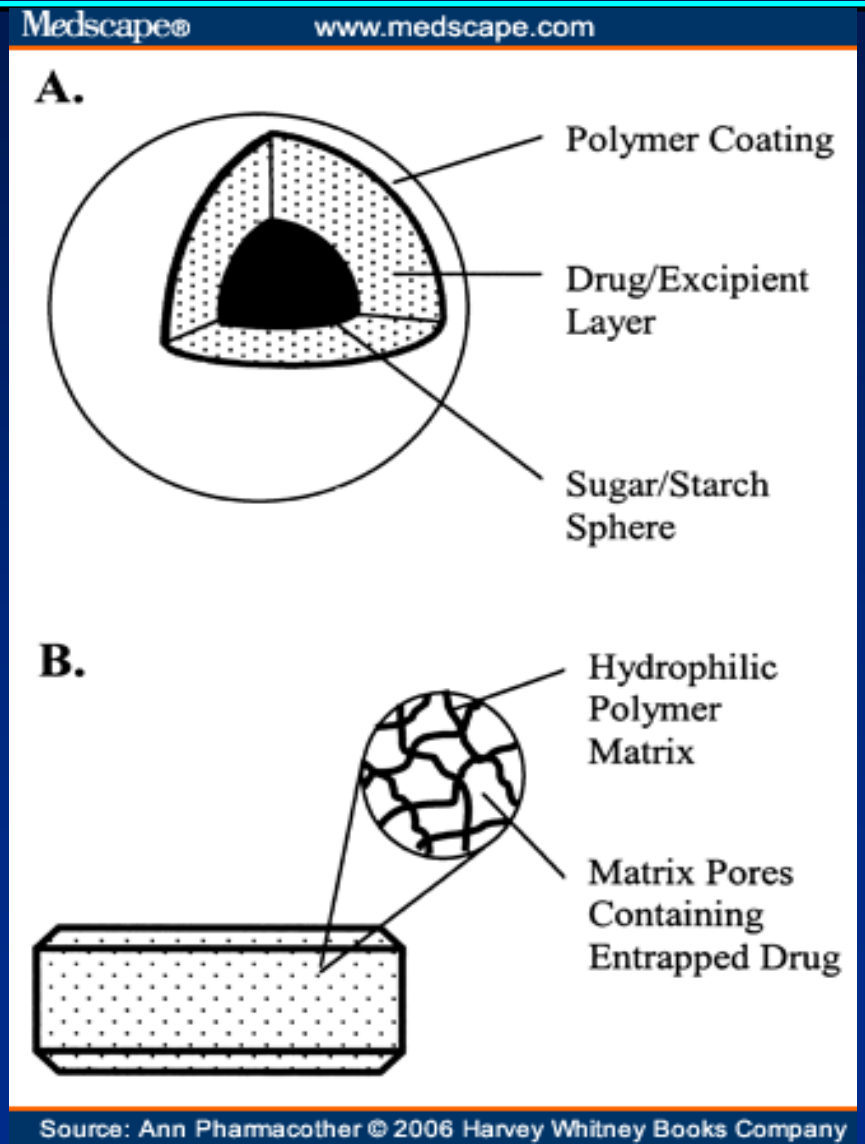
Factors Affecting Bioavailability

- Physical properties of the drug
  - (hydrophobicity, pKa, solubility
- Formulation (excipients used, release methods)
- Relationship to food/meals
  - Interaction with foods – grapefruit juice (CYP3A4), acid/base
- Gastric emptying rate
- Circadian differences
- First-pass metabolism
- Gut (and brain) transporters (e.g. P-glycoprotein)
- Individual differences – Age, Gender ,GI tract disease

Half-lives of Commonly Prescribed Opiates

Opiate Drug	Half-life (hours)
Morphine (morphine-6-glucuronide	3 (2)
Hydromorphone	2 - 3
Oxycodone	2 - 3
Fentanyl	3.7
Codeine	3 - 4
Meperidine (Normeperidine)	3 - 4 (14 - 21)
Pentazocine	2 - 3
Nalbuphine	5
Butorphanol	2.5 – 3.5
Buprenorphine	3 - 5
Methadone	24
Levorphanol	12 - 15
Propoxyphene (Norpropoxyphene)	30 - 40

Oral Modified-Release Opioid Products



Representation of
(A) an extended-release bead formulation
(B) a sustained-release matrix tablet prepared using a hydrophilic polymer.

