Pharmacology of Synthetic Drugs NIST Emerging Trends in Synthetic Drugs Workshop

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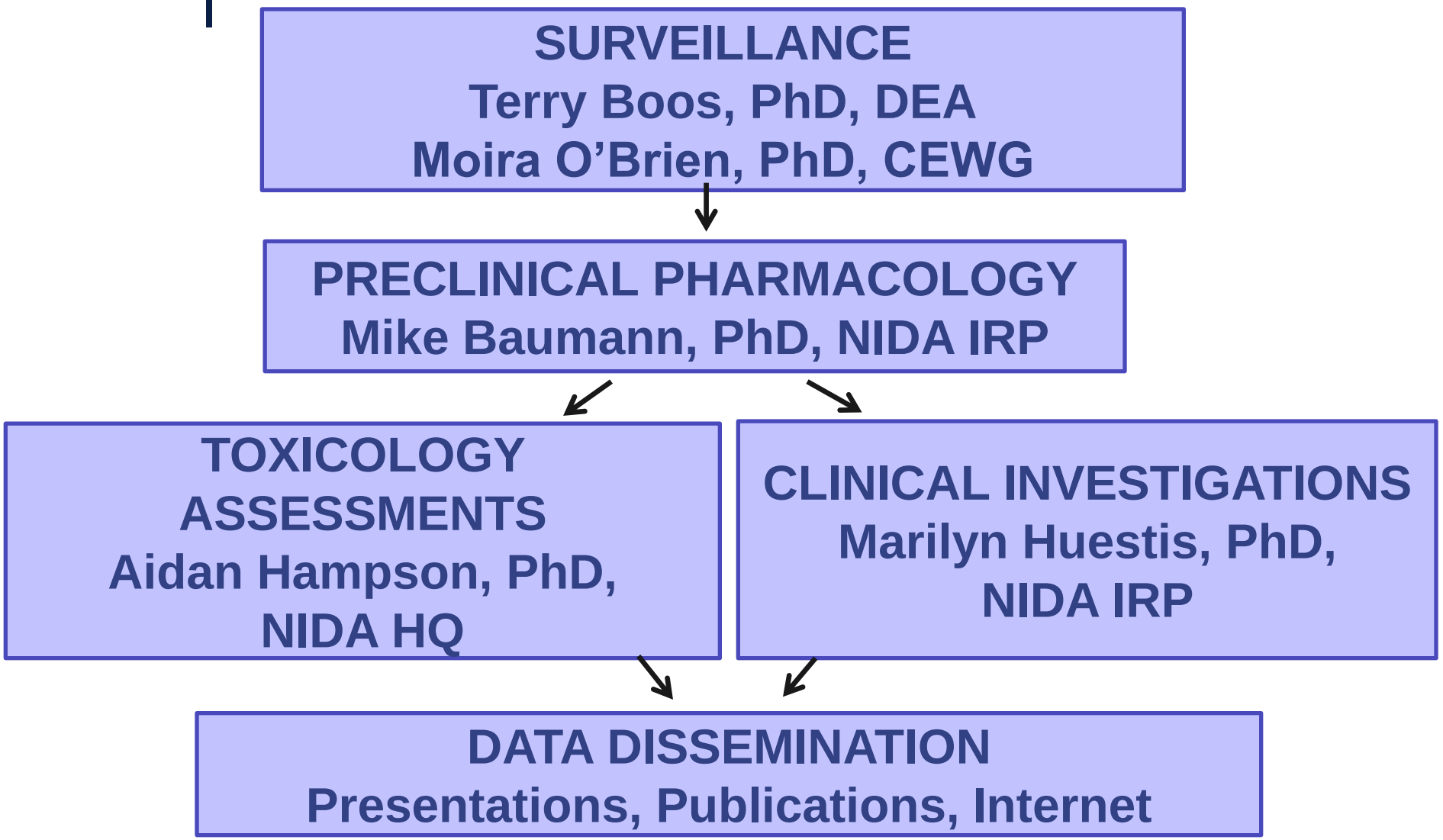
Chemistry & Drug Metabolism Research Program

- Utilize pharmacological & toxicological tools to
  - Address mechanisms underlying human drug abuse & addiction
  - Investigate behavioral & physiological drug toxicities
  - Develop new prevention strategies & treatment medications
- Conduct controlled drug administration studies in humans to determine onset, peak & duration of drug effects & time course of markers in biological matrices

Chemistry & Drug Metabolism Research Program

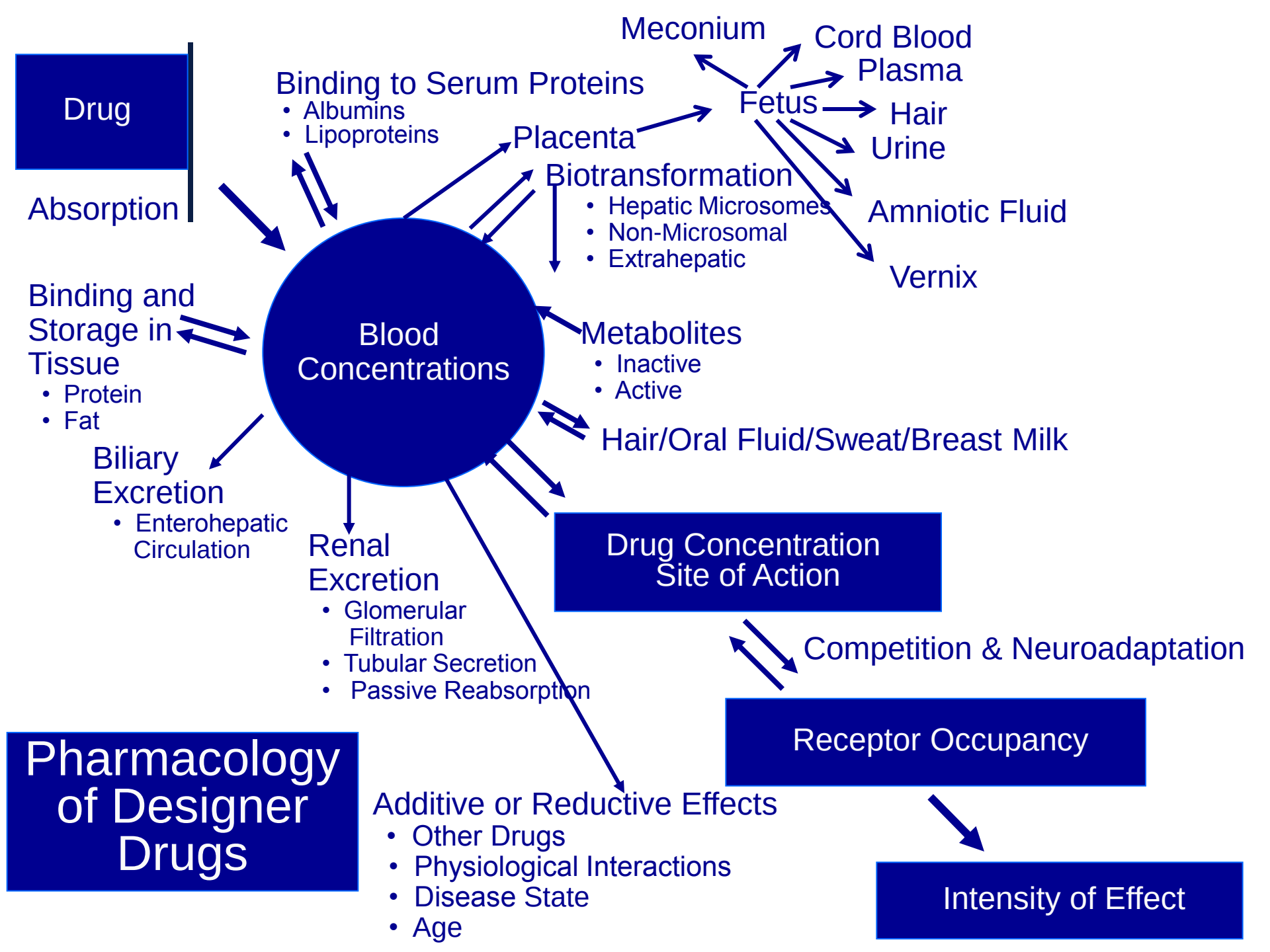
- Data provide a framework for understanding mechanisms of drug action & toxicity, & for predicting drug effects in individual patients
- Research directly impacts public health & safety
  - Data for evidence-based drug policy & legislation
  - Identify new metabolic pathways & metabolites (designer drugs)
  - Improve monitoring tools to deter & identify drug use
  - Document medication efficacy when assessing new pharmacological or behavioral drug treatments
  - Create new tools for drug abuse practitioners

National Institute on Drug Abuse IRP Designer Drug Initiative



National Institute on Drug Abuse Intramural Research Program Designer Drug Initiative

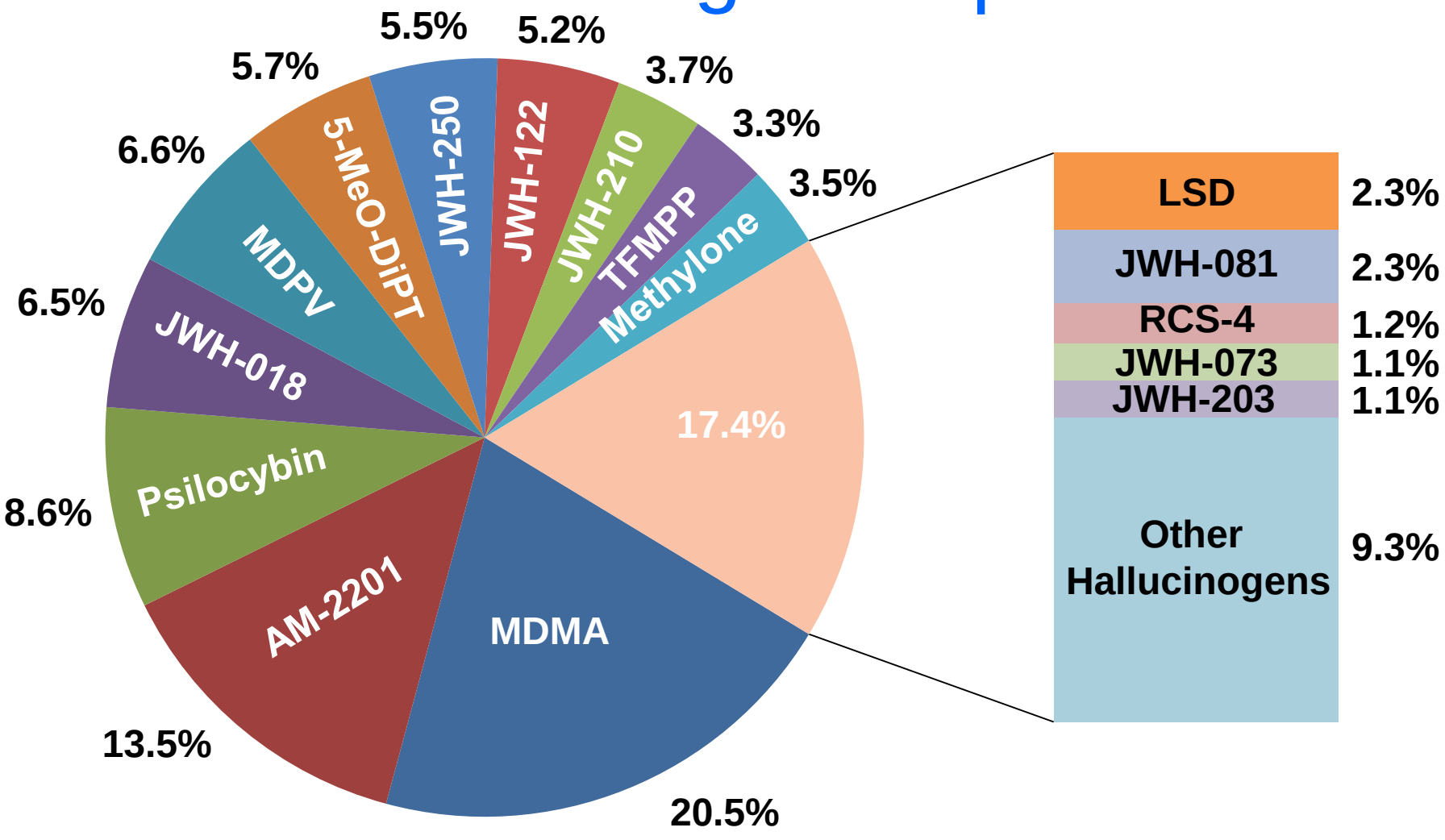
- Characterize pharmacokinetics of designer drugs in humans
  - Cultured hepatocyte incubation with designer drugs
  - Human liver microsome incubation with designer drugs
  - High resolution mass spectrometric analysis of phase 1 & 2 metabolites
  - High resolution time of flight designer drug screen


Drug
Absorption
Binding to Serum Proteins
• Albumins
• Lipoproteins
Placenta
Biotransformation
• Hepatic Microsomes
• Non-Microsomal
• Extrahepatic
Meconium
Cord Blood
Plasma
Fetus
Hair
Urine
Amniotic Fluid
Vernix
Binding and Storage in Tissue
• Protein
• Fat
Blood Concentrations
Metabolites
• Inactive
• Active
Hair/Oral Fluid/Sweat/Breast Milk
Biliary Excretion
• Enterohepatic Circulation
Renal Excretion
• Glomerular Filtration
• Tubular Secretion
• Passive Reabsorption
Drug Concentration Site of Action
Competition & Neuroadaptation
Receptor Occupancy
Intensity of Effect
Additive or Reductive Effects
• Other Drugs
• Physiological Interactions
• Disease State
• Age
Pharmacology of Designer Drugs

Designer Drug Problem Isn't New

- 1970's- Synthetic hallucinogens
  - LSD analogs: LSD acetyl amide *(Orange sunshine)*
  - Phencyclidine analogs: tenocyclidine *(TCP)*
- 1980's- Synthetic opioids
  - Fentanyl analogs: α-methylfentanyl
  - Meperidine analogs: MPPP, MPTP-induced Parkinsonism
- 1990's- Synthetic stimulants
  - Cathinones: methcathinone
  - Aminorex: 4-methylaminorex

NFLIS 2011
Hallucinogen Reports



N = 45,382

K2 Spice Zohai
Bombay Blue Black
Mamba Genie Skunk
Moon Rocks Blaze
Yucatan Fire Genie

