Designer drugs of abuse: The science behind the headlines

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Presentation Outline

- Designer drugs, or NPS
- Designer Drug Research Unit (DDRU)
- Neuron structure and function
- Cannabinoid NPS (e.g., "Spice")
- Stimulant NPS (e.g., "Bath salts")
- Hallucinogen NPS (e.g., "NBOMes")
- Opioid NPS (e.g., acetyl fentanyl)
- Summary

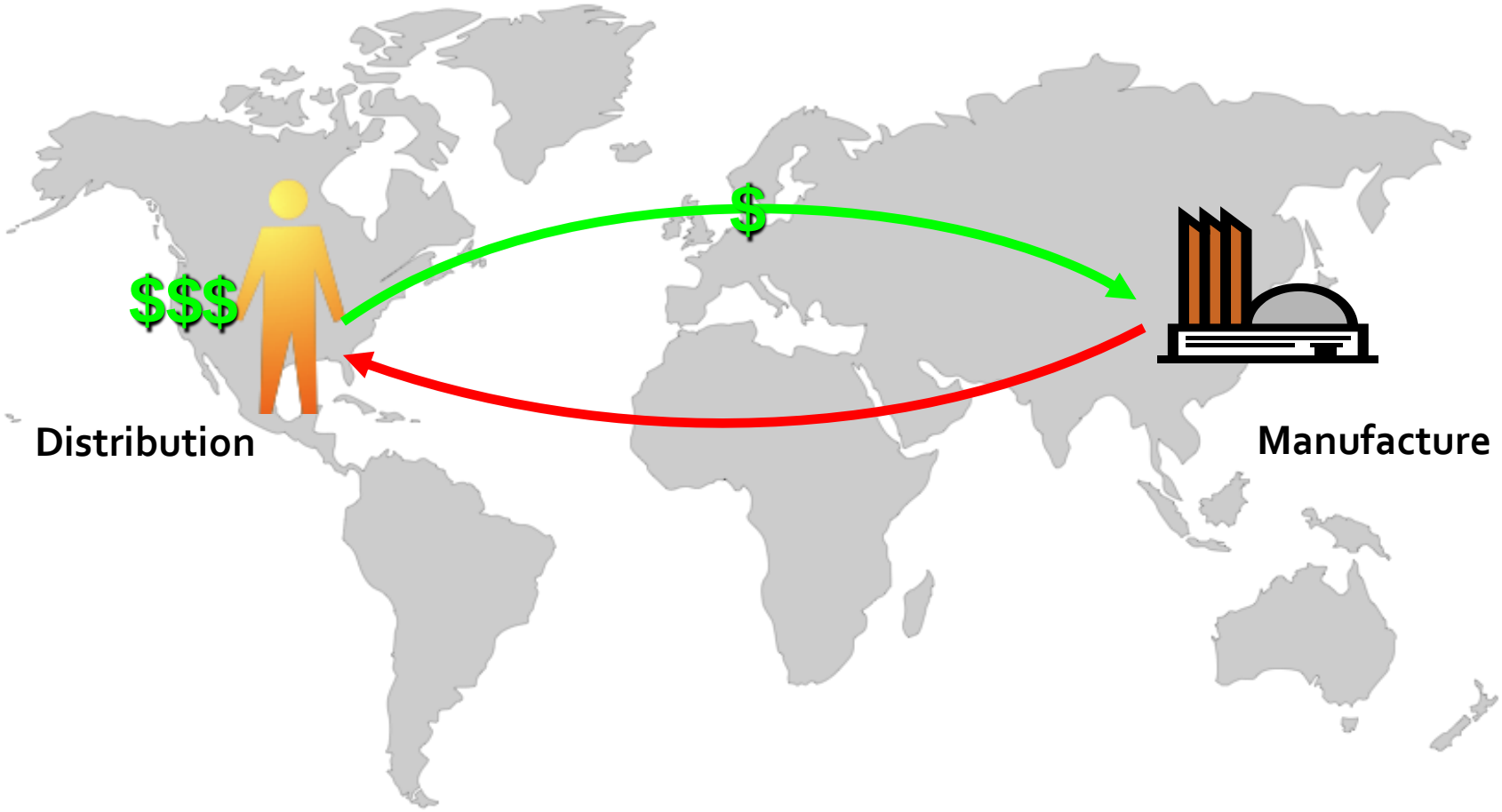
Designer drugs are synthetic alternatives to more traditional drugs of abuse

- Man-made psychoactive drugs created by chemists who hijack biomedical literature
- Sold under false pretenses as harmless non-drug products
- Easy to obtain from the Internet, smoke shops, gas stations, street dealers
- Used without detection, since urine toxicology tests do not usually identify these drugs

The number of designer drugs, or new psychoactive substances (NPS), is increasing

In the 2015 *World Drug Report*, the United Nations Office of Drugs and Crime (UNODC) noted that NPS continue to proliferate in the global drug marketplace, in terms of both quantity and diversity. By December 2014, a total of **541 different NPS** had been reported by 95 countries and territories to the UNODC early warning system.

NPS are manufactured by Asian companies and sold in bulk to distributors via the Internet



The Internet has facilitated the widespread availability and misuse of NPS

- Biomedical research has identified the mechanism of action for classic drugs of abuse (e.g., cocaine)
- Online databases describe recipes for making novel drugs to target specific mechanisms
- Marketing and sales of new synthetic drugs on websites allow anonymous purchases
- "Trip reports" about drug use experiences are shared on Internet forums
  - *Bluelight*, *Erowid*, *Lyceum*, etc.

NPS can be classified based on the drugs they intend to mimic

- Synthetic cannabinoids, e.g. "Spice"
  - Induce marijuana-like effects
- Synthetic stimulants, e.g. "Bath salts"
  - Induce cocaine-like effects
- Synthetic hallucinogens, e.g. "NBOMes"
  - Induce LSD-like effects
- Synthetic opioids, e.g. Acetyl fentanyl
  - Induce morphine-like effects

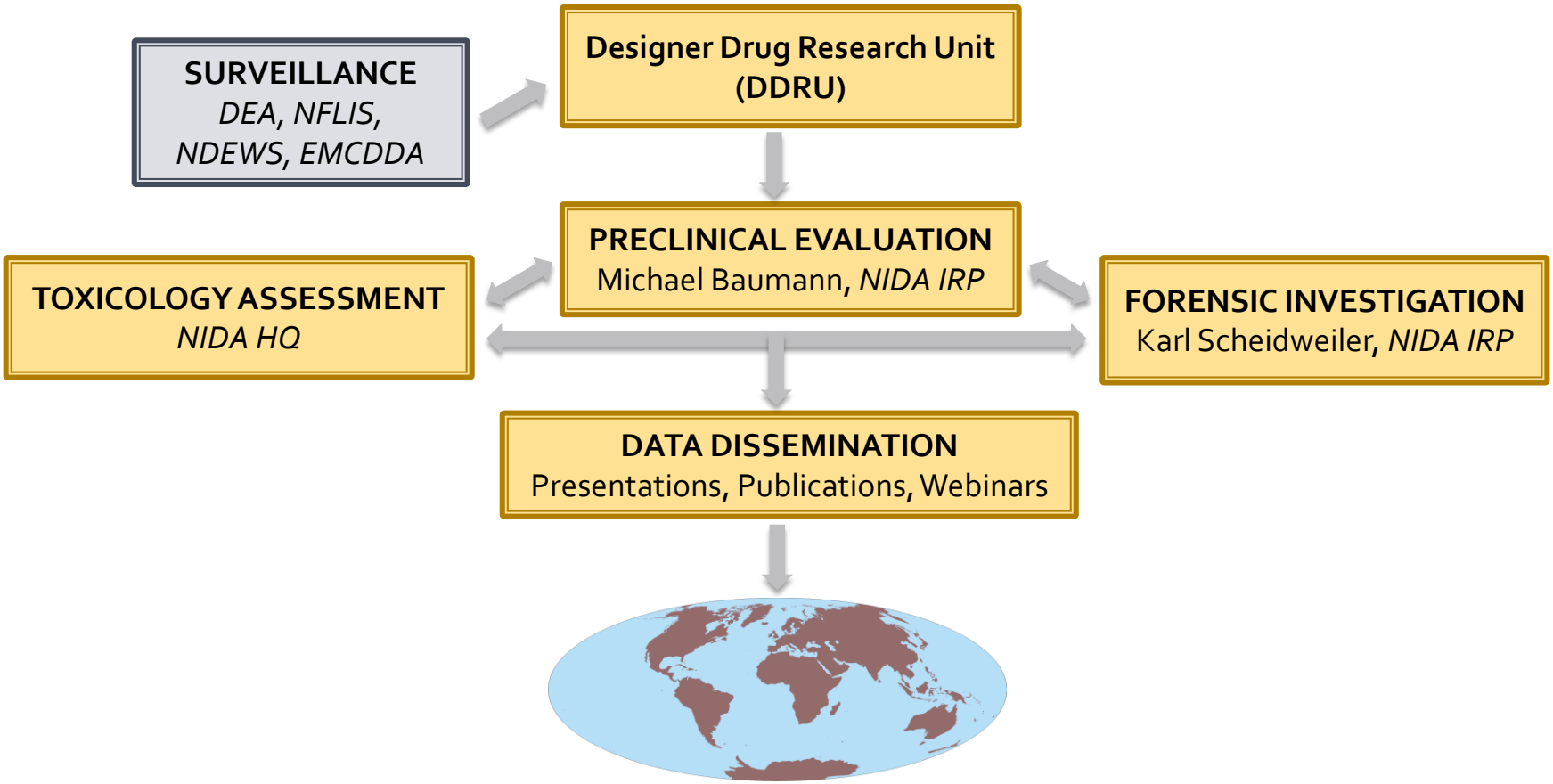
Mission and goals of the Designer Drug Research Unit (DDRU) at NIDA IRP

The ***MISSION*** of the DDRU is to collect, analyze, and disseminate the most up-to-date information about NPS.