Alcohol affects bioavilability of Oral Modified-Release Opioid Products

Product	Dosage Form	Strength	Dosing Frequency	Bioavail-ability (%)	Time to Steady-State (days)	Interaction with Alcohol
Morphine sulfate						
Avinza	immediate+ extended-release capsules	Immediate and extended release beads	24 h	<40	2–3	**Yes**
Kadian	sustained-release capsules	Polymer coated pellets	12–24 h	20–40	~2	**Yes**
Oramorph	sustained-release tablets	Matrix	8–12 h	~40	1–2	?
MS Contin	controlled-release tablets	hydrophilic/ hydrophobic matrix	8–12 h	~40	1	?
Oxycodone HCl						
OxyContin	controlled-release tablets	immediate and extended hydrophobic matrix	12 h	60–87	1–1.5	?
Hydrocodone						
Palladone	extended-release tablets	matrix pellet formulation	24 h	~30	1–1.5	**Yes**

Morphine Metabolism

- Glucuronidation – renal elimination
  - Morphine-6-glucuronide (potent analgesic)
  - Morphine-3- glucuronide (excitatory side-effect)

- Demethylation
  - Normorphine (excitatory side effects)
    - CYP3A4 (grapfefuit juice), CYP2C8 (quercetin)

Pharmacokinetics of alcohol

- Alcohol is converted by alcohol dehyrdogenase (ADH) to acetaldehyde **$CH_3CH_2OH + NAD \rightarrow CH_3CHO + NADH$**
- Acetaldehyde is converted by aldehyde dehydrogenase (ALDH) to acetic acid, then to CO2 and water in the Krebs cycle **$CH_3CHO + NAD \rightarrow CH_3COOH + NADH$**
- The rate of metabolism is Zero order – i.e. it is not concentration dependent (about 7 g/hr) at BACs > 0.02 g/L
- Cytochrome P450 Ethanol Oxidation by CYP2E1, CYP3A4

  CYP2E1 is inducible and greater in chronic heavy drinkers, accounting for an increased rate of metabolism at high BACs

Alcohol Morphine Metabolic Interactions

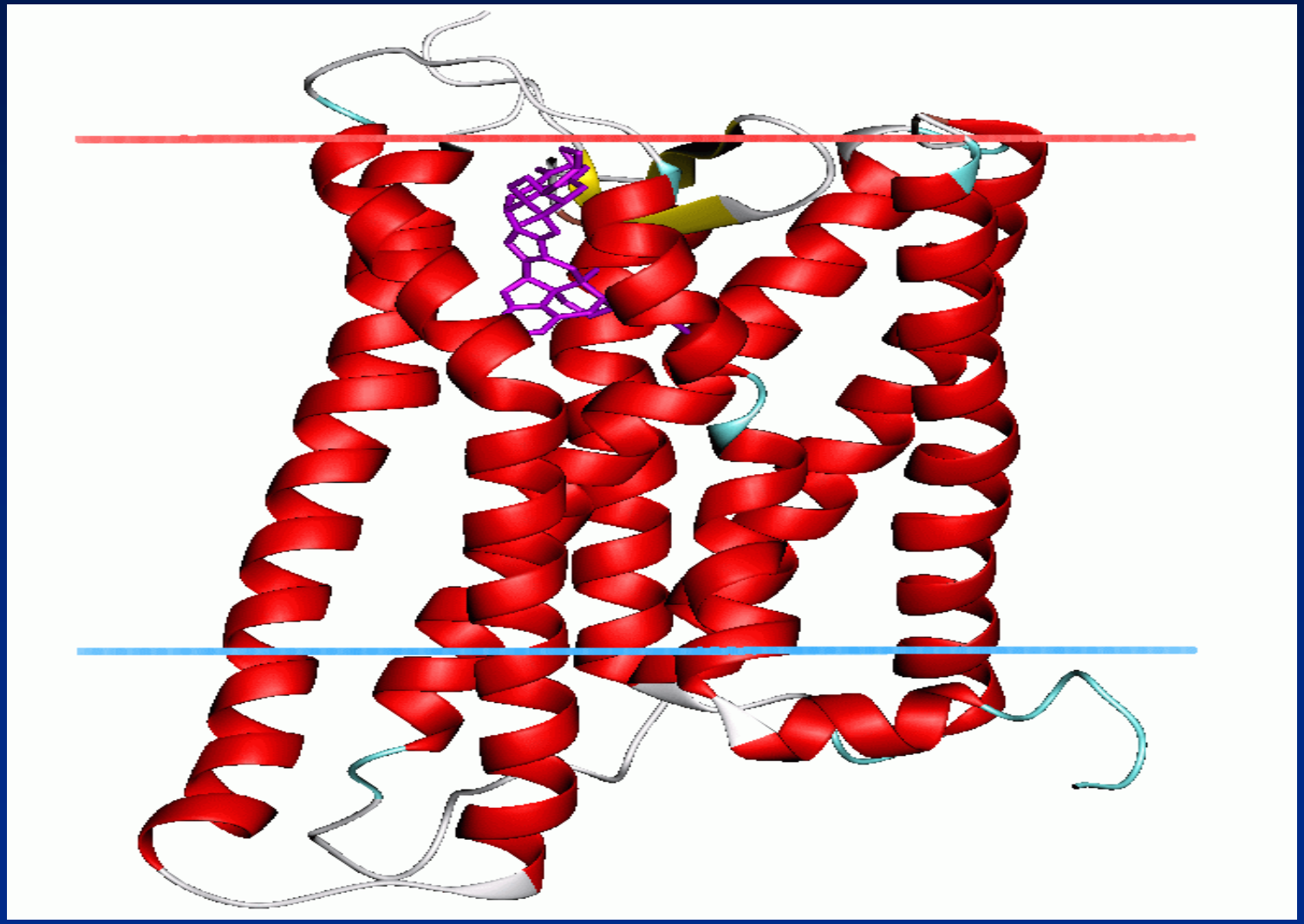
- Glucuronidation
  - Ethanol metabolism produces reduced NAD (NADH)
  - NADH reduces ability of liver to produce UDP-glucuronic acid, necessary for glucuronidation of morphine and other drugs
- Demethylation
  - Acute ethanol can inhibit CYP3A4, potentiating morphine
  - Chronic ethanol induces CYP3A4, increasing morphine metabolism and reducing effects