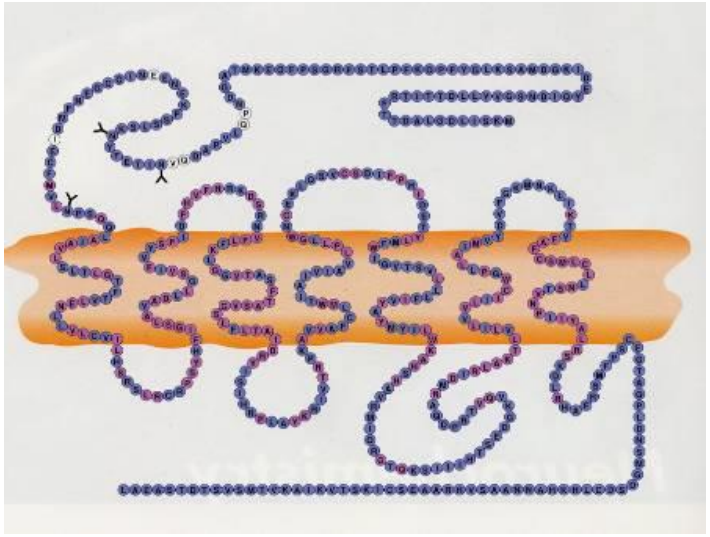
Synthetic Cannabinoids
JWH, AM, HU, XLR, UR

Synthetic Cannabinoids Pharmacology

- Primarily smoked, delivers drug rapidly to brain
- High abuse liability
- Agonists at CB1 &/or CB2 receptors with wide variability in binding affinity
- Binding evaluated in rodent brain, Chinese hamster ovarian cells, human embryonic kidney cells, human receptor preparations
- Most more potent than Δ9-tetrahydrocannabinol (THC)

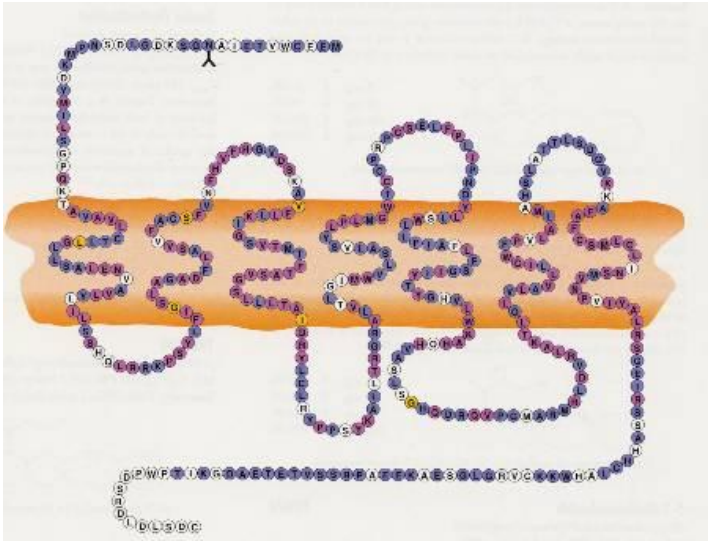
Cannabinoid Receptors

CB_1



Central nervous system
Cardiovascular system
Reproductive system

CB_2



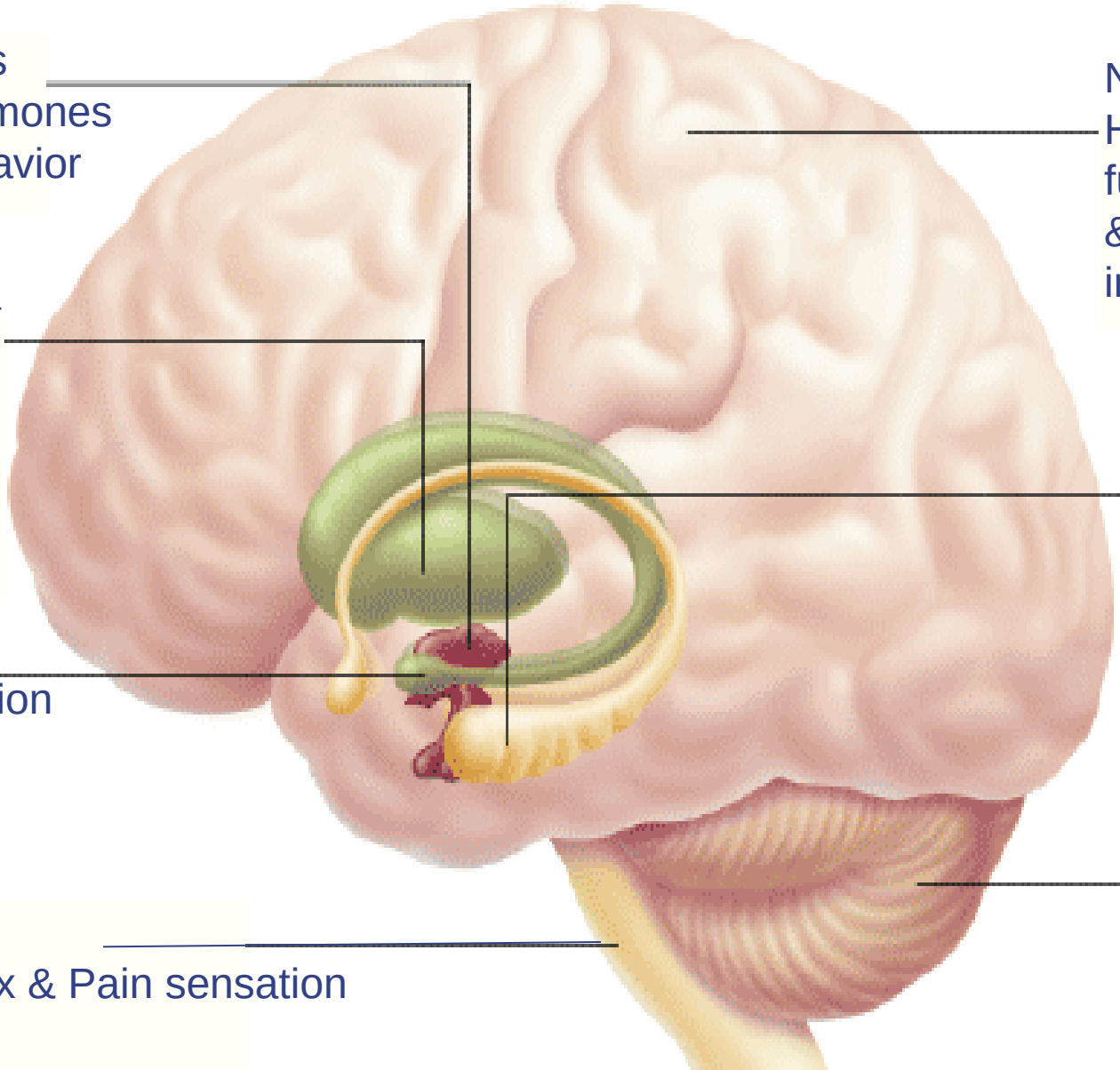
Immune system
Spleen, Tonsils &
Lymphoid tissues

Non-CB1, Non-CB2 Receptors

SC Receptor Binding Affinity
compared to THC (CB_1 K_i = 5 – 80 nM)

Drug	CB_1 K_i (nM)	CB_2 K_i (nM)	THC CB_1 K_i / SC CB_1 K_i
AM694	0.1	1.4	50 - 805
AM2201	1.0	2.6	5 - 80
HU210	0.1	0.5	50 - 800
JWH018	9.0 ± 5.0	2.9 ± 2.7	0.5 – 9.0
JWH073	8.9 ± 1.8	38.0 ± 24.0	0.6 – 9.0
JWH081	1.2 ± 0.03	12.4 ± 2.2	4.2 – 67.1
JWH250	11.0 ± 2.0	33.0 ± 2.0	0.5 – 7.3
UR144	150	1.8	< 1

High CB1 Receptor Density



Hypothalamus
Appetite, Hormones
& Sexual behavior

Basal Ganglia
Motor control
& planning

Amygdala
Anxiety, Emotion
& Fear

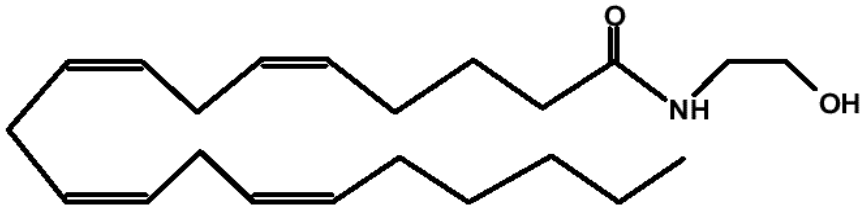
Brain Stem
& Spinal Cord
Vomiting reflex & Pain sensation

Neocortex
High cognitive
function
& Sensory data
integration

Hippocampus
Memory &
Learning

Cerebellum
Motor control
& coordination

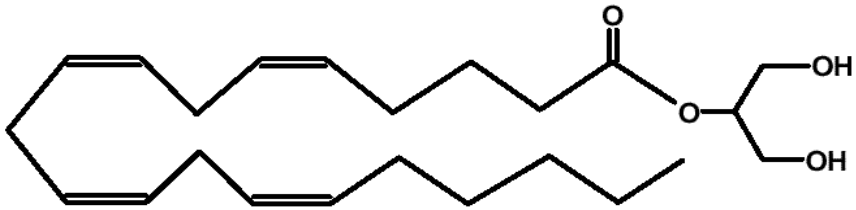
Endogenous Cannabinoids



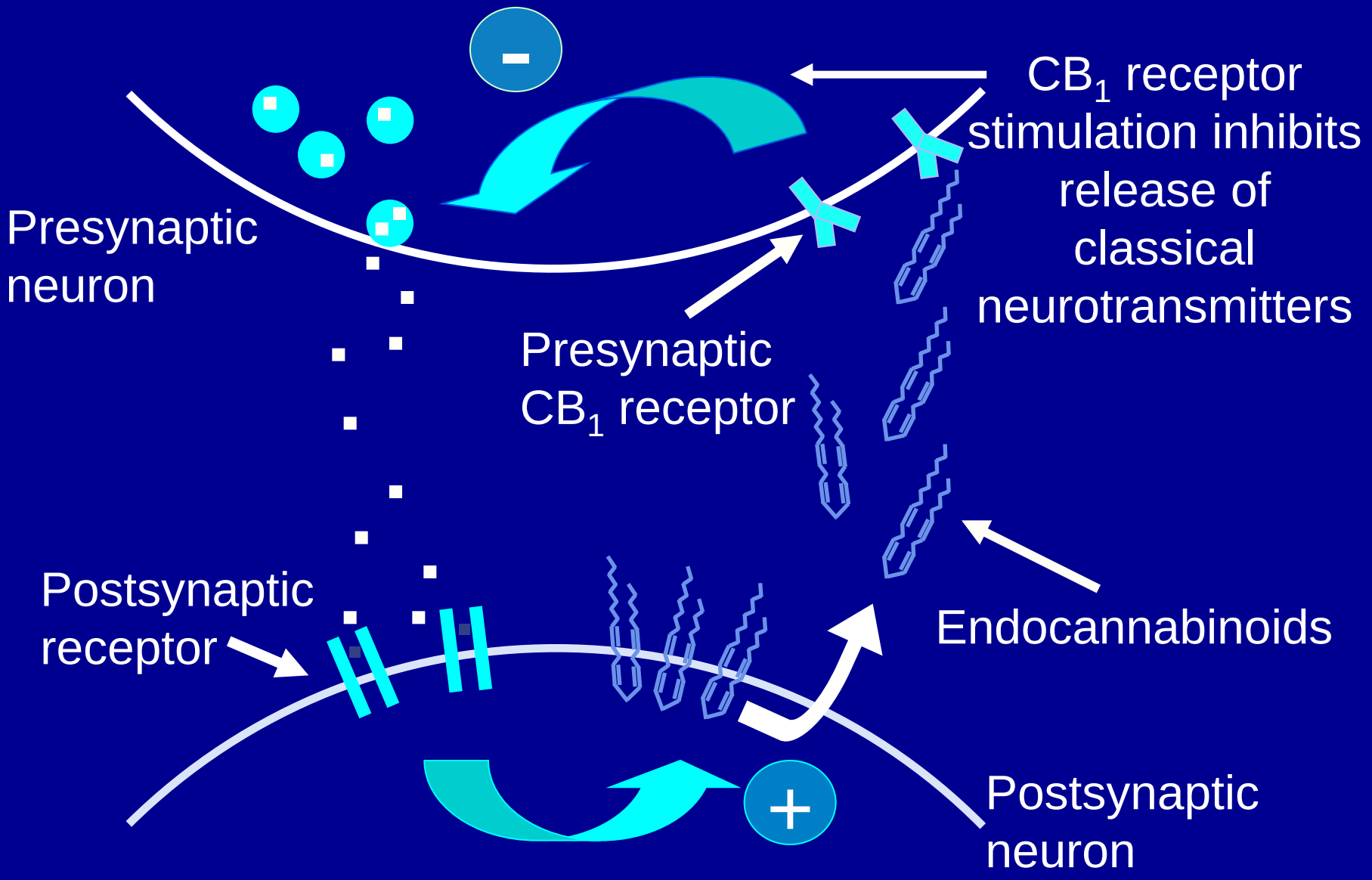
Anandamide (AEA)

- Different routes of synthesis
- Different modes of degradation (FAAH & MAGL)
- Different efficacy

2-Arachidonyl glycerol (2AG)



Endocannabinoid Signaling



Synthetic Cannabinoids Pharmacology

- Limited pharmacodynamic research on rodents & non-human primates
- Few human data
  - 1 limited controlled administration study
  - Multiple self-administered single dose studies
  - Emergency room & police reports
  - Internet posts

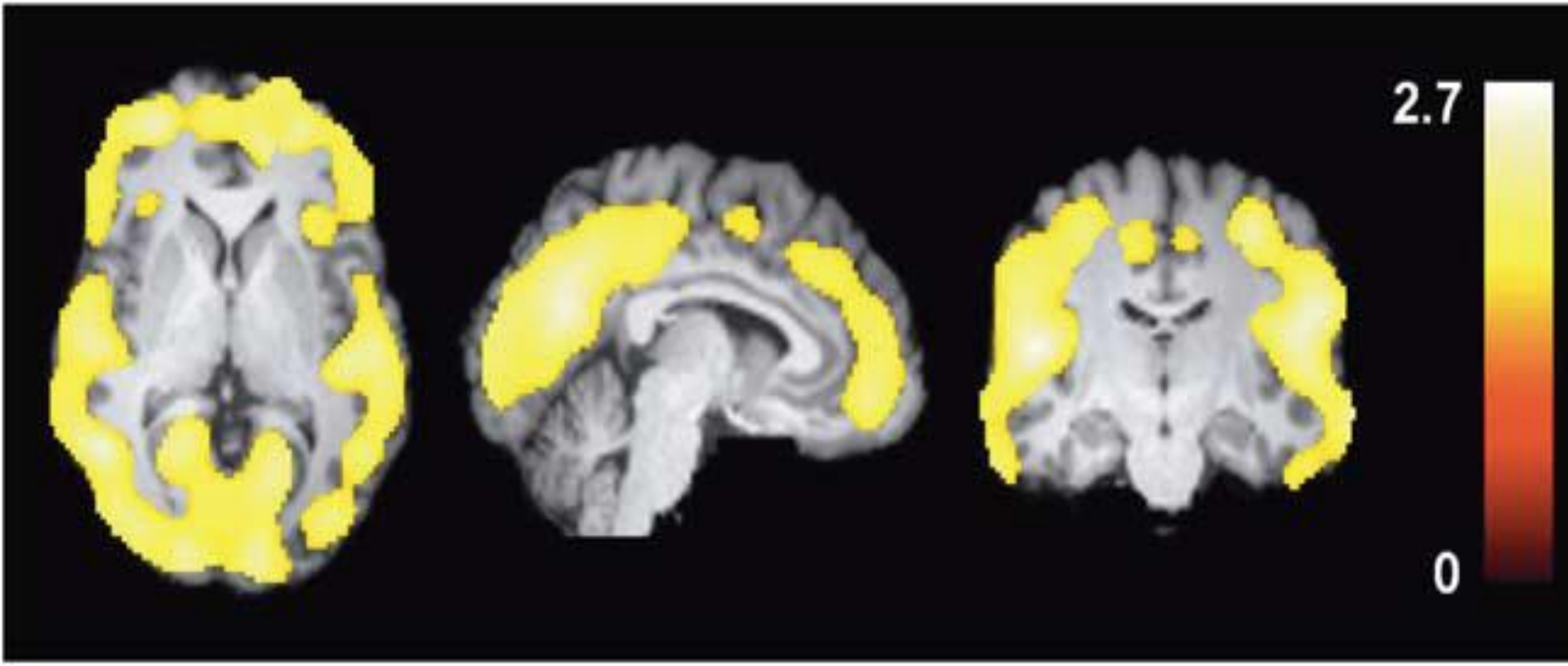
Preclinical Acute vs Chronic Exposure (14 day)