The ***GOALS*** of the DDRU include:

- 1) SURVEILLANCE – to identify those NPS that pose risks
- 2) PRECLINICAL EVALUATION – to determine the molecular mechanisms and pharmacological actions of NPS in animal models
- 3) TOXICOLOGY ASSESSMENTS – to evaluate the toxic potential of NPS using predictive, in vitro, and in vivo methods
- 4) FORENSIC INVESTIGATION – to develop forensic assays, and examine PD/PK effects of NPS in animal models under controlled conditions
- 5) DATA DISSEMINATION – to make findings available to the scientific community and the public via presentations, publications and Internet.

Organizational Chart for the DDRU at NIDA IRP



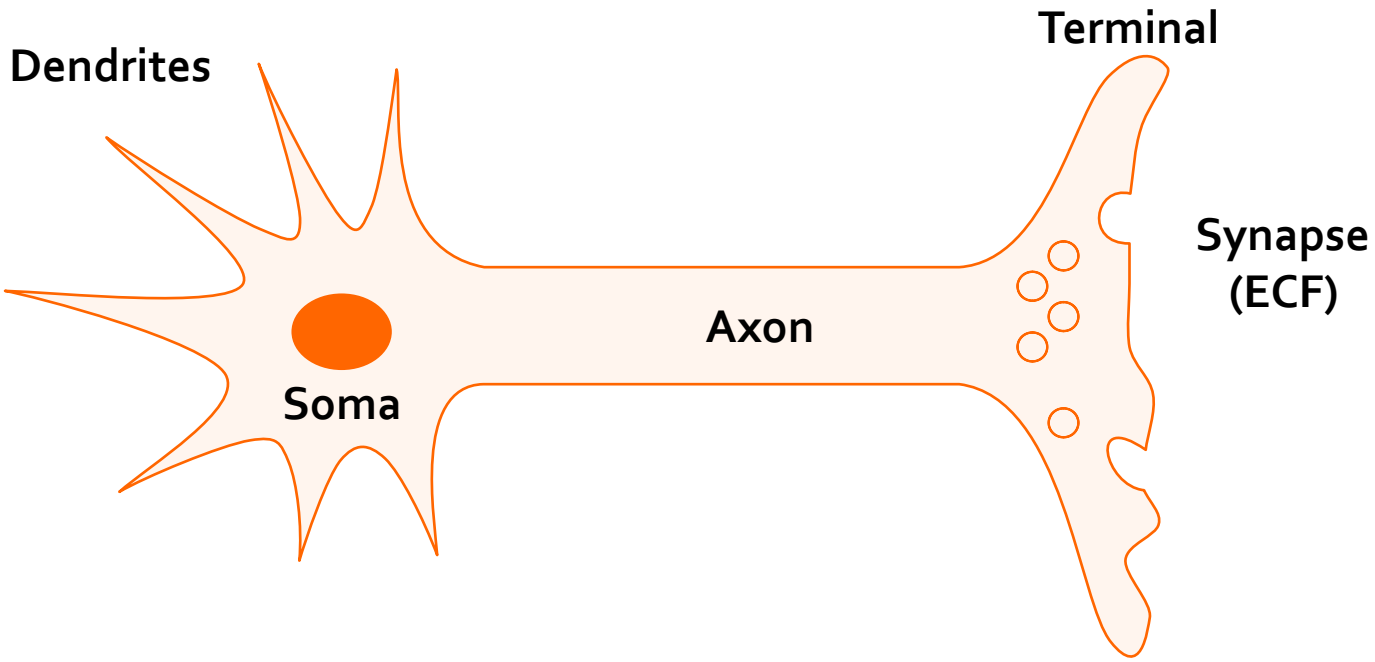
Surveillance… which NPS require investigation?

- Poison Control Centers (AAPCC)
- Drug Enforcement Administration (DEA)
  - Terrance Boos, PhD
  - *National Forensic Laboratory Information System (NFLIS)*
- National Drug Early Warning System (NDEWS)
  - Eric Wish, PhD & Erin Artigiani, MS
- European Monitoring Centre for Drugs & Drug Addiction (EMCDDA)
  - Simon Brandt, PhD

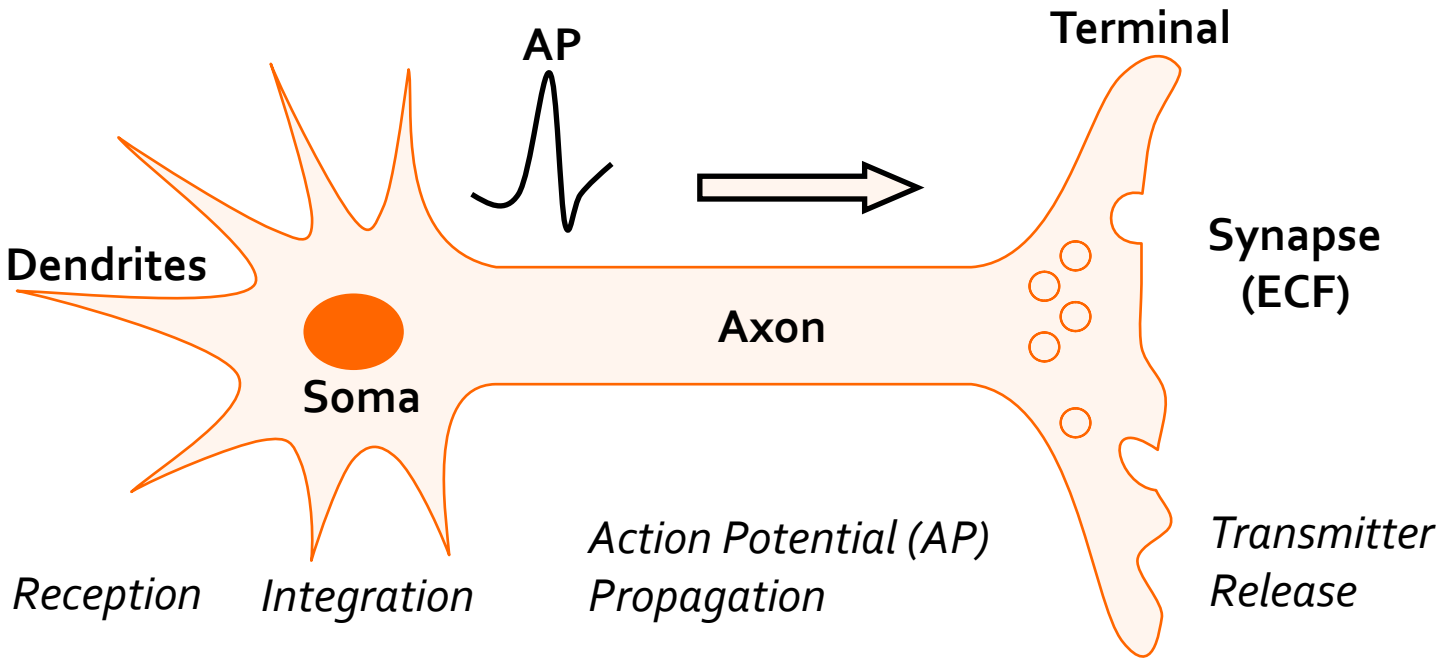
Workflow for the DDRU preclinical laboratory involves multiple steps

- Identification of specific problematic NPS
- Synthesis of purified drugs and metabolites
  - Kenner Rice, PhD (NIDA IRP)
  - Simon Brandt, PhD (EMCDDA)
- *In vitro* testing at receptors and transporters
  - John Partilla, BS & Donna Walther, MS (NIDA IRP)
- *In vivo* testing in rodent models
  - Josh Elmore, BS & Hailey Walters, BS (NIDA IRP)
  - Chuck Schindler, PhD (NIDA IRP)

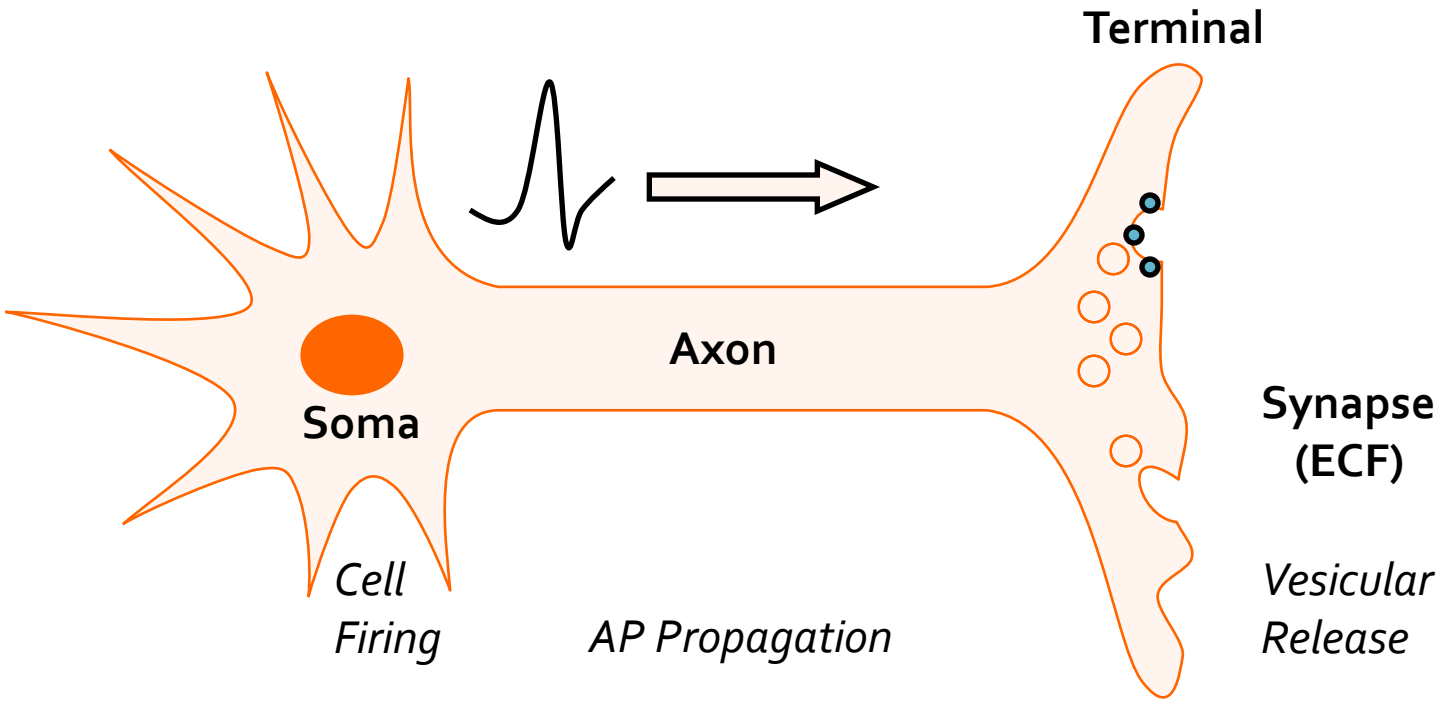
Nerve cells, or neurons, are the functional units of the brain