Pharmacokinetic interactions between methadone and alcohol

- Chronic ethanol induces cytochromes P450 2E1, 3A4 and 1A2. CYP3A4 and CYP1A2 can contribute to an increased rate of methadone metabolism in alcoholics (Meskar et al. 2001), leading to reduced methadone efficacy.
- Alcoholics can also develop severe liver disease and chronic liver disease may alter methadone disposition (Kreek, 1988).

- Pharmacodynamics
  - The processes by which drugs exert an effect at their site of action
  - Includes acute and chronic effects on brain cells, including receptors and other cellular components

Mu-opioid receptor and bound opiate



Pharmacodynamics of Opiates

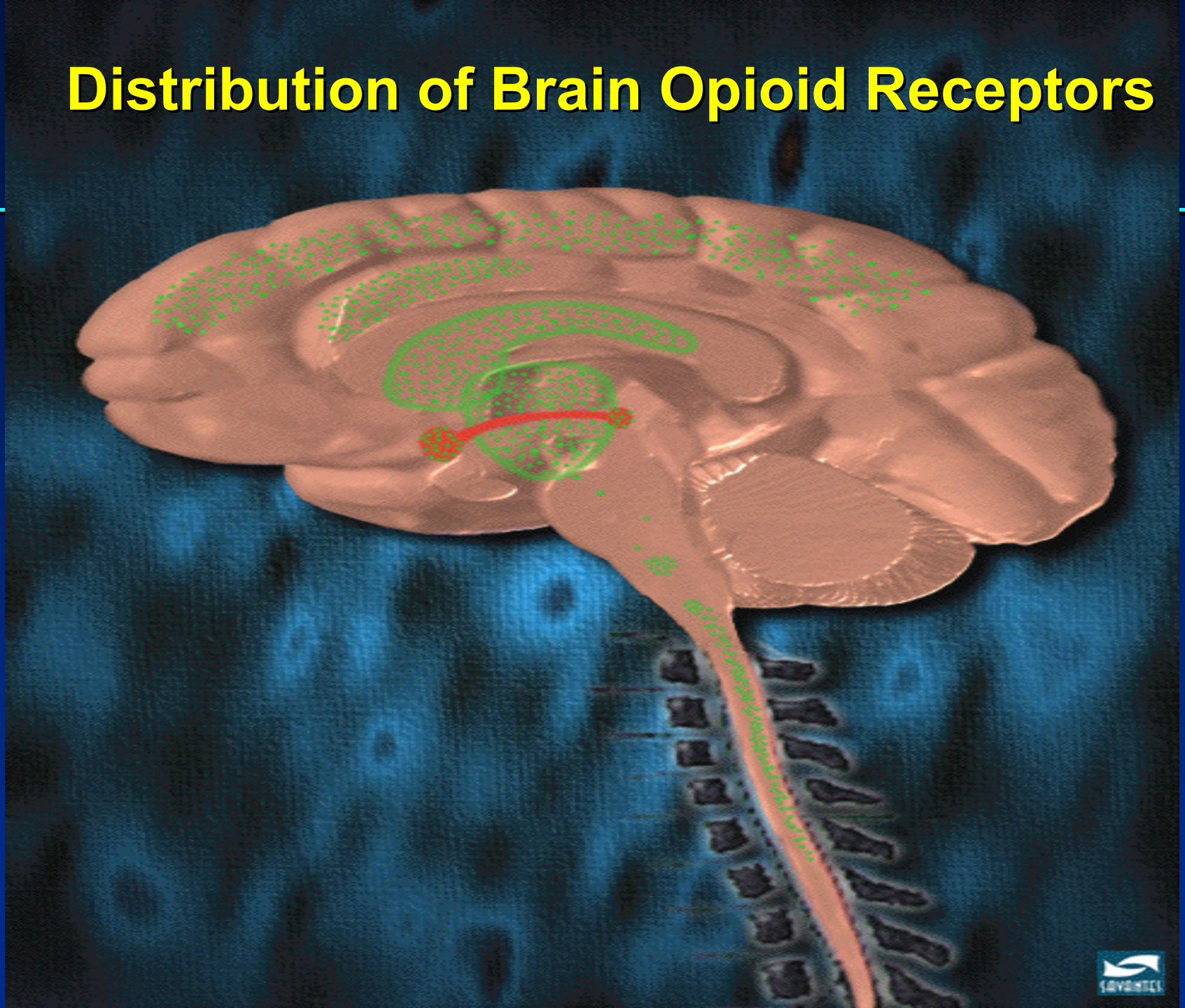
- Depends on drug-receptor interactions
  - Binding of ligands to receptor complexes
  - Signal transduction across the cell membrane due to changes in the receptor complex
  - Change is proportional to % receptors occupied or by rate of reversible binding (attachment) of ligand
  - Effects are agonistic or antagonistic