- Acute
  - Analgesia
  - Anti-emetic
  - Anti-epileptic
  - Anxiolytic (low dose)/ Anxiogenic (high dose)
  - Decrease locomotion/ catalepsy (high dose)
  - Hypothermia/Hypotension
  - May produce relapse in formerly drug-dependent animals
- Chronic
  - Cognitive impairment
  - Anti-inflammatory
  - Immunosuppressive
  - Anxiogenic
  - Facilitated sensitization to other drugs

Acute vs Chronic Human Exposure

- Acute
  - Agitation & anxiety
  - Chest pain & tachycardia
  - Hypertension
  - Muscle twitches
  - Nausea & vomiting
  - Short-term memory & cognitive impairment
  - Shortness of breath
  - Paranoia/Hallucinations
  - Reddened conjunctivae & dilated pupils
- Chronic
  - Psychosis/Paranoia
  - Withdrawal
    - Increased craving
    - Hypertension
    - Muscle twitches
    - Restlessness
    - Sweating
    - Tachycardia

[^{18}F]FMPEP-d_2 Labels CB1 Cannabinoid Receptors in Brain of Chronic Daily Cannabis Smokers

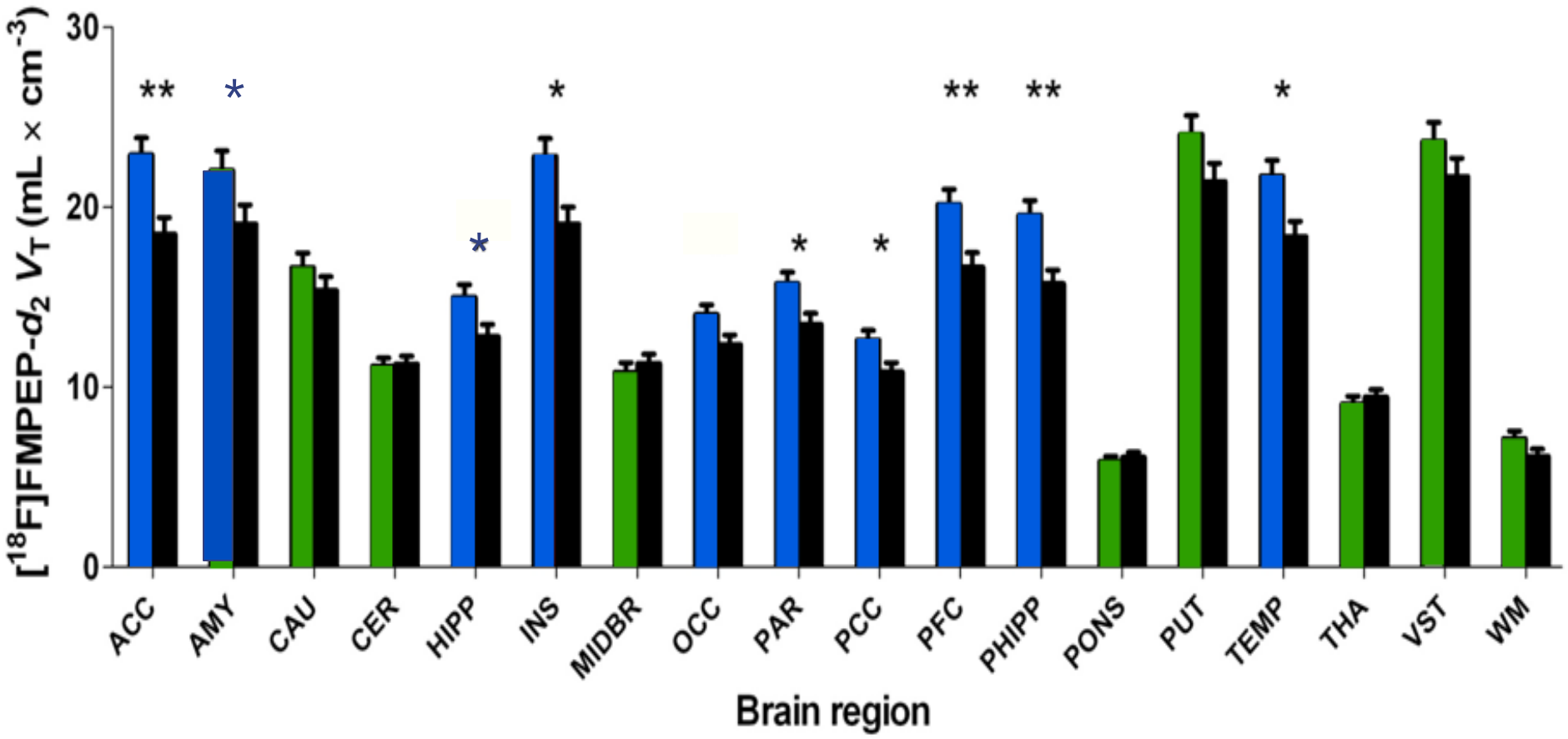


Molecular Psychiatry 2012

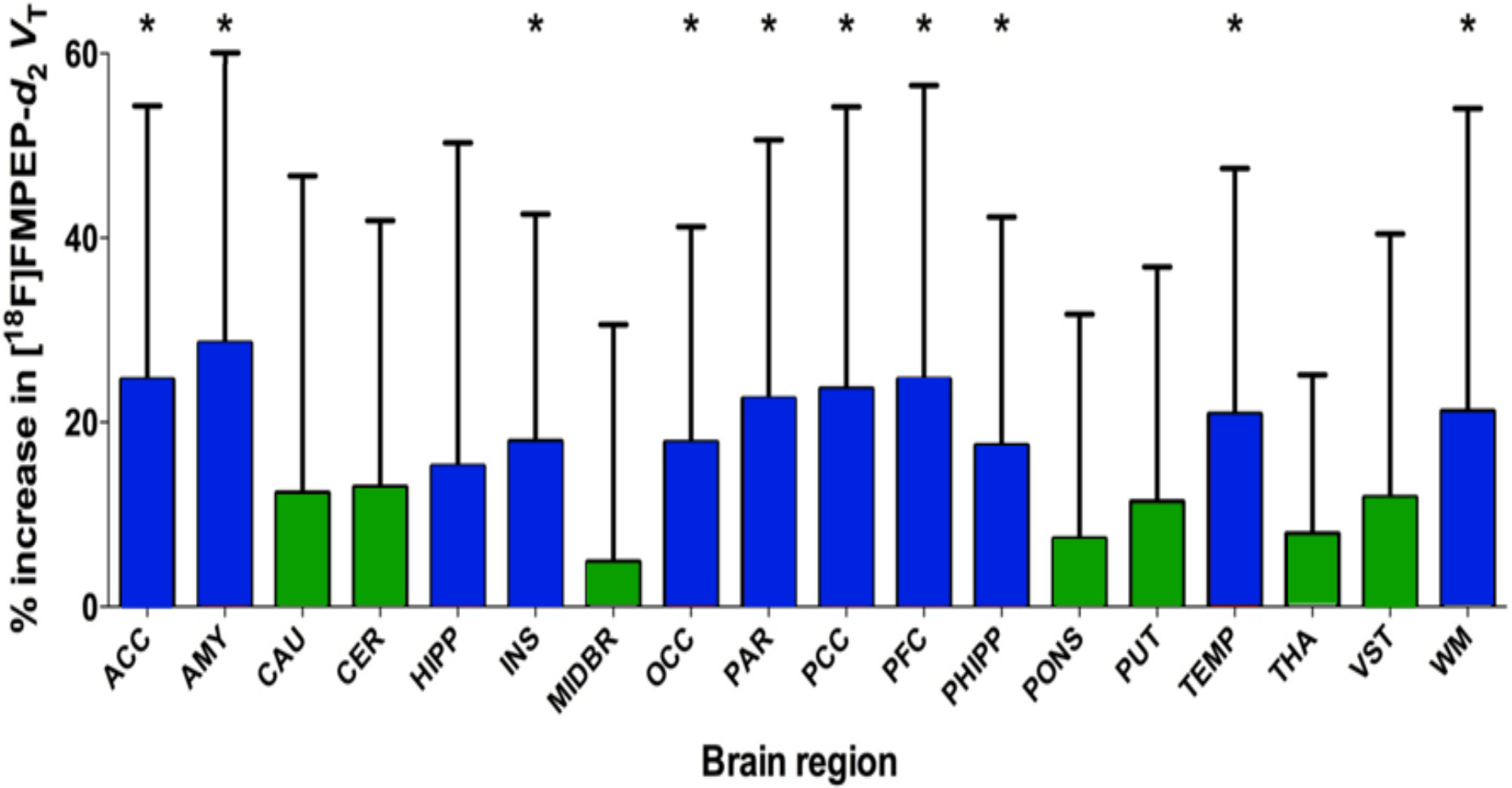
Effects of Chronic Cannabis Exposure on Cannabinoid Receptor Density

- New CB-1 cannabinoid receptor ligand for PET studies, [18F]FMPEP-d2
- Collaboration with Bob Innis & Jussi Hirvonen of NIMH
- Imaged chronic daily cannabis smokers on admission to monitor CB1-cannabinoid receptor density
- Imaged chronic daily cannabis smokers after 30 days sustained abstinence

CB_1-Cannabinoid Receptors Specifically Downregulated in Cortical Regions of Chronic Daily Cannabis Smokers (N=30) as Compared to Controls (N=28)



CB_1 Cannabinoid Receptors Significantly Increased after Sustained Cannabis Abstinence (N=14)



Synthetic Cannabinoids Pharmacokinetics

- Teske et al 2010
  - 50µg/kg smoked JWH-018 to 1 M & 1 F
  - Serum collected 5 min to 48 h, LOD 0.07 µg/L
  - JWH-018 identified 5 min up to 48 h F, 24 h M
- Logan et al 2011
  - Smoked 3 puffs JWH-018 & JWH-073 within 30 min
  - Parent & metabolites identified 30 min (1st sample - 4h in blood)

Synthetic Cannabinoids Pharmacokinetics

- Metabolism
  - Phase I (hydroxylation, carboxylation, dealkylation)
  - Phase II (glucuronidation)
  - Parent compound rarely found in urine
  - Critical to define metabolism of new designer drugs to permit identification of exposure

Synthetic Cannabinoids in Human Biological Specimens

Drug	Matrix	Concentration	Herbal Product
AM-2201	Femoral blood Oral fluid Serum	0.3 ng/g 0.33 – 22 ng/mL 9.5 ng/mL	Haze Unknown Unknown
AM-694	Femoral blood Serum	0.09 ng/g 0.20 ng/mL	Unknown Sweed
JWH-015	Serum	<10 ng/mL	Maya
JWH-018	Blood Femoral blood Hair Oral Fluid Serum	0.1 – 199 ng/mL 0.05 ng/g 5.1 – 5.7 pg/mg 0.15–.53 ng/mL 0.13 – 11 ng/mL	Unknown Haze Unknown Unknown K2 Summit, Smoke, Spice, Maya, Ninja

Synthetic Cannabinoids in Human Biological Specimens

Drug	Matrix	Concentration	Herbal Product
JWH-019	Oral Fluid Serum	<0.15 ng/mL 11 ng/mL	Unknown Unknown
JWH-072	Urine	111 ng/mL	Unknown
JWH-073	Blood CSF Hair Serum	.1–68.3 ng/mL 19 ng/mL 0.7–21 pg/mg 0.11–71 ng/mL	Unknown Unknown Unknown Maya
JWH-081	Blood Hair Serum	1.2–42 ng/mL 5.1–31 pg/mg 6 ng/mL	Jamaican Gold, Ninja Strong Unknown Unknown
JWH-122	Serum	0.17–40 ng/mL	Monkees go bananas, Tropical car, Lava Red, & others
JWH-210	Serum	0.20–190 ng/mL	Maya, Push, Bonzai Remix, Spice, Jamaican Gold

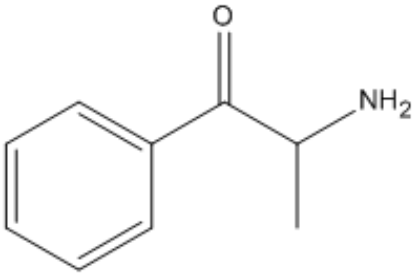
Synthetic Cannabinoids in Human Biological Specimens

Drug	Matrix	Concentration	Herbal Product
JWH-250	Hair Serum	0.5–14 pg/mg 0.10–14 ng/mL	Unknown Monkees go bananas, Bonzai
JWH-307	Serum	53 ng/mL	Unknown
MAM2201	Plasma	49 ng/mL	Samurai King
RCS-4	Serum	0.3 ng/mL	Unknown
JWH-018 N-pentanoic acid	Urine	11.6–11,182 ng/mL	Unknown
JWH-018 N-5-OH-pentyl	Urine	2.5–5,350 ng/mL	Unknown

Bliss Panic Bath Salts
MPH Red Dove Kick
Blue Silk Power Surge
Zoom Ivory Wave
Vanilla Sky

