

An aerial photograph of the University of Porto campus, showing various buildings, a large green dome, and the Douro River in the background. The text is overlaid in yellow on the top half of the image.

New psychoactive substances: are we challenged by new paradigms or just a face lift of old drugs of abuse?

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The Alfândega International Congress Centre



EUROTOX
PORTO 2015

Annual Congress of the European Societies of Toxicology 2015
Bridging Sciences for Safety

13–16 September 2015
Porto, Portugal



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NEW PSICOACTIVE SUBSTANCES

“Legal highs”

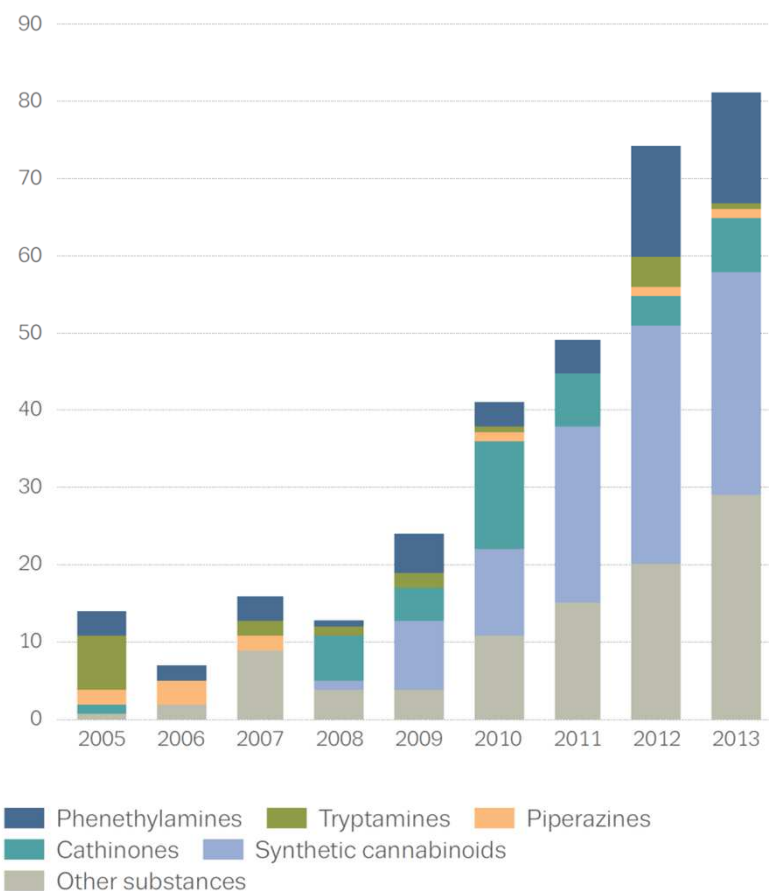


The worldwide **status quo** on drug abuse has changed dramatically in recent years, with the appearance of a wide range of **new psychoactive substances**, collectively known as “legal highs”, sold via the **internet** or at “**smart shops**” or “**head shops**”



European Monitoring Centre
for Drugs and Drug Addiction

Number and main groups of new psychoactive substances notified to the EU Early Warning System, 2005–13



European Drug Report

Trends and developments

2014

The unprecedented speed of appearance and distribution of the NPS worldwide makes it difficult or even impossible to assess its hazards and social risks and therefore a good understanding of the potential harm of these substances is still to be evaluated.

Fallacies about NPS

1. “NPS are different from classical drugs of abuse, and its use involves lower health risks”
2. “NPS sold in *smartshops* are more pure than street drugs”

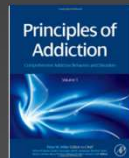
Are we challenged by new paradigms from the pharmacological and toxicological point of view?

NO

The receptors/transporters are the same



Only variations in potency and/or mixed effects are to be expected



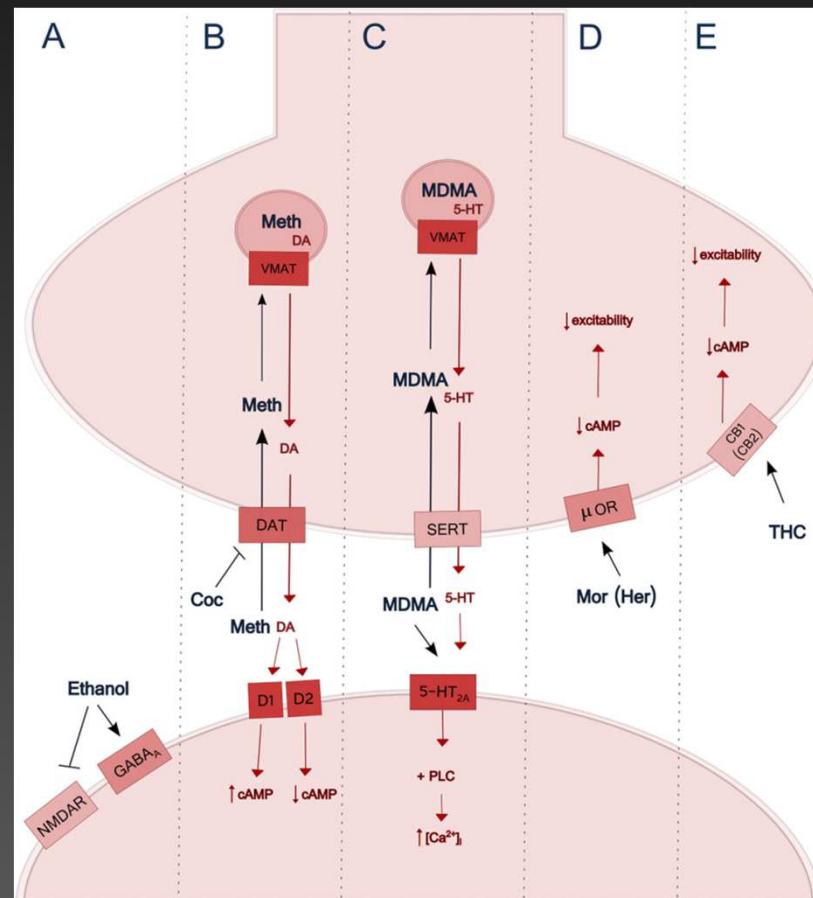
CHAPTER

17

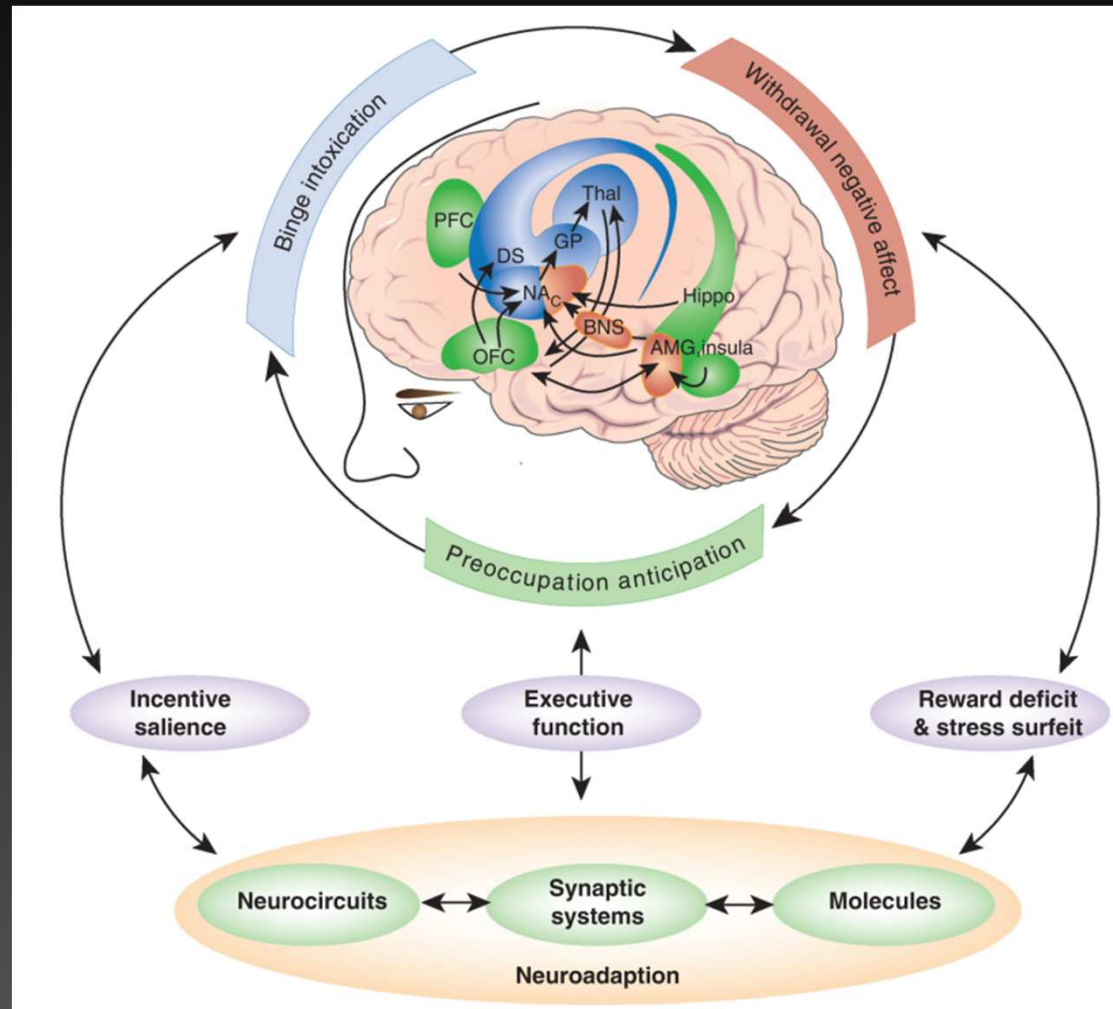
Medical Toxicology of Drugs of Abuse

Teresa Cunha-Oliveira*, Ana Cristina Rego*,
Félix Carvalho[§], Catarina R. Oliveira*

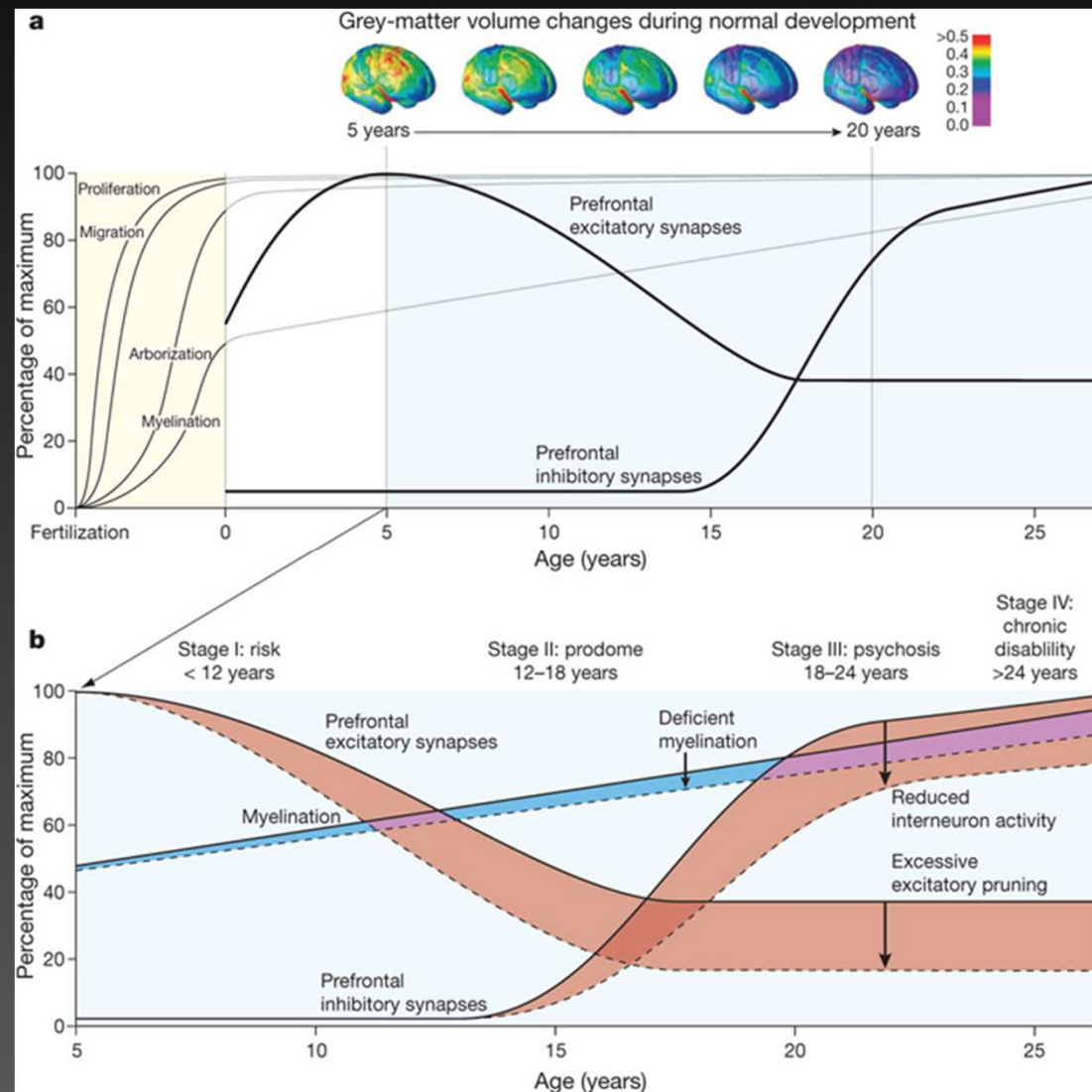
*CNC, University of Coimbra, Coimbra, Portugal [§]University of Porto, Porto, Portugal



Dependence pathways are the same



Development of **psychotic** and **schizophrenic** states are a strong risk caused by drug use during the development of the pre-frontal cortex



Nature. 2010;
468(7321):187-93.

