

Preclinical Assessment of Abuse Potential

Roger D. Porsolt Ph.D.

President

Porsolt & Partners Pharmacology

Plan

■ Definitions

■ Drug abuse

- Drug tolerance
- Similarity to drugs of abuse
 - Overt behavior
 - Drug discrimination
- Positive reinforcing properties
 - Conditioned place preference
 - Self-administration

■ Conclusions



Dependence Liability

- **Psychological**
Drug craving: difficulty in stopping drug use or sustaining abstinence
- **Physical**
Occurrence of withdrawal symptoms on drug cessation



Abuse Liability

- **Likelihood that a drug with psychoactive or CNS effects will sustain patterns of non-medical self-administration that result in disruptive or undesirable consequences.**



Dependence does not predict abuse

	Abuse	Dependence
Morphine	✓	✓
U50488	x	✓
Δ9-THC	✓	x



Substance characteristics leading to abuse potential

- **Central action**
- **PK parameters (rapid onset, short duration of action)**
- **High solubility**
- **High safety margin**
- **Tolerance after prolonged use (dose escalation)**
- **Similarity to other drugs of abuse (drug discrimination)**
- **Positive reinforcing properties (conditioned place preference, self-administration)**



Drug Classes Associated with Abuse Liability and Scheduled by DEA

- **Opioids**
- **Sedative hypnotics**
- **Cocaine, amphetamine and other CNS stimulants**
- **Hallucinogens, phencyclidine and similar agents**
- **Cannabinoids (marijuana and related compounds)**
- **Nicotine-like drugs**
- **Chemical precursors of controlled substances**
- **Anabolic steroids**



Drug Schedules

Schedule	Definition	Examples
I	<ul style="list-style-type: none"> - No current accepted medical use - High abuse potential 	Heroin, methaqualone, psilocybin, marijuana
II	<ul style="list-style-type: none"> - Current accepted medical use - High abuse potential 	Cocaine, PCP, morphine, fentanyl, methadone
III	<ul style="list-style-type: none"> - Current accepted medical use - Medium abuse potential 	Opium, acetaminophen + codeine, amphetamine, barbiturates
IV	<ul style="list-style-type: none"> - Current accepted medical use - Low potential for abuse 	Benzodiazepines, zolpidem, modafinil, barbital, pemoline
V	<ul style="list-style-type: none"> - Accepted medical use - Very low abuse potential 	Codeine preparations, promethazine, opium preparations



Preclinical Abuse Liability: Advantages of Studies in Non-Humans

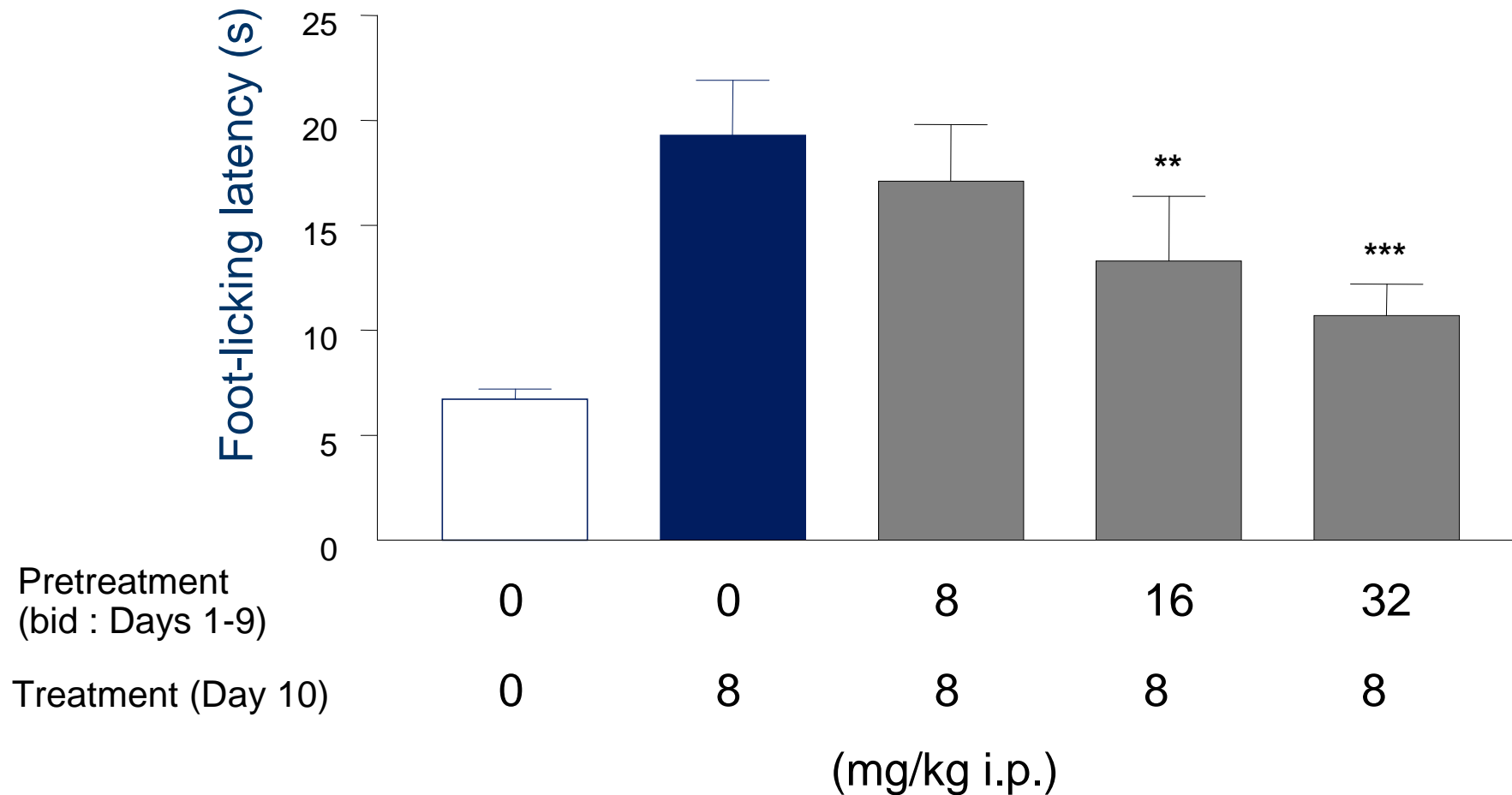
- Relatively inexpensive
- Can occur early in drug development
- Broad range of dosing conditions
- Different routes of administration
- Compare a wide variety of drugs
- Mechanism studies