Neurons are capable of firing electrical impulses called action potentials (APs)

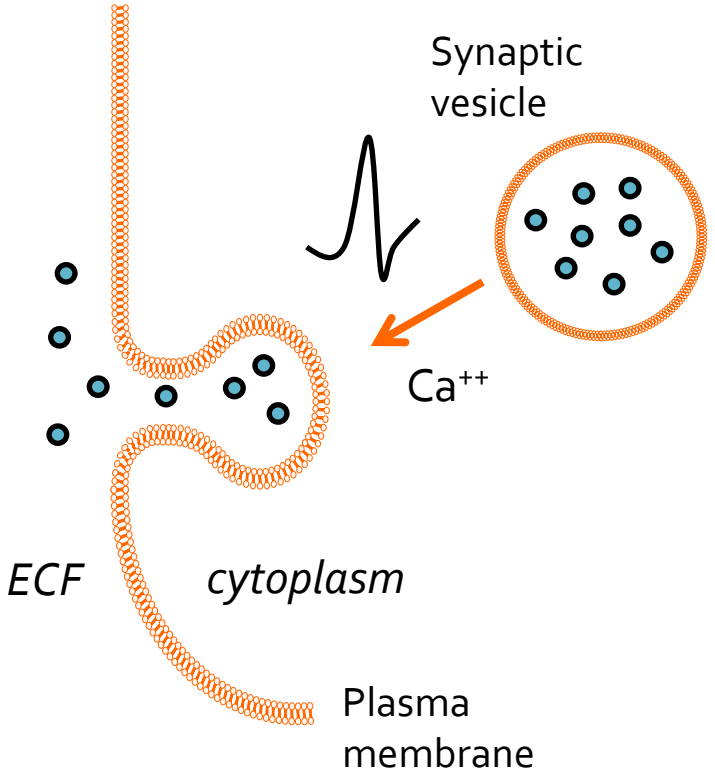


The pattern of AP firing is coupled to the release of neurotransmitter molecules

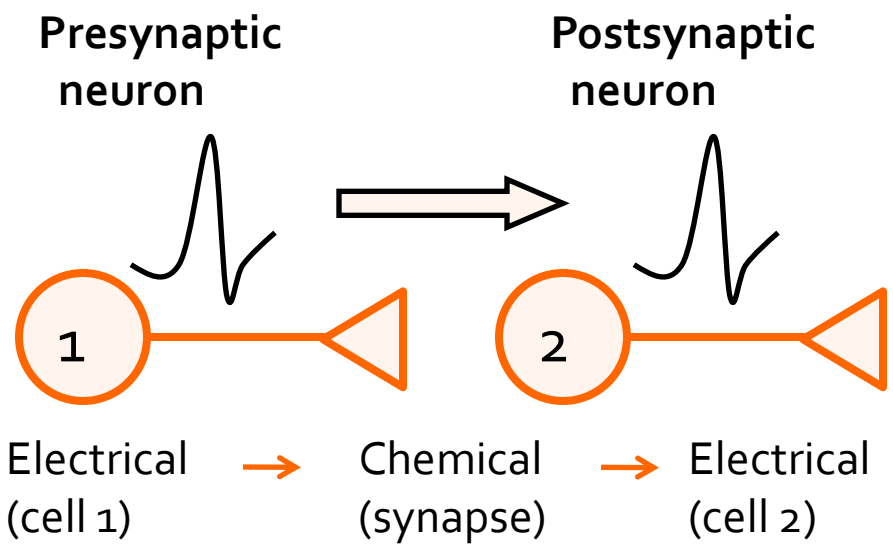


Neurotransmitters are released by exocytosis, a process requiring calcium ions

- AP triggers fusion of vesicular membrane with plasma membrane
- Contents of vesicle are released into synaptic cleft (i.e., ECF)
- Process is dependent upon intracellular Ca^{++}

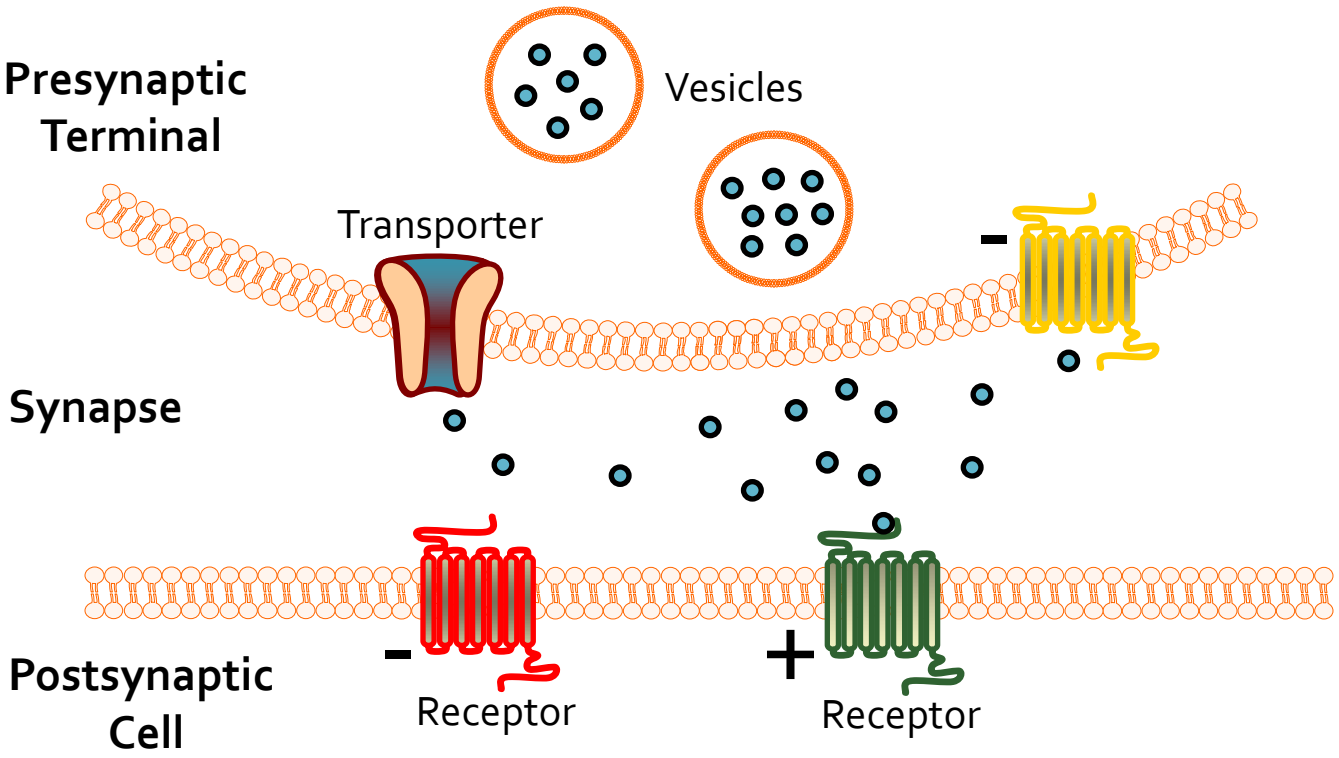


The space between neurons, or "synapse", is the site of chemical transmission

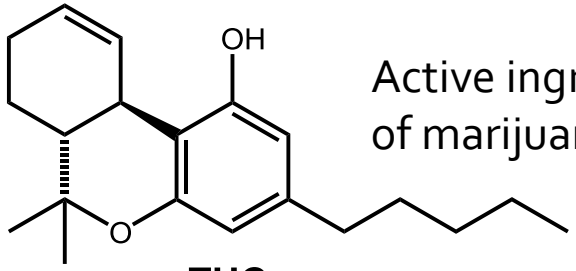


At the synapse, electrical signaling (i.e., AP) is converted to chemical signaling as neurotransmitter molecules are released into the extracellular space

Released neurotransmitters bind to receptors on pre- and post-synaptic cells

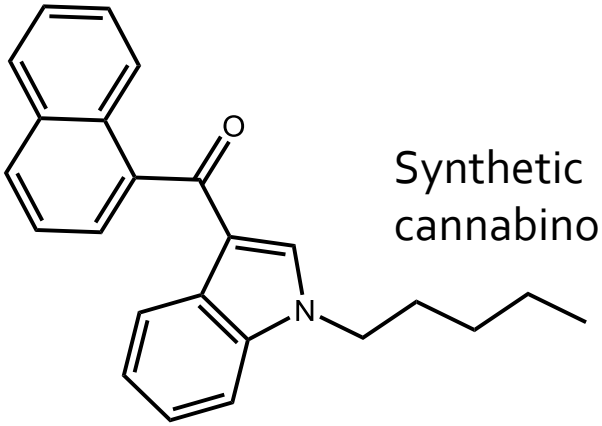


Synthetic cannabinoid products *(e.g., Spice)* consist of plant material laced with drug