Synthetic Cathinones
MDPV, Mephedrone, Butylone

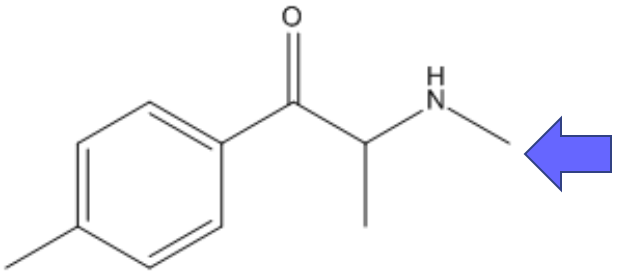
1st Generation Synthetic Cathinones



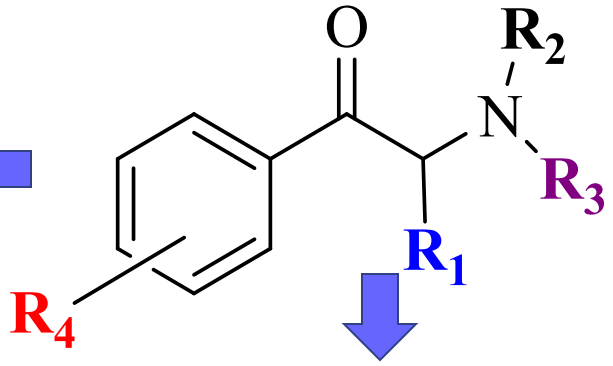
Cathinone

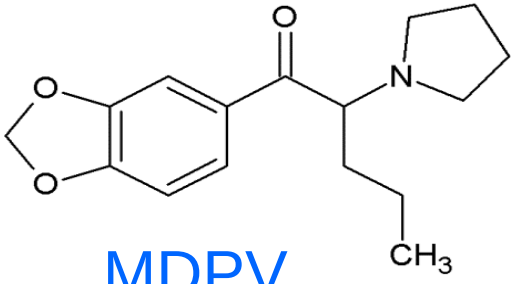
Phenyl ring substitution

3,4 methylenedioxy
& pyrrolidinyl substitution



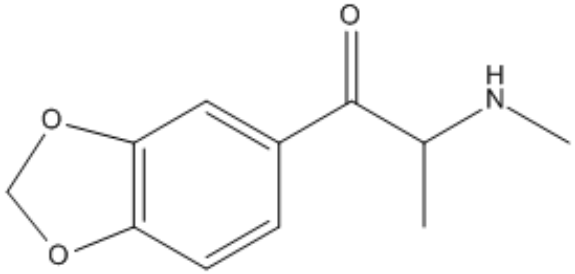
Mephedrone





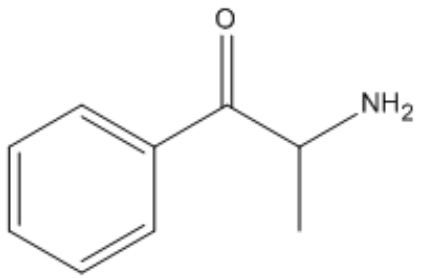
MDPV

3,4 methylenedioxy
substitution

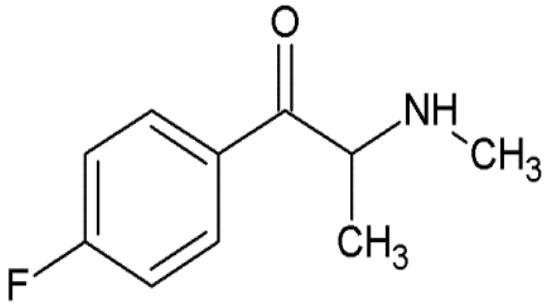


Methylone

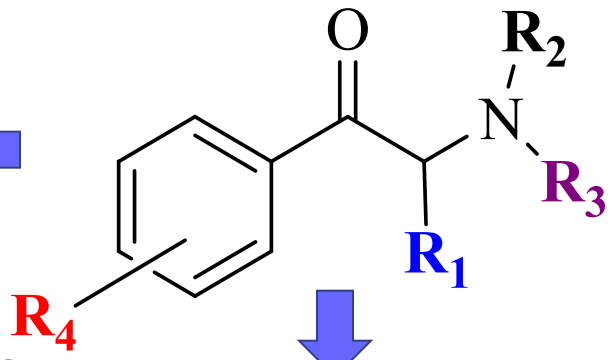
2nd Generation Synthetic Cathinones

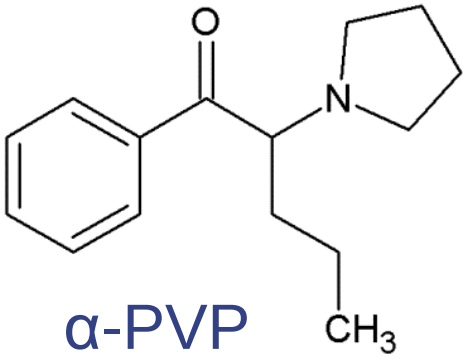


Cathinone

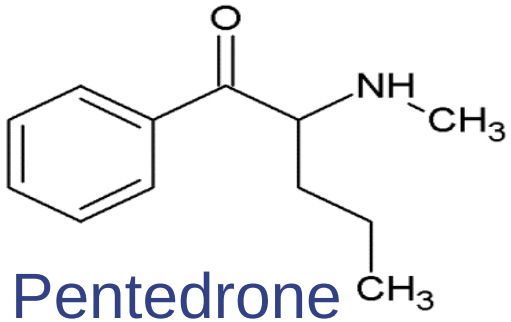


4-Fluoromethcathinone
(4-FMC)





α-PVP



Pentedrone

Naphyrone, 3-FMC, Buphedrone, MDPPP, 4-MEC, Methedrone, Benzedrone, MDPBP, Ethylone, Butylone, & **more**!

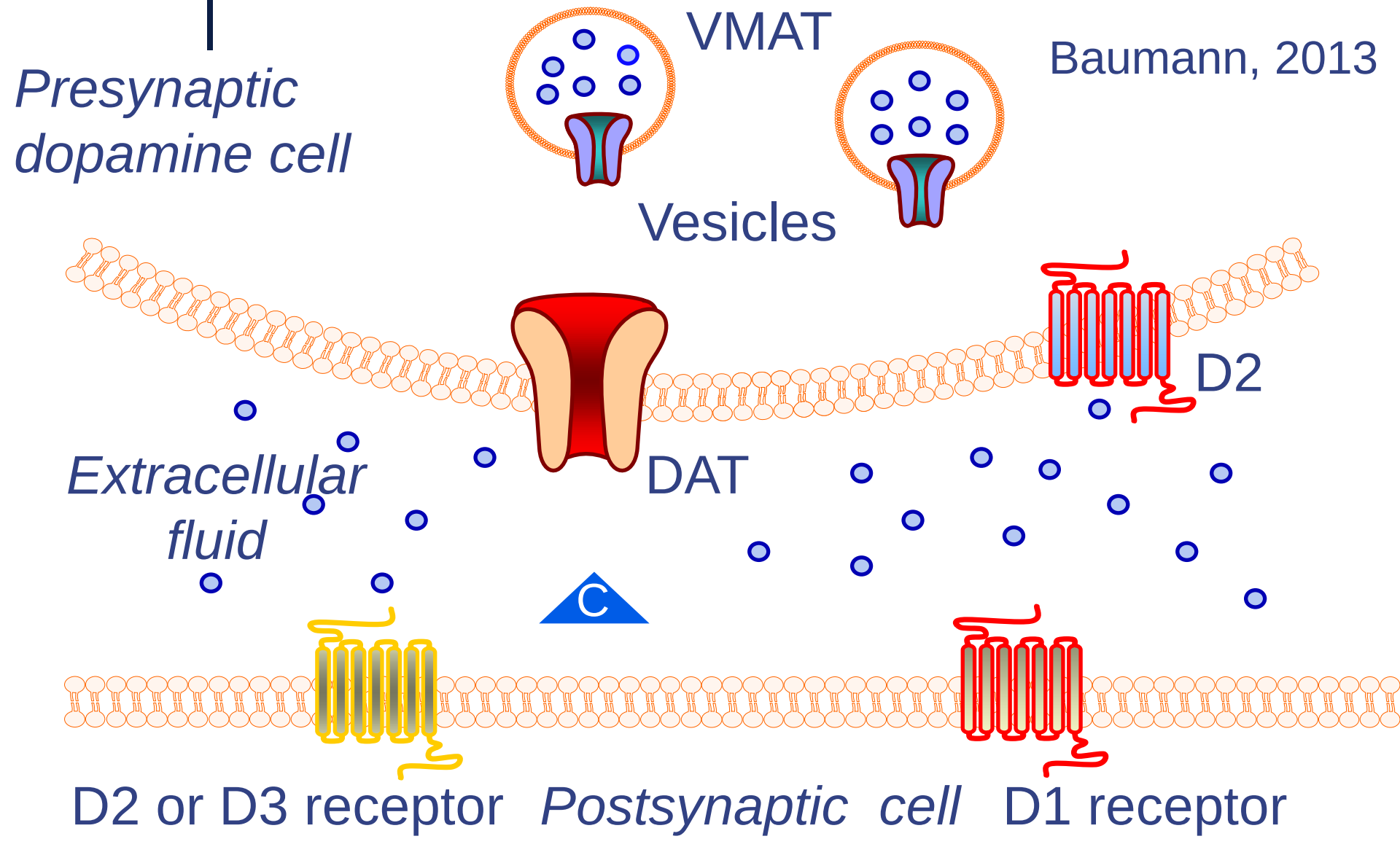
Misuse of Synthetic Cathinones Growing Public Health Concern

- 1st US poison control case in July 2010
- Within 1 year >4,000 cases reported
- >90% of cases in emergency departments
- Keto moiety typically less potent
- Pyrrolidophenones typically potent (MDPV)
- Longer the alkyl substituent lower the potency

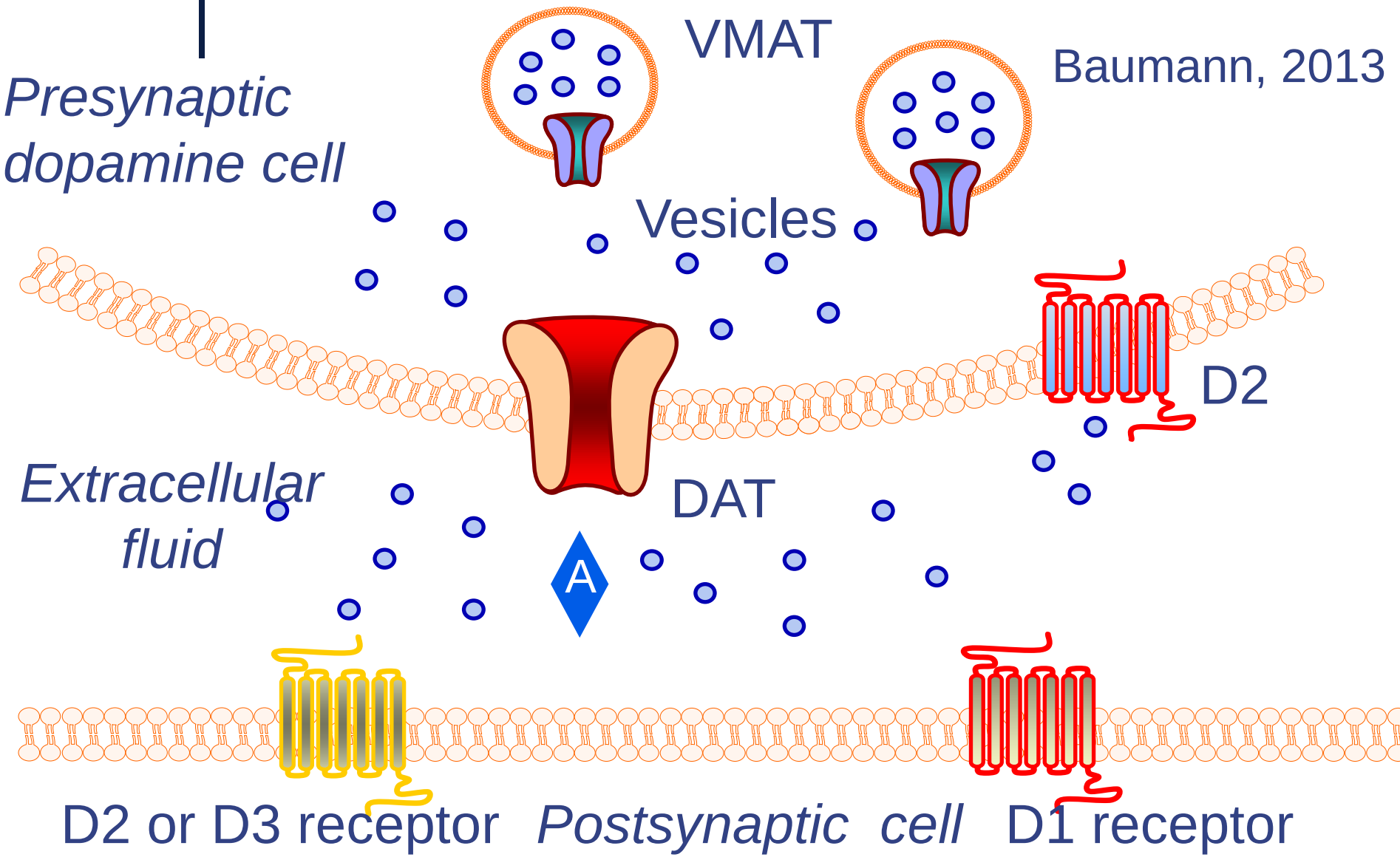
Synthetic Cathinones

- Intranasal, injection & oral (dabbing, bombing) administration
- Doses vary with route & potency (5 mg – 5 g)
- Increase in designer cathinone use may be driven by lack of *Ecstasy (Brundt et al., 2010*

Cocaine Blocks Dopamine Reuptake by Dopamine Transporter (DAT)



Amphetamine Enters Cell as DAT Substrate, Releasing Dopamine by Reverse Transport



Designer Cathinones Interact with Monoamine Transporters

- Two types of interaction with transporters
  - Transporter blockers inhibit transmitter reuptake
  - Transporter substrates *(i.e., releasers)* enter cells & reverse normal direction of flux, cause transmitter release
- Drugs that interact with DAT are highly addictive
  - Cocaine is a DAT blocker
  - Amphetamine is a DAT substrate