Fallacies about NPS

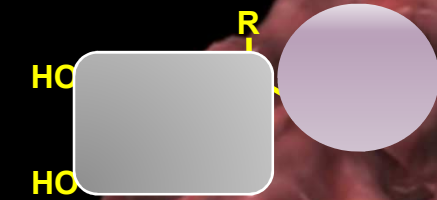
“NPS are different from classical drugs of abuse, and its use involves lower health risks”

In reality:

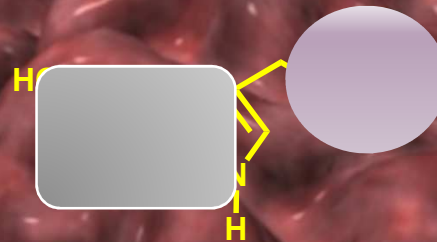


If **chemical structures** of NPS are **similar** to those of illegal drugs, or whether they have the **same pharmacodynamics**, the negative effects will be at least similar, if not even worse

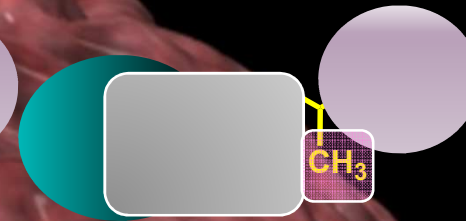
Chemical structure of cathinone/amphetamine derivatives



Catecholamines



Serotonin



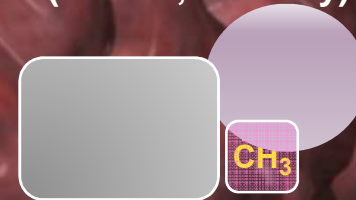
Methylenedioxymethamphetamine (MDMA; Ecstasy)



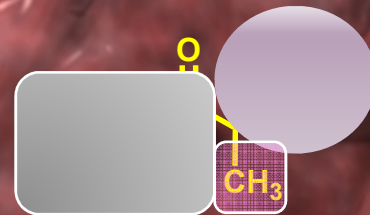
4-Methylthioamphetamine



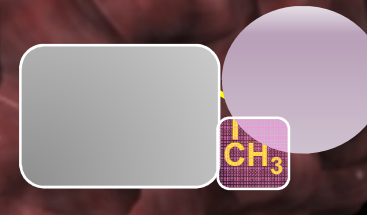
Phenylethylamine



Amphetamine



Cathinone



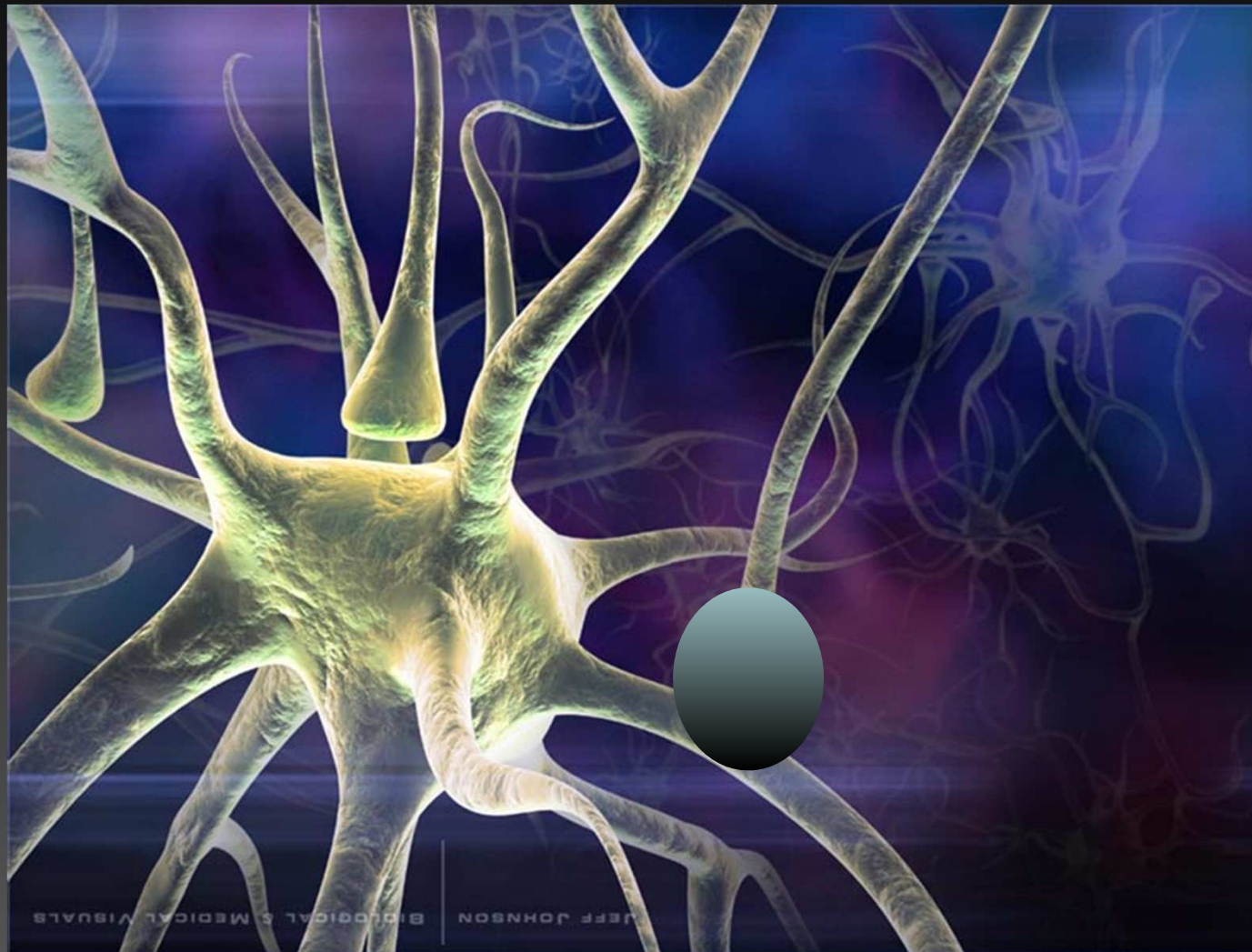
Methamphetamine



Catha edulis

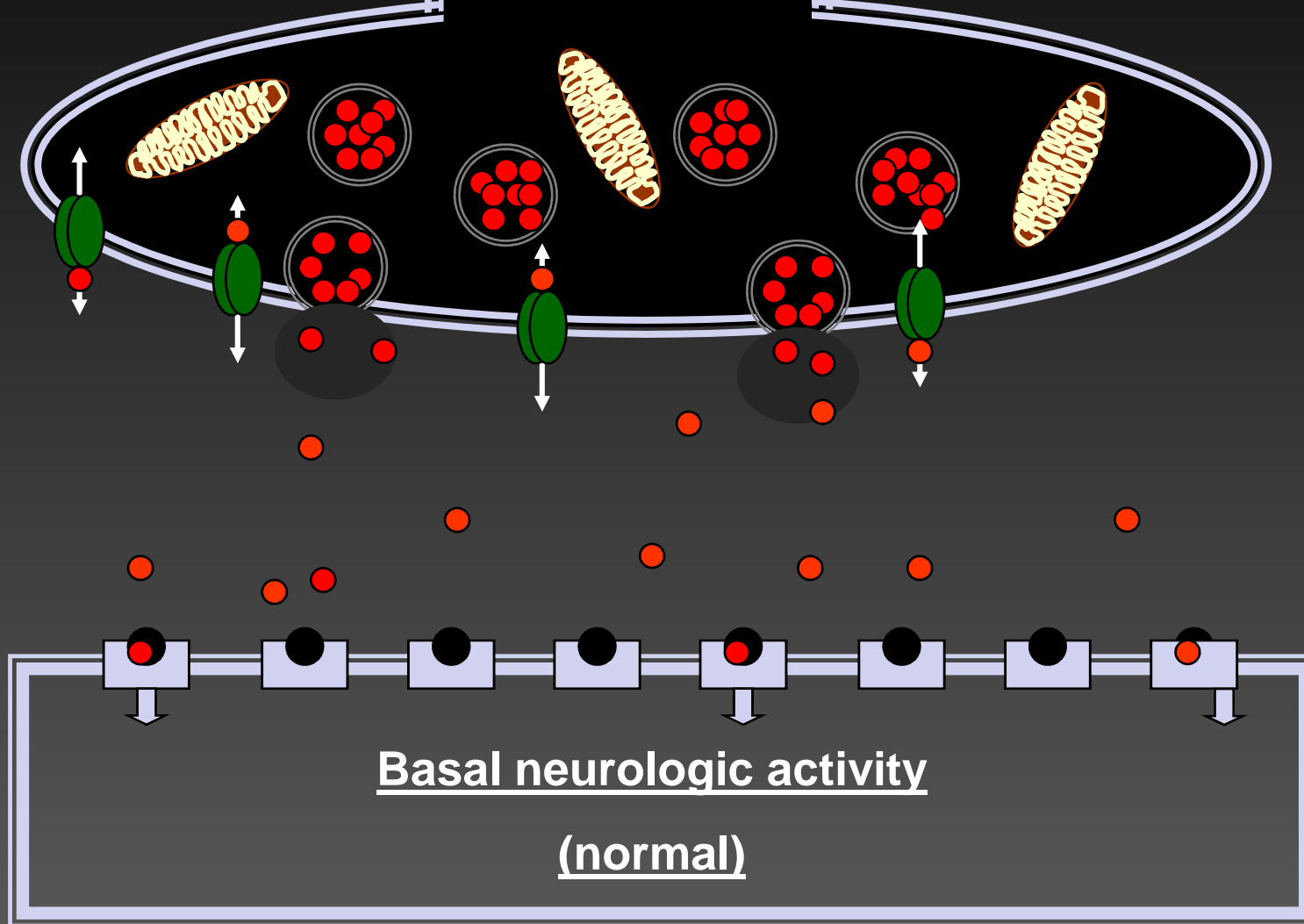


Mechanism of action of amphetamine derivatives – release of neurotransmitters from nerve endings