DRUG TOLERANCE



Hot Plate Test in the rat: Tolerance after repeated morphine treatment



SIMILARITY TO DRUGS OF ABUSE

Overt Behavior



Irwin Test in the Mouse

MK 801 (p.o.)

0.125 (mg/kg)	1 (mg/kg)	4 (mg/kg)	32 (mg/kg)
No change	Excitation +++	Excitation +++	Sedation ++
	Straub	Straub	Straub
	Stereotypies	Stereotypies	Stereotypies
	Convulsions	Convulsions	Convulsions
	Hyperthermia +	Hyperthermia +	Tremor
			↓ Reactivity to touch
			Motor incoordination
			↓ Muscle tone

Phencyclidine (p.o.)

1 (mg/kg)	4 (mg/kg)	16 (mg/kg)	64 (mg/kg)
↓ Reactivity	Excitation ++	Excitation +++	Convulsions
	↓ Traction	Stereotypies	Death (3/3)
	↓ Reactivity to touch	Convulsions	
		Tremor	
		↓ Fear	
		↓ Traction	
		Motor incoordination	
		↓ Muscle tone	
		↑ Respiration	

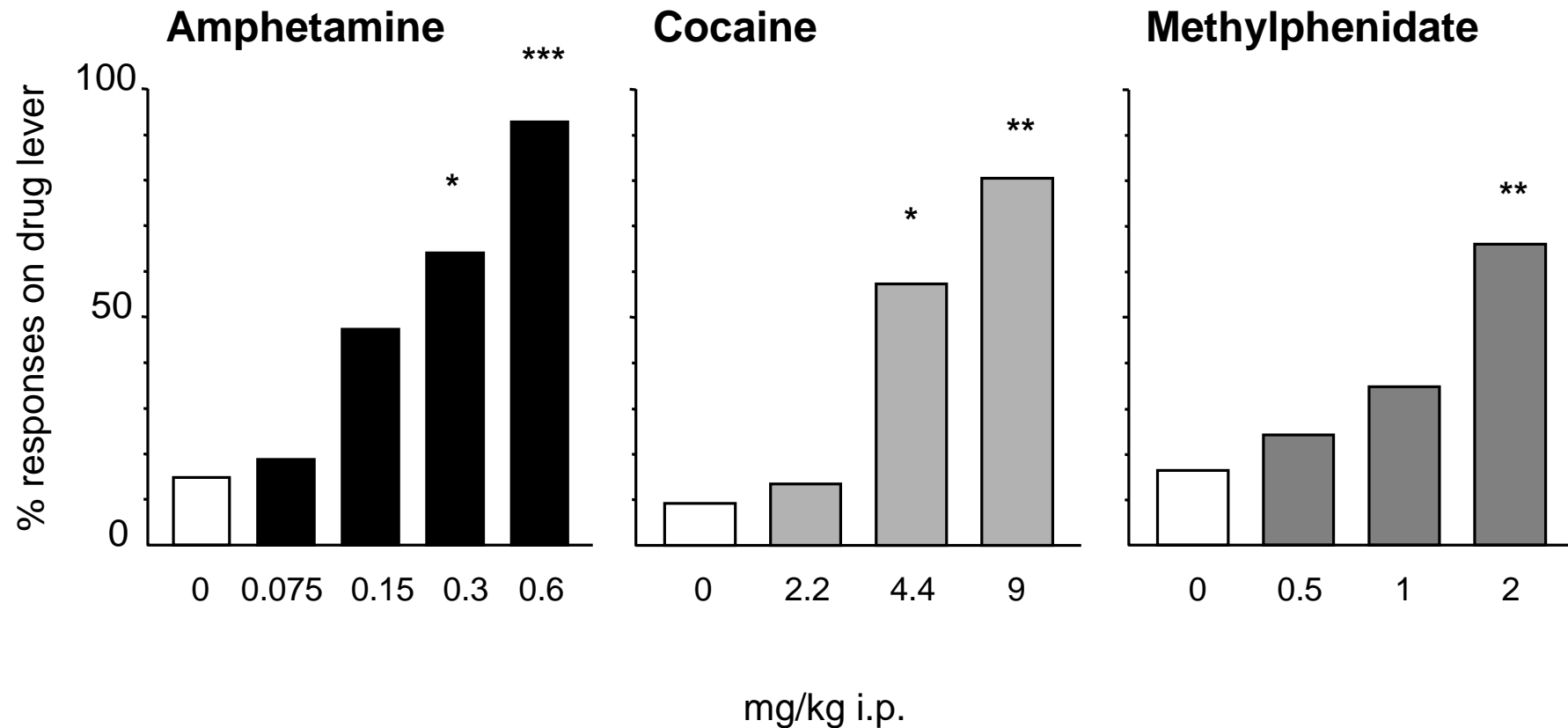


SIMILARITY TO DRUGS OF ABUSE

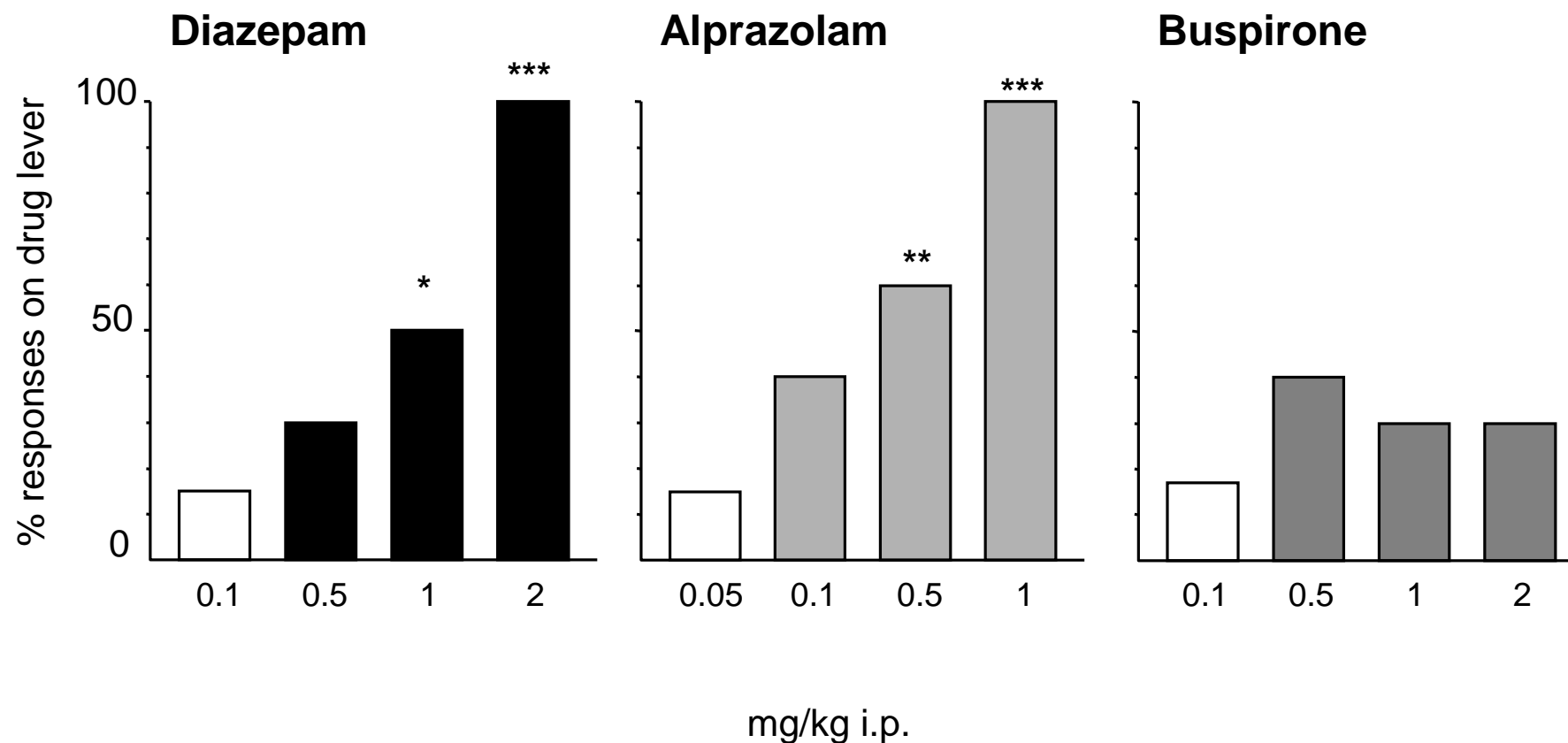
Drug Discrimination



Amphetamine (0.6 mg/kg i.p.) Discrimination Test in the rat



Diazepam (2 mg/kg i.p.) Discrimination Test in the rat



Drug Discrimination

- Strengths: pharmacologic specificity

Test drug	Training Drug		
	Cocaine	Heroin	Midazolam
Cocaine	✓	x	x
Amphetamine	✓	x	x
Heroin	x	✓	x
Morphine	x	✓	x
Midazolam	x	x	✓
Pentobarbital	x	x	✓
Test substance	?	?	?