Active ingredient of marijuana

THC



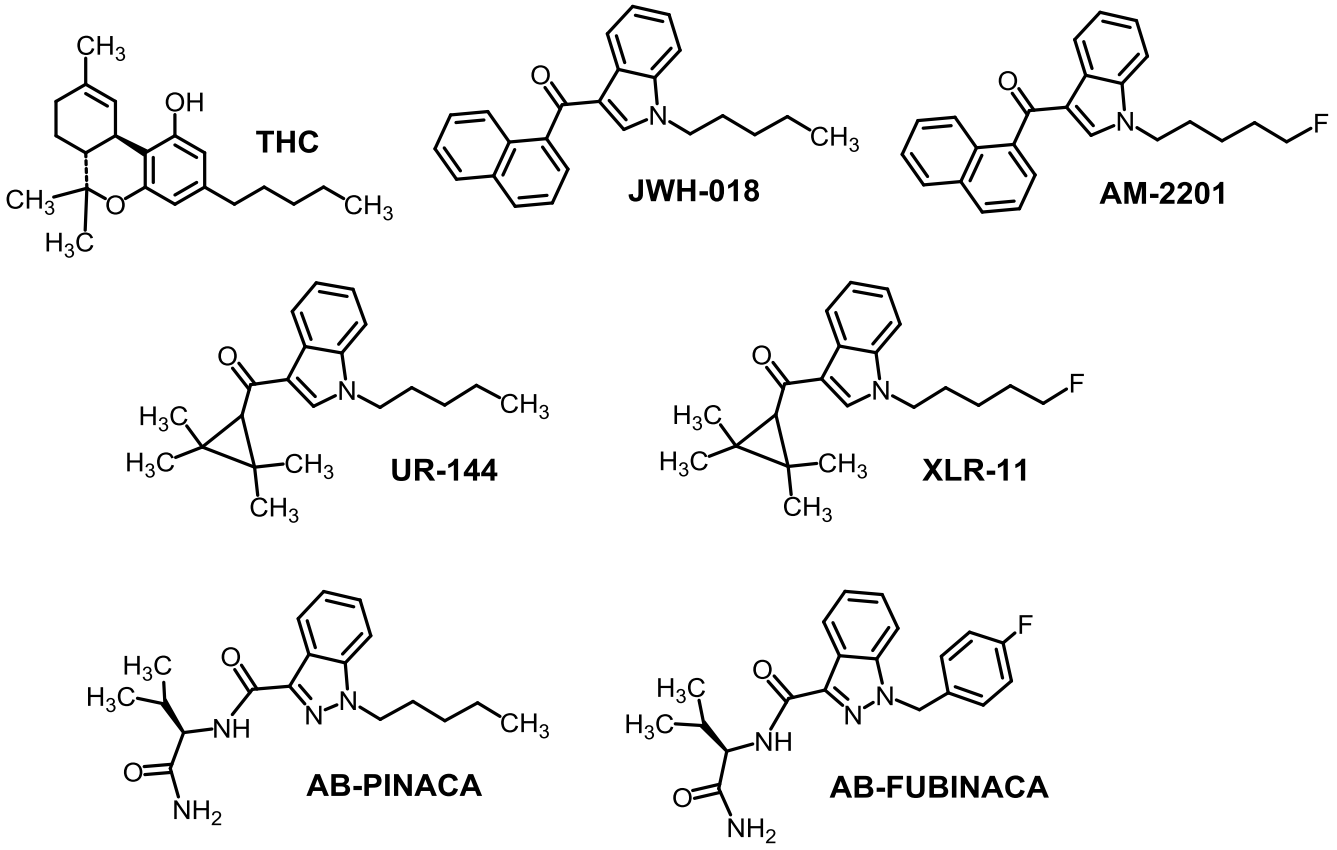
Synthetic cannabinoid

JWH-018

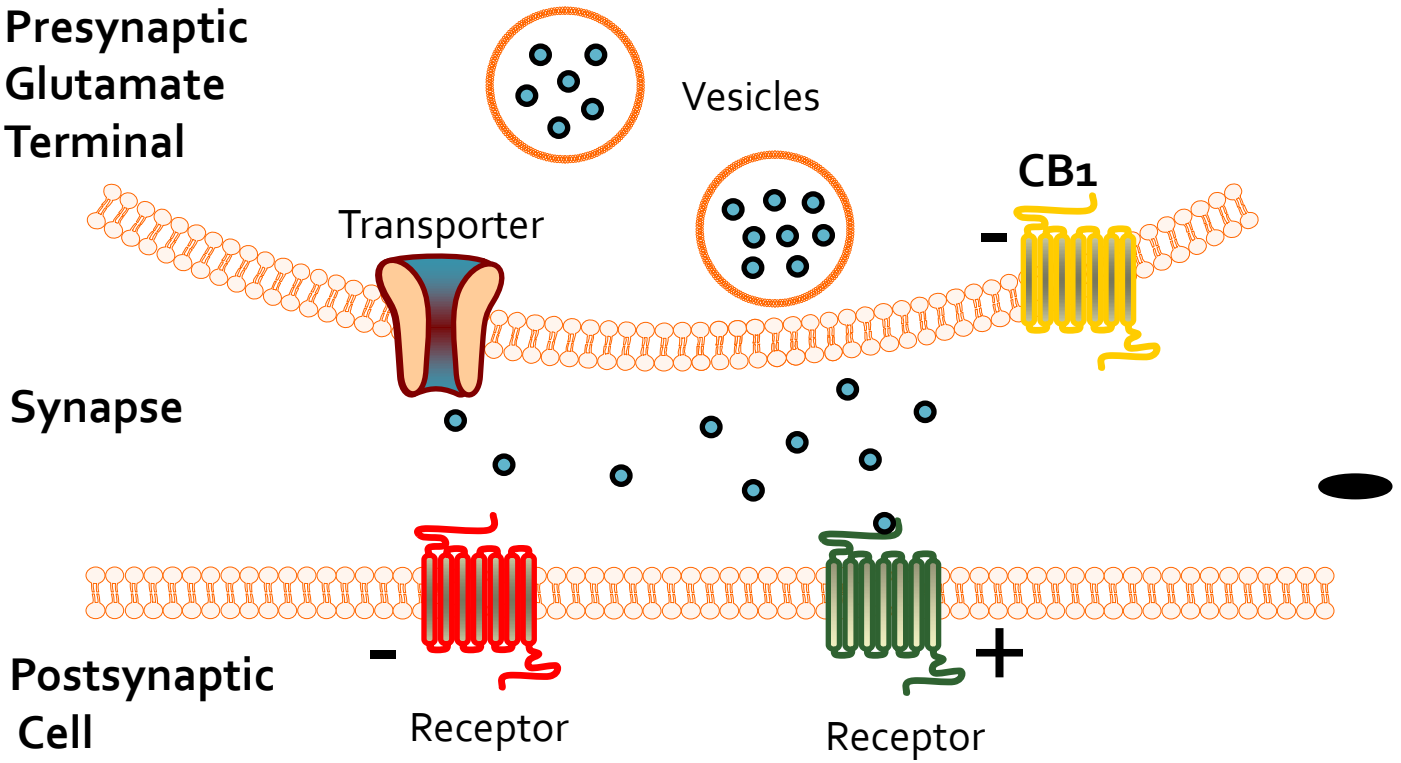
Effects of cannabinoid NPS mimic the effects of marijuana but are stronger

- Methods of use
  - Inhalation of smoke using bongs, pipes or joints
  - Vaping of liquid
- Psychoactive effects
  - Positive mood and euphoria
  - Perceptual distortions similar to the effects of marijuana
  - Can be much more more potent than THC
- Adverse effects
  - Increased heart rate, vomiting, kidney injury
  - Hallucinations, panic attacks, persistent psychosis

Legislation banning *Spice* cannabinoids has fostered the appearance of new analogs

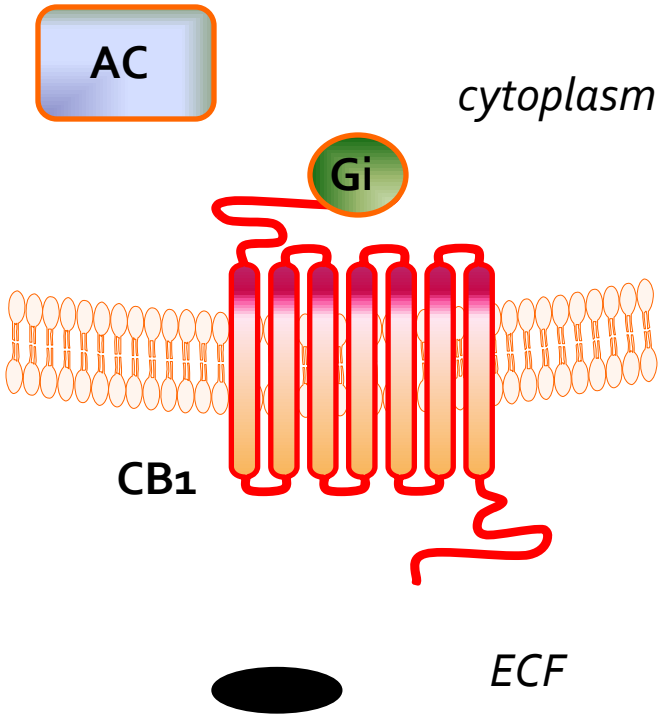


Synthetic cannabinoids bind to CB1 receptors on presynaptic nerve terminals



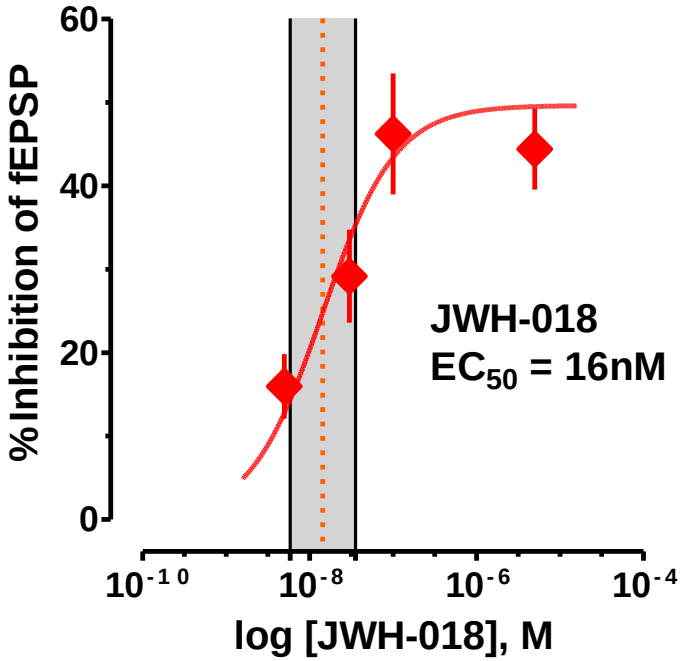
Synthetic cannabinoid binding to CB1 receptors inhibits presynaptic cell activity