Opioid Receptors and Ligands

Receptor subtypes	Agonists	Antagonists	Second messengers
mu-opioid	Morphine Beta-Endorphin	Naloxone, Naltrexone	(-)cAMP, (+)gK+
delta-opioid	DPDPE enkephalins	Naltrindol	(-)cAMP, (+)gK+
kappa-opioid	ketocyclasocin dynorphinA 1-32	Norbinaltorphimine	(-)gCa^{2+}

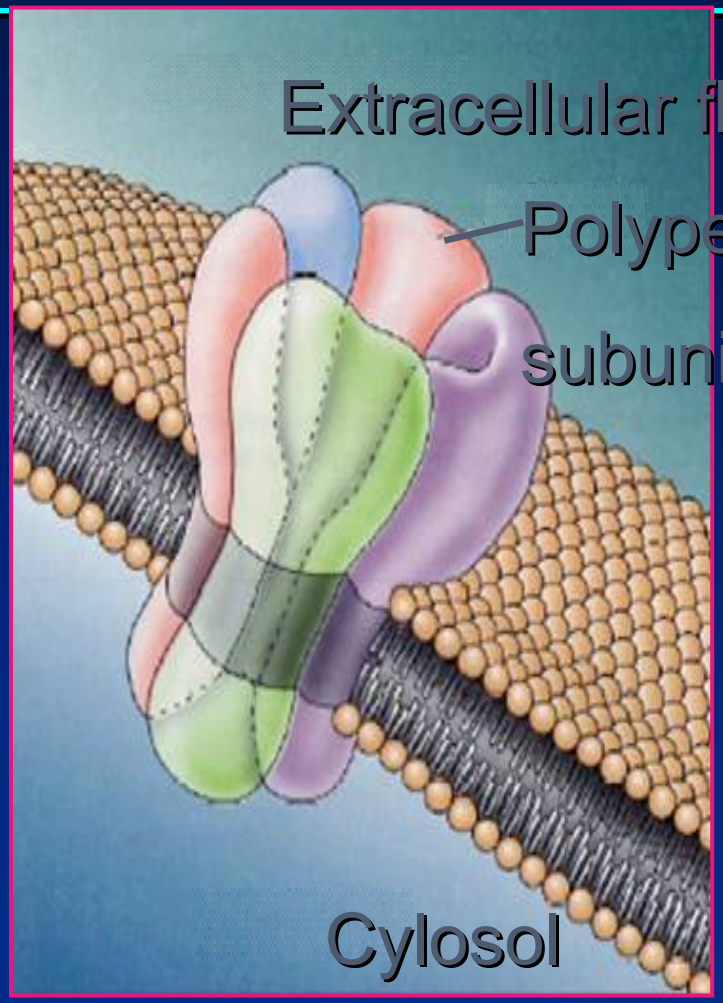
Antagonists have no effect on activity by themselves, but block the activity of agonists and partial agonists