POSITIVE REINFORCING PROPERTIES

Conditioned Place Preference

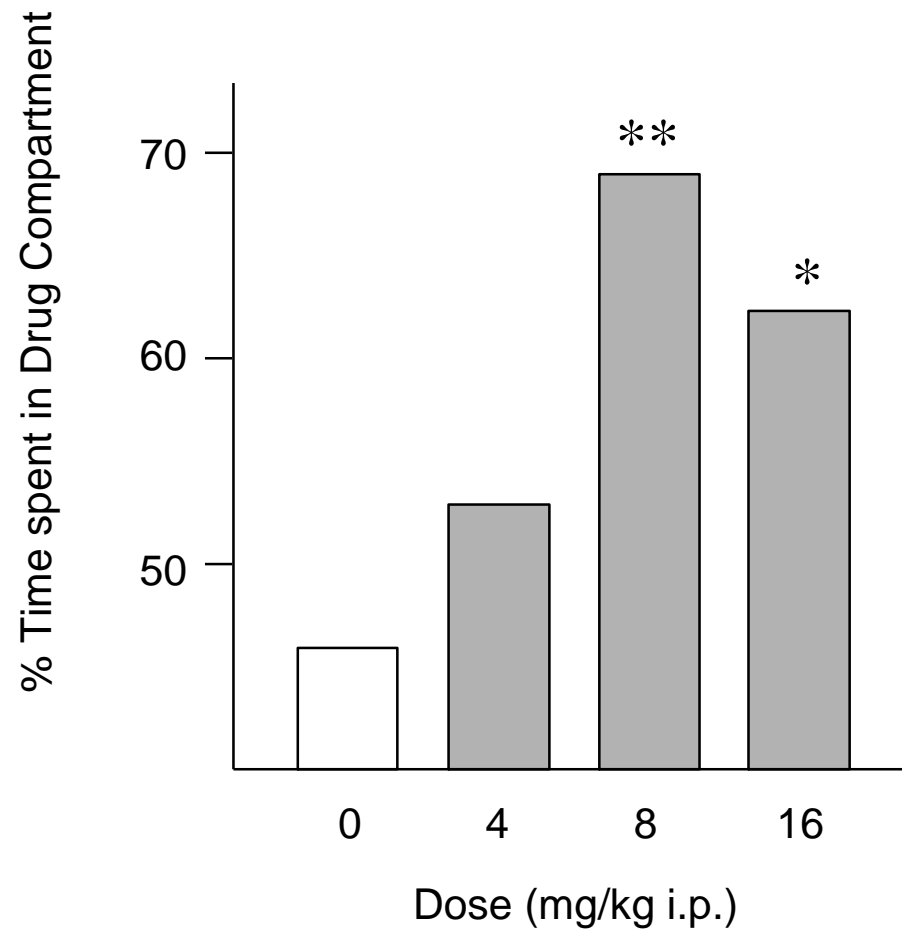


Place Preference Test in the rat



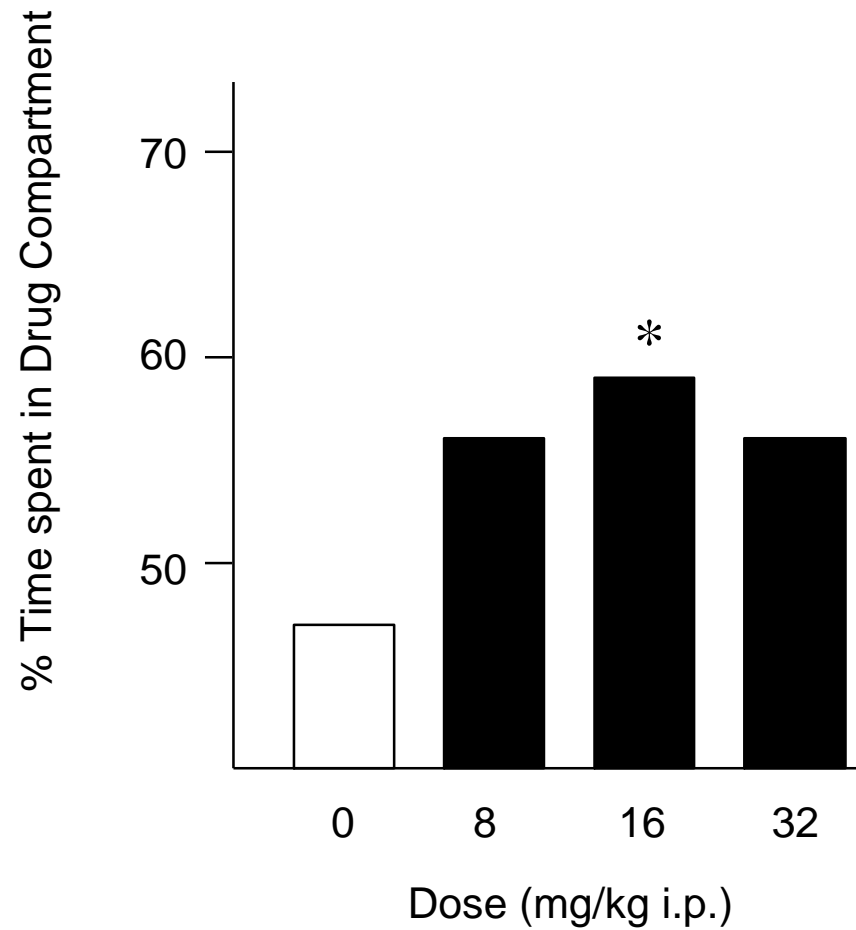
Place Preference in the rat