- CB1 receptors are coupled to Gi
- Receptor binding inhibits activity of adenylate cyclase (AC)
- Cell firing and neurotransmitter release are ***inhibited***



The synthetic cannabinoid, JWH-018, inhibits presynaptic glutamate release

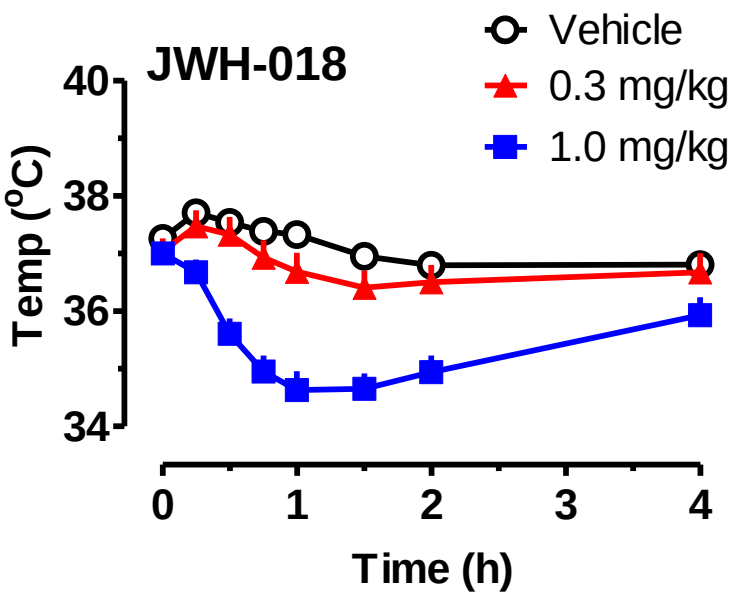
- JWH-018 decreases glutamate release and corresponding EPSPs
- Effects are dose-dependent and long-lasting
- JWH-018 is at least 5-times more potent than THC



Hoffman et al., 2016

The synthetic cannabinoid, JWH-018, produces marked hypothermia in male rats

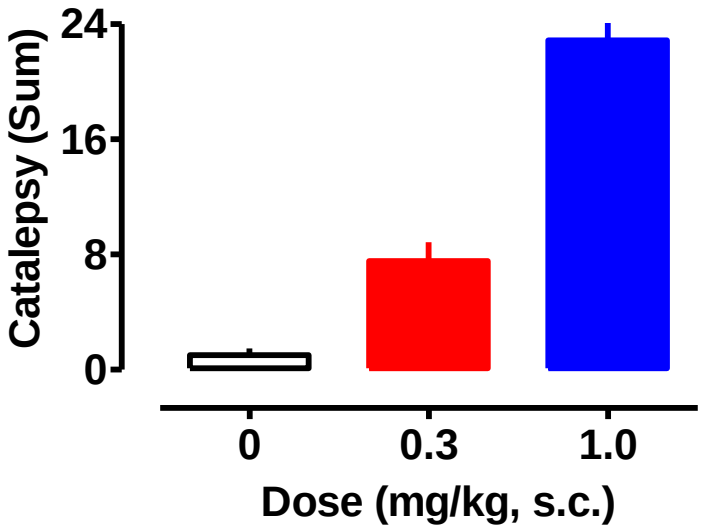
- JWH-018 decreases body temperature (i.e., hypothermia)
- Effects are dose-dependent and long-lasting
- JWH-018 is at least 5-times more potent than THC



Elmore et al., unpublished

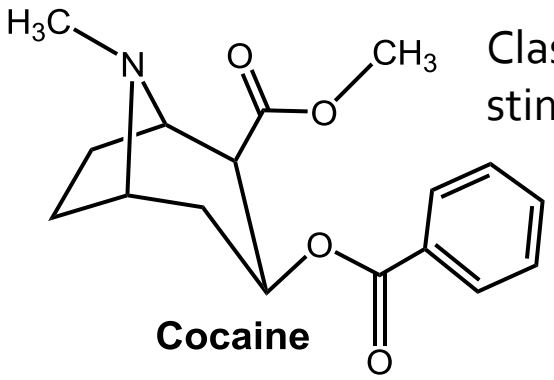
JWH-018 produces catalepsy in male rats

- JWH-018 causes a lifeless immobility (i.e., catalepsy)
- Effects are dose-dependent and long-lasting
- JWH-018 is at least 5-times more potent than THC



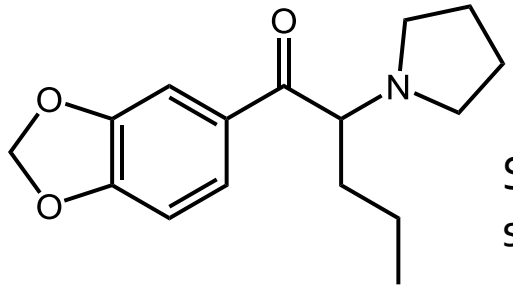
Elmore et al., unpublished

Synthetic stimulant products *(e.g., Bath salts)* consist of dry powders or crystals



Classic stimulant

Cocaine



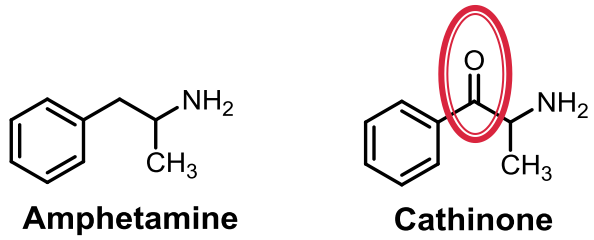
Synthetic stimulant

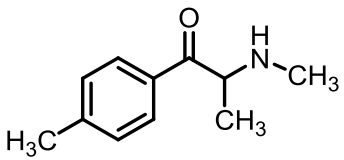
3,4-Methylenedioxypyrovalerone (MDPV)

Effects of stimulant NPS mimic the effects of cocaine but are stronger

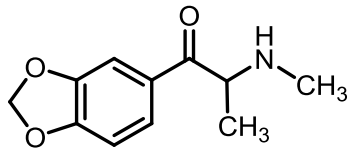
- Methods of use
  - Oral ingestion, snorting, intravenous injection
- Psychoactive effects
  - Euphoria and increased energy similar to cocaine
  - Can be much more more potent than cocaine
- Adverse consequences
  - Increased heart rate and blood pressure, hyperthermia
  - Agitation, delirium, psychosis, death

Legislation banning *Bath salts* stimulants has fostered the appearance of new analogs