Distribution of Brain Opioid Receptors



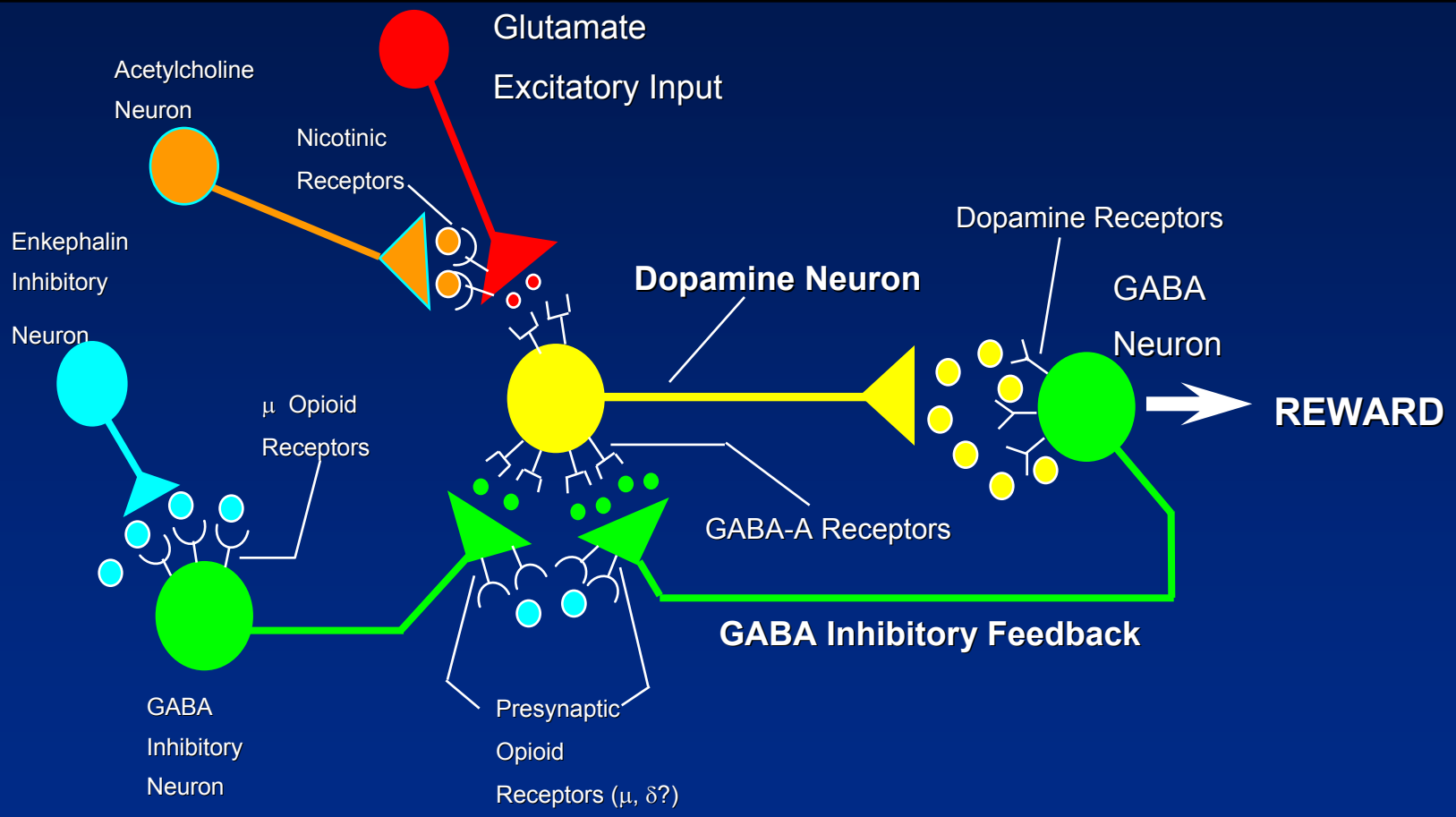
Ethanol is a Drug With Complex Pharmacodynamics

- Ethanol has no single mechanism of action (ie, no one active site)
- High doses nonspecifically disrupt membrane functioning ("fluidization")
- Low doses act on membrane proteins (receptors, transporters, etc), binding to hydrophobic pockets or displacing water
- Individuals differ in their sensitivity to alcohol effects based on genetic differences



Kenna et al., *Am J Health Syst Pharm* 2004;61:2272.