• Serotonin

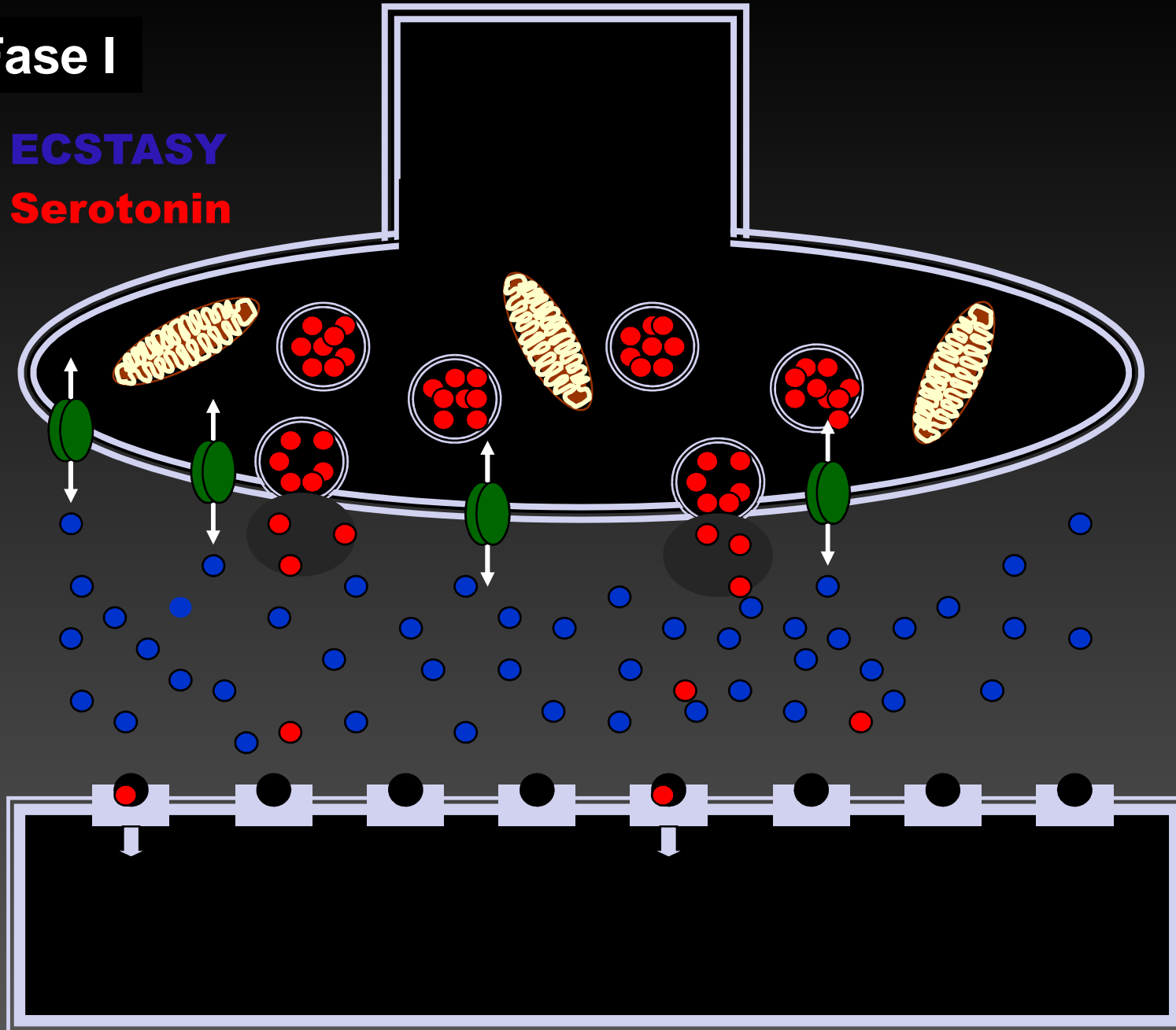
 SERT



Fase I

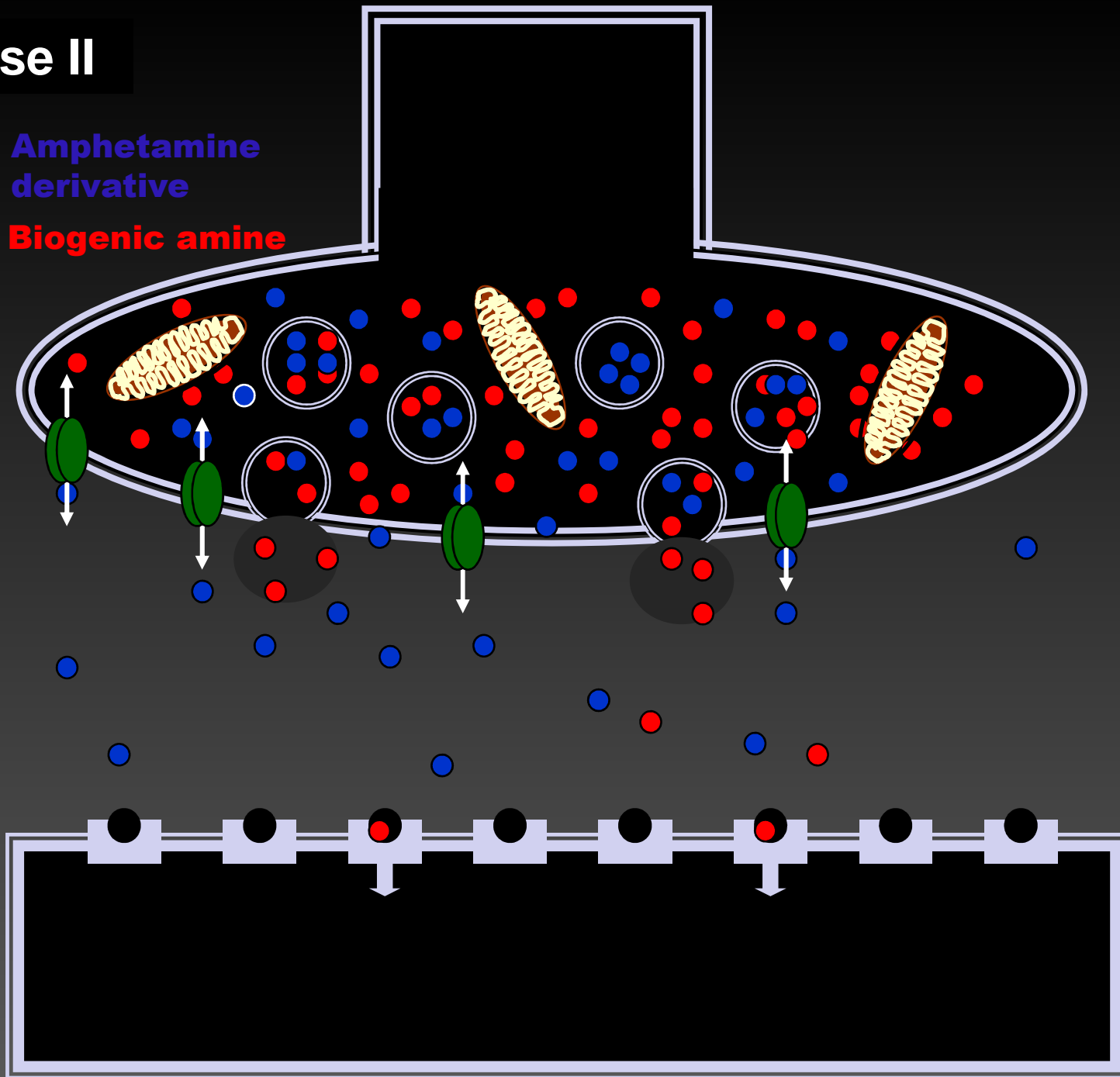
● **ECSTASY**

● **Serotonin**



Fase II

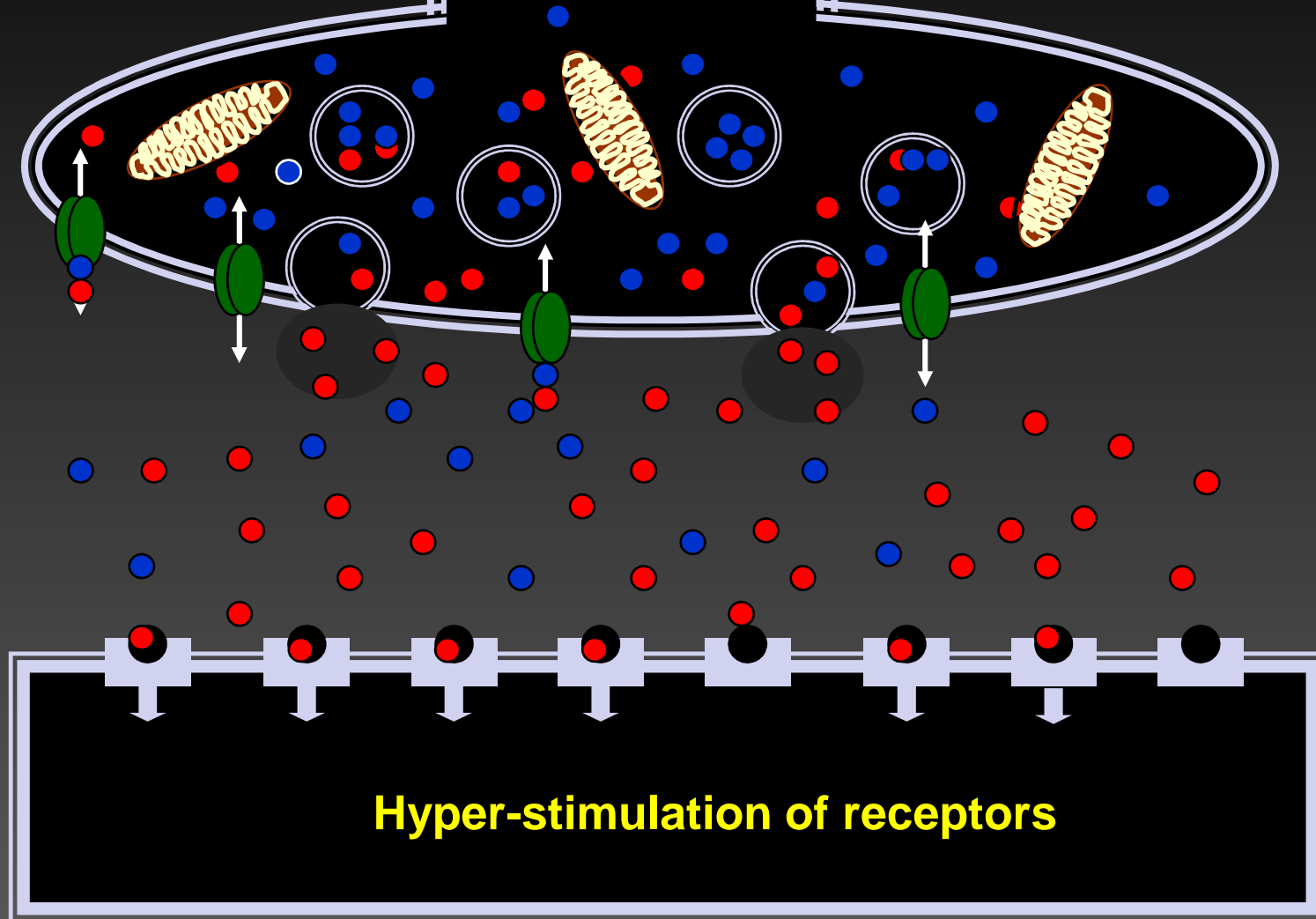
- Amphetamine derivative
- Biogenic amine



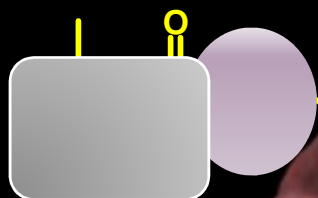
Fase III

- **ECSTASY**
- **Serotonin**

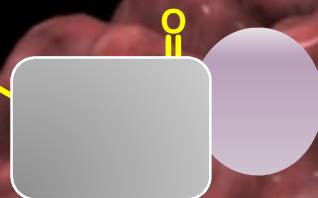
Pharmacological effect
of short duration



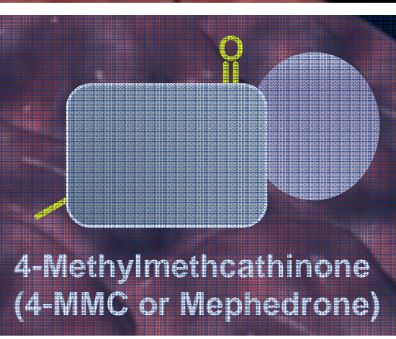
Cathinone/amphetamine-like “legal highs”



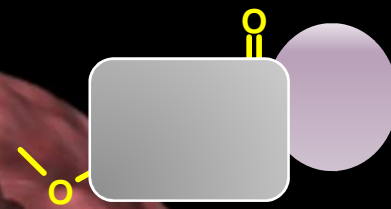
2-Methylmethcathinone
(2-MMC)



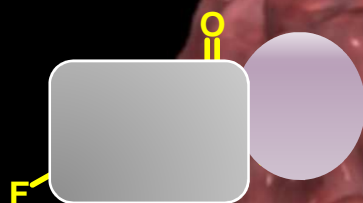
3-Methylmethcathinone
(3-MMC)



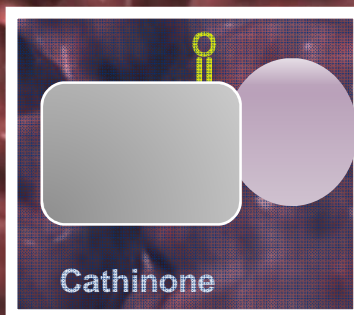
4-Methylmethcathinone
(4-MMC or Mephedrone)



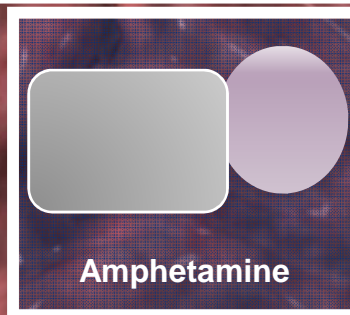
4-Methoxymethcathinone
(Methedrone)



Flephedrone



Cathinone



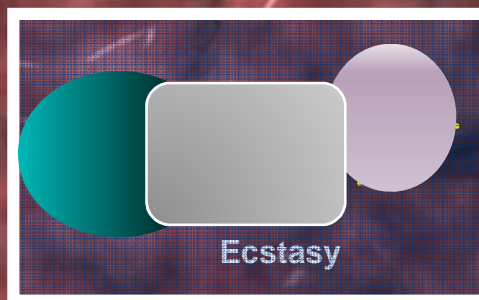
Amphetamine



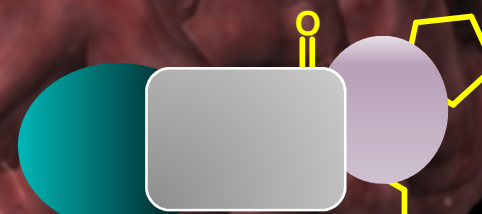
Buphedrone



3,4-Methylenedioxy-N-methylcathinone
(Methylone)



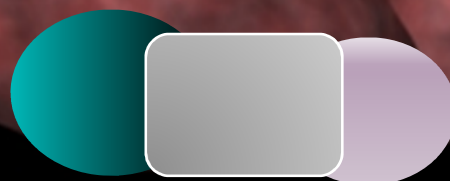
Ecstasy



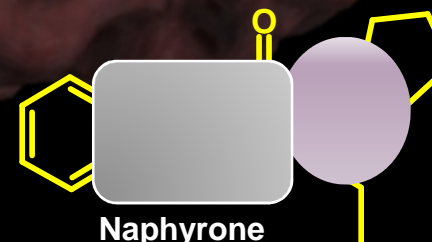
Methylenedioxypyrovalerone
(MDPV)



Butylone

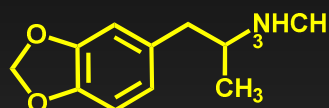


5,6-Methylenedioxy-2-aminoindane (MDAI)

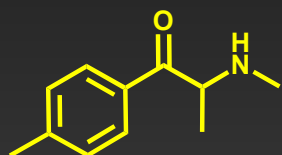


Naphyrone

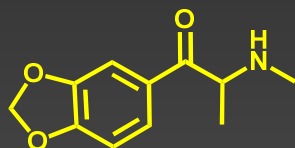
Mephedrone and Methylone Increase Extracellular Serotonin and Dopamine, similarly to MDMA