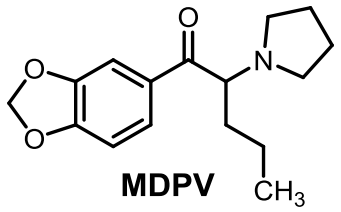




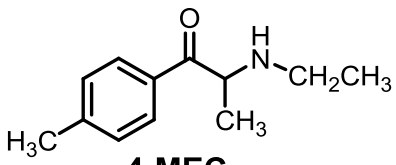
Mephedrone



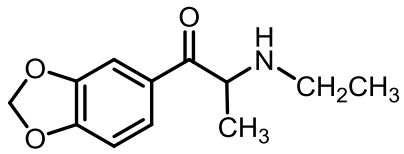
Methylone



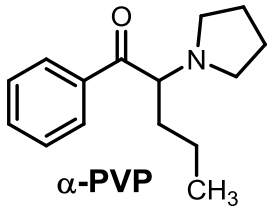
MDPV



4-MEC

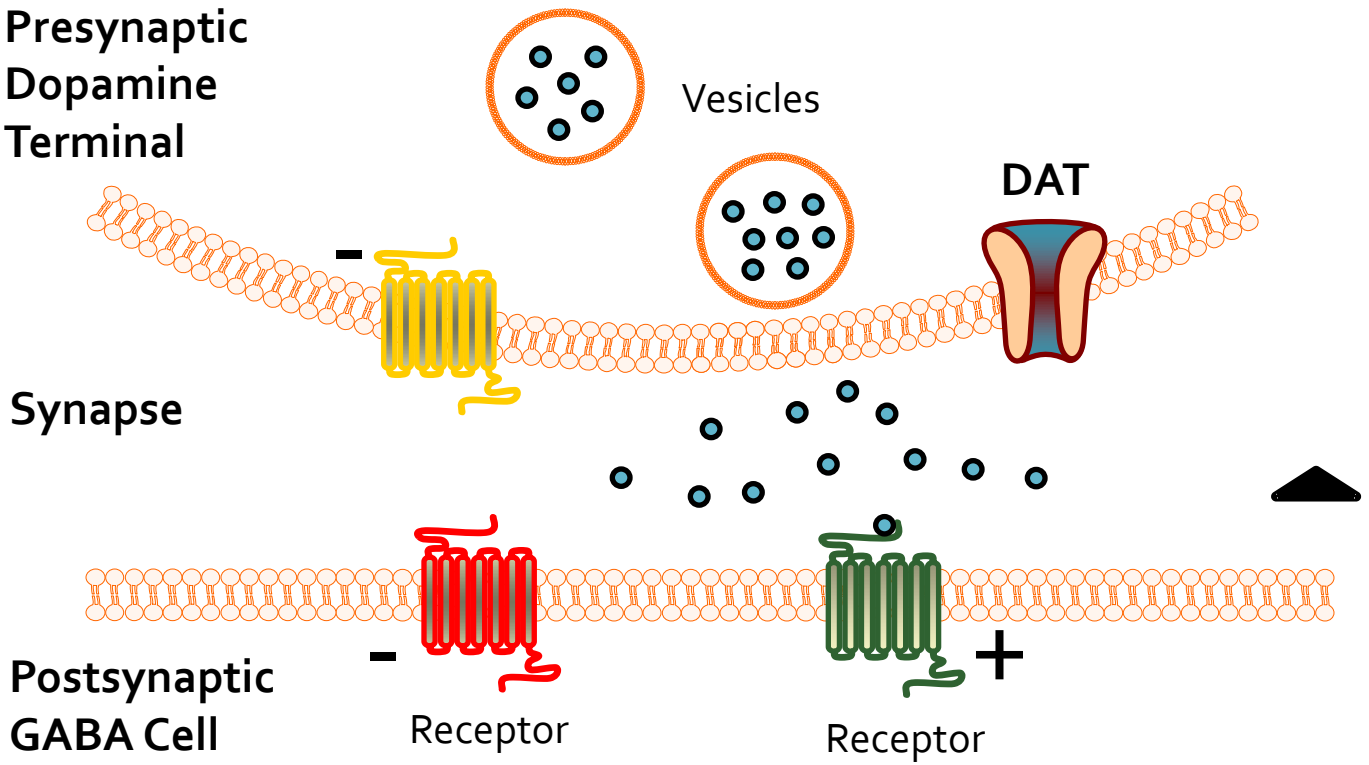


Ethylone



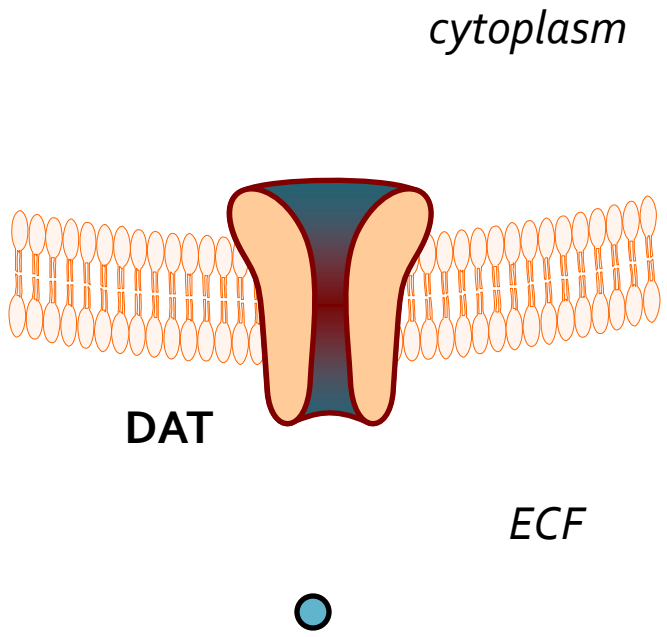
α-PVP

Synthetic stimulants bind to dopamine transporters (DAT) to block dopamine uptake



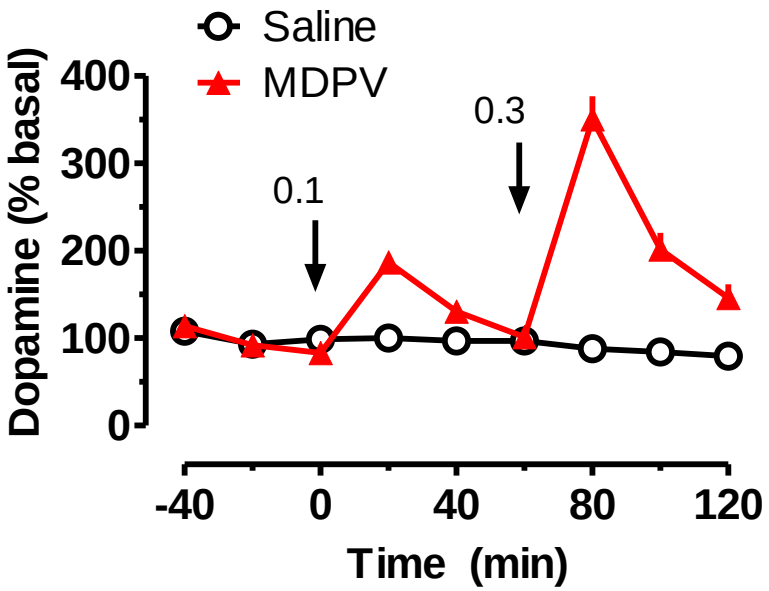
DAT proteins function to move extracellular dopamine back into cells

- DATs are channel-like proteins located in cell membranes
- DAT is responsible for dopamine reuptake
- Drugs that disrupt DAT will produce increases in dopamine in the extracellular fluid (ECF)



The synthetic stimulant, MDPV, increases extracellular dopamine in rat brain

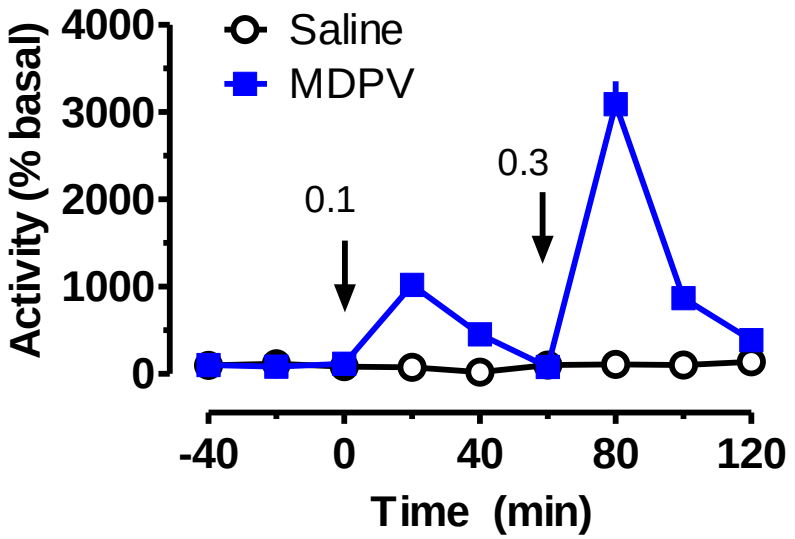
- MDPV increases extracellular concentrations of dopamine in reward circuits
- Effects are dose-dependent and rapid
- MDPV is at least 10-times more potent than cocaine



Schindler et al., 2015

MDPV produces marked increases in locomotor activity

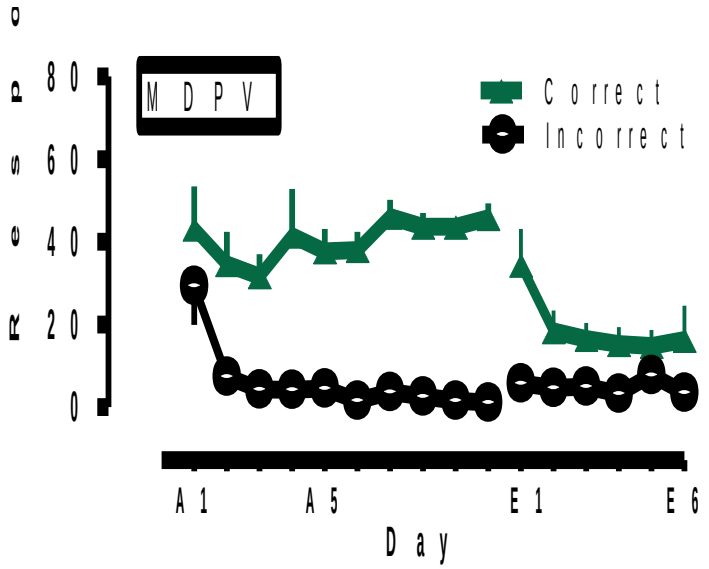
- MDPV markedly increases forward locomotion in rats
- Motor effects correspond to elevations in dopamine
- MDPV is at least 10-times more potent than cocaine



Schindler et al., 2015

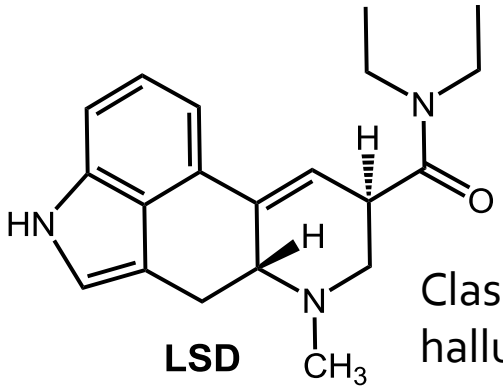
MDPV is readily self-administered by male rats

- Rats learn quickly to self-administer MDPV
- Acquisition of self-administration behavioral indicates abuse liability
- MDPV is at least 10-times more potent than cocaine



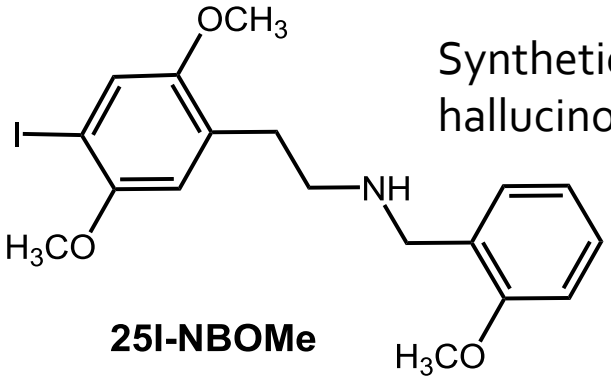
Schindler et al., 2015

Synthetic hallucinogen products *(e.g., NBOMEs)* consist of liquid or paper laced with drug