Neurochemical Systems and Drugs of Abuse



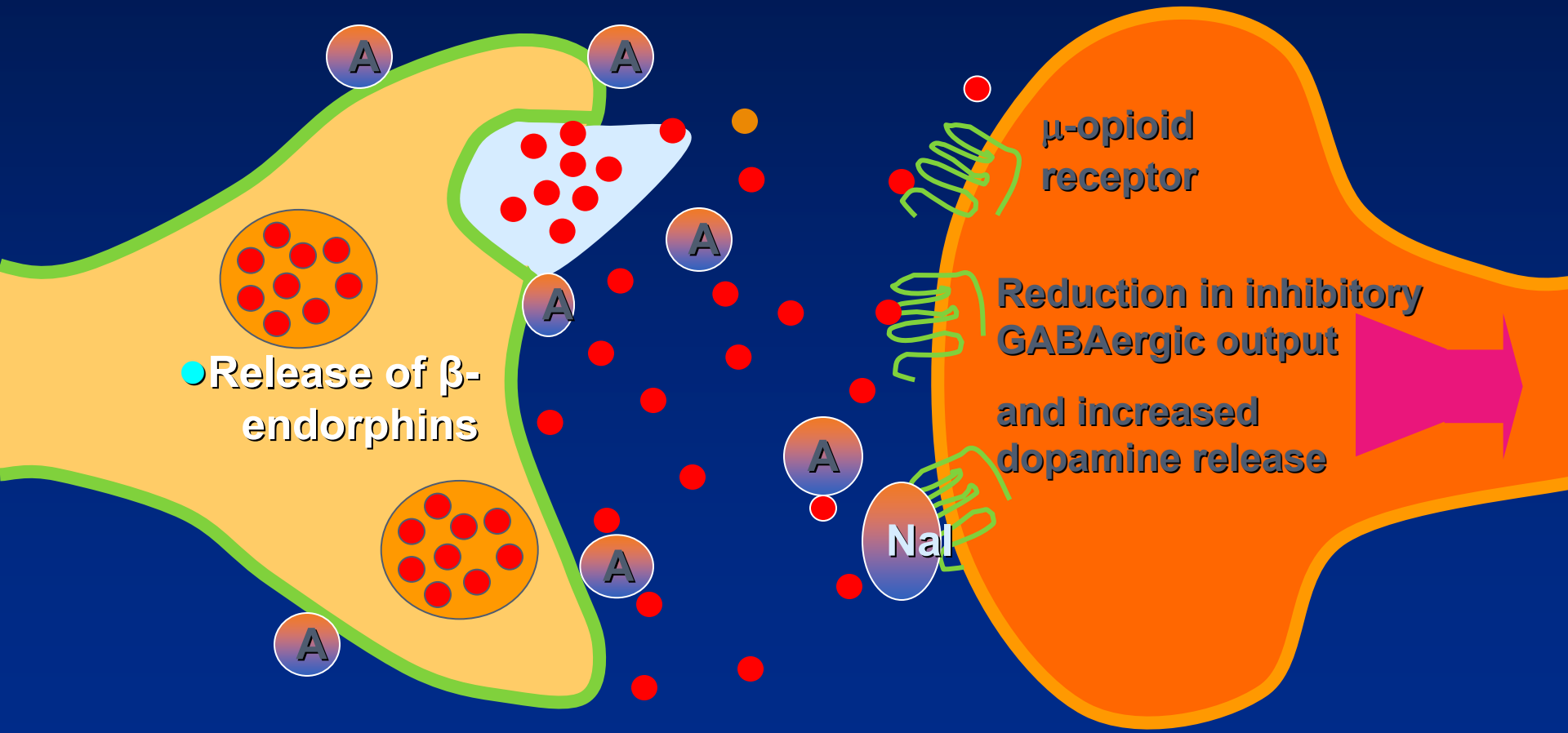
Pharmacodynamic interactions between methadone and alcohol

- Alcohol consumption results in the release of the body's naturally occurring opiates, endorphins both in the brain and in the periphery.
  - If opiates are consumed simultaneously with alcohol the exogenous and endogenous opioid effects can be additive.
- All opiate receptors are G-protein linked receptors. Ethanol facilitates receptor-G-protein coupling, potentiating the effects of opiates.