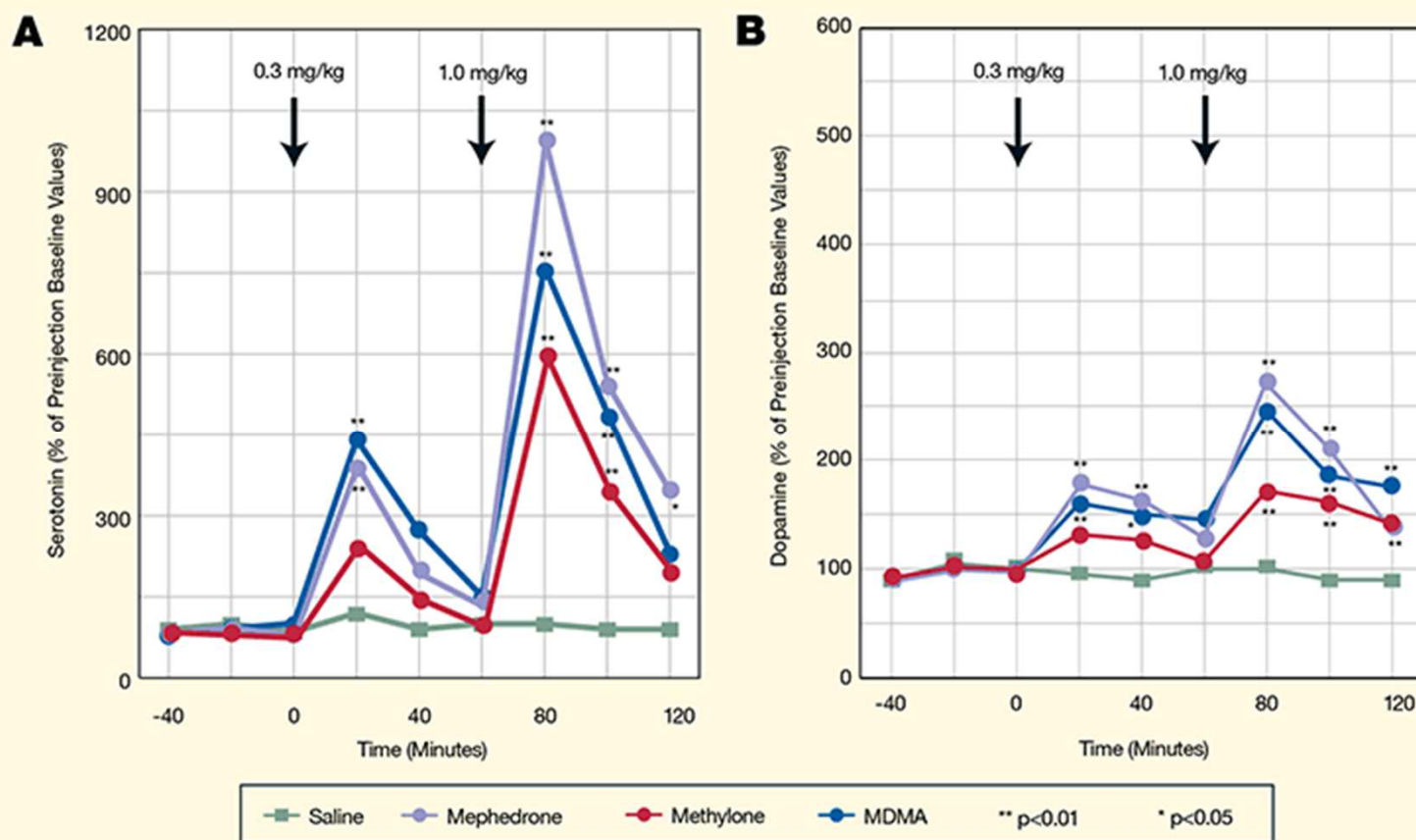
MDMA



Mephedrone



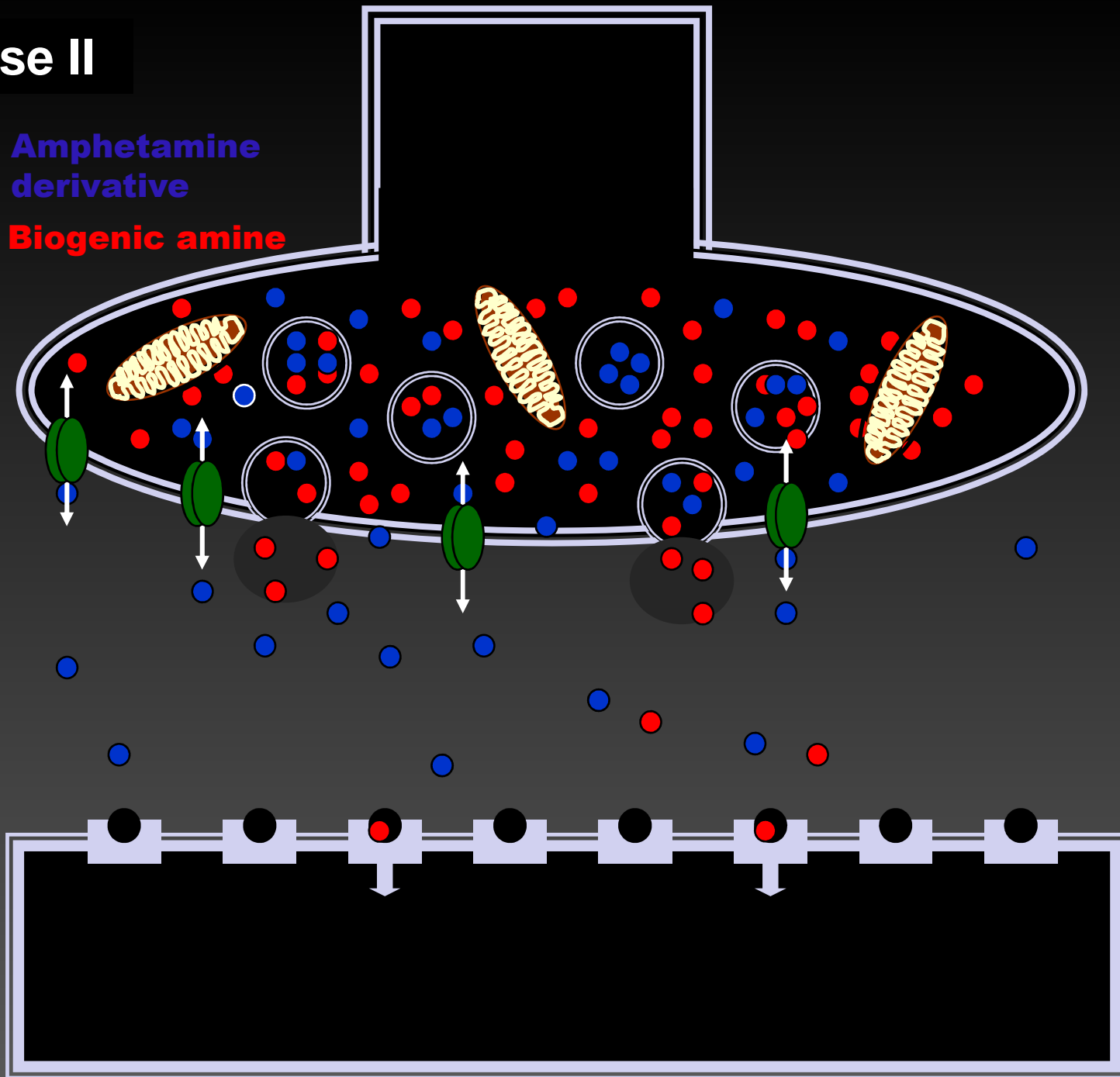
Methylone



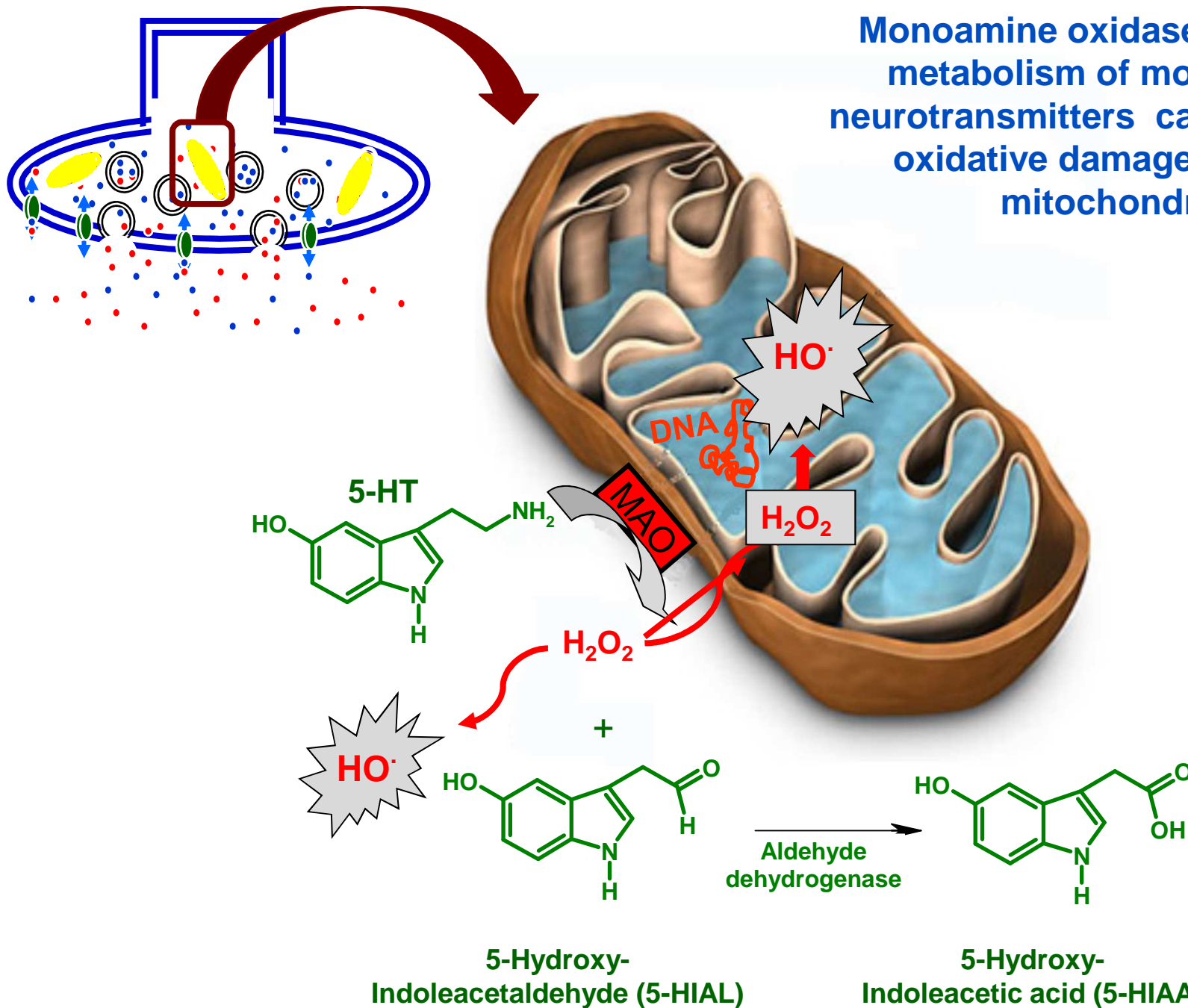
Baumann, M.H., et al. The designer methcathinone analogs, mephedrone and methylone, are substrates for monoamine transporters in brain tissue. *Neuropsychopharmacology* 37(5):1192–1203, 2012

Fase II

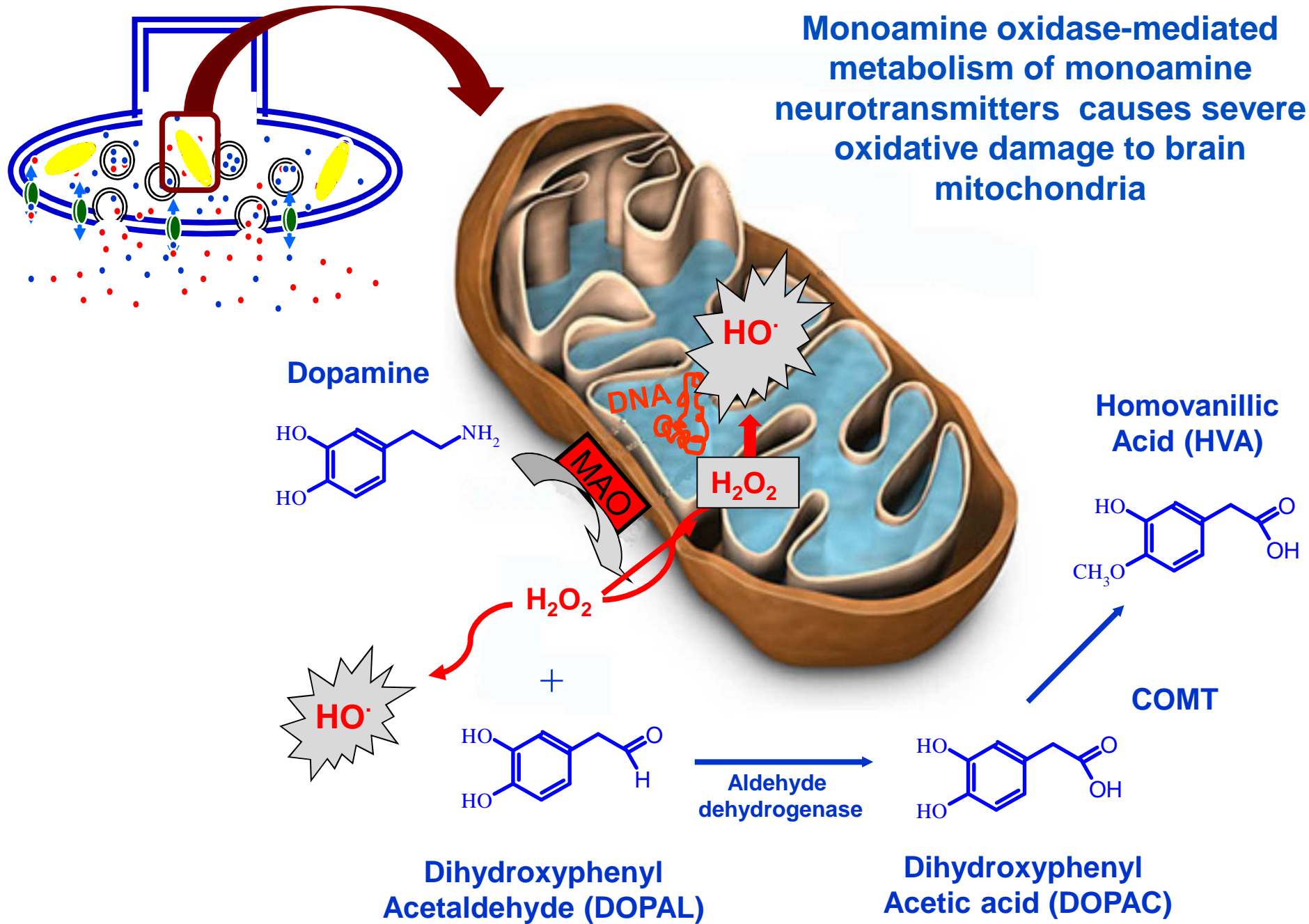
- Amphetamine derivative
- Biogenic amine



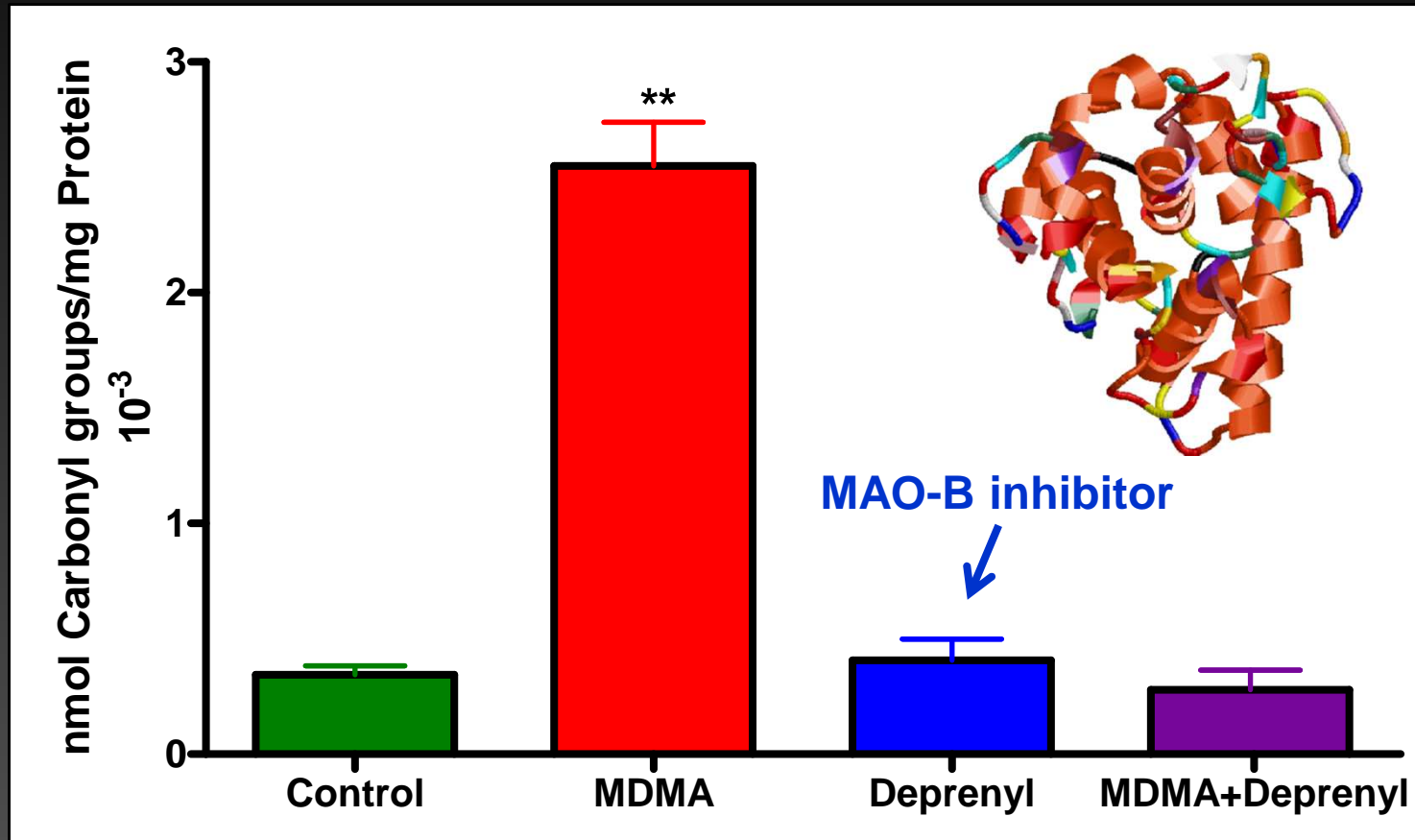
**Monoamine oxidase-mediated
metabolism of monoamine
neurotransmitters causes severe
oxidative damage to brain
mitochondria**



Monoamine oxidase-mediated metabolism of monoamine neurotransmitters causes severe oxidative damage to brain mitochondria