LSD

Classic hallucinogen



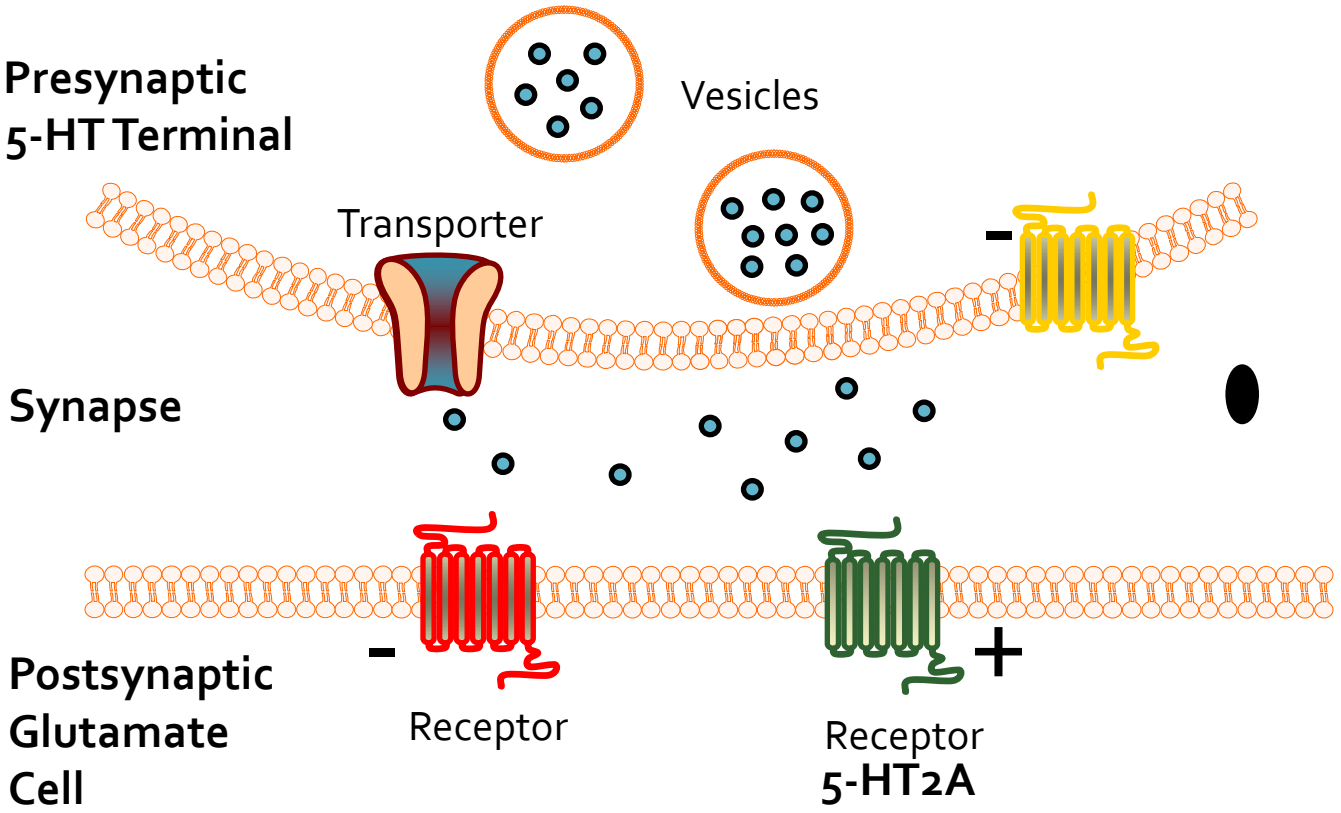
25I-NBOMe

Synthetic hallucinogen

Effects of hallucinogenic NPS mimic the effects of LSD but are stronger

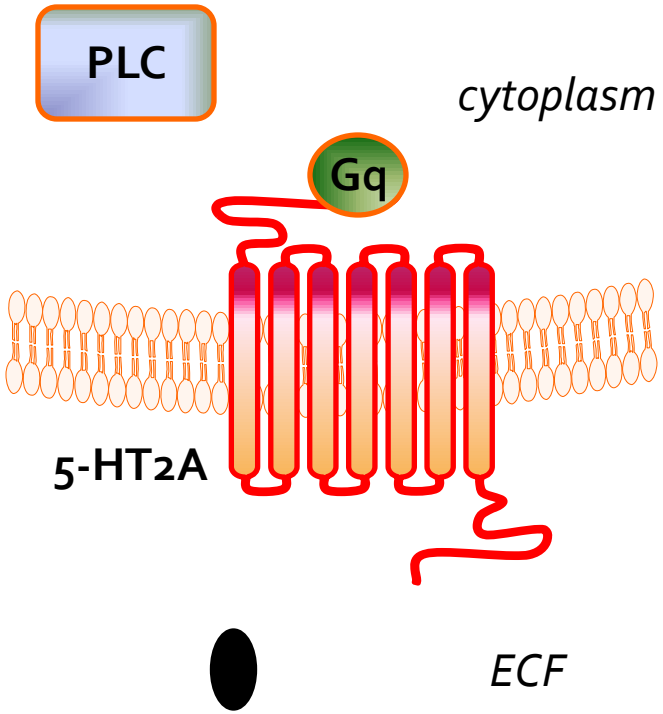
- Methods of use
  - Oral ingestion
- Psychoactive effects
  - Perceptual distortions similar to effects of LSD
  - 25I-NBOMe is much more potent than LSD
- Adverse consequences
  - Increased heart rate and blood pressure, hyperthermia
  - Agitation, delirium, death

Synthetic hallucinogens bind to 5-HT2A receptors on postsynaptic nerve cells

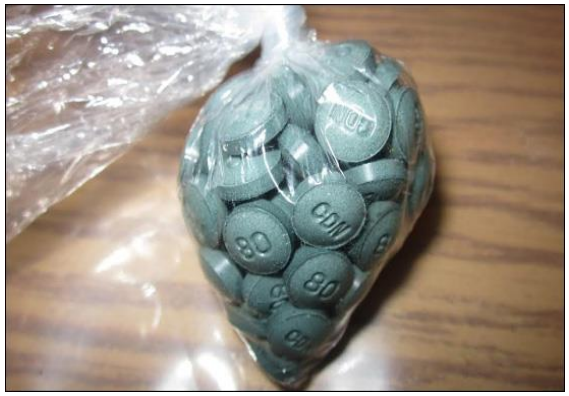


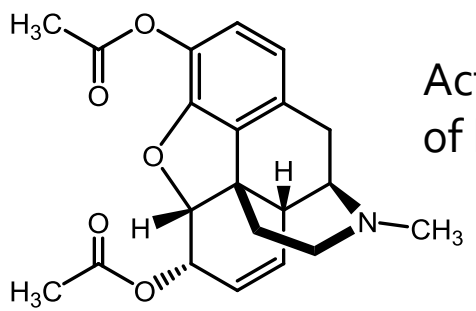
Synthetic hallucinogen binding to 5-HT2A receptors stimulates postsynaptic cell activity

- 5-HT2A receptors are coupled to Gq
- Receptor binding enhances activity of phsopholipase C (PLC)
- Cell firing and transmitter release are ***stimulated***



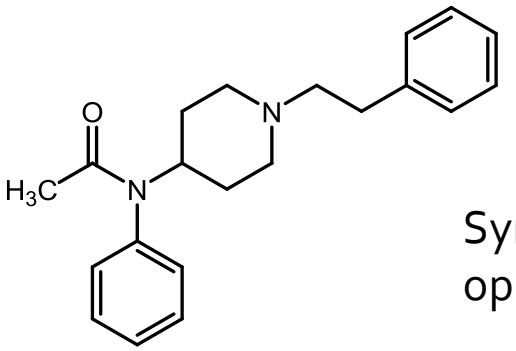
Synthetic opioids are used as adulterants for heroin or as individual drugs of abuse





Diacetylmorphine

Active ingredient of heroin



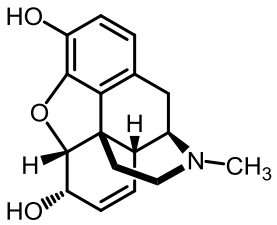
Acetyl fentanyl

Synthetic opioid

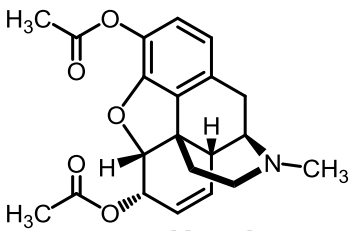
Effects of opioid NPS mimic the effects of heroin but are sometimes stronger

- Methods of use
  - Intravenous injection via needle and syringe
  - Insufflation, oral, smoking (free base)
- Psychoactive effects
  - Acute "rush", euphoria and pain relief
  - Can be much more more potent than heroin
- Adverse effects
  - Tolerance, dependence, addiction, blood-borne infection
  - Constipation, respiratory depression

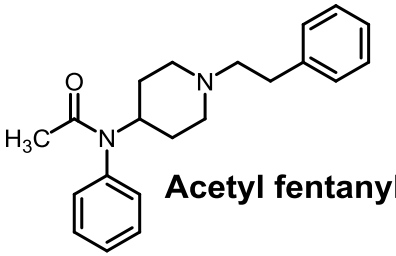
A variety of synthetic opioids have emerged in the recreational drug marketplace