Pharmacodynamic interactions between methadone and alcohol

- Both alcohol and opioids can sensitize ventral tegmental dopamine neurons and facilitate use of the other agent (Brodie 2002; Leite-Morris et al 2004).
- Recent in vivo PET neuroimaging studies find that abstinent alcoholics show significantly elevated μ-opioid receptor availability in the ventral striatum and prefrontal cortex (Heinz et al 2005), suggesting that alcohol can increase opioid receptors.

Alcohol Increases the Activity of Endogenous Opioids (endorphins)



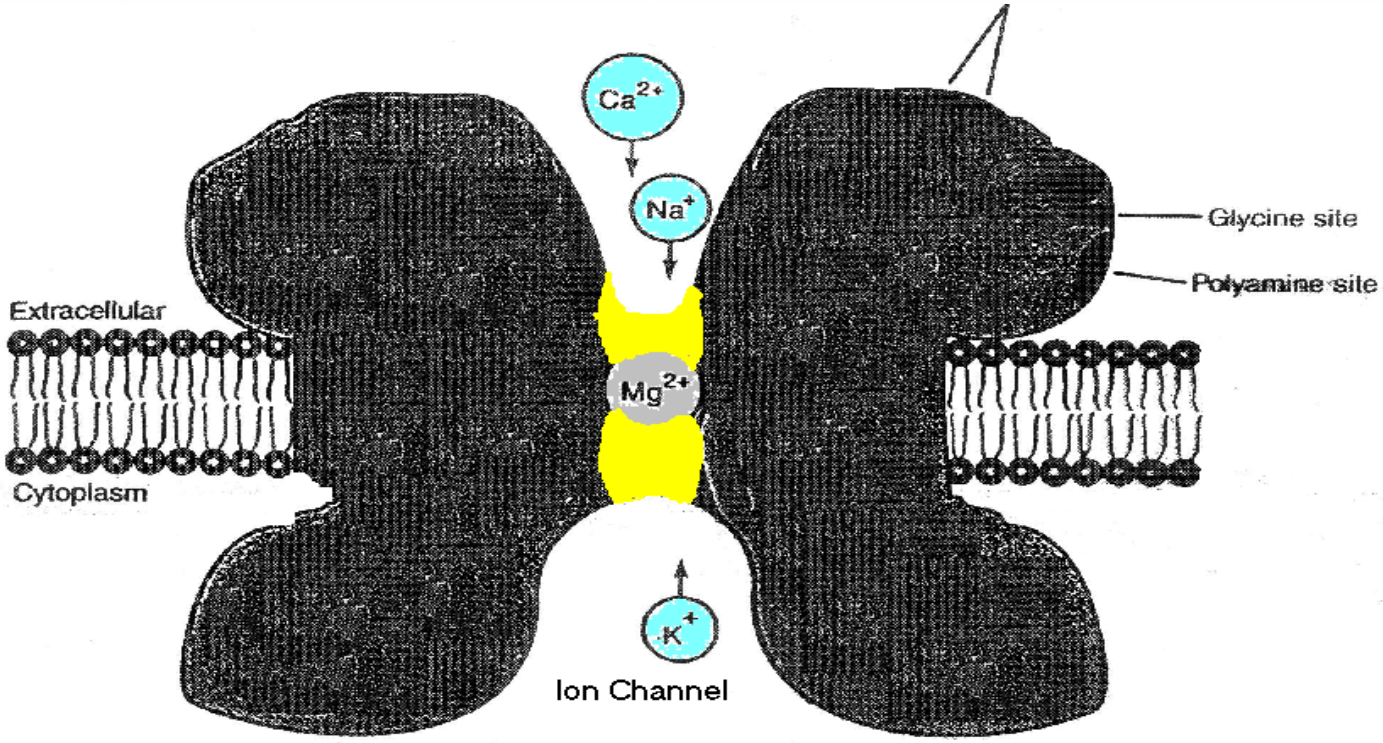
Adapted from Kenna et al., *Am J Health Sys Pharm* 2004;61:2272.