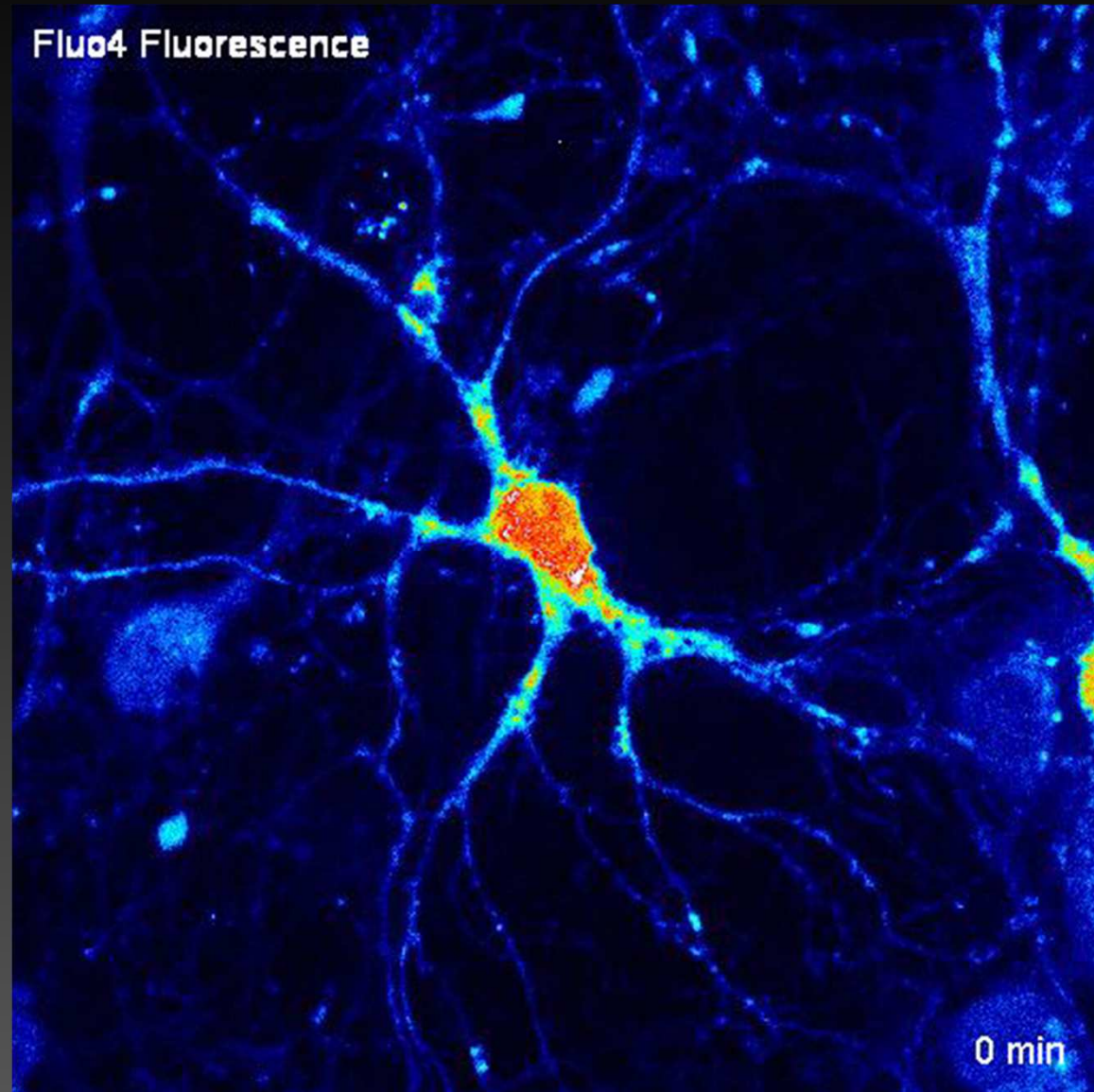


Oxidation of brain mitochondrial proteins and prevention by a MAO-B inhibitor

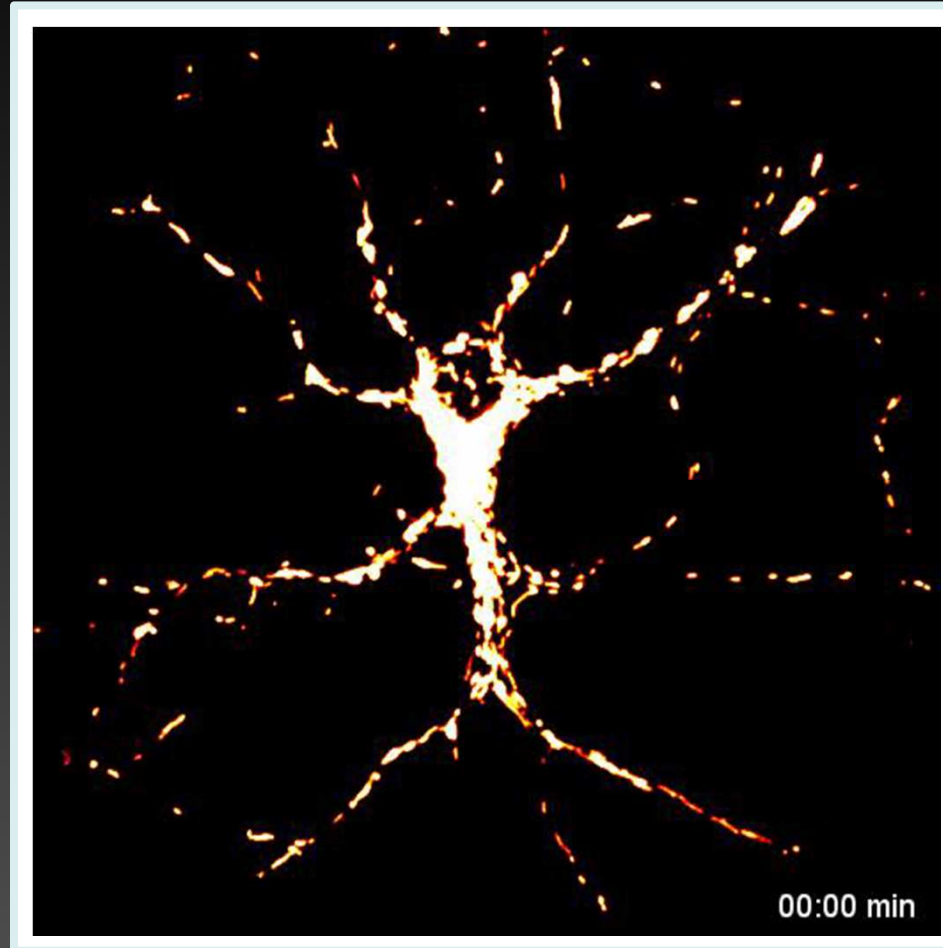


Ema Alves, Teresa Summavielle, Cecília Juliana Alves, Joana Gomes-da-Silva, José Custódio Barata, Eduarda Fernandes, Maria de Lourdes Bastos, Maria Amélia Tavares, Félix Carvalho (2007) Monoamine oxidase-B mediates ecstasy-induced neurotoxic effects to adolescent rat brain mitochondria. *Journal of Neuroscience* 27(38):10203–10210.

Ecstasy – Increase of free intracellular calcium in hippocampal neurons



In neurons, mitochondria are highly dynamic organelles



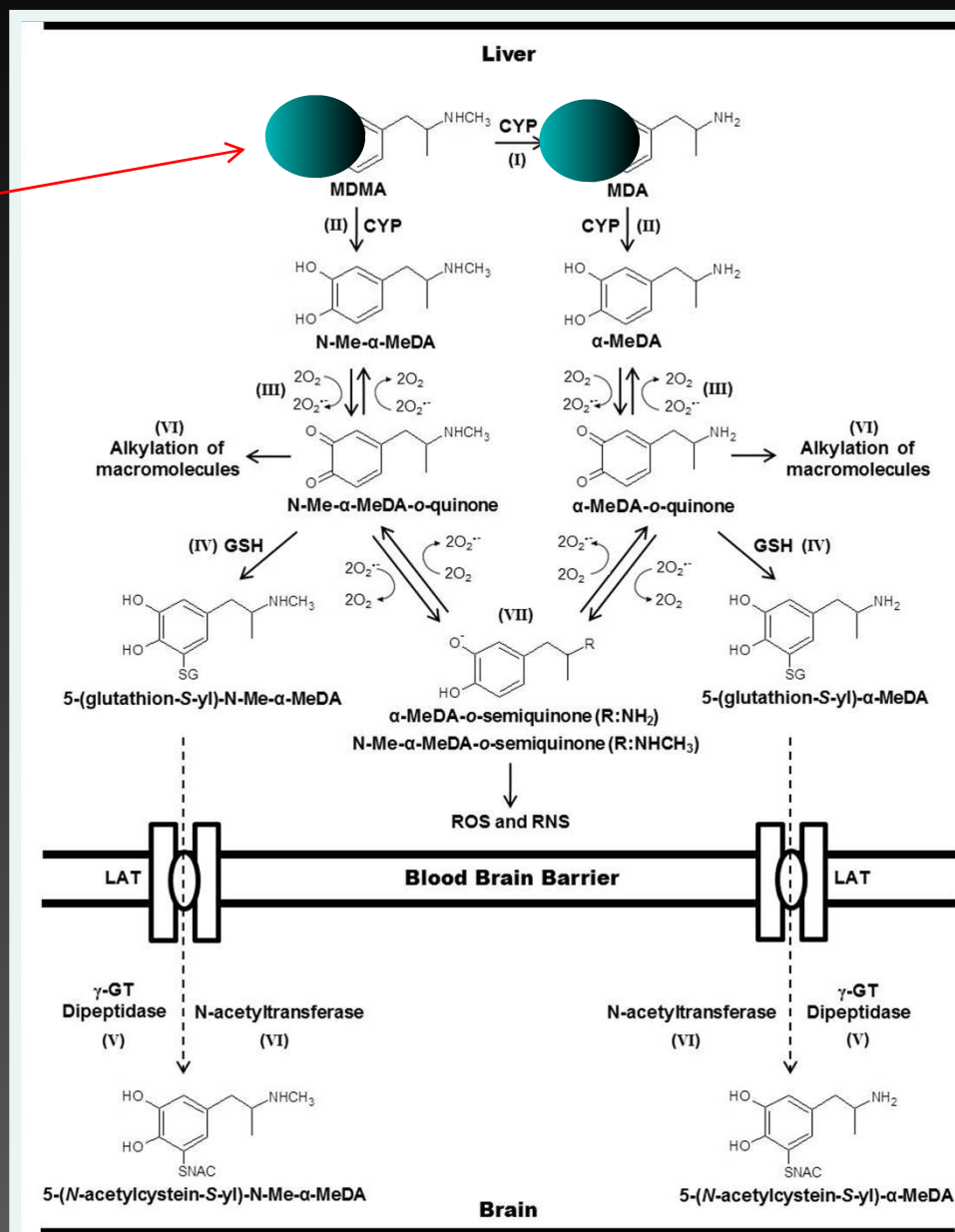
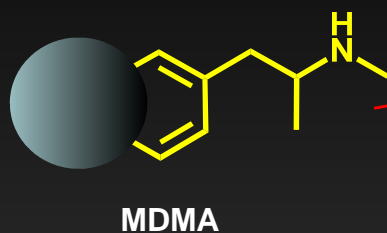
Mitochondrial movement in a hippocampal neuron, at 6DIV, under control conditions. Live-imaging was performed in a hippocampal neuron transfected with MitDsRed.

Ecstasy dramatically impairs mitochondrial trafficking in hippocampal neurons

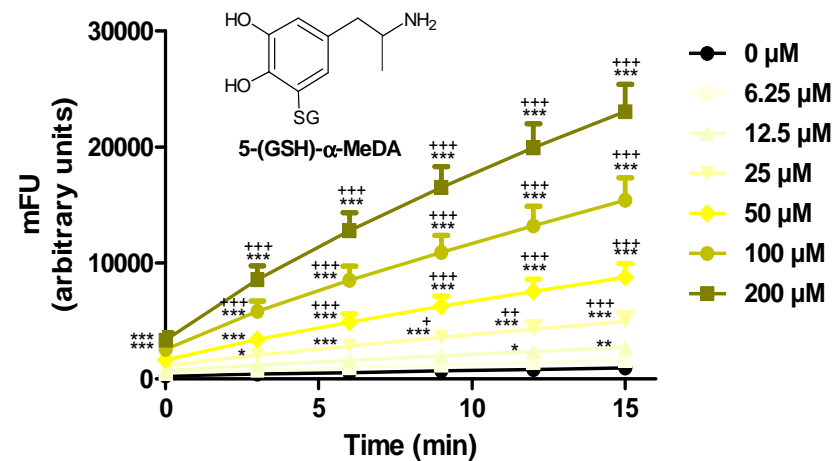
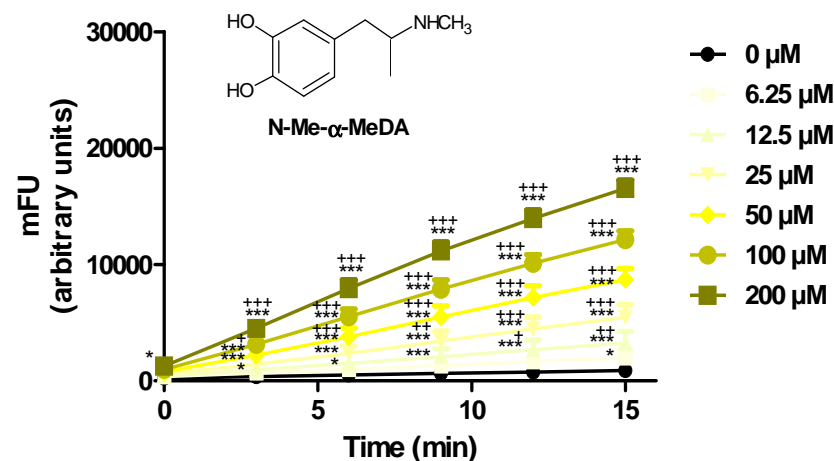
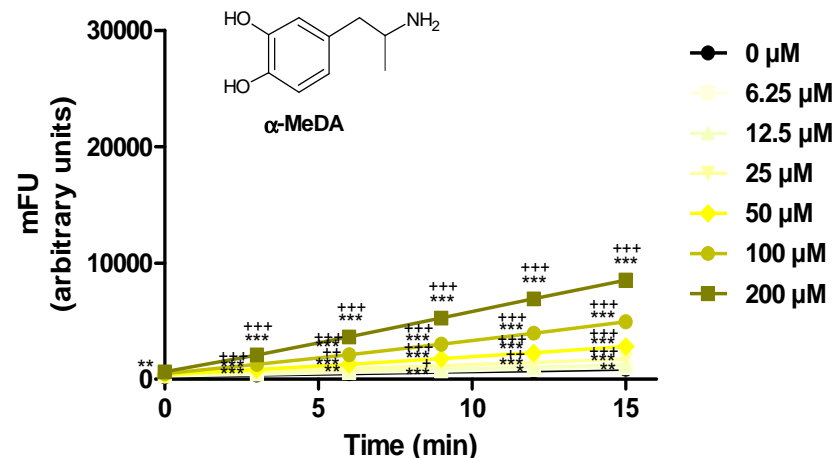
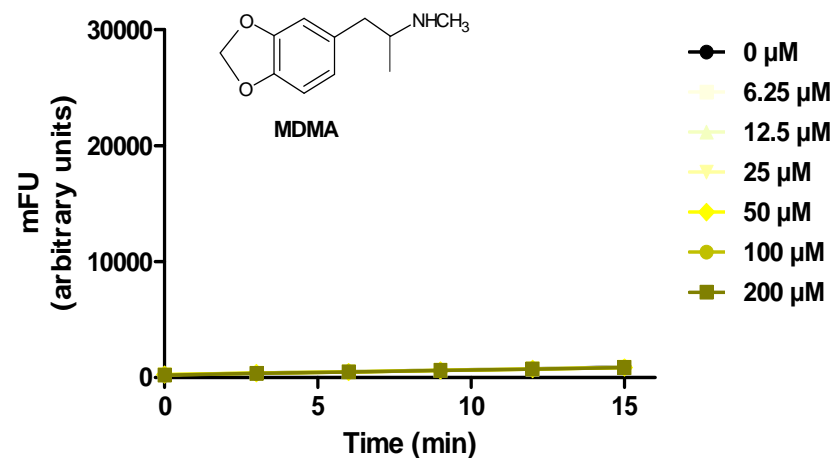


(A-B) Axonal transport of mitochondria in a hippocampal neuron, at 6DIV, under control conditions (A) or after exposure to MDMA for 90 min (B). Live-imaging of axonal mitochondria was performed in a hippocampal neuron transfected with MitDsRed.