Morphine

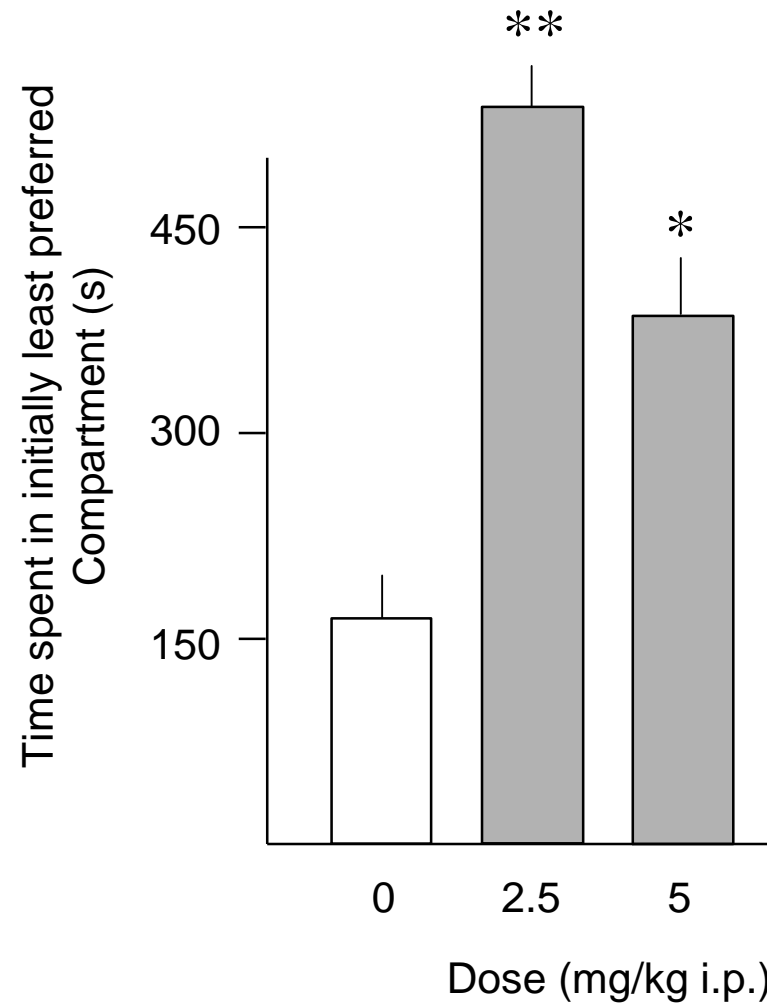


Place Preference in the rat

Cocaine

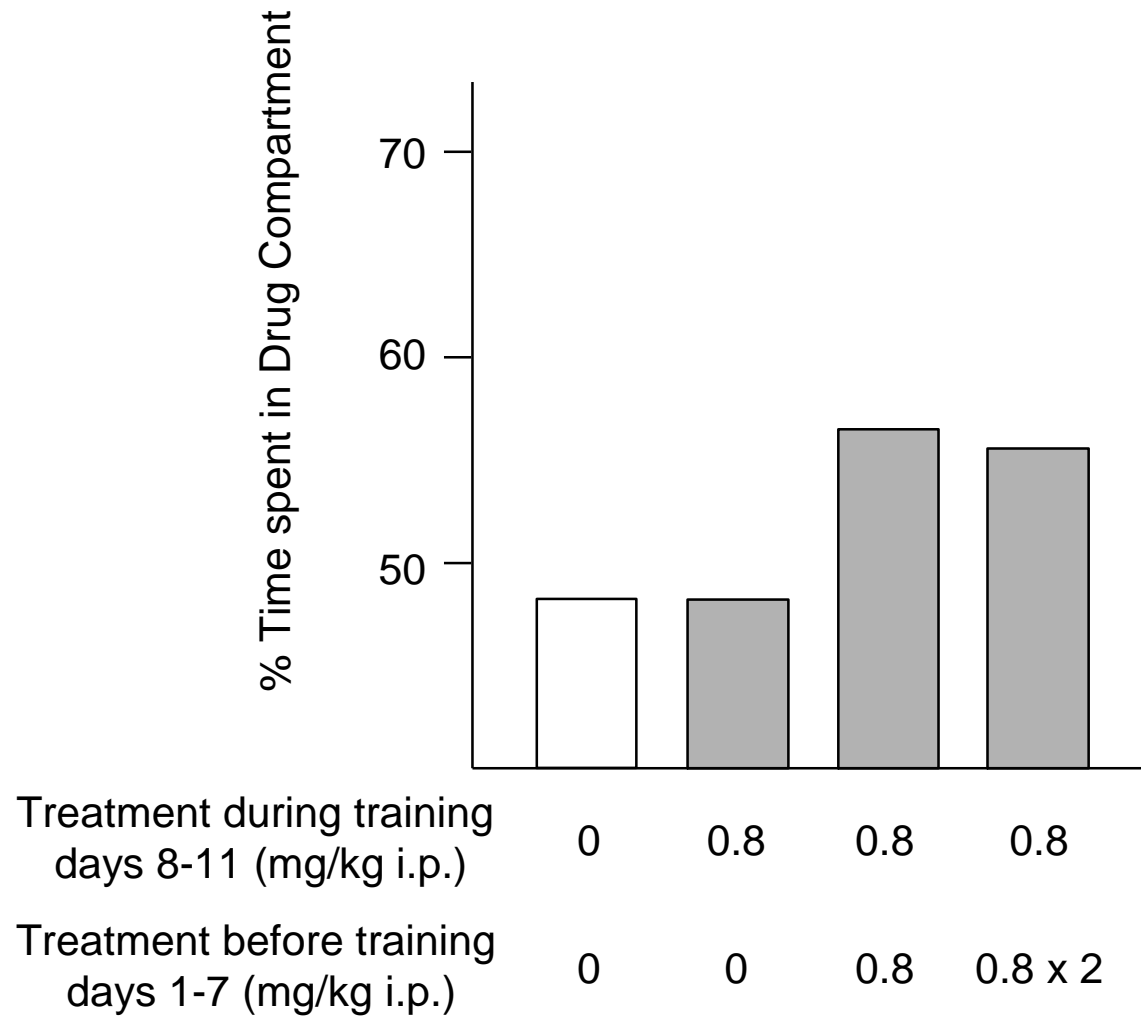


Place Preference in the rat Diazepam (from Gray et al, 1999)