Pharmacodynamic interactions between opiates and alcohol

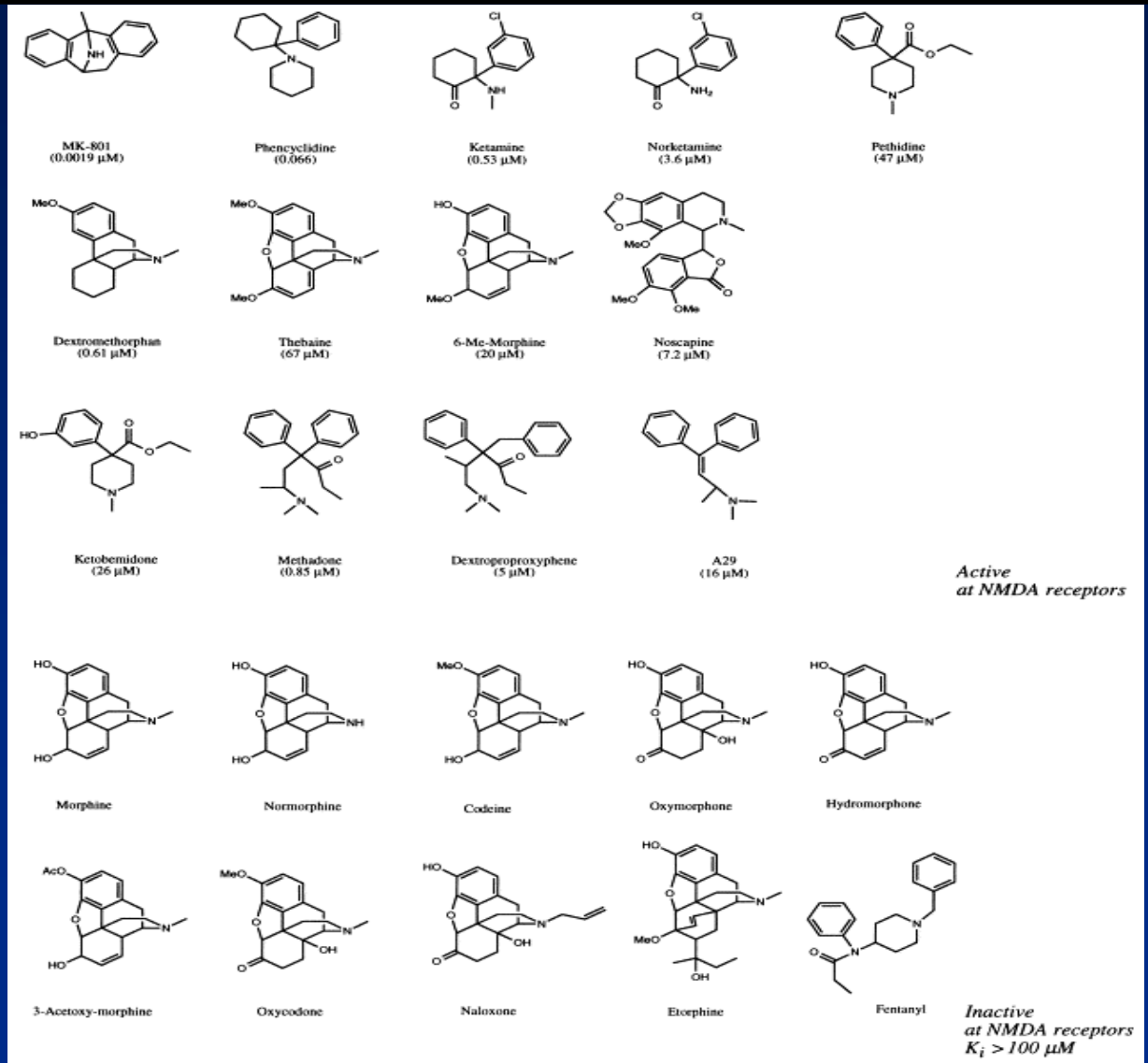
- Synthetic opioids, including methadone have nonopioid actions, including inhibition *N*-methyl-D-aspartate (NMDA) receptors (Callahan et al 2004).
- One of alcohol's major effects is inhibition of NMDA receptors, as well.
- Acutely, alcohol and opiates can enhance each others inhibitory effects on NMDA receptors, leading to increased sedation.
- Chronically, alcohol and opiates can upregulate NMDA receptors potentially leading to increased withdrawal symptoms of both alcohol and opiates.

The NMDA- Glutamate Receptor

inhibited by acute alcohol and up-regulated (supersensitive) during alcohol withdrawal



Opioids as NMDA Antagonists



Summary of Opiate Alcohol Interactions

Pharmacokinetic Interactions

- Liberation of modified release oral formulations
- Metabolism – Acute and chronic effects
  Glucuronidation, CYP3A4, liver disease

Pharmacodynamic Interactions

- Acute release of endorphins by alcohol
- Changes in opiate receptors with chronic alcohol
- Ethanol facilitation of opiate effects at the receptor by actions on G-protein coupling
- NMDA receptor inhibition by alcohol and opiates