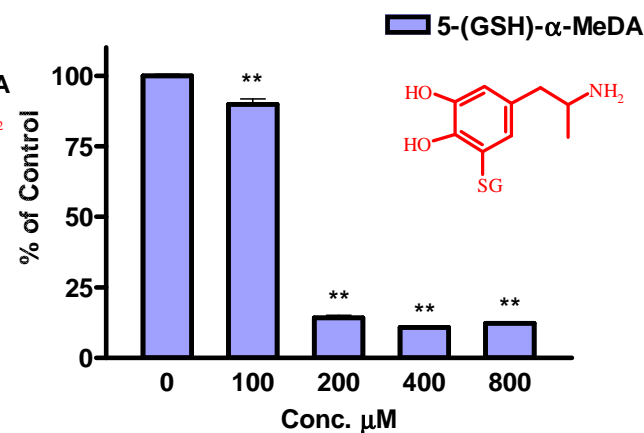
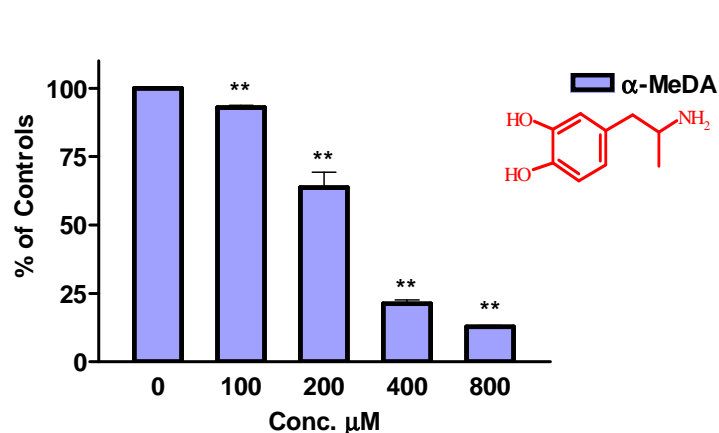
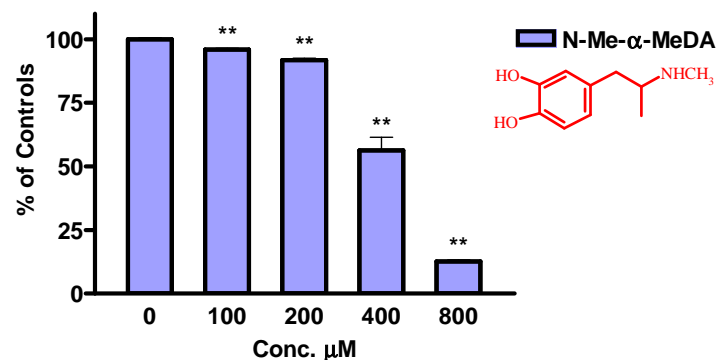
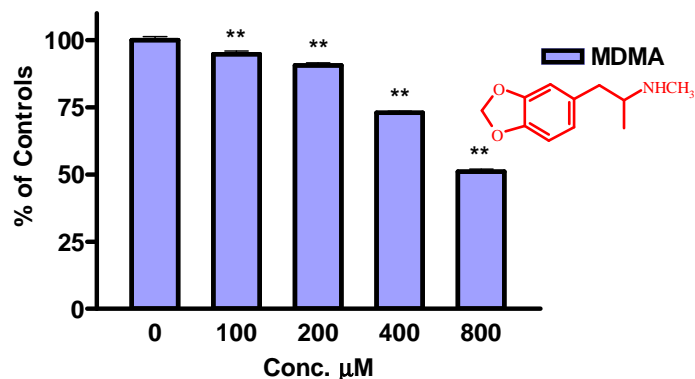
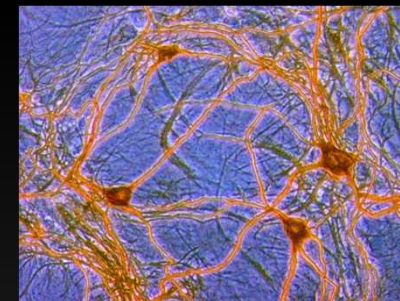
MDMA is metabolized in the liver, resulting in the formation and release of toxic metabolites to the circulation



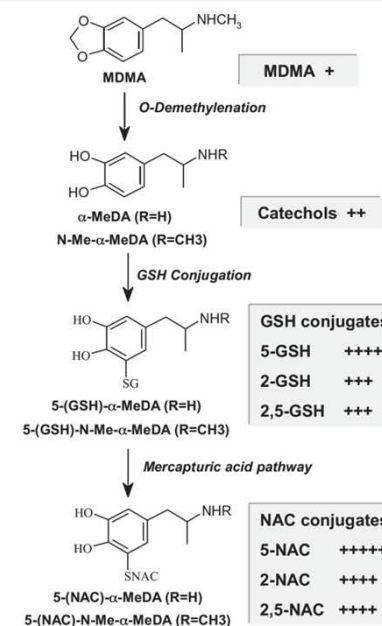
Production of hydrogen peroxide in Mouse brain synaptosomes



The metabolites of ecstasy are much more neurotoxic

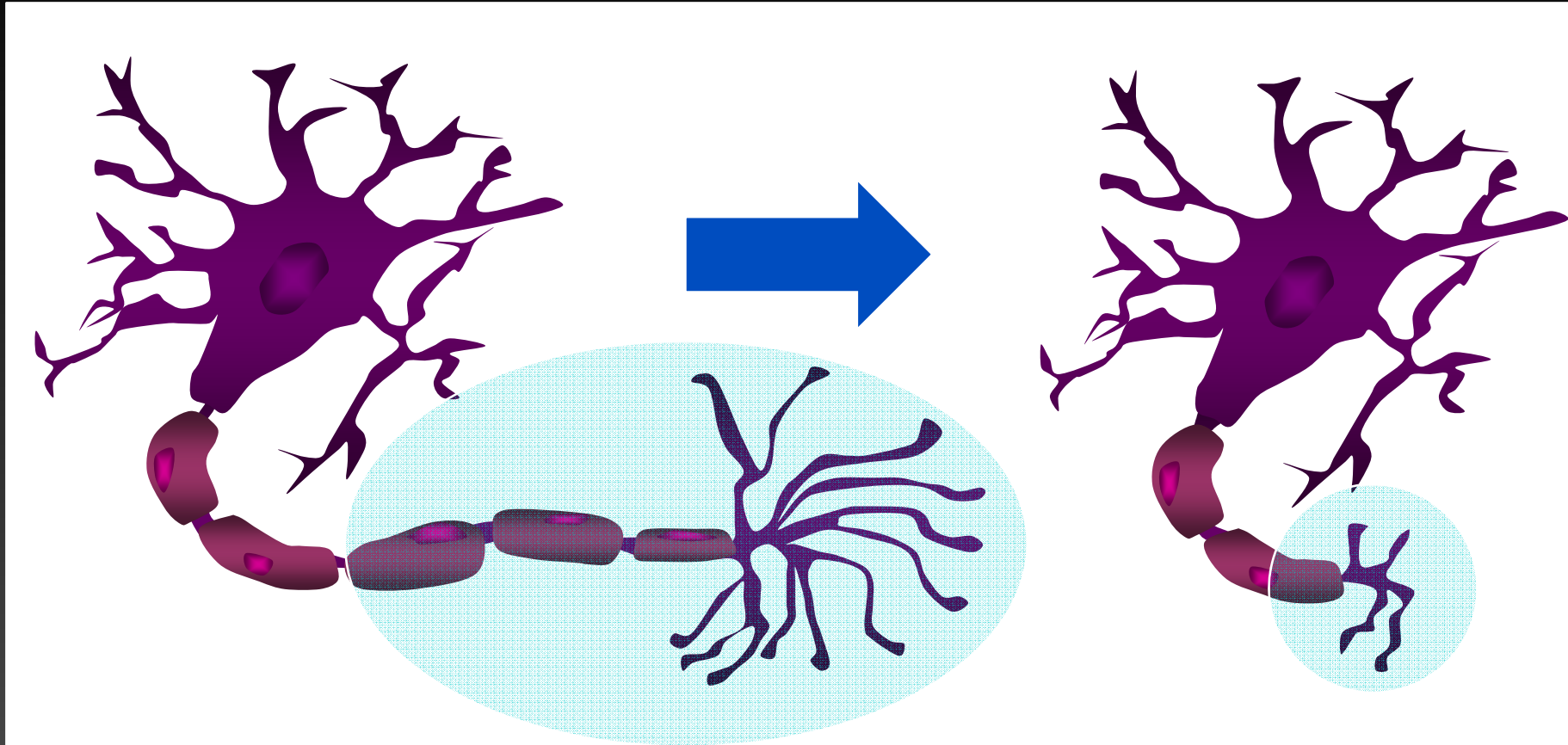


MDMA Metabolites Neurotoxicity Profile



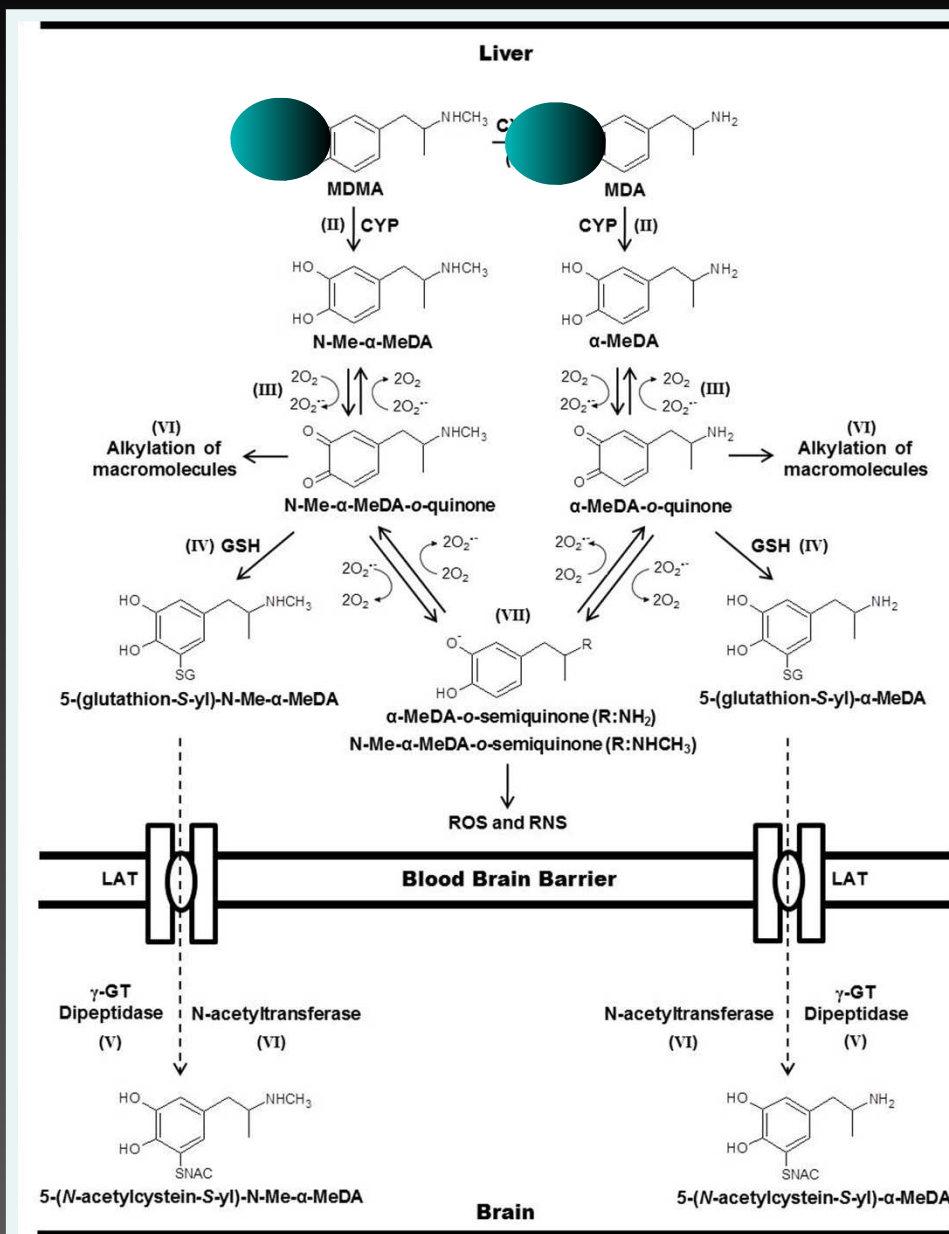
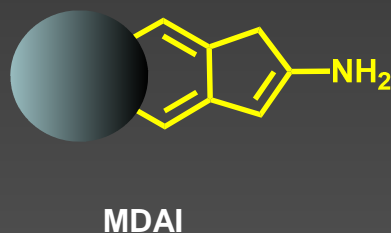
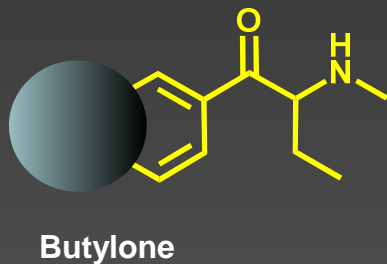
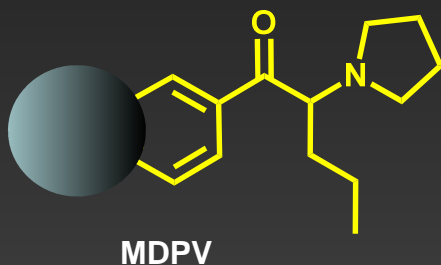
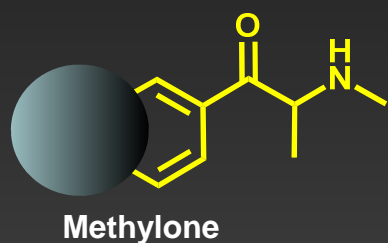
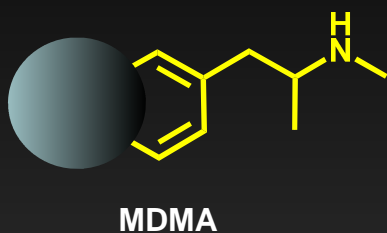
João Paulo Capela, Andreas Meisel, Artur Abreu, Paula Branco, Luísa Ferreira, Ana Lobo, Fernando Remião, Maria de Lourdes Bastos, Félix Carvalho (2006) Neurotoxicity of ecstasy metabolites in rat cortical neurons, and influence of hyperthermia.
Journal of Pharmacology and Experimental Therapeutics 316(1):53-61.

Neurotoxicity of ECSTASY



Exposure to MDMA may elicit long-term changes in the neurochemistry and behaviour resulting from selective neurotoxicity of serotonergic axon terminals

The same type of metabolism is expected for NPS with the 3,4-methylenedioxy group