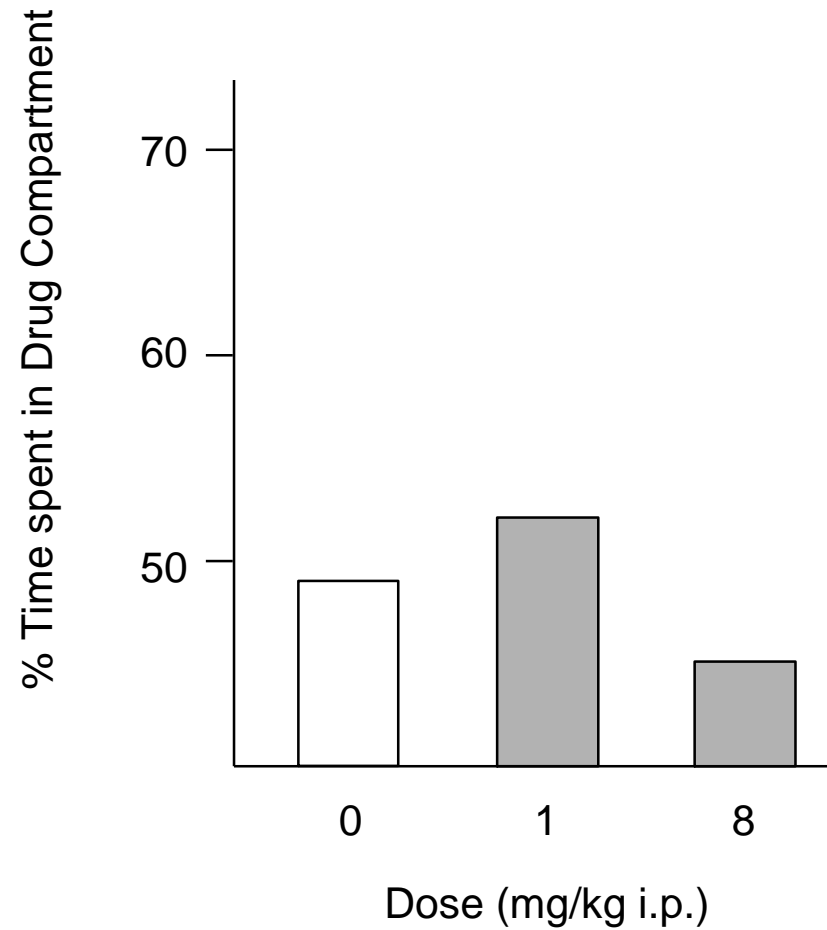


Place Preference in the rat

Nicotine



Place Preference in the rat Δ^9 -tetrahydrocannabinol



POSITIVE REINFORCING PROPERTIES

Self-Administration



Self-Administration Methodology

■ Substitution procedures

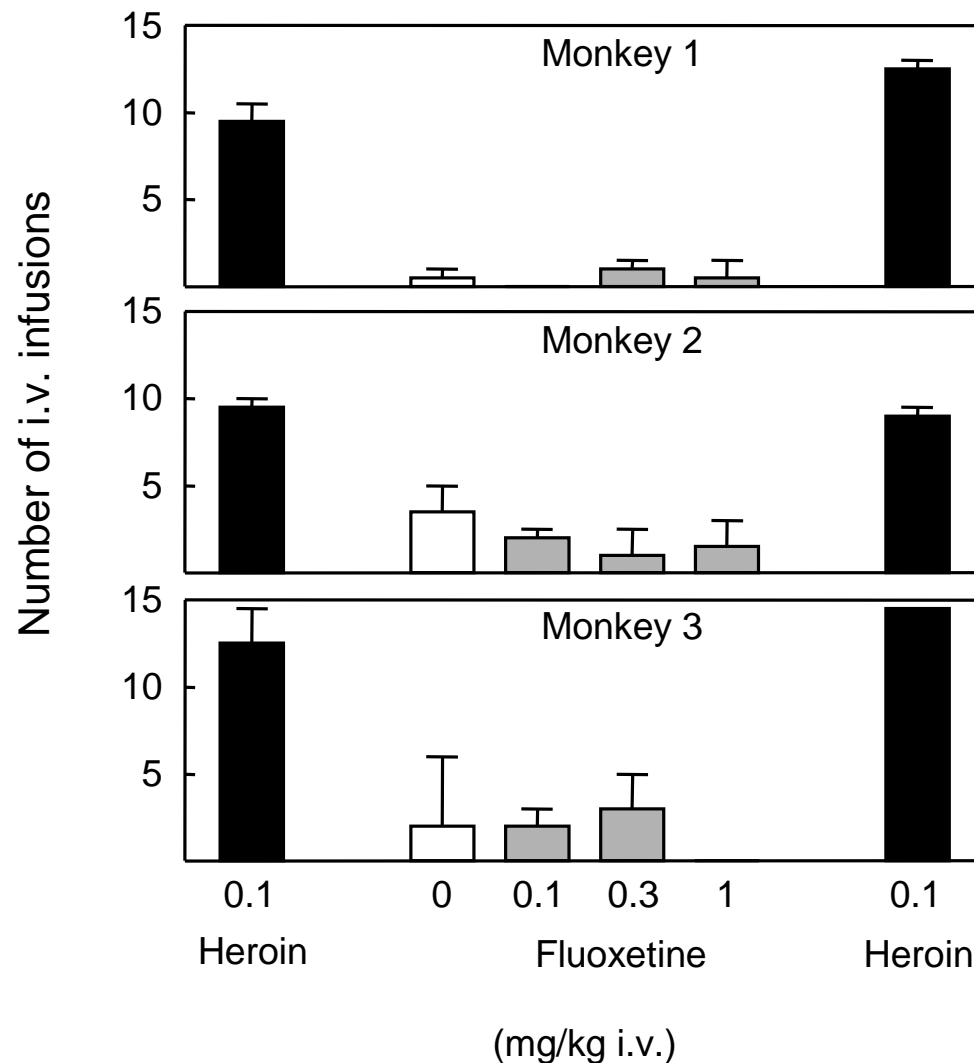
- established baseline (drug abuser)
- reuse of animals (particularly primates)
- high sensitivity (false positives ?)
- possible negative contrast