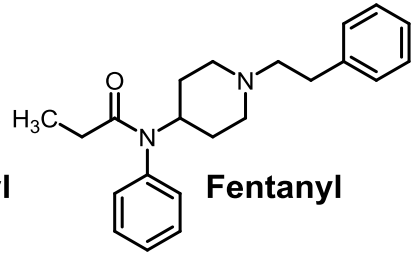
Morphine



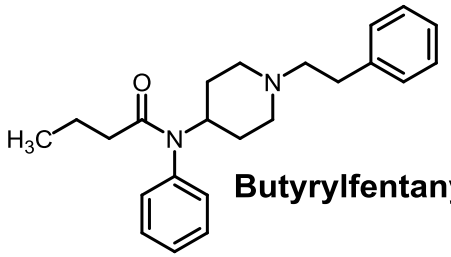
Heroin



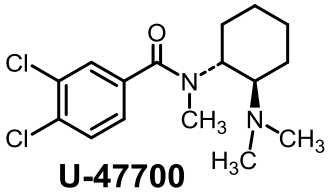
Acetyl fentanyl



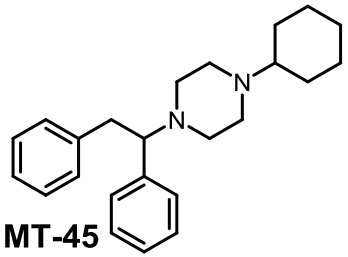
Fentanyl



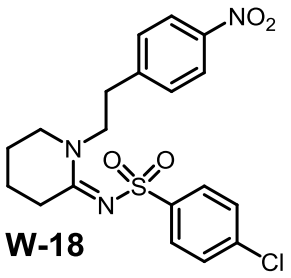
Butyrylfentanyl



U-47700

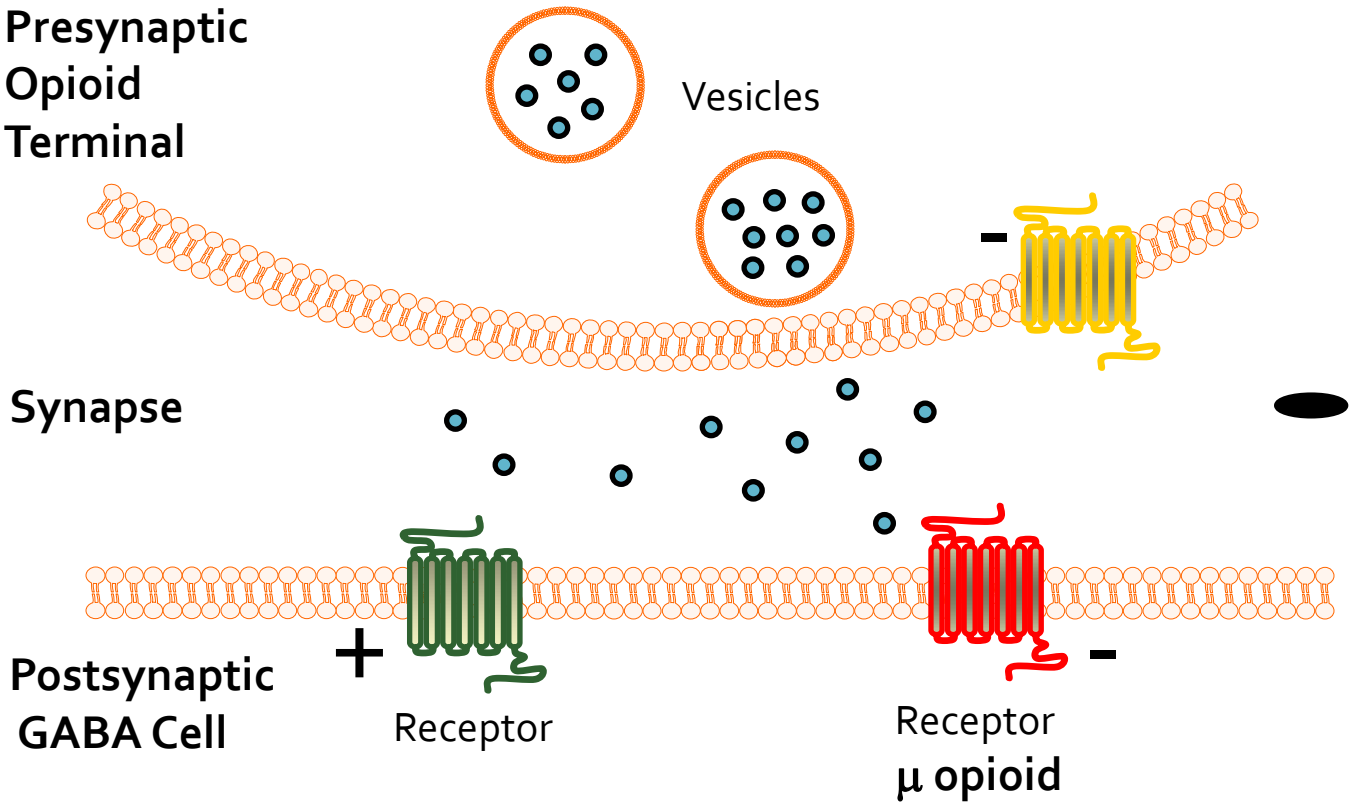


MT-45



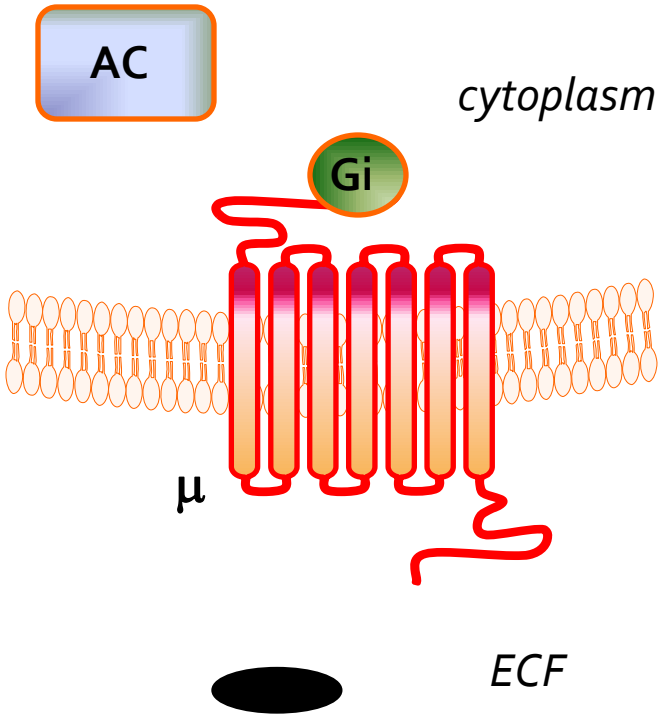
W-18

Synthetic opioids bind to μ-opioid receptors on post-synaptic nerve terminals



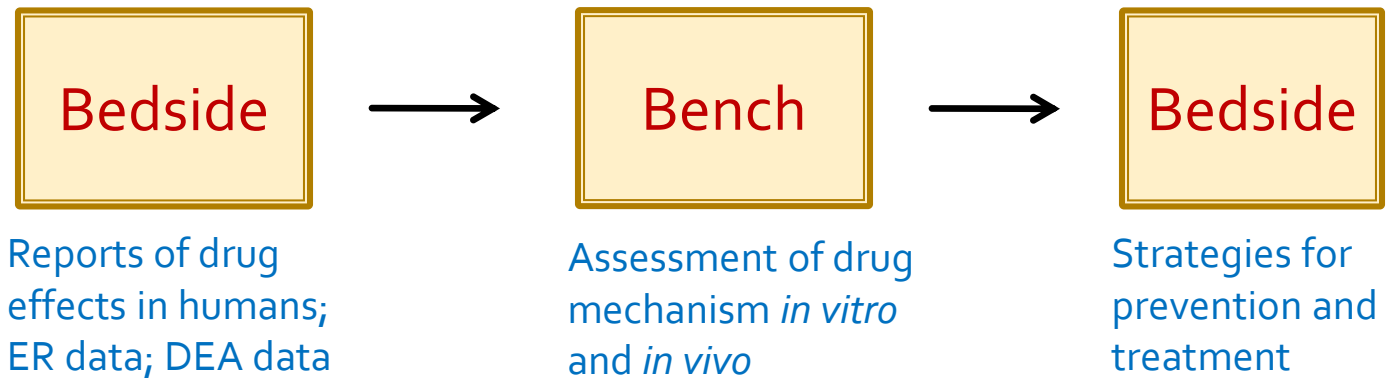
Synthetic opioid binding to μ receptors inhibits postsynaptic cell activity

- μ receptors are coupled to Gi
- Receptor binding inhibits activity of adenylate cyclase (AC)
- Cell firing and neurotransmitter release are ***inhibited***



Translational laboratory research plays a critical role in public health and safety

- E.g., Translational research with 5-HT medications
  - Role of SERT in IPAH *(Rothman et al., 1999)*
  - Role of 5-HT_{2B} receptors in CVD *(Rothman and Baumann, 2009)*
- Translational research with NPS



Preclinical findings have been used to influence public health policy and legislation

- Scheduling decisions by DEA and DHHS
  - Emergency Scheduling
  - Final Scheduling
- US legislation such as H.R. 3537
  - Draft bill to render specific NPS illegal
- European Drug Monitoring Center
  - EMCDDA Annual Reports
  - EMCDDA-Europol Joint Report on α-PVP
  - Risk Assessment Report for MDPV
  - Risk Assessment Report for 4,4'-DMAR

The use of NPS presents a number of dangerous health risks

- NPS can produce life-threatening adverse medical consequences
- Biological effects of NPS resemble those of the drugs they intend to mimic, but NPS are often much more potent
- Users can not be sure of the precise chemical constituents of products
- NPS can contain toxic impurities, byproducts or adulterants

Essential collaborators

- NIDA IRP
  - Chuck Schindler, PhD *[behavior & telemetry]*
  - Eugene Kiyatkin, MD *[in vivo physiology]*
  - Carl Lupica, PhD and Alex Hoffman, PhD *[electrophysiology]*
  - Marilyn Huestis, PhD *[PD/PK studies]*
- Research Triangle Institute
  - Julie Marusich, PhD *[behavior]*
- Virginia Commonwealth University
  - Steve Negus, PhD *[intracranial self-stimulation]*
- Medical University of Vienna
  - Harald Sitte, PhD *[in vitro assays]*