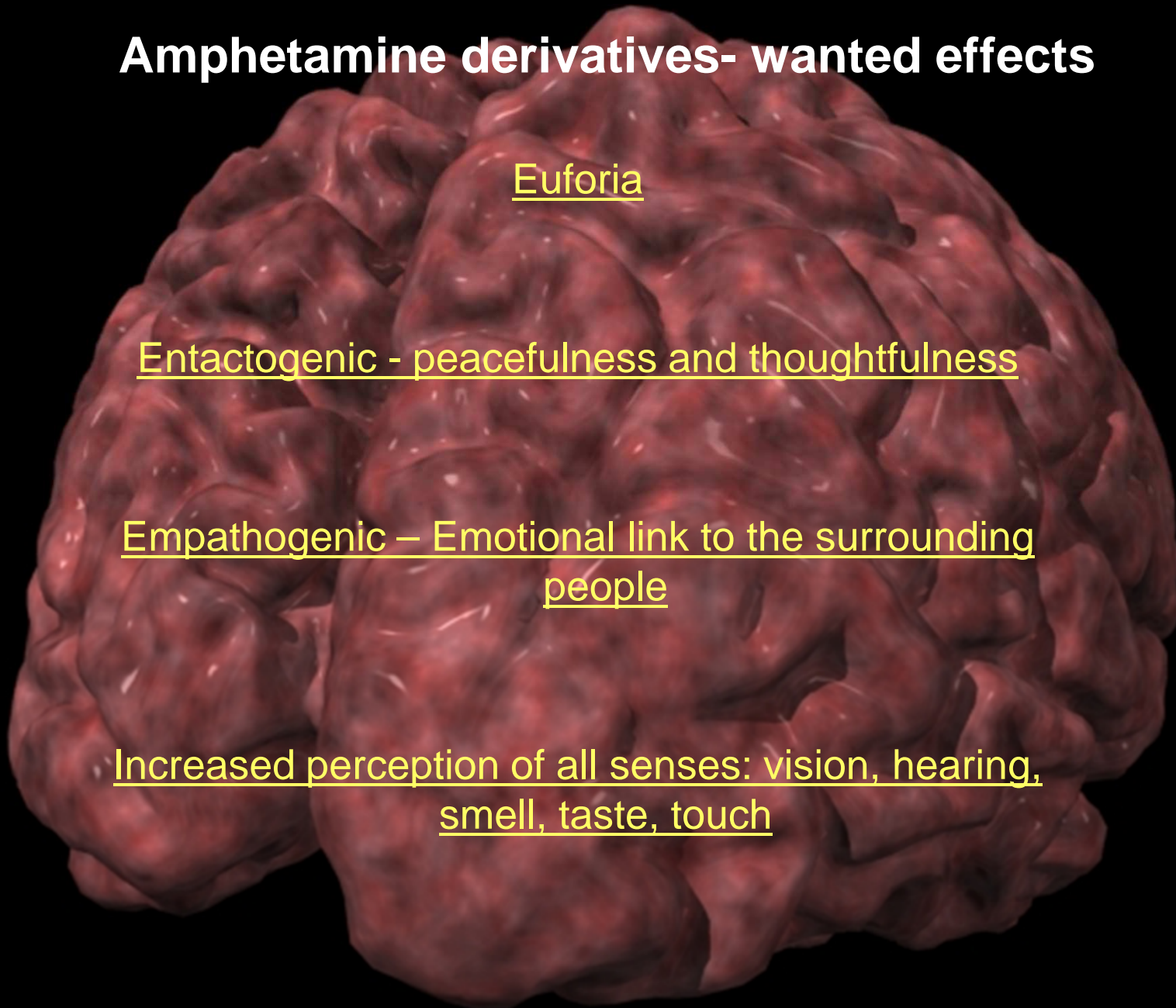
Amphetamine derivatives- wanted effects

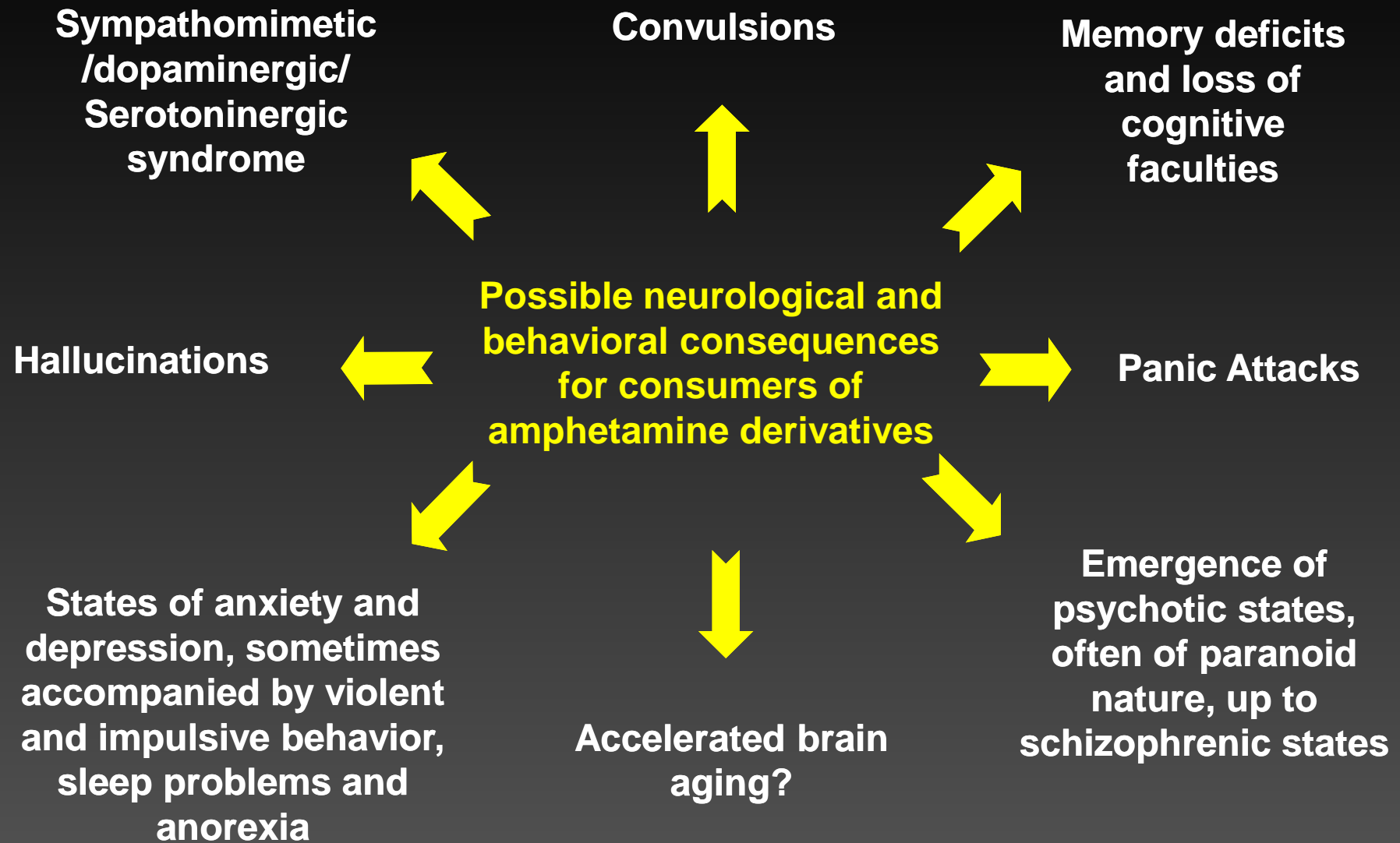
Euforia

Entactogenic - peacefulness and thoughtfulness

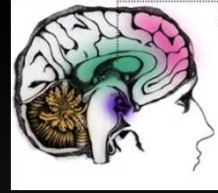
Empathogenic – Emotional link to the surrounding people

Increased perception of all senses: vision, hearing, smell, taste, touch





Neurotoxicity



**Teratogenicity and
embryotoxicity**

Hyponatremia



Hepatotoxicity



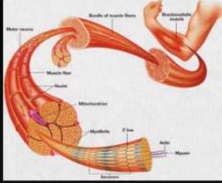
Nephrotoxicity



Hyperthermia

**Severe
toxicity of
ecstasy-like
drugs**

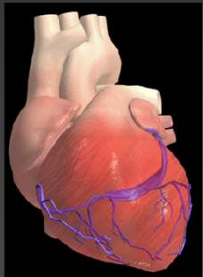
Rhabdomyolysis



**Disseminated
Intravascular
Coagulation**

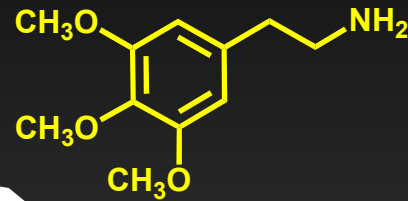


**Toxicity to the
cardiovascular
system**

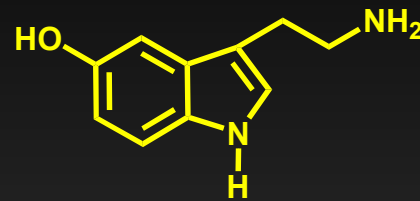


chemical structure of serotonin and of other hallucinogens

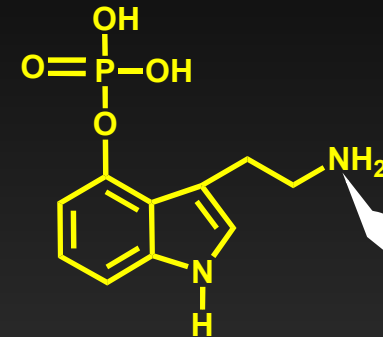
Peyote cactus



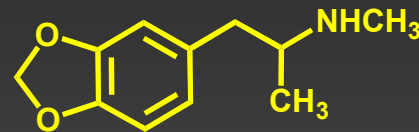
Mescaline



Serotonin



psilocybin



MDMA

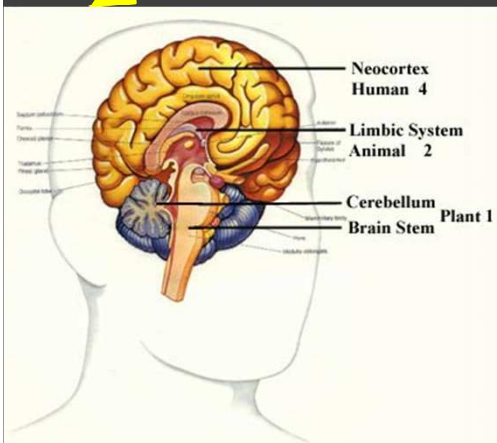


Lysergic acid
diethylamide
(LSD)

Synthesized by
Hofmann, in 1938

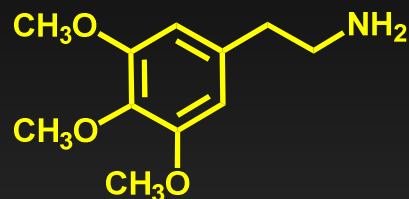


Magic mushrooms
Psilocybe cubensis
Psilocybe mexicana

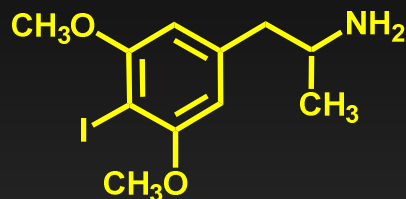


Stimulation of 5-HT_{2A} receptors, especially
in pyramidal neurons of the neocortex

DOI (2,5-Dimethoxy-4-iodoamphetamine, an hallucinogenic mescaline derivative and agonist of 5-HT_{2A} receptors induces apoptosis in cortical neurons – prevented by 5-HT_{2A} antibodies

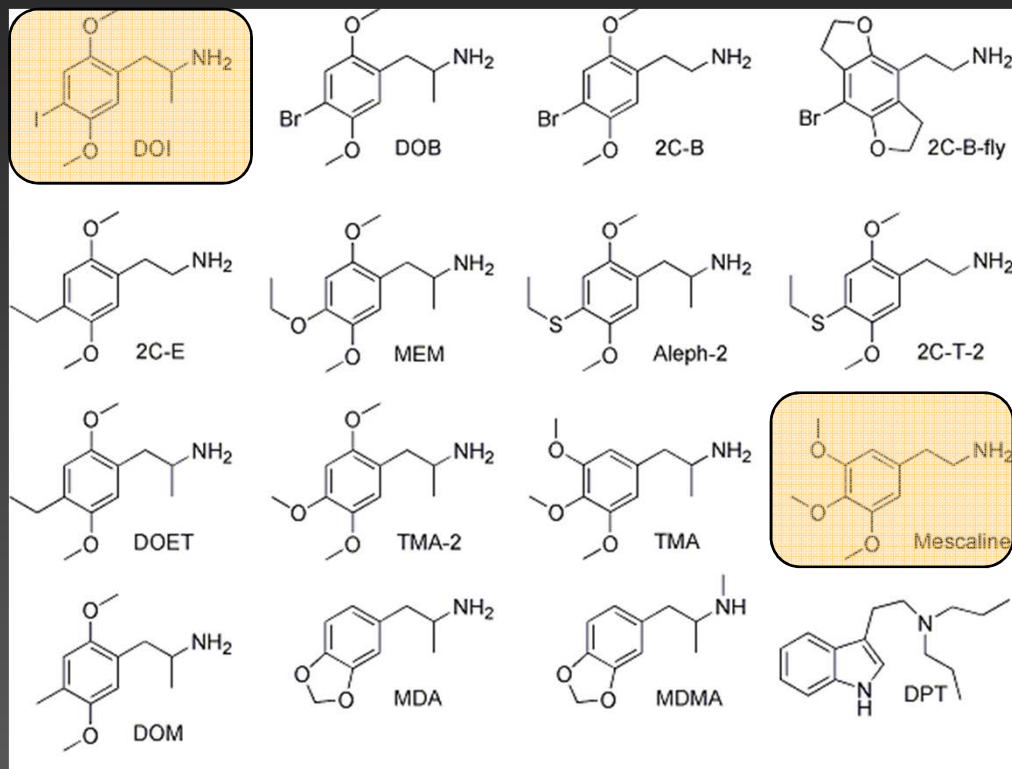
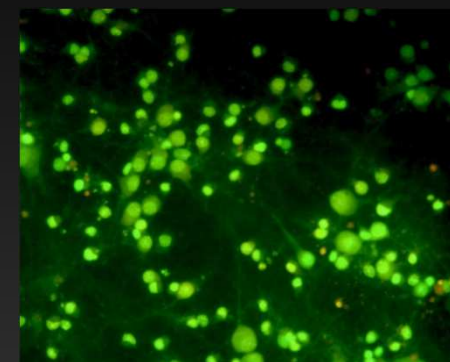


Mescaline

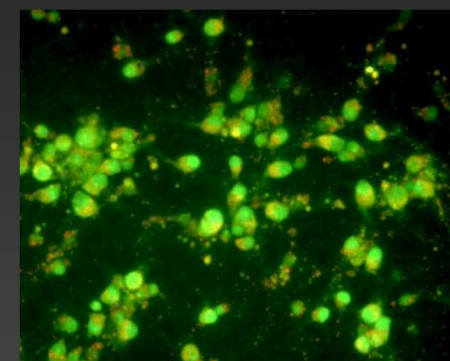


DOI

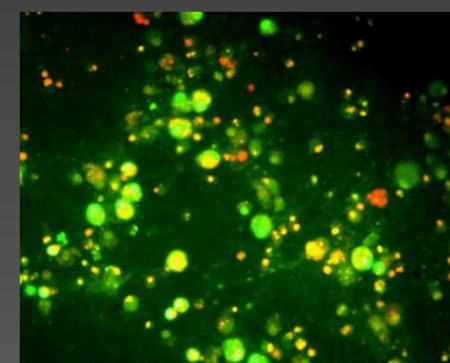
Control



10μM



50μM



Are we challenged by new paradigms from the Analytical Chemistry point of view?

YES

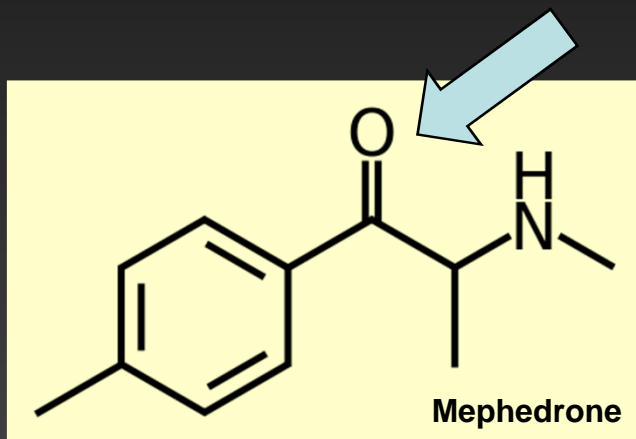
Structures and solubility of NPS are different from classical drugs

The profile of NPS metabolites will sustain several differences

Mixtures of different NPS are frequent

Pharmacokinetic features

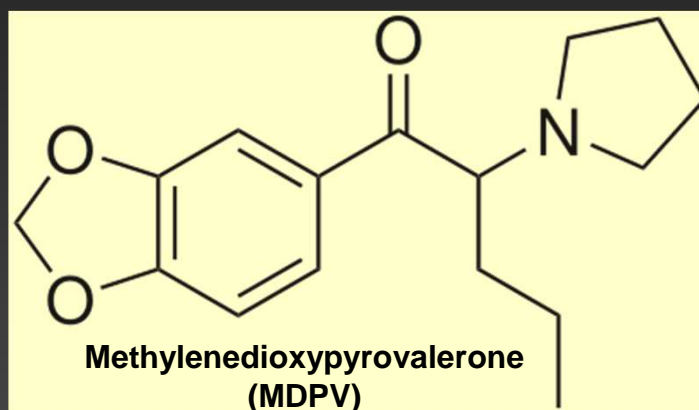
Generally, the presence of the β -keto group increases the polarity of the synthetic cathinones, resulting in a decrease of their ability to cross the blood-brain barrier (BBB)



Higher or repeated doses are used...