■ Initiation procedures

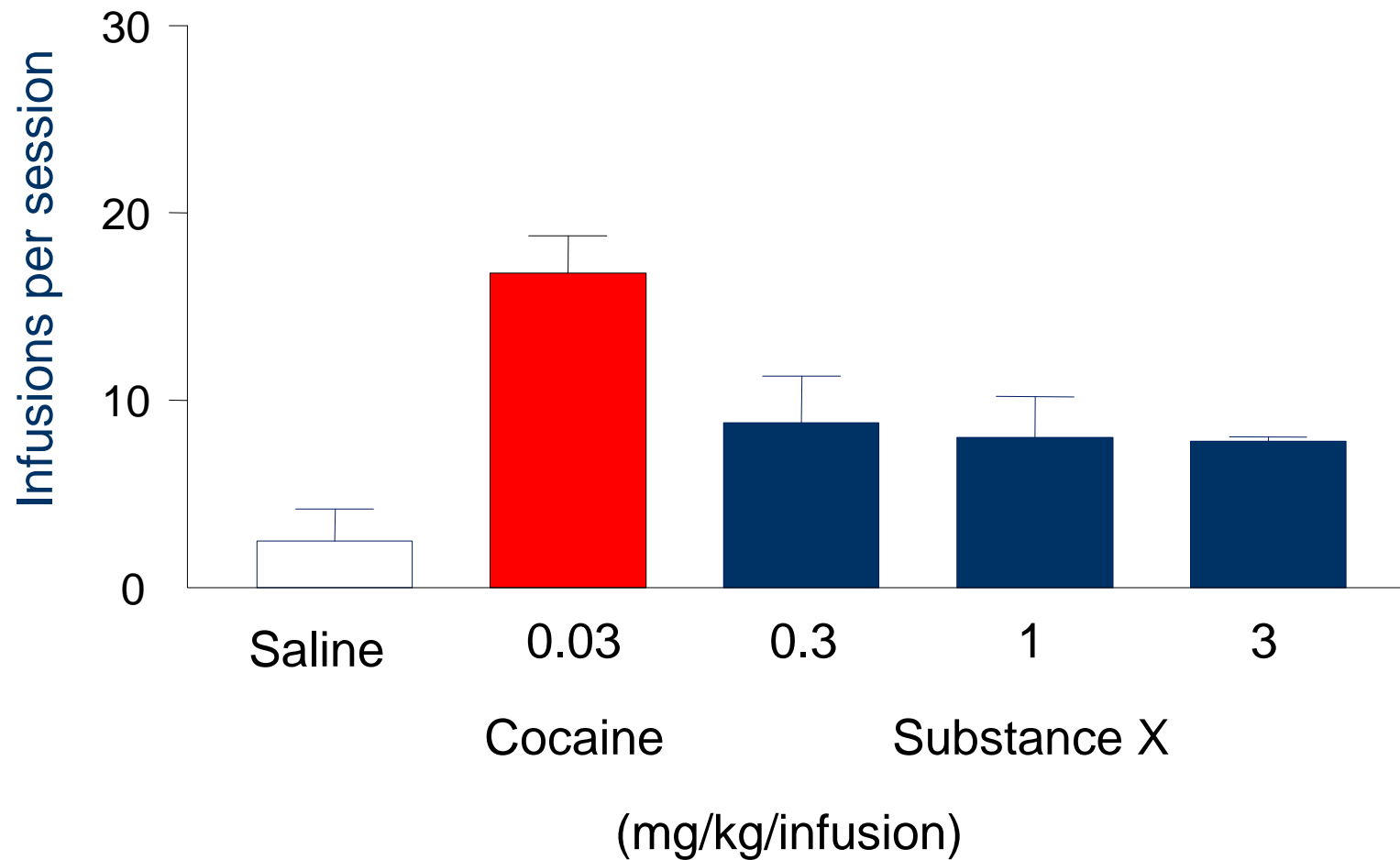
- new animals per test substance (drug naive)
- lower sensitivity (false negatives ?)