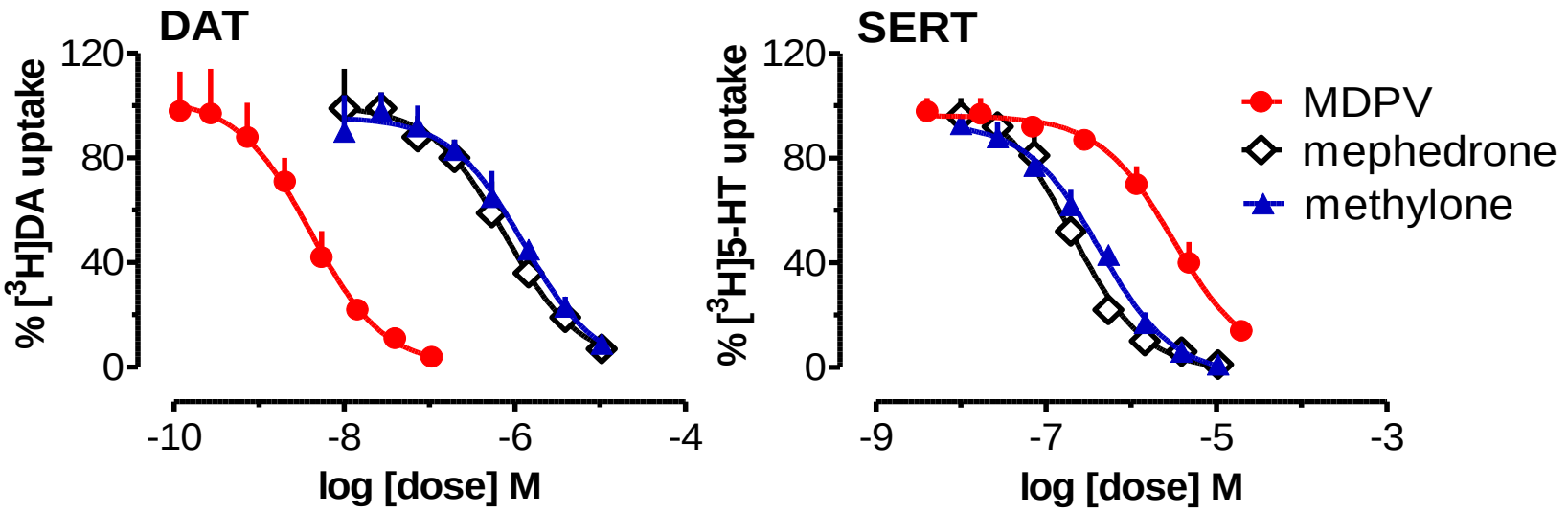
Mechanisms of Action

- Mephedrone & methylone are substrates or monoamine releasers at transporters (like MDMA) *Baumann et al., 2012*
  - Dose-related increase in extracellular dopamine & serotonin (5-HT)
  - Methylone similar profile but ~ ½ as potent as mephedrone
- Pyrovalerone is dopamine transporter blocker (like cocaine) *Meltzer et al., 2006*

Mechanisms of Action

- MDPV potent dopamine & norepinephrine blocker (100X greater) than weak 5-HT effects
  - Surprising, due to 3,4-methylenedioxy group
  - Pyrovalerone has similar effects
  - Norepinephrine (NET) effects explain potential dangerous cardiovascular effects
  - MDPV inhibits dopamine clearance with higher potency & efficacy than cocaine (10-fold)

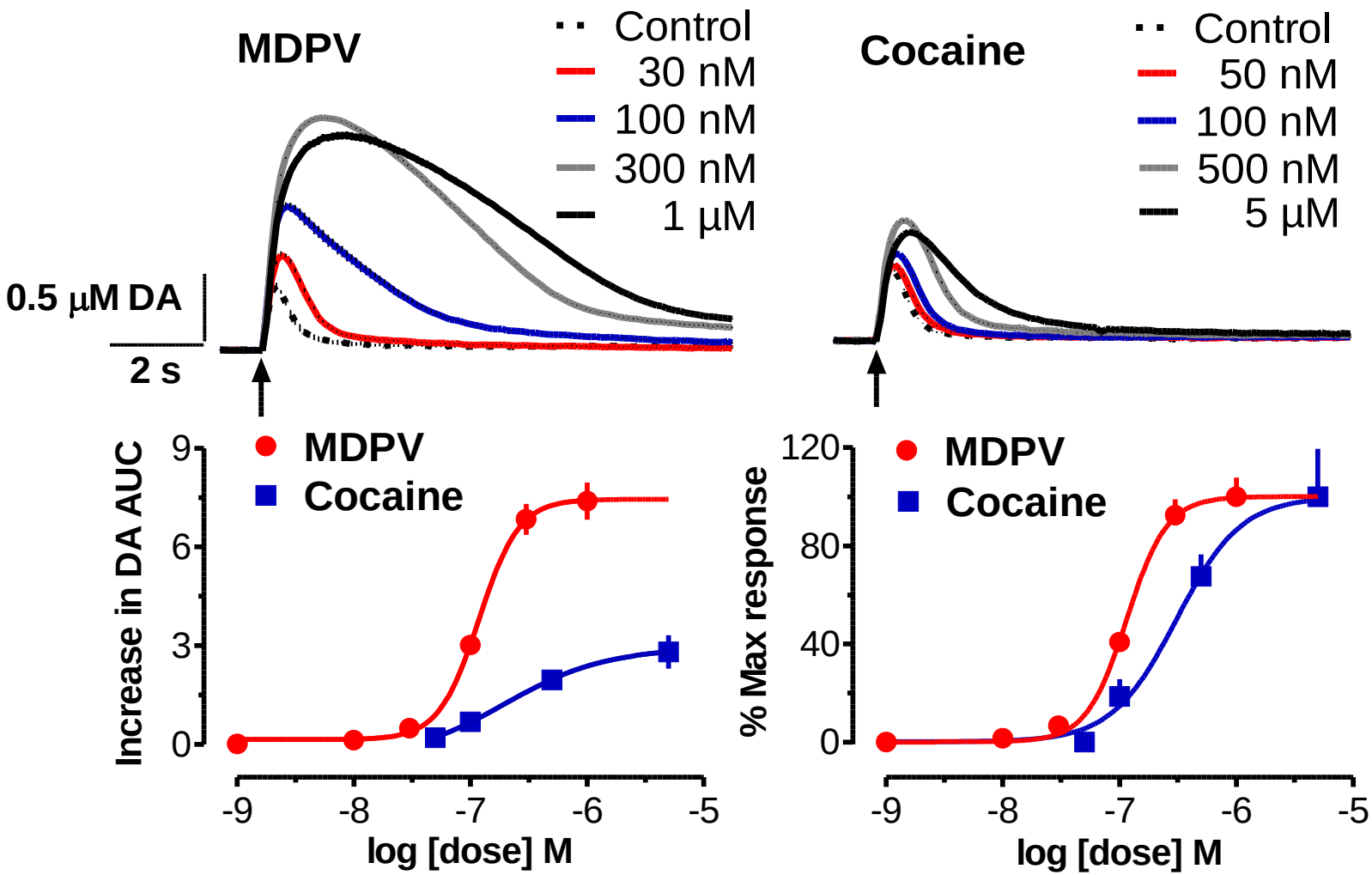
MDPV Potent Dopamine Uptake Blocker, Weaker Serotonin Effects



Drug	Dopamine IC50, nM	5-HT IC50, nM	DA/5-HT ratio
MDPV	**4.4 ± 0.3**	**2556 ± 653**	**580**
Mephedrone	765 ± 53	416 ± 29	0.5
Methylone	1684 ± 275	668 ± 144	0.4

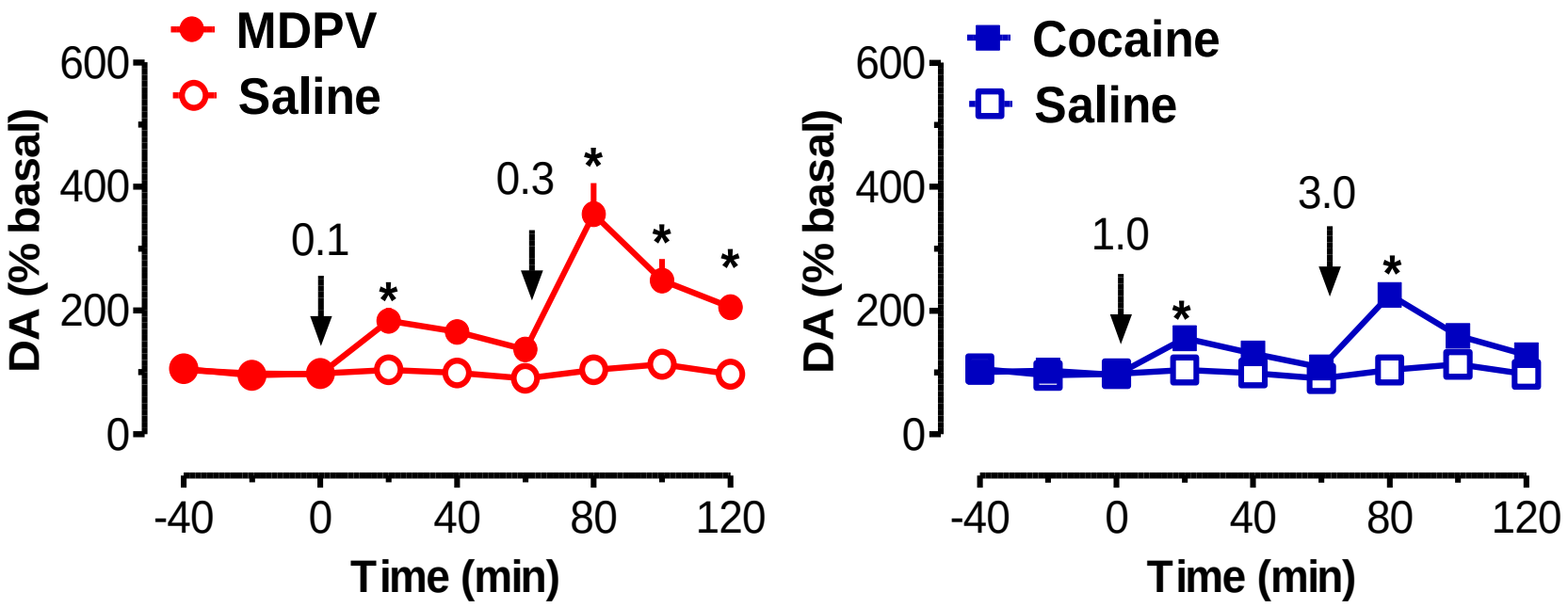
Baumann et al., 2012

MDPV Greater Potency & Efficacy than Cocaine for Inhibiting Dopamine Clearance



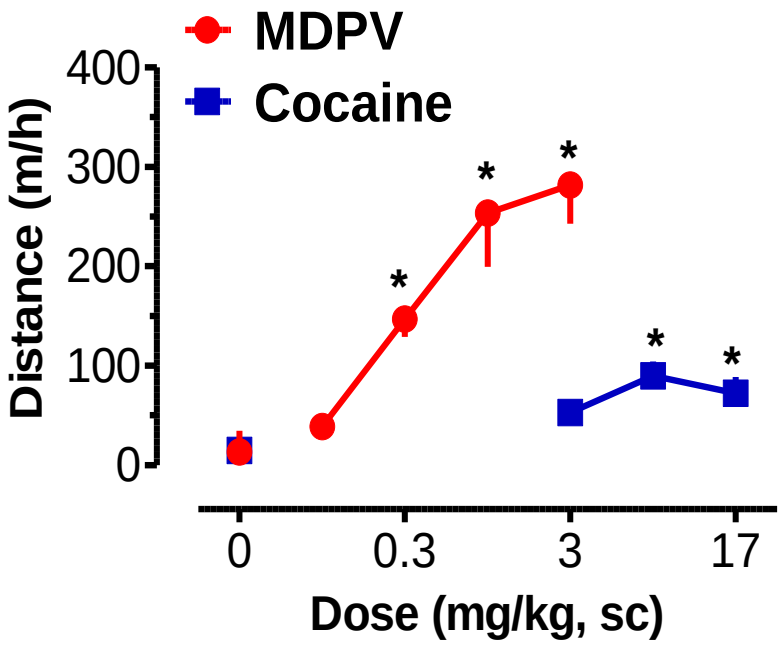
Baumann et al., 2012

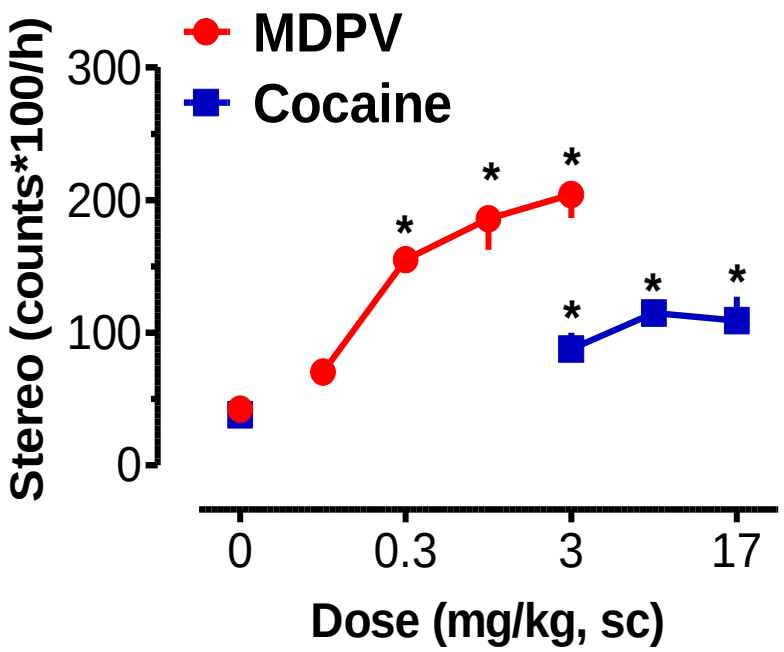
MDPV Increases Dialysate Dopamine Levels in Rat Nucleus Accumbens



- MDPV at least 10-fold more potent than cocaine
- MDPV effects sustained compared to cocaine

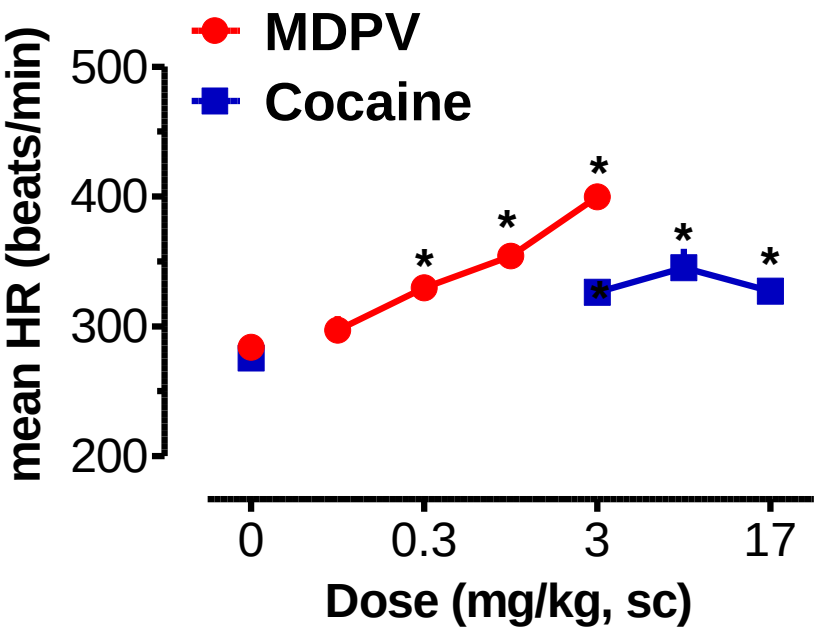
MDPV Elicits Robust Dose-related Hyperactivity in Rats