Pharmacokinetic features

The **polarity issue** occurs mainly with the N-alkylated derivatives, but **not so much with the pyrrolidine family of cathinones**, since the presence of the pyrrolidine ring greatly reduces the polarity of these compounds



Mixtures

Plant extracts with opioid activity KRATOM

Mitragynine



7-Hydroxymitragynine



30 and 17 x more
potent than mitragynine
and morphine
respectively

Mitragyna speciosa (Kratom)



Agonists of opioid
receptors delta and mu

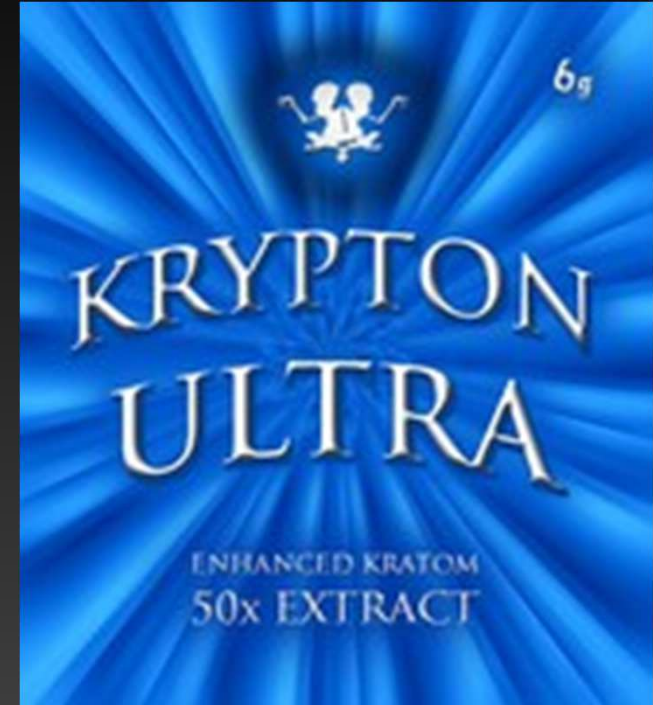
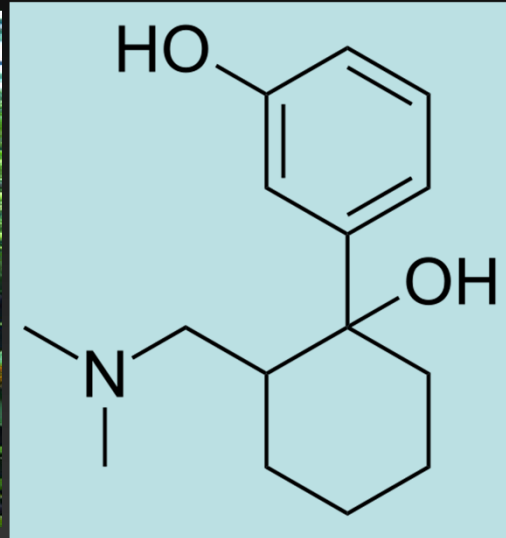
At low doses – adrenergic agonists
At high doses – opioid agonists



Mixtures

Plant extracts with opioid activity

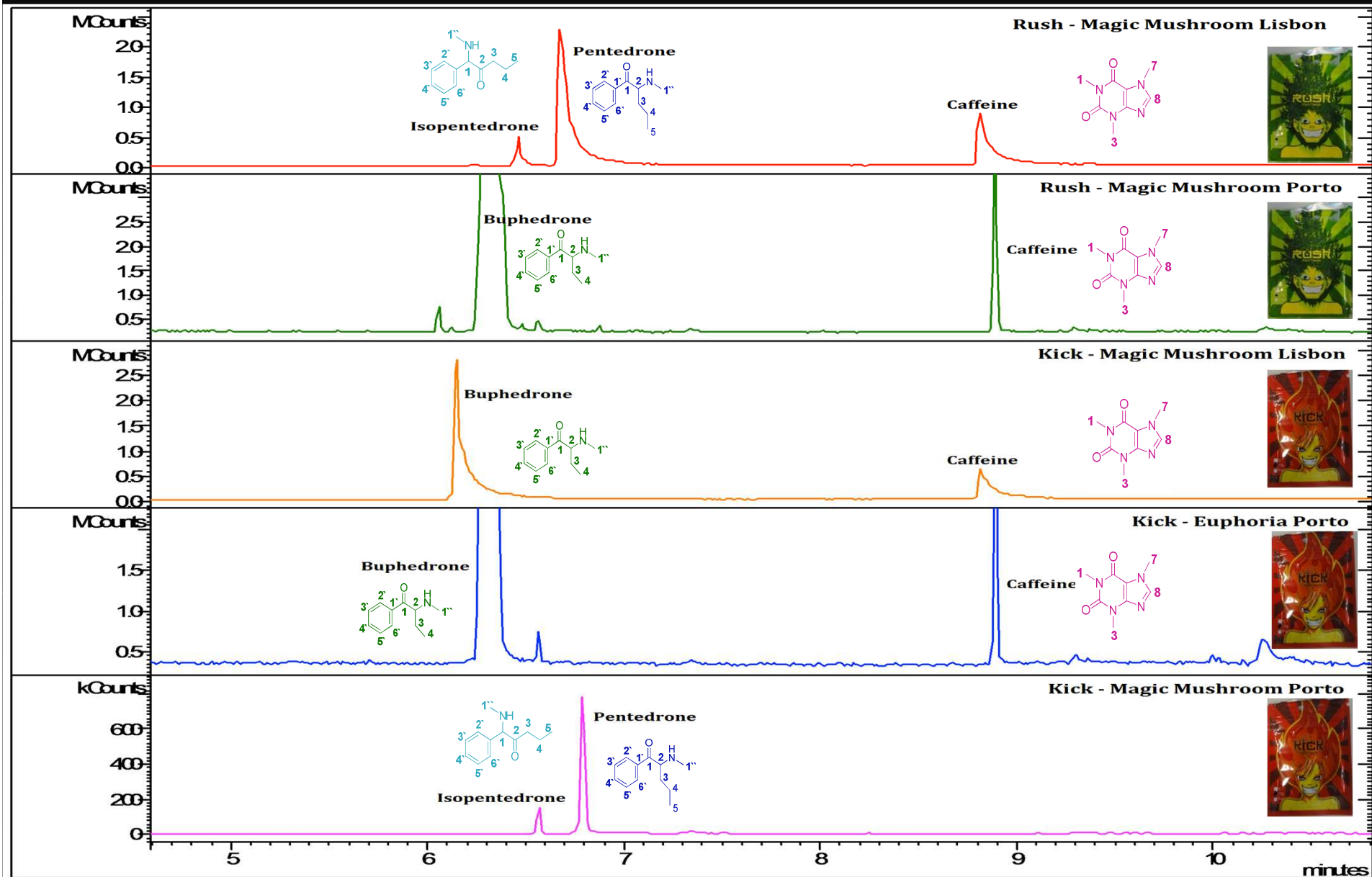
KRATOM + O-Desmethylnaloxadol



Considered the cause of several deaths in Sweden

Mixtures

Mixtures of different NPS are frequent



Mixtures

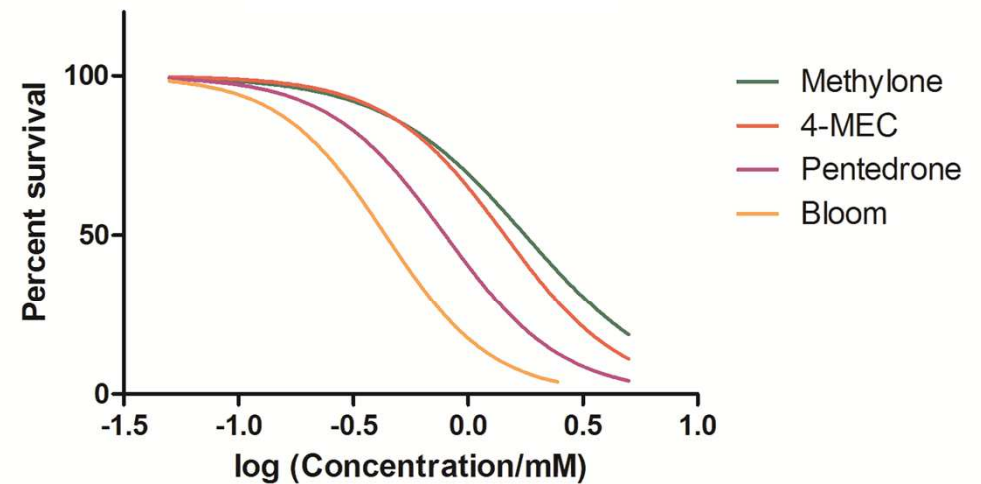
Mixtures have been shown to be more toxic

PRIMARY CULTURES OF RAT HEPATOCYTES

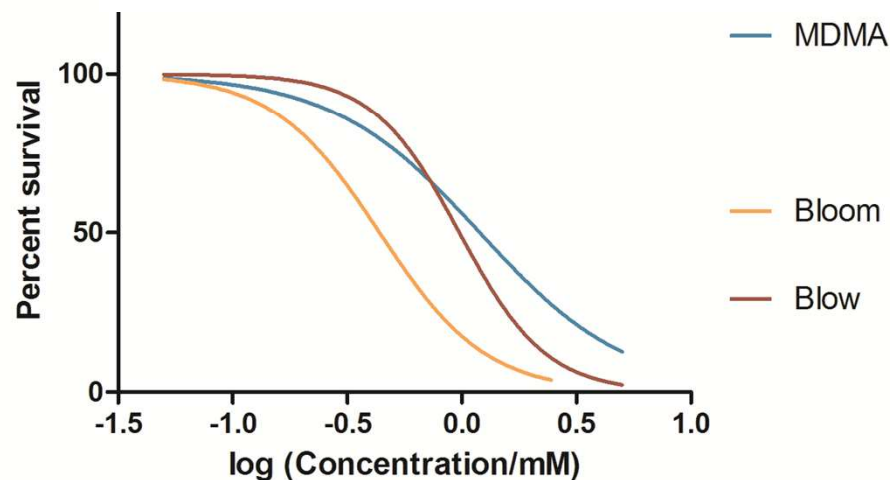
Bloom

Toxicity of Bloom, Blow and MDMA

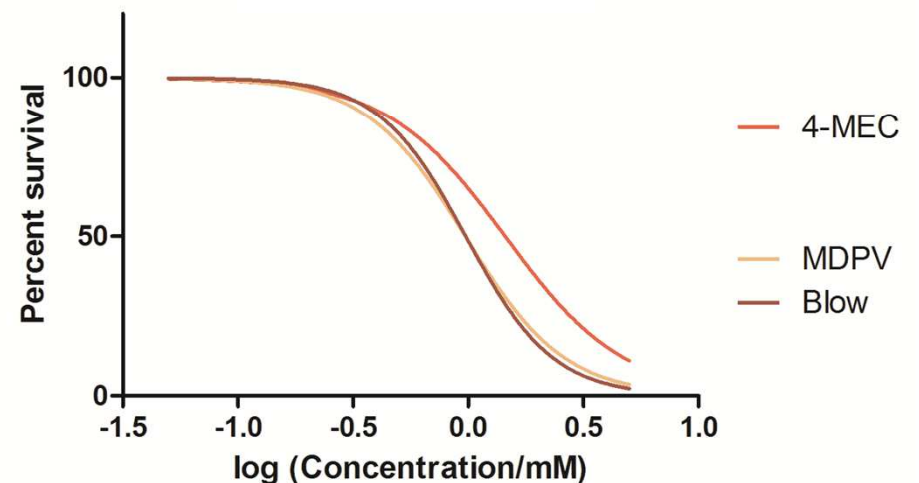
4-MEC - 4-Methylethcathinone
MDPV - Methylenedioxypropylvalerone



Bloom vs Blow vs MDMA



Blow



Acknowledgements



Center of Chemistry and Biochemistry (CQB), Faculty of Sciences, University of Lisbon



Laboratory of Scientific Police, Lisbon, Portugal



Institute for Molecular and Cell Biology



Faculty of Health Sciences, University Fernando Pessoa



Laboratories of Toxicology and Applied Chemistry, Faculty of Pharmacy, University of Porto

FCT Fundação para a Ciência e a Tecnologia
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E ENSINO SUPERIOR Portugal

“Fundação para a Ciência e a Tecnologia” (FCT), Portugal

- ▶ **FCT - Project (PTDC/SAU-FCF/102958/2008), unde the framework of “Programa Operacional Temático Fatores de Competitividade (COMPTE) do Quadro Comunitário de Apoio III” and “Fundo Comunitário Europeu (FEDER) (FCOMP-01-0124-FEDER-011079)”.**
- ▶ **FCT - PhD Grant (SFRH/BD/64939/2009) and Post-Doc Grant (SFRH/BPD/30776/2006).**
- ▶ **REQUIMTE (Rede de Química e Tecnologia) Associated Laboratories.**



EUROTOX
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13–16 September 2015
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Thank you very much for your attention

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Universidade do Porto





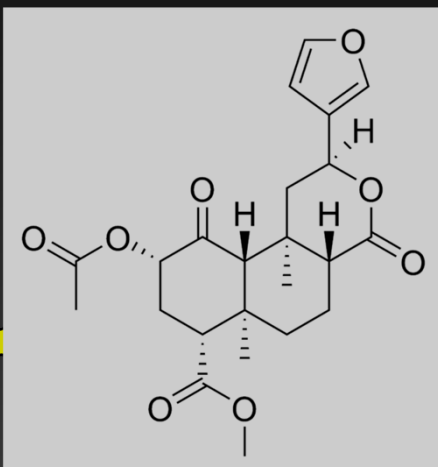




Plant extracts with opioid activity



SALVINORIN A:



Salvia divinorum



Agonist of kappa opioid receptors

Kappa opioid agonists cause hallucinogenic effects often unpleasant (or even dysphoric)

Effects appear within one minute after administration of the drug :

Dysphoria, hallucinations, dissociation, uncontrolled laughter, depersonalization.

CATHINONE/AMPHETAMINE DERIVATIVES

OTHER TOXIC EFFECTS IN ANIMAL STUDIES

Cardiovascular toxicity

Mephedrone increases the heart rate and blood pressure in rats, and cardiac contractility in guinea pigs

Thermoregulation

Cathinone, **ephedrone** and **methyldone** induce hyperthermia in rats

MDPV evokes a dose-dependent hyperthermia in mice, but only at a warm ambient temperature

Mephedrone induces hypothermia in single doses, and hyperthermia in a binging session

Addictive and reinforcing effects

Mephedrone and **MDPV** elicit self-administration patterns in rats

Methyldone shows a dose-dependent reinforcer efficacy in rats

CATHINONE/AMPHETAMINE DERIVATIVES

SUBJECTIVE EFFECTS AND ADVERSE TOXIC REACTIONS IN HUMANS

Synthetic cathinones

Subjective effects: **euphoria, increased empathy, decreased sense of hostility, and increased libido**

Unwanted effects: **sweating, nausea, vomiting, headaches, dizziness and confusion**

Toxic effects

Cardiovascular – hypertension and tachycardia, hyperthermia, peripheral vasoconstriction, palpitations, chest pain, tremor and seizure

Neurological – agitation, hallucinations, aggressiveness, anxiety, restlessness, depression with suicidal ideations, psychosis, anhedonia and dependence

Other – mydriasis, hyponatraemia, acute liver failure, acute kidney injury and rhabdomyolysis