Intravenous self-administration of fluoxetine compared with saline and heroin in 3 monkeys



Mean self-administration of cocaine and Substance X in 4 rhesus monkeys



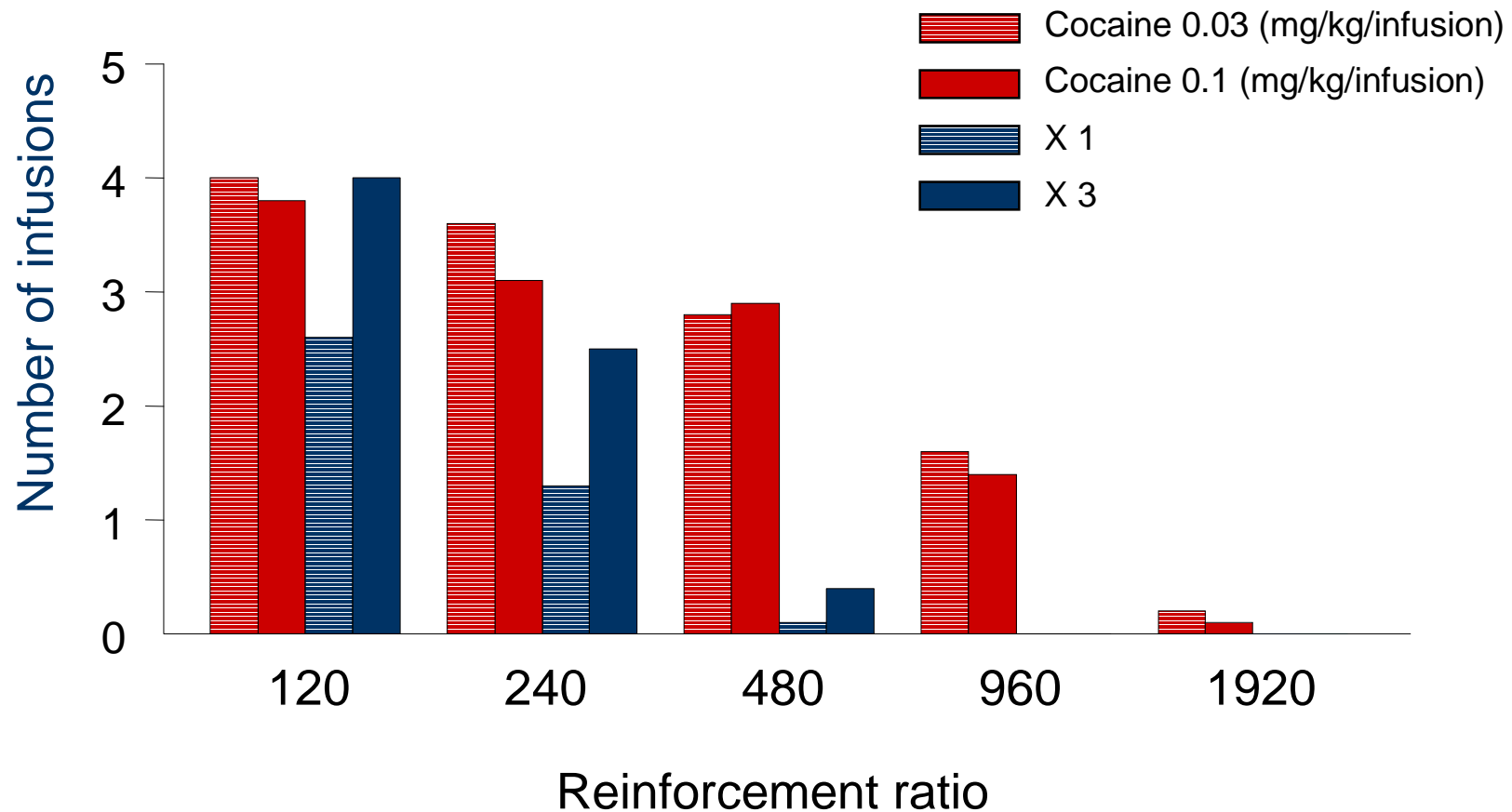
Breaking points for some known or potential drugs of abuse in monkeys trained on an FR50 schedule

Test Drug	Breaking point
Cocaine	750
Methylphenidate	675
Ephedrine	275
Bupropion	100
Modafinil	100

Data from Beardsley (2006)



Mean number of drug reinforcements received at each reinforcement ratio in 3 rhesus monkeys



Self-administration

■ Weaknesses

■ False negatives

- GHB
- LSD

■ False positives

- Bupropion
- Modafinil
- Nomifensine

	Rat	Monkey	Human
Cocaine	✓	✓	✓
Heroin	✓	✓	✓
PCP	✓	✓	✓
GHB	x	x	✓
LSD	x	x	✓
Bupropion	✓	✓	x
Modafinil	NT	✓	x
Nomifensine	✓	NT	x



Conclusions

- Drugs for most CNS applications or with CNS mechanism of action will have to be assessed for abuse liability
- Drug discrimination a sensitive but indirect assessment of abuse liability
- Conditioned place preference is not a sensitive nor a direct assessment of abuse liability
- Self-administration, particularly in the primate, is the most direct and sensitive assessment of abuse liability



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