Psychomotorstimulants
(psychostimulants)

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2020

PSYCHOSTIMULANTS

cocaine

Amphetamines (AMs)

stimulant

amphetamine,
methamphetamine,
methylphenidate,
katine,
MDMA (ecstasy),
etc.

stimulant
+
hallucinogenic

mescaline,
DOM,
MDA,
MDMA (high dose),
etc.

MECHANISM of ACTION

5-HT transmission

hallucination

CA transmission

NE
in the periphery

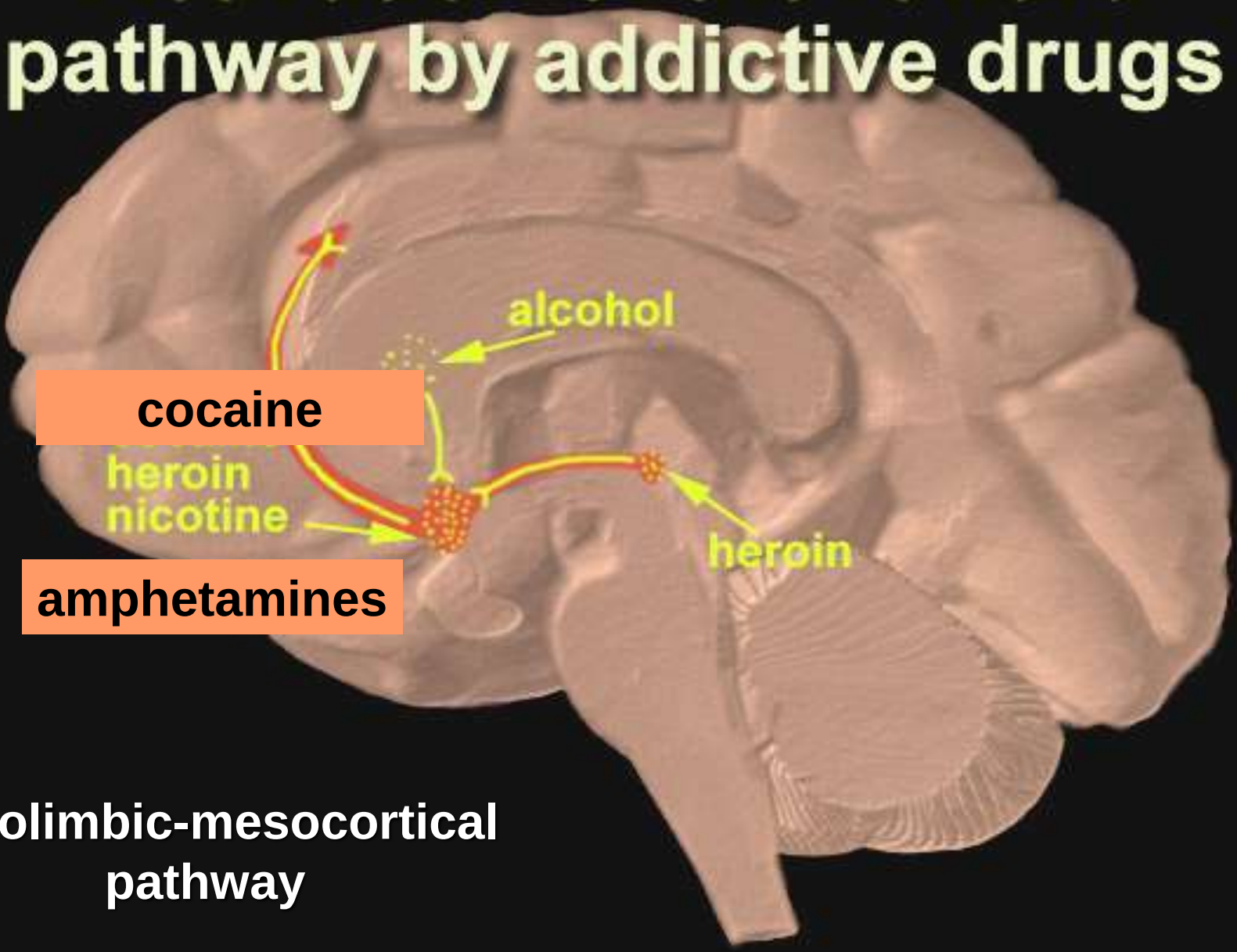
increase of
sympathetic tone

DA
in the brain

stimulant
effect

dependence

Activation of the reward pathway by addictive drugs



mesolimbic-mesocortical pathway

MECHANISM of ACTION of COCAINE and ATS

indirectly activate the dopamine transmission

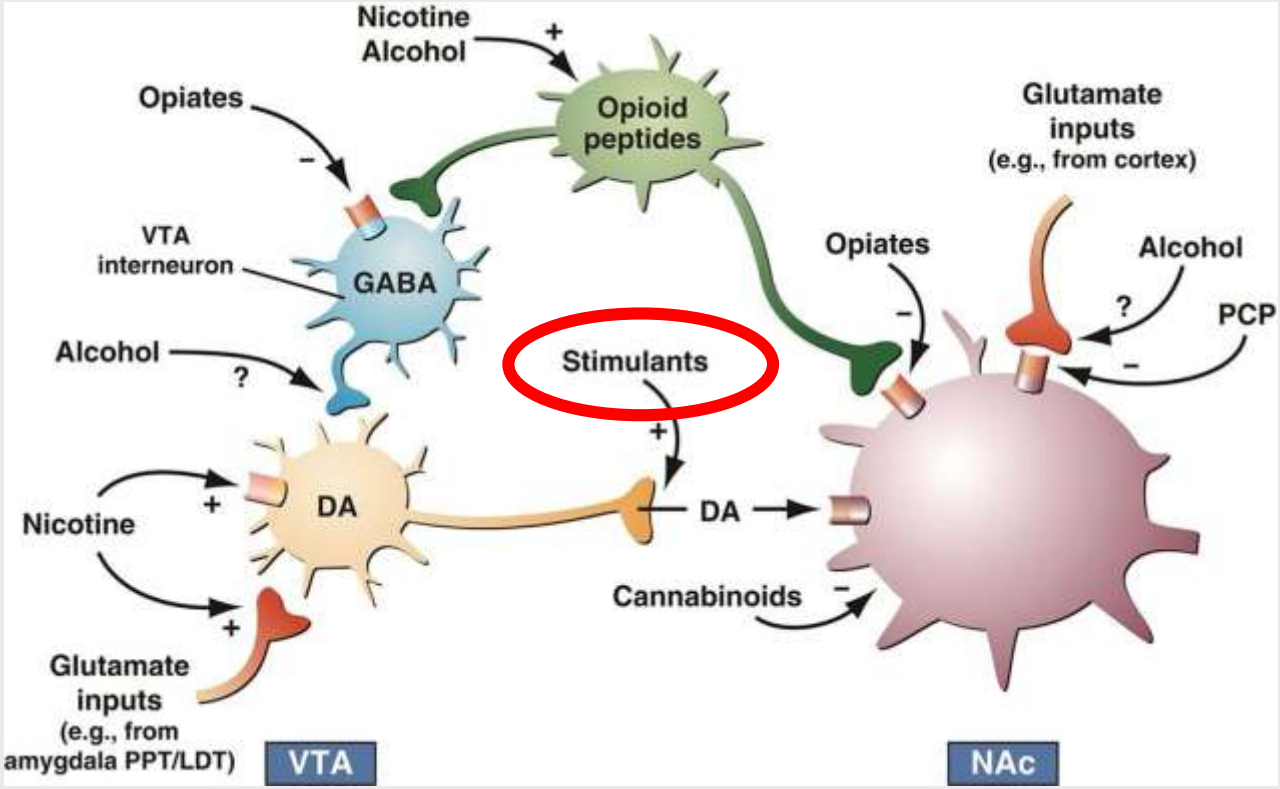
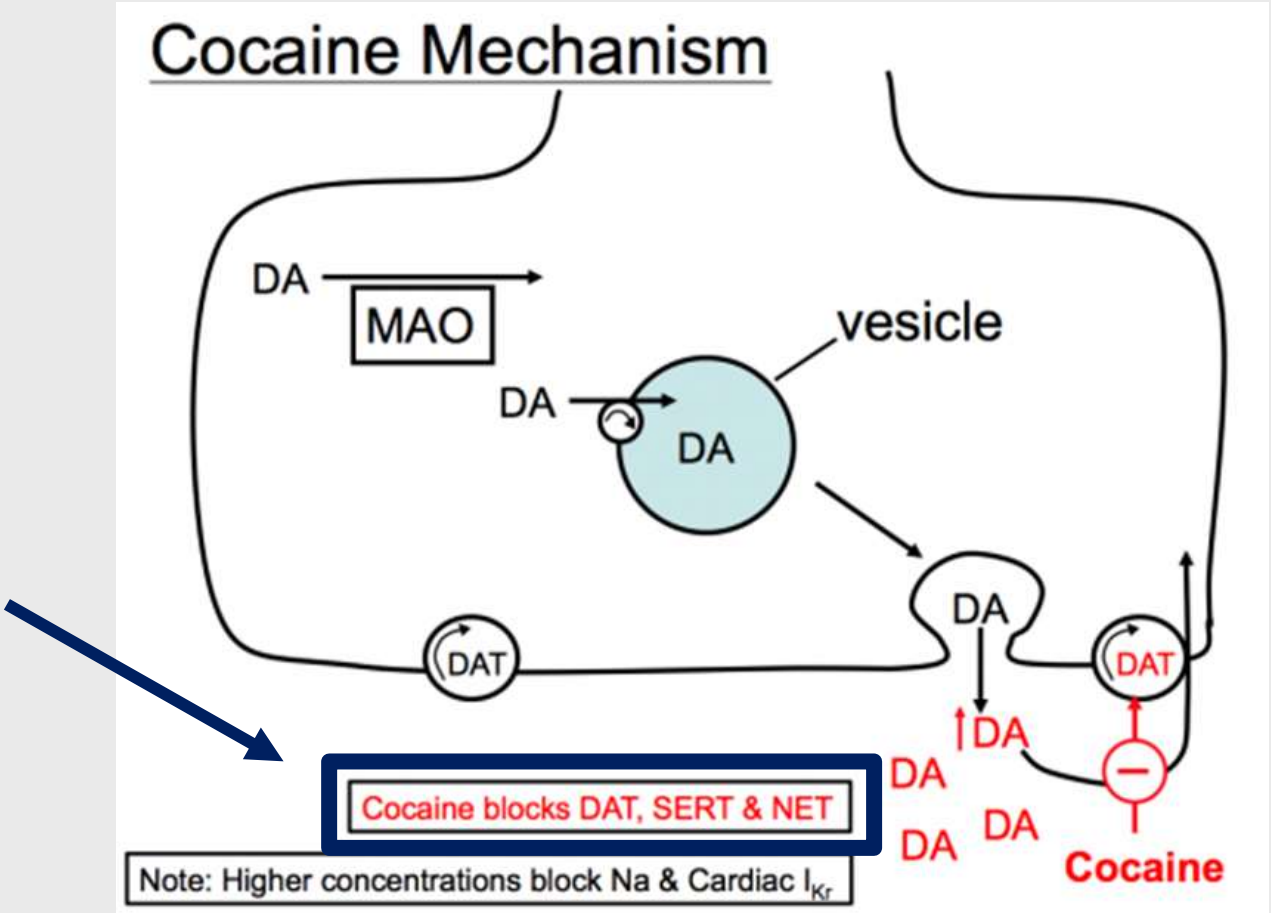