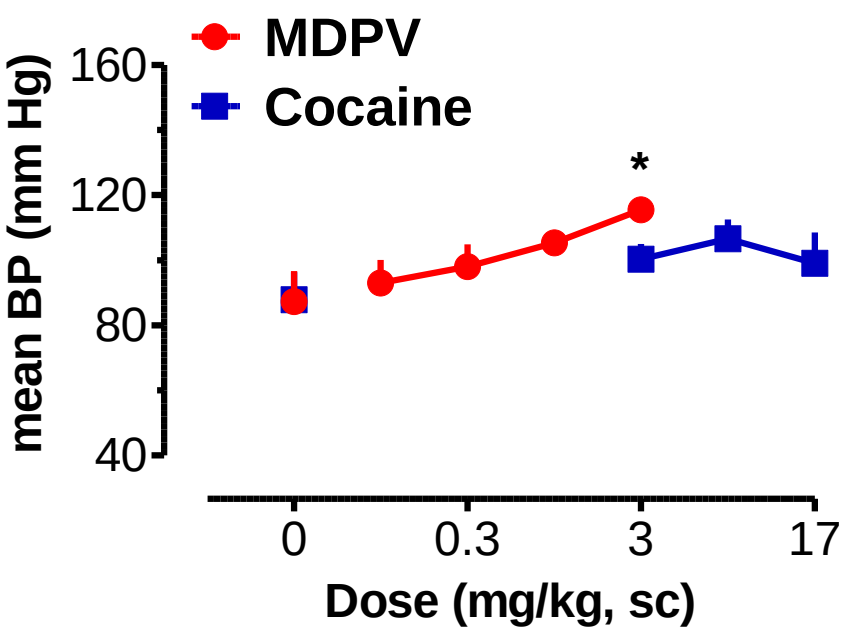




- MDPV at least 10-fold more potent than cocaine
- MDPV more efficacious than cocaine

MDPV Increases Heart Rate & Blood Pressure in Rats More Than Cocaine





- MDPV at least 10-fold more potent than cocaine
- MDPV more efficacious than cocaine

Preclinical Cathinone Exposure

- Rapid onset of increased:
  - Locomotion
  - Heart rate
  - Blood pressure
  - Body temperature
  - Ataxia (3-FMC)
  - Convulsions (methylone)
  - Exploration (methylone, 3-FMC)
  - No dopamine neurotoxicity

Preclinical Cathinones Pharmacology

- Fantegrossi 2013
  - MDPV dosing to mice at warm temperatures
  - Potentiated motor activity,
  - Self-injurious behavior at high doses
  - Profound stereotypy
  - Only hyperthermic effects at warm temperatures; greater risk with drug use in warm environment

Preclinical Cathinones Pharmacology

- Mephedrone & methylone: no long lasting effects on brain monoamines but high doses cause selective brain serotonin depletion
- Preclinical locomotor & self-injurious behavior predict agitation, psychosis & violence in humans
- MDPV users prone to develop excited delirium, also seen in PCP users, possibly due to MDPV lipophilicity of & ability to cross BBB (Penders 2013)

Human Cathinone Exposure

- Effects similar to MAMP, cocaine & MDMA
- Phenethylamine core responsible for stimulatory effects
- Methylenedioxy group for empathogenic effect Penders et al 2012
  - Low doses: euphoria & increased alertness
  - High doses: life threatening excited delirium, agitation, psychosis, hallucinations, tachycardia & death
  - Renal failure & skeletal muscle breakdown

Human Cathinone Effects

- Borek 2012
  - Multiorgan failure
- No human studies examining acute vs chronic cathinone exposure

Emergency Room Symptoms N=236

Agitation	82%
Combative/violent behavior	57%
Tachycardia	56%
Hallucinations	40%
Paranoia	36%
Confusion	34%
Myoclonus/movement disorders	19%
Hypertension	17%
Chest pain	17%
CPK elevations	9%

Spiller et al., 2011

1st Responder Reports Spiller et al 2011

- Adult male shoots out windows of house while aiming at “strangers”
- Adult female, confused & agitated, leaves 2 year old child in middle of highway because child has “demons”
- Adult male jumps out of window to flee from non-existent “pursuers”
- Adult male breaks all windows in house & wanders barefoot through broken glass

Cathinone Pharmacokinetics

- No controlled human studies, but *in vivo* rat & *in vitro* human liver microsomes (HLM) & hepatocytes data
- Phase I (demethylenation, O-methylation, N-dealkylation, reduction of keto moiety)
  - CYP2D6, CYP2B6, CYP1A2, CYP2C19
- Phase II (glucuronidation & sulfation)
  - Unchanged parent compounds in urine at high concentrations, some conjugates

Fatal Cathinone Concentrations

Drug	Matrix	µg/L	Other Drugs	Case	Ref.
Butylone	Blood	22,000	ND	Suicide overdose	Rojek 2012
Mephedrone	Blood	5,500	ND	Fatality	Adamowicz 2013
Methylone	Heart blood	1,100	MDPV 30µg/L	Fatality	Cawrse 2012
Methylone	Peripheral blood	670	ND	Fatality	Cawrse 2012
Methylone	Peripheral blood	560	ND	Fatality	Pearson 2012
Methylone	Heart blood	111	ND	Fatality	Cawrse 2012

Synthetic Cathinones Concentrations

Drug	Matrix	µg/L	Other Drugs	Case	Ref.
MDPV	Blood	220	Opiates, Bupropion	Fatality	Microgram Nov 2012
MDPV	Heart blood	470	Methylone: 60µg/L	Fatality	Cawrse 2012
MDPV	Serum	670	ND	Fatality	Murray 2012
MDPV (N=259)	Blood	16-8400	23% MDPV only	Driving	Kriikku 2011
MDPV	Blood	24-241	Not reported	Poison center	Spiller 2011
MDPPP	Serum	154	JWH-072:16 MDA:11µg/L	ED visit	Thorton 2012
Flephedrone	Serum	346	MDPV:	ED visit	Thorton

Summary & Conclusions

- MDPV is primary synthetic cathinone found in US cases
- Could be due to improved stability
- MDPV produces observed adverse effects
- MDPV at least 10-fold more potent than cocaine *in vivo* at blocking dopamine uptake
- MDPV has unique pharmacology for cathinones
- Antagonism of excess DA signaling may aid in management of synthetic cathinone ED cases

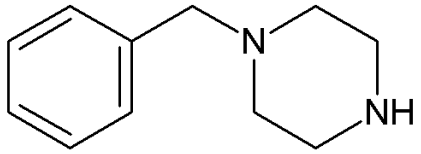
A2 Blast Bolts BZP Cosmic Kelly ESP Euphoria Exodus Fast Lane Happy Pills Legal E Nemesis Party Pill

Synthetic Piperazines

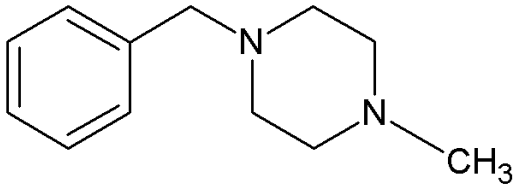
BZP, TFMPP, mCPP

Piperazine Structures

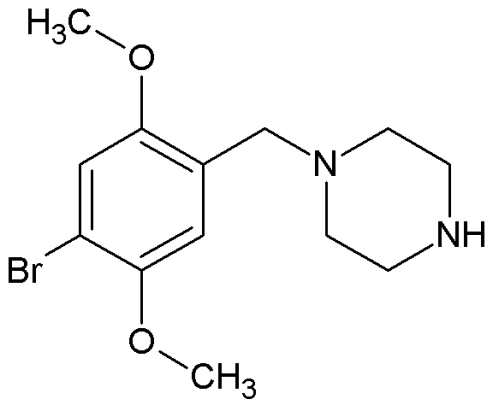
Benzylpiperazines



1-BZP

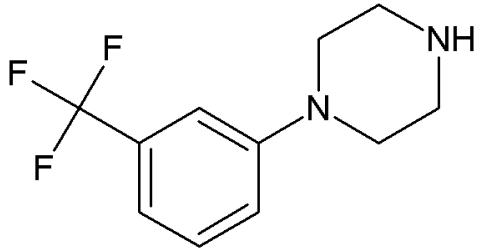


MBZP

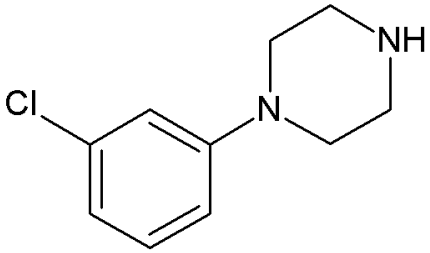


2C-B-BZP

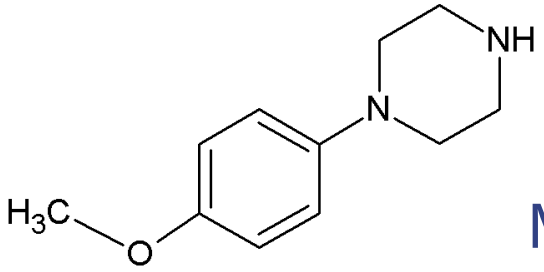
Phenylpiperazines



TFMPP



mCPP



MeOPP

Piperazines

- BZP developed in 1950's to treat worms & 1970's as anti-depressant
- Stopped due to amphetamine-like effects
- Recreational use 1st reported in 1990s
- BZP & TFMPP temporarily placed into Schedule I (2002)
- TFMPP removed from the list in 2004
- Both drugs often found in MDMA tablets

Piperazine Mechanisms of Action

- Stimulate release & inhibit reuptake of dopamine, serotonin & norepinephrine
- In animals, potency lower than d-AMP, d-MAMP & d-MDMA
- BZP effects are dose-related as it is both a partial agonist & antagonist at 5-HT receptor
- Little human data, but observed effects showed similar symptoms to MDMA exposure

Preclinical Piperazine Pharmacology

- BZP induced dose-dependent anxiety, locomotion & hyperactivity
- At high 10 mg/kg dose, BZP produced seizures in rats
- 0.13 – 0.5 mg/kg IV BZP substituted for 0.06 – 0.5 mg/kg cocaine in self-administration study in rhesus monkeys
- In drug discrimination studies, BZP substituted for amphetamines in rodents & primates

Preclinical Piperazine Pharmacology

- TFMPP alone did not increase locomotion
- TFMPP did not substitute for cocaine or amphetamines
- BZP & TFMPP induced lower self-administration than BZP alone

Human Piperazine Pharmacodynamics

- Lin et al 2009
  - 200 mg BZP in 27 females
  - Similar effects
  - No pharmacokinetics samples
  - 200mg BZP vs placebo increased blood pressure, heart rate & feelings of self-confidence

Human Piperazine Pharmacodynamics

- Lin et al 2011
  - Randomized, double blind, N=36 males
  - Evaluated 2 h prior and after dosing
  - ARCI, VAS & POMS
  - No pharmacokinetics samples
  - 100/30mg BZP/TFMPP (single dose) vs placebo increased blood pressure, heart rate & feelings of self-confidence (similar to 200 mg BZP alone)

Human Piperazine Pharmacodynamics

- Thompson et al. 2010
  - Within-subject, cross-over design, 4 treatments
    - 300mg/74mg BZP/TFMPP & placebo alcohol
    - 300mg/74mg BZP/TFMPP & 57.6 g alcohol
    - Placebo piperazine & 57.6 g alcohol
    - Placebo piperazine & placebo alcohol
  - Evaluated driving performance & physiological effects

Human Piperazine Pharmacodynamics

- Only 35/64 subjects completed due to adverse events
  - 4/10 BZP/TFMPP only & 3/7 BZP/TFMPP with EtOH experienced adverse events
  - Agitation, anxiety, vomiting, insomnia, migraine, hallucinations, & increased BP & heart rate
  - No effects when placebo &/or EtOH only

Human Piperazine Pharmacodynamics

- BZP/TFMPP improved driving performance
  - Decreased standard deviation of lateral position (SDLP) 4.2 cm
- EtOH decreased driving performance when combined with BZP/TFMPP by increasing SDLP by 2.3 cm (non-significant increase)

Piperazine Pharmacokinetics

- Antia et al *J For Science* 2010
  - 200 mg oral BZP: C_{max} 262 µg/L, T_{max} 75 min
    - Detectable in plasma < 30h
  - 60 mg oral TFMPP: C_{max} 24.1 µg/L, T_{max} 90 min

Piperazine Pharmacokinetics

- Metabolism/Elimination
  - Phase I (hydroxylation); metabolized by CYP2D6, CYP1A2 & CYP3A4
  - Phase II (glucuronidation & sulfate conjugate)
  - BZP major metabolites 3 & 4-OH-BZP, O & N-BZP-sulfate found in urine for more than 24 h
- TFMPP has two half-lives 2.0 & 6.0 h
- TFMPP metabolites 4-OH-TFMPP

Piperazine Pharmacokinetics

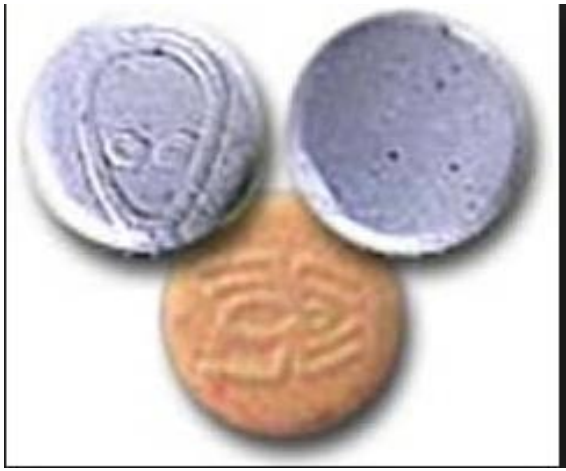
- Metabolism/Elimination
  - mCPP is a metabolite of trazodone, nefazodone, enziprazole & etoperidone
  - When mCPP ingested, p-OH-mCPP metabolite detected in blood, plasma, urine