Figure from Koob, Focus, 2011, originally adapted from Nestler, Nat Neurosci, 2005

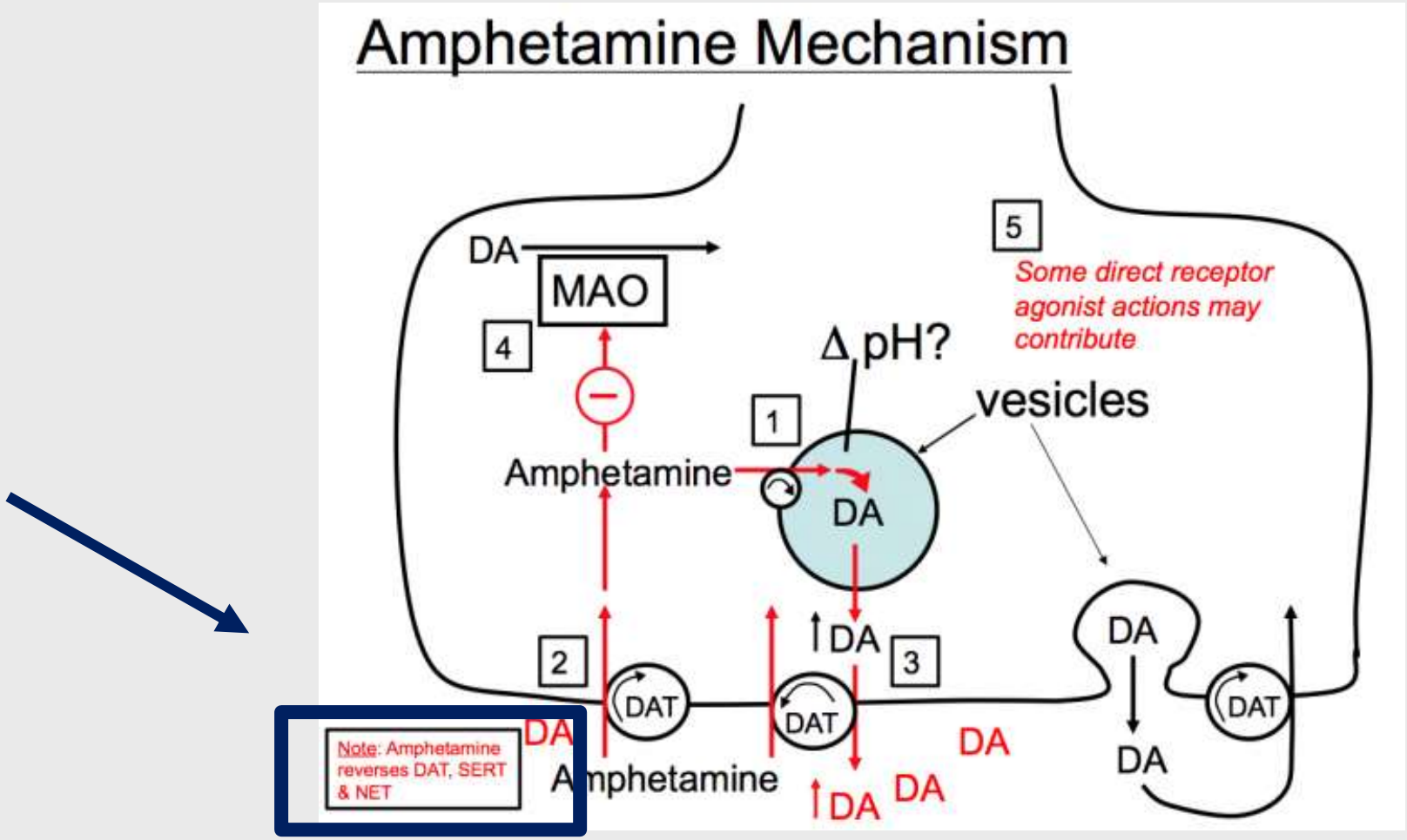
MECHANISM of ACTION of COCAINE

Binding to DAT - inhibition of reuptake



MECHANISM of ACTION of ATS

reverse transport



MECHANISM of ACTION II

- **Amphetamine enhances mainly the DA release, but other derivatives (Methamphetamine, MDMA) influence the NA and the 5-HT release, too**

- **Further effect of AMs:**
  MAO inhibition
  inhibition of transmitter reuptake

- **Cocaine inhibits mainly the DA reuptake, but influences the NA and 5-HT reuptake as well**

EFFECTS of PSYCHOSTIMULANTS

well being

euphoria - ”rash”, „high”