Piperazine Fatalities

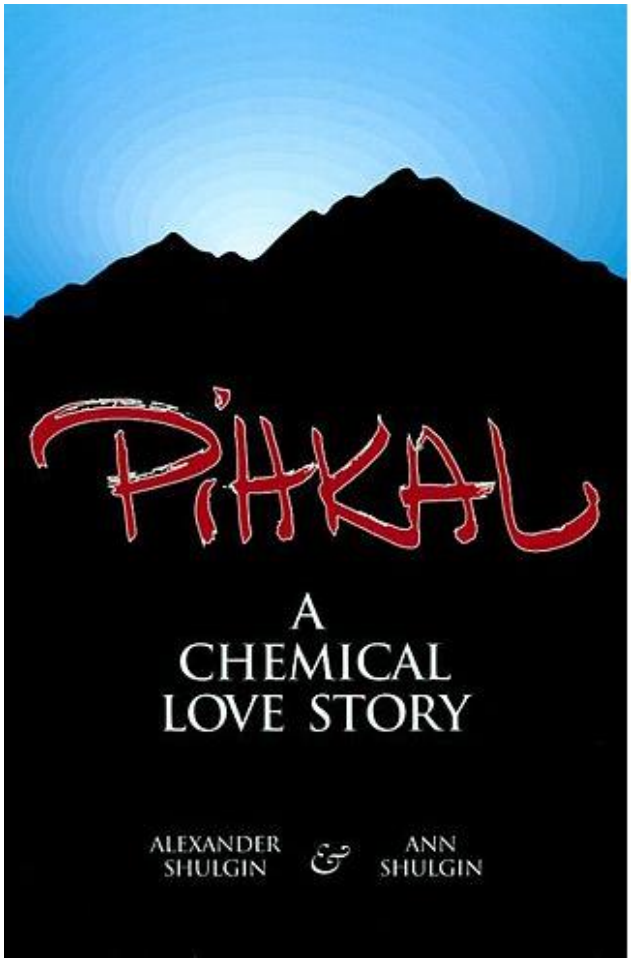
- Elliot et al 2011
  - BZP postmortem: 0.5 – 1.4 mg/L (femoral blood); 4.9 - 15.7 mg/L (urine)
  - TFMPP postmortem: 0.05 – 0.15 mg/L (femoral blood); 0.9 – 1.0 mg/L (urine)
  - Other drugs reported: benzodiazepines, cocaine, ketamine, amphetamine &/or EtOH

Summary & Conclusions

- BZP is a more potent stimulant than TFMPP
- BZP & TFMPP improved driving performance at low doses, but produced adverse effects such as agitation, anxiety, hallucinations, insomnia, & migraine
- Need more pharmacokinetic data on mCPP



Synthetic Hallucinogens
Tryptamines (5-MeO-DiPT, Foxy) & Phenethylamines (DOM, 2C-B)

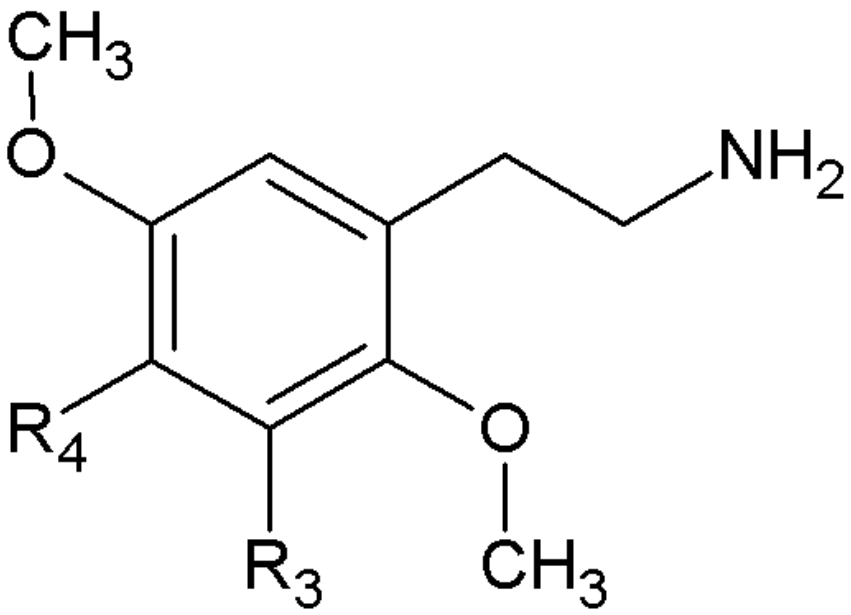


Phenylethylamines I Have Known & Loved

by Alexander & Ann Shulgin

1991

Phenethylamine 2C Structures



2,5-dimethoxyphenethylamine (2C-H)

2C-B (R4: Br)
2C-C (R4: Cl)
2C-D (R4: CH_3)
2C-E (R4: CH_2CH_3)
2C-I (R4: I)
2C-N (R4: N_2O)
2C-P (R4: $CH_2CH_2CH_3$)
2C-T (R4: S)
2C-T2 (R4: S-CH_2CH_3)
2C-T4 (R4: S-isopropyl)
2C-T7 (R4: S-propyl)

PIHKAL

- Shulgin synthesized >200 psychoactive compounds in his laboratory at UCSF
- Book covers synthesis, bioassay, dosages & effects
- Synthetic Drug Abuse & Prevention Act 2012
  - Nine 2C on Schedule I

2C Mechanisms of Action

- Little data on pharmacological & toxicological properties of 2C series
- Have affinity to 5-HT_2 receptors & act as agonists or antagonists at different receptor subtypes

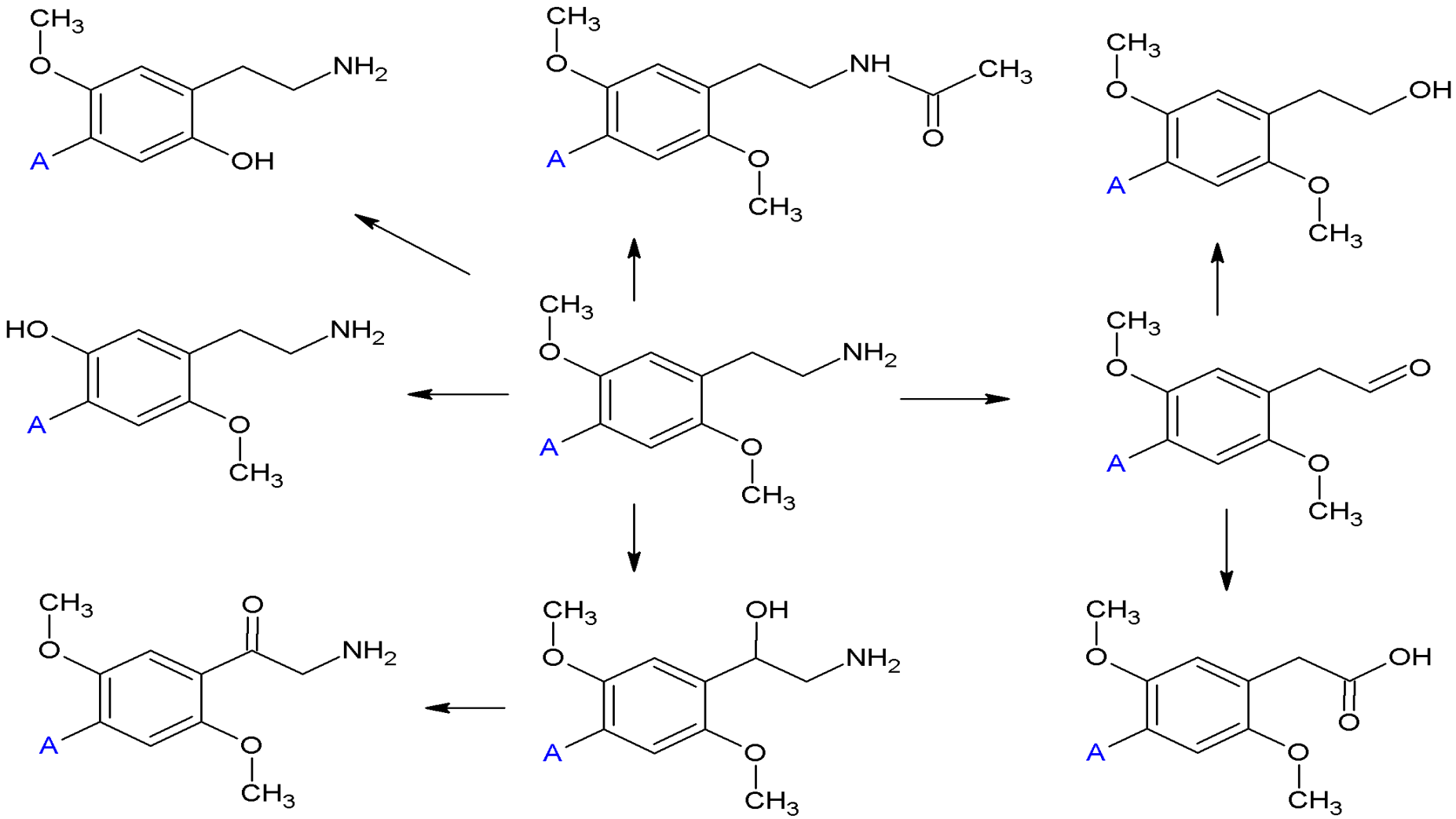
2C Pharmacology

- Clinical Effects Dean et al. 2013 *J Med Tox*
  - Route of administration: oral, insufflation
  - Hallucinations, euphoria, empathy, nausea, vomiting, agitation, tachycardia, hypertension, respiratory depression & delirium, seizures, psychosis & suicidal thoughts
  - Excited delirium: delirium with agitation → violence
  - Hyperactivity → hyperthermia → cardiopulmonary arrest
  - 2C intoxication & overdose reported

2C	Chemical Name	Dosage mg	Duration h
2C-B	4-Bromo-2,5-dimethoxyphenethylamine	12–24	4–8
2C-C	4-Chloro-2,5-dimethoxyphenethylamine	20–40	4–8
2C-D	4-Methyl-2,5-dimethoxyphenethylamine	20–60	4-6
2C-E	4-Ethyl-2,5-dimethoxyphenethylamine	10-25	8-12
2C-G	3,4-Dimethyl-2,5-dimethoxyphenethylamine	20–35	18-30
2C-G-3	3,4-Trimethylene-2,5-dimethoxyphenethylamine	16-25	12-24
2C-G-5	3,4-Norbornyl-2,5-dimethoxyphenethylamine	10-16	32-48
2C-I	4-Iodo-2,5-dimethoxyphenethylamine	14–22	6–10
2C-N	4-Nitro-2,5-dimethoxyphenethylamine	100–150	4–6
2C-P	4-Propyl-2,5-dimethoxyphenethylamine	6-10	10-16

2C	Chemical Name	Dosage mg	Duration h
2C-SE	4-Methylseleno-2,5-dimethoxyphenethylamine	~100	6–8
2C-T	4-Methylthio-2,5-dimethoxyphenethylamine	60-100	3-5
2C-T-2	4-Ethylthio-2,5-dimethoxyphenethylamine	12-25	6-8
2C-T-4	4-Isopropylthio-2,5-dimethoxyphenethylamine	8–20	12–18
2C-T-7	4-Propylthio-2,5-dimethoxyphenethylamine	10–30	8–15
2C-T-8	4-Cyclopropylmethylthio-2,5-dimethoxyphenethylamine	30–50	10–15
2C-T-9	4-(t)-Butylthio-2,5-dimethoxyphenethylamine	60–100	12–18
2C-T-13	4-(2-Methoxyethylthio)-2,5-dimethoxyphenethylamine	25–40	6–8
2C-T-15	4-Cyclopropylthio-2,5-dimethoxyphenethylamine	>30	Few h
2C-T-17	4-(s)-Butylthio-2,5-dimethoxyphenethylamine	60–100	10–15

2C-B Metabolism by Human Hepatocytes Meyer & Maurer *Current Drug Metabolism* 2010



2C Metabolism

- Meyer & Maurer Current Drug Metabolism 2010
  - Primarily *O*-demethylation in position 2 or 5 of aromatic ring &/or reduction to alcohol
  - 2Cs containing sulfur undergo sulfoxidation
  - Monoamine oxidases (MAO-A & MAO-B) important for deamination
  - Phase II: glucuronidation &/or sulfation

2C Deaths

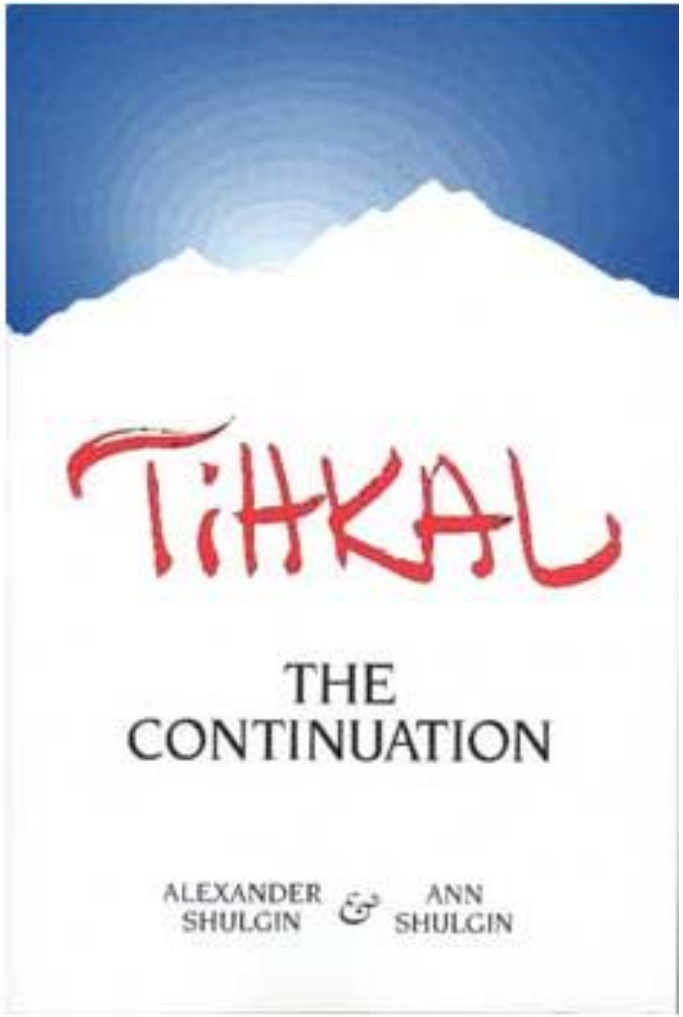
Age/sex	Agent	Route	Dose	Symptoms
20 y M	2C-T-7	Snorted	35 mg	Vomiting, hallucinations, agitation, aggression, nasal bleeding, possible seizure activity, pulmonary edema, cardio/pulmonary arrest
17 yr M	2C-T-7	Snorted	?	Agitation, violence, aggression, possible hyperthermia (removal of clothing), rigidity, cardio-pulmonary arrest
Age ? M	2C-T-7 & MDMA	?	? 2CT-7; 200 mg MDMA	Agitation, aggression, violence, seizures, hallucinations, cardio/pulmonary arrest, cerebral hemorrhage

2C Deaths

Age/sex	Agent	Route	Dose	Symptoms
19 y M	2C-E	Snorted	?	Aggressive/agitation, hyperthermia, DIC, multi-organ failure
17 y M	2C-I-NBOMe	Oral	?, mixed with chocolate	Hyperventilation, foaming at mouth
18 y M	2C-I-NBOMe	?	?	?
22 y M	2C-T-21	Oral	? dipped tongue into powder	Hyperthermia (108 °C), seizures, coma

Summary

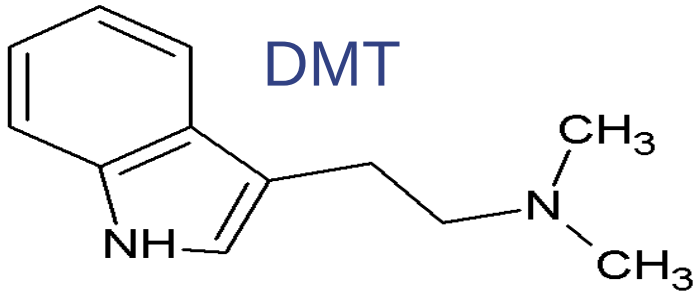
- Phenethylamines 2C series produce effects similar to Ecstacy
- Human pharmacokinetic data limited
- 2C-B metabolism produces multiple metabolites in human hepatocytes



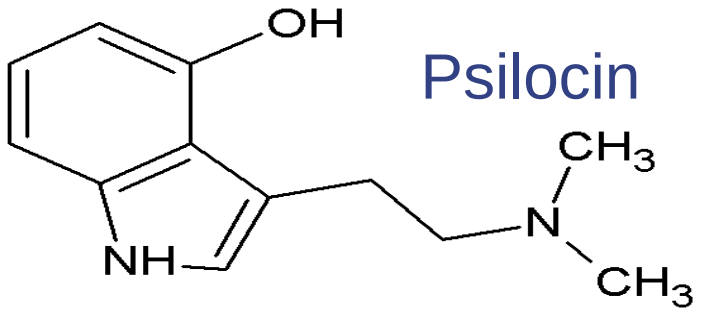
Tryptamines I Have Known & Loved

Tryptamines

DMT



Psilocin



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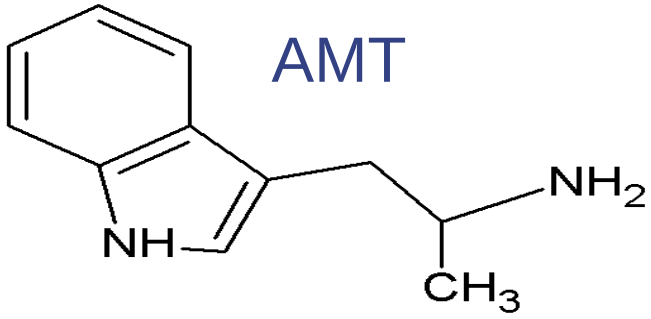
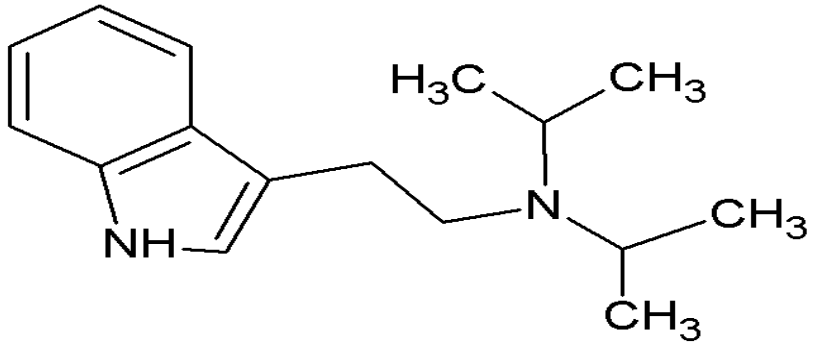


DiPT*



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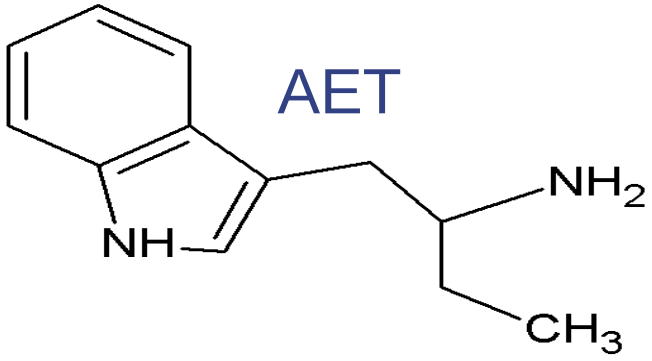
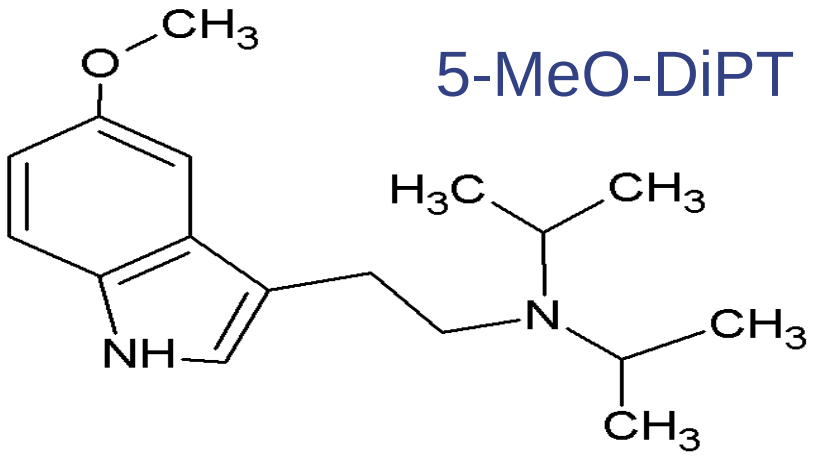


5-MeO-DiPT



* Not DEA scheduled

Tryptamines

- Tryptamines produce hallucinations in humans
- Endogenous tryptamines are derived from tryptophan & converted via biological pathways
- High affinity for 5-HT_2 serotonin receptors
- Little binding affinity data available for synthetic tryptamines
- Only 5-MeO-DiPT studied in rodent brain

Tryptamines

- 5-MeO-DiPT one of 25 most frequently identified drugs, increased 36-fold between 2010-2011 (NFLIS)
- Tryptamines Schedule I in 2004
- Psilocybin, a natural occurring tryptamine, is converted to psilocin (also Schedule I)
- Often found with BZP, TFMPP, MDMA & synthetic cathinones
- LSD is considered part of tryptamine family

Tryptamines Pharmacology

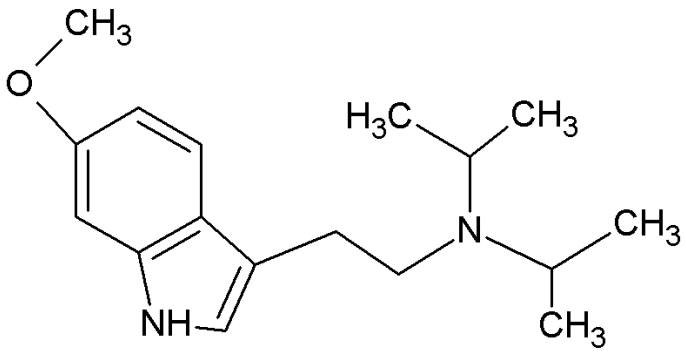
- Administered orally, insufflation & smoking
- Self-reported human effects (Shulgin, 1997)
  - Entheogenic (feeling divine within), euphoric, sensual, visual hallucinations, “out of body” experience, reduced limb control, nausea, anxiety, bruxism, dilated pupils, tachycardia, headache & sweating
- Subjective effects reported within 30 min, peak 1 – 1.5 h, duration 3 – 6 h

Preclinical Tryptamines Pharmacology

- Fantegrossi *Biochemistry & Behavior* 2006
  - 0.3 – 10 mg/kg ip dose to rats induced dose-dependent head-twitch-response
  - 5-MeO-DiPT>DMT>control
  - 30 mg/kg induced convulsions
  - 5-MeO-DiPT produced LSD-like discriminative stimulus effects

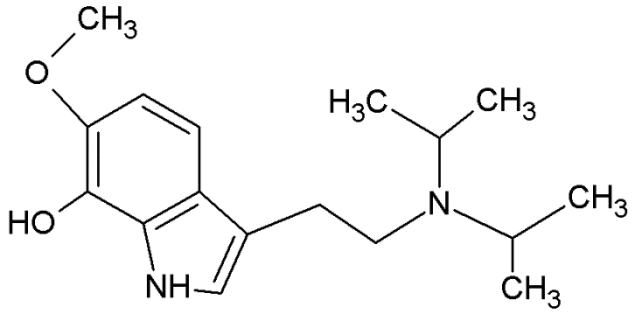
5-MeO-DiPT Pharmacokinetics

Meyer & Maurer *Current Drug Metabolism* 2010



5-MeO-DiPT

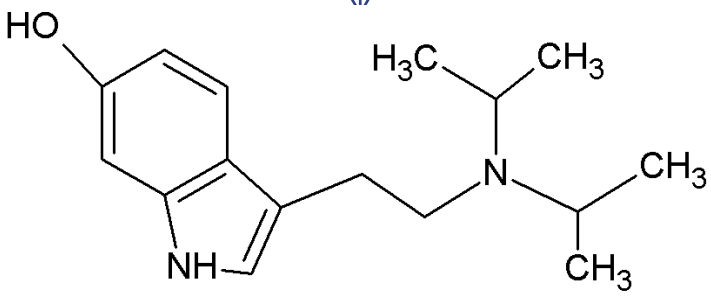
CYP1A1



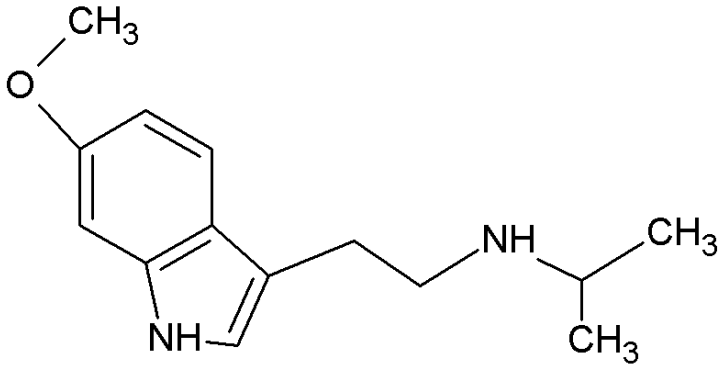
6-OH-5-MeO-DiPT

CYP1A2
CYP2C9/19
CYP3A4

CYP2D6



5-OH-DiPT



5-MeO-IPT

Tryptamines Pharmacokinetics

- Shen et al *Biochemical Pharmacology* 2010
  - 5-MeO-DMT pharmacokinetics from human liver microsomes, hepatocytes & *in vivo* studies in rats
  - Phase I metabolism *O*-demethylation for 5-MeO-DMT
  - After IV & IP administration in rat blood 5-MeO-DMT shows nonlinear pharmacokinetics
  - Phase II: not characterized

Tryptamines Pharmacokinetics

- 5-MeO-DiPT pharmacokinetic studies in human & rat liver microsomes, *in vivo* rat studies
- 5-MeO-DiPT Phase I metabolism primarily *O*-demethylation & hydroxylation; side chain *N*-dealkylation
- Phase II: glucuronidation & sulfation
- Limited pharmacokinetics for other designer tryptamines

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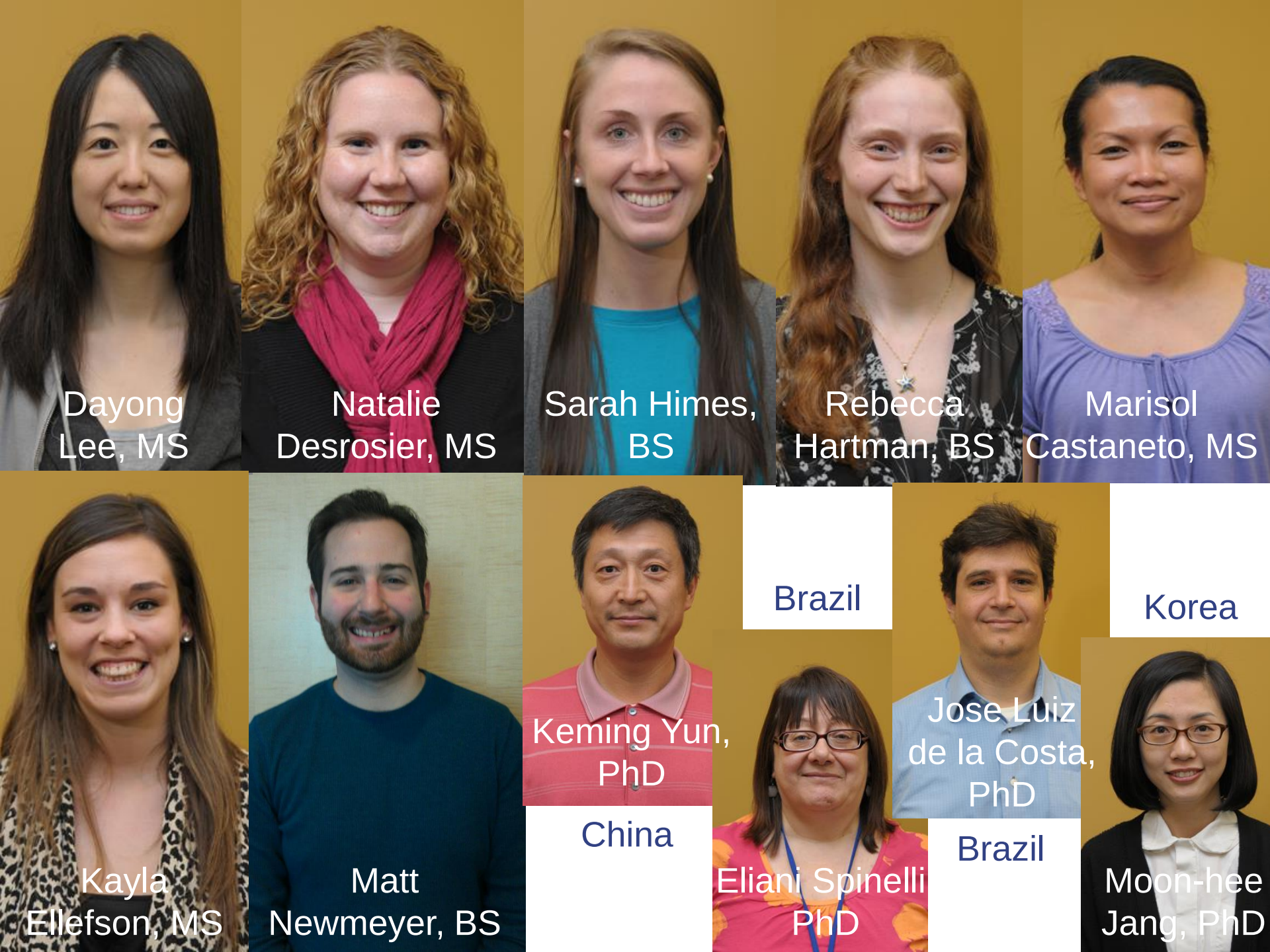
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Brazil
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Brazil
Korea
Moon-hee Jang, PhD

Thank you for your attention & NIST for arranging this important conference on Emerging Trends in Designer Drugs