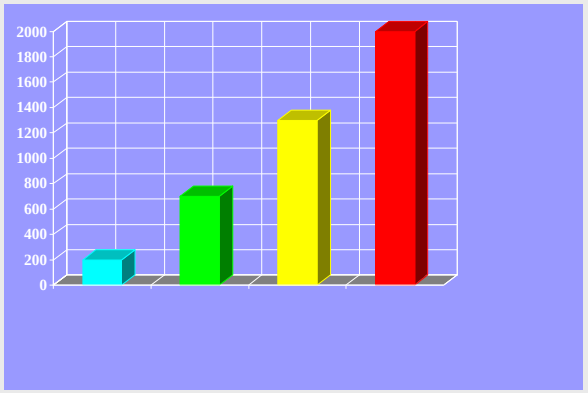
increase of physical abilities

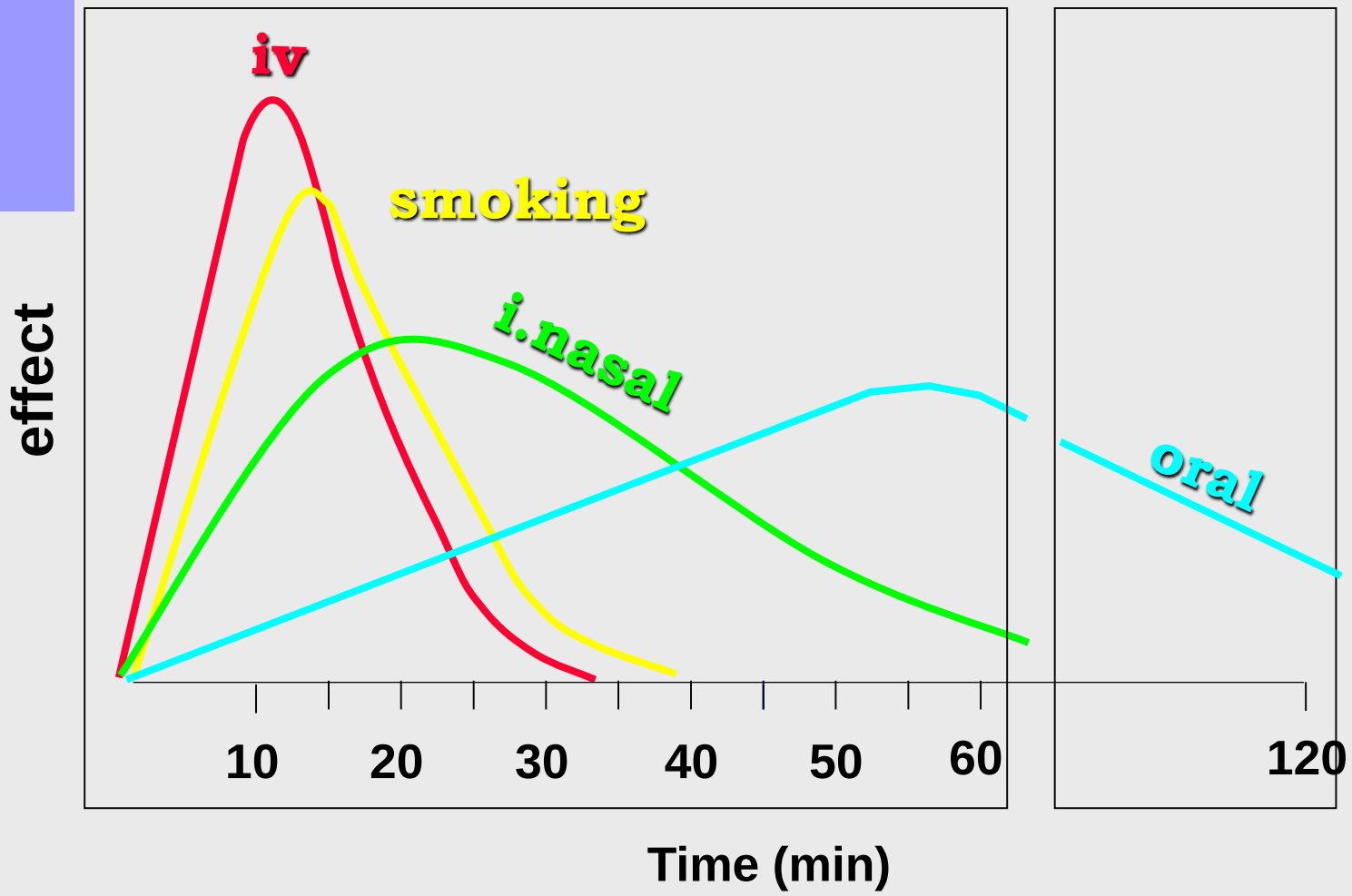
increase of mental capacity (controversial)

effect depends on dose

route of administration
first or repeated administration
accompanying circumstances

THE INTENSITY AND TIME COURSE OF COCAINE INTOXICATION





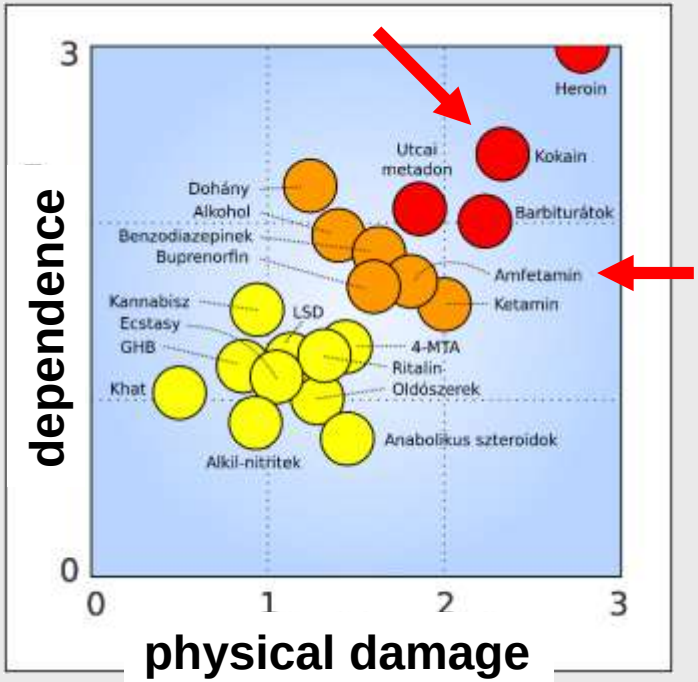
DRUGS of ABUSE

DEPENDENCE POTENTIAL

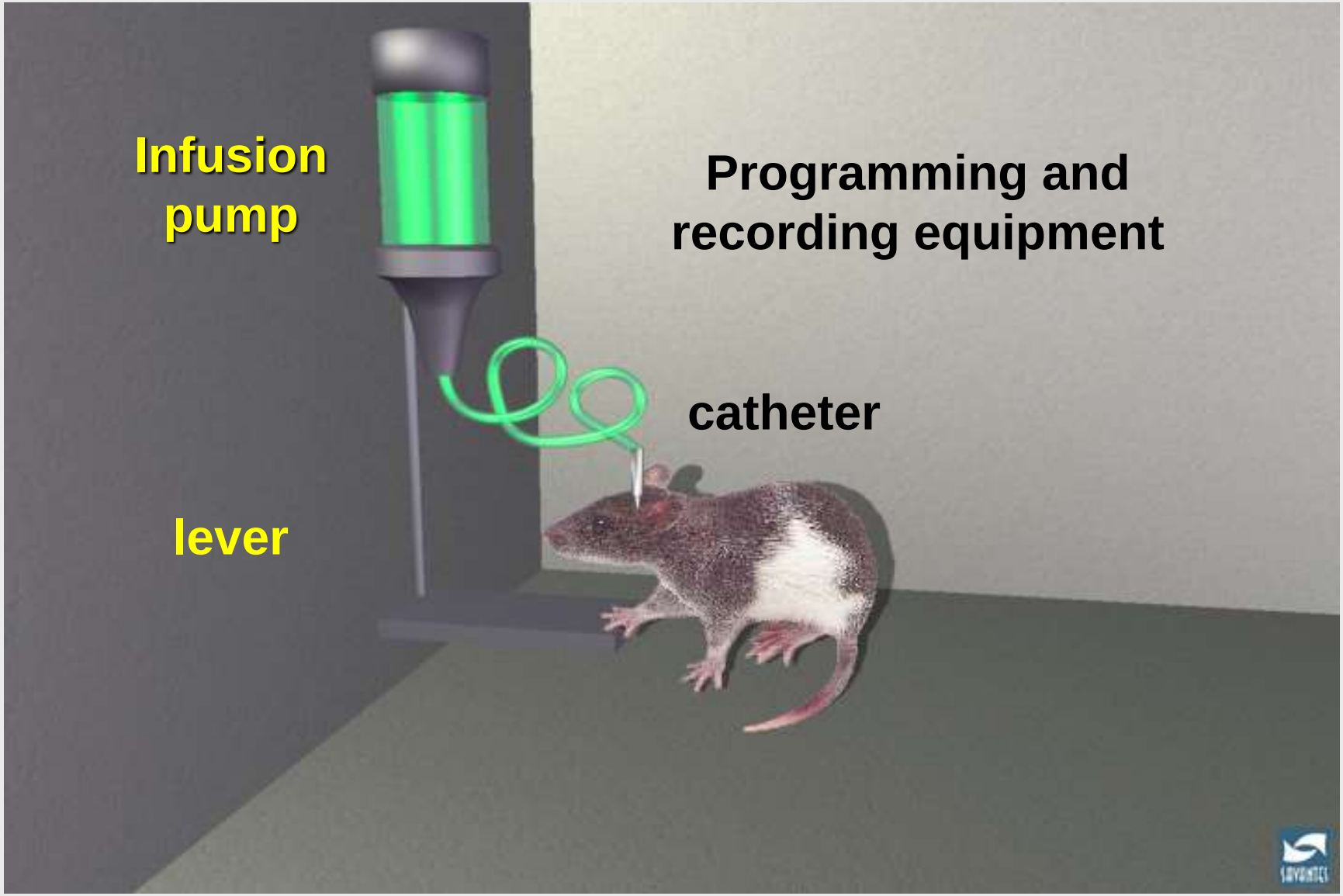
Stimulants

cocaine — **very strong**

amphetamines — **strong**



SELF-ADMINISTRATION



SELF-ADMINISTRATION

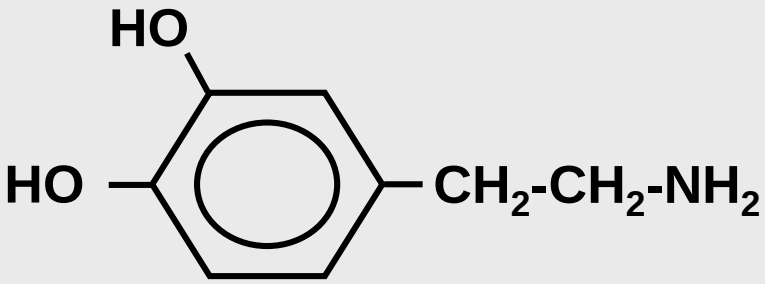
positive

equal		unequal	
continuous increase	no increase	frequent	not frequent
Morphine	Nicotine	Cocaine	Caffeine
Meperidine	Diazepam	Amphetamines	
Codeine	Chlordiaze-	Inhaled	
Pentazocine	poxide	anesthetics	
Alcohol*		THC	

* Only alcohol preferring strains

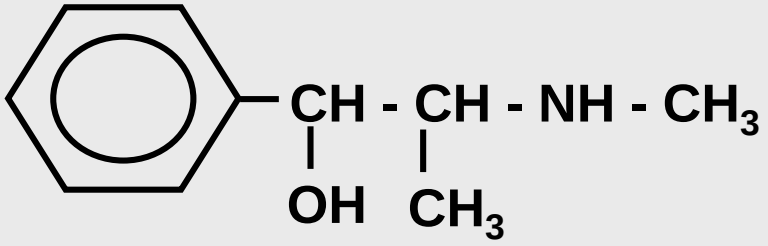
Drug	Psychic Dependence	Physical Dependence	Tolerance
Morphine & Derivatives	+++	+++	+++
Amphetamine-like	++	(+)	++ (in case of regular use)
Cocaine	+++	(+)	(+)

AMPHETAMINES (ATS)

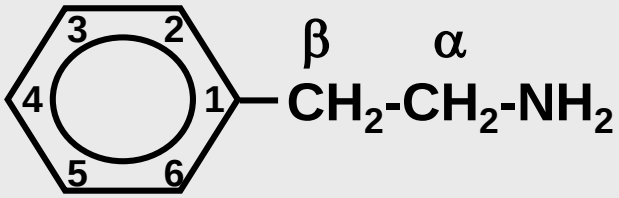


Dopamine

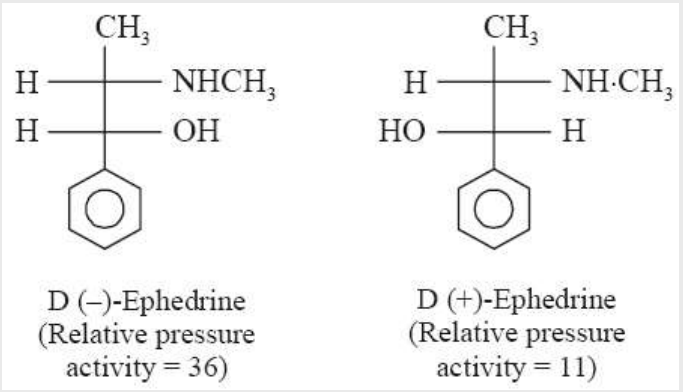
Ephedra viridis, mormon tea



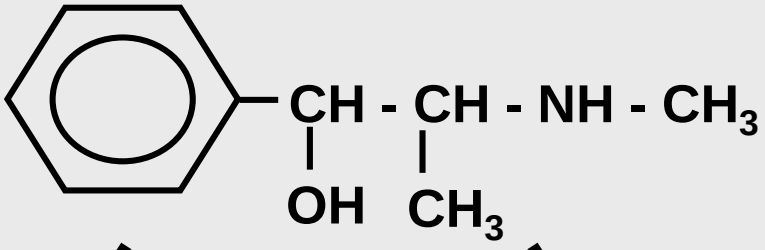
Ephedrine



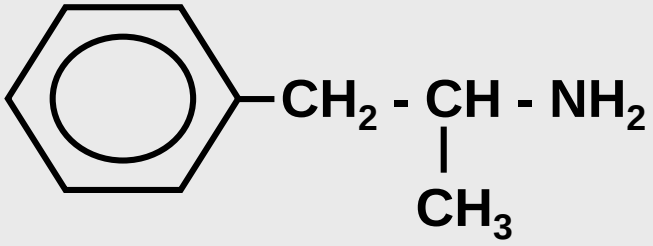
Phenylethylamine (PEA)



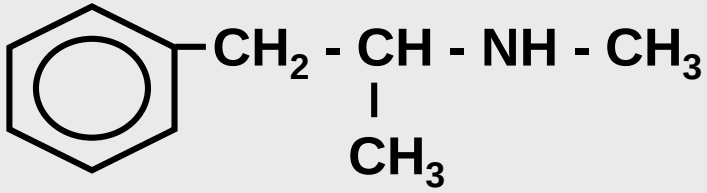
dextrorotatory form is biologically more active



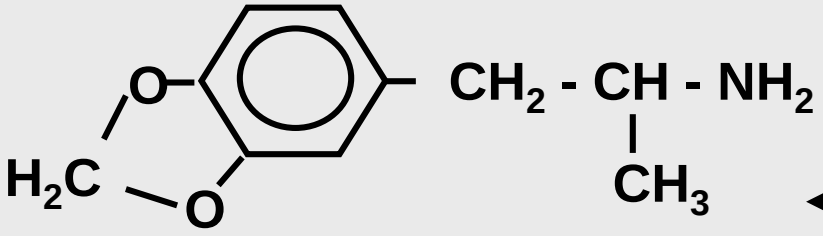
Ephedrine



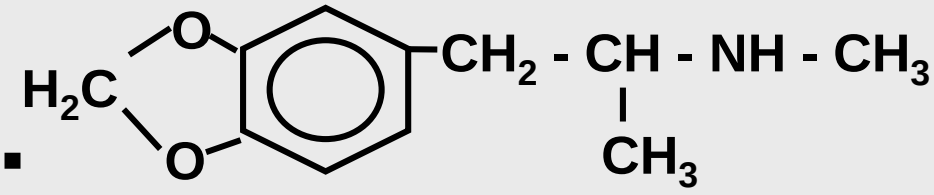
Amphetamine (speed)



Methamphetamine (speed in U.S.A.)

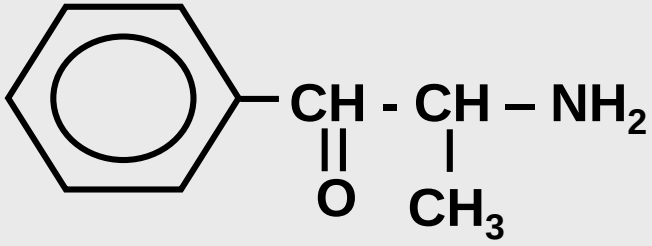


Methylenedioxyamphetamine (MDA)

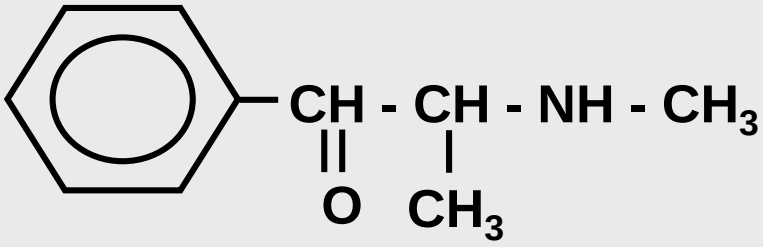


Methylendioxy-methamphetamine (MDMA, „ecstasy", Adam, E, essence)

MDA (DOM, etc.) - hallucinogenic AM



cathinone



methylcathinone

Alkaloid of Khat (*Catha edulis)*

Designer drug

Mephedrone (4MMC)

Very toxic

- tolerance quick
- aggression
- toxic metabolites

„DESIGNER" DRUGS I

Designer drugs are structural or functional analogs of controlled substances that has been designed to mimic the pharmacological effects of the original drug, while avoiding classification as illegal

Psychoactive substances

Performance enhancing drugs (designer steroids)

- ***Stimulants (amphetamine-like)***

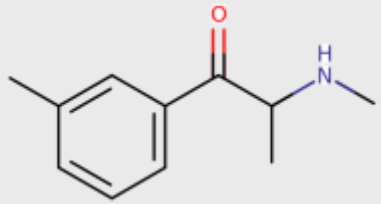
Methylone, MDPV (Methylene-dixypyrovaleron)
Benzofury, 4Mec (amphetamine group)
MDAI 5,6-Methyilene-dioxy-2 aminoindan
4-Fa 4-fluoroaphfetamine

Dimethocaine larocaine (local anesthetic, about half as potent as cocaine)- used to be used in UK and Ireland

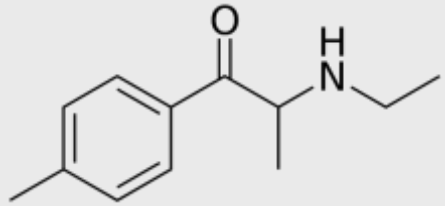
„DESIGNER” DRUGS II

Other Chat derivatives

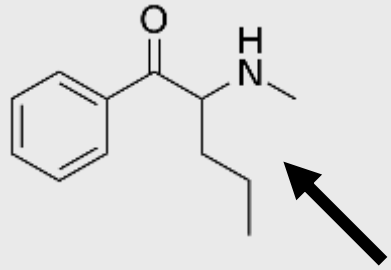
3-Methylmethcathinone (3MMC)



4-Methylethcathinone (4MEC)

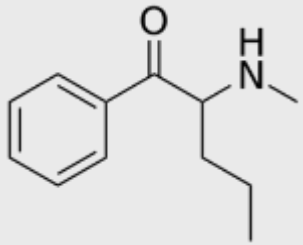


Pentedrone (α-methylamino-valerophenone)
penta crystal – cocaine-like effect



„DESIGNER" DRUGS III

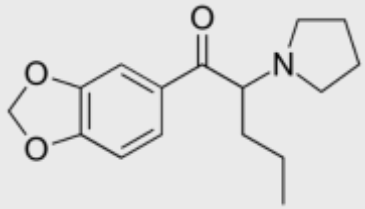
MPDV and derivatives



Pentedrone

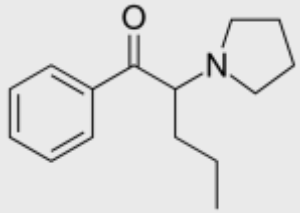
MPDV (methylenedioxypyrovalerone)

Bath salt

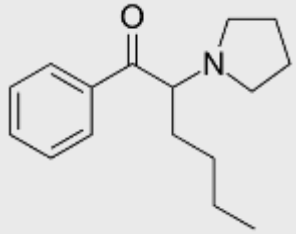


pyrrolidine

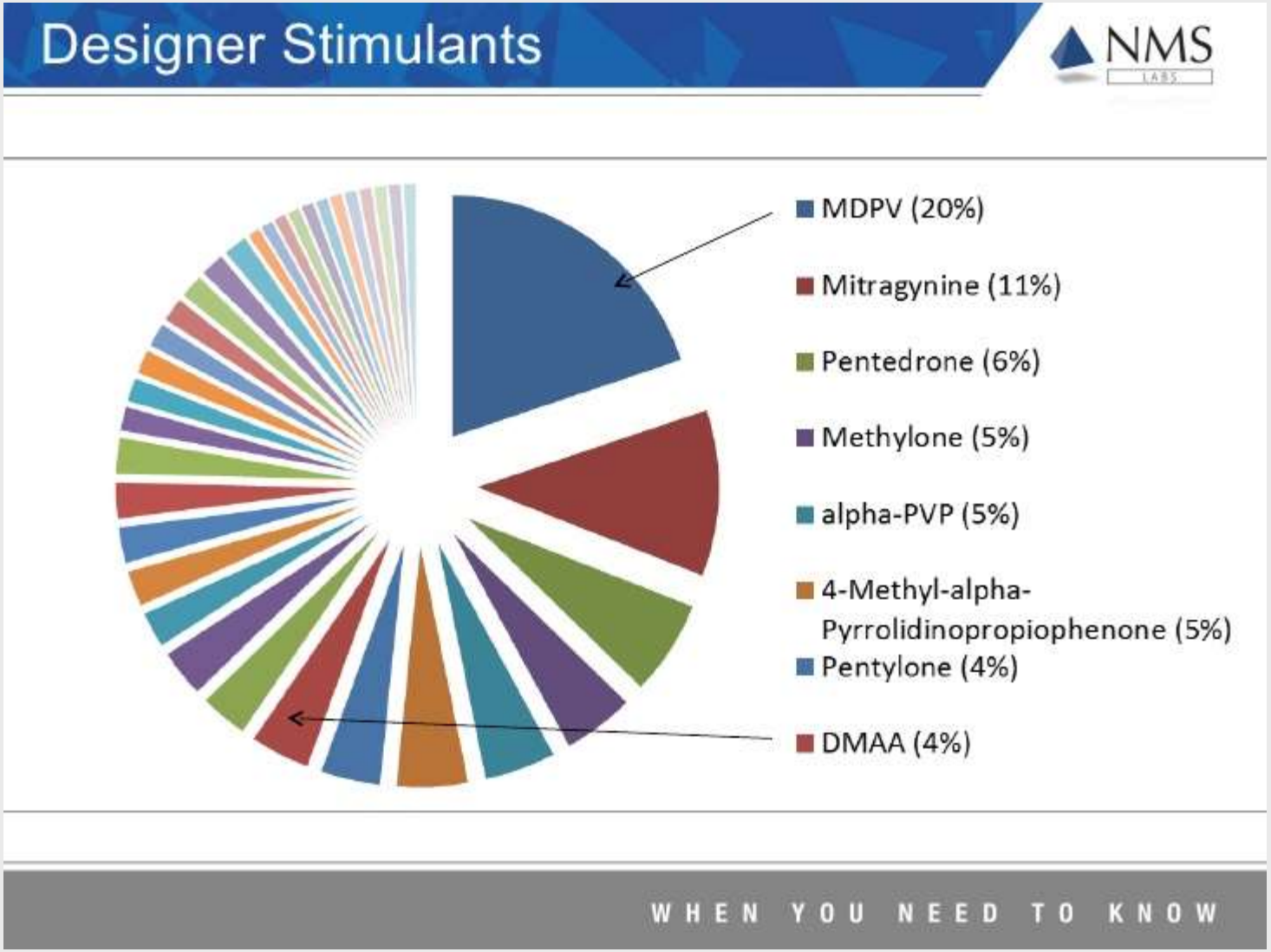
***alpha*-pyrrolidinopentiophenone (α-PVP)**



***alpha*-pyrrolidinohexiophenone (α-PHP)**



2012



https://image.slidesharecdn.com/designerdrugspringupdatebklwebinarmay2012-120525134751-phpapp02/95/trends-report-on-changes-in-the-designer-drug-market-spring-2012-29-728.jpg?cb=1337954029

Confiscated and determined drugs in Hungary

	2010	2011	2012	2013	2014
1	THC	THC	THC	THC	THC
2	amfetamin	amfetamin	**pentedron**	AKB-48F * (apinaca)	AB-CHMINACA*
3	**mefedron**	**4-MEC**	AM-2201*	**pentedron**	amfetamin
4	kokain	**MDVP**	amfetamin	amfetamin	MDMB-CHMICA *
	MDVP (10)	**Mefedron** (8)	Kokain (8) **4-MEC (9)**	**3-MMC (6)** **A-PVP (8)** MDMA (9) **Mefedron (10)**	**Pentedron (5)** **A-PVP (7))** MDMA (9)

Csesztregi Tamás Bűnügyi Szakértői és Kutatóintézet
Szerves Kémiai Analitikai Szakértői Osztály

ATS EUPHORIA

- Rush (~ orgasm like reaction; sex drive is enhanced)

- Subjects become confident, hyperactive, talkative (MDMA – entactogen – „touching within”)

- Mental alertness
- Fatigue — physical, mental } is reduced

(military persons, pilots, students - exams ??)

Exhaustion (lack of sleep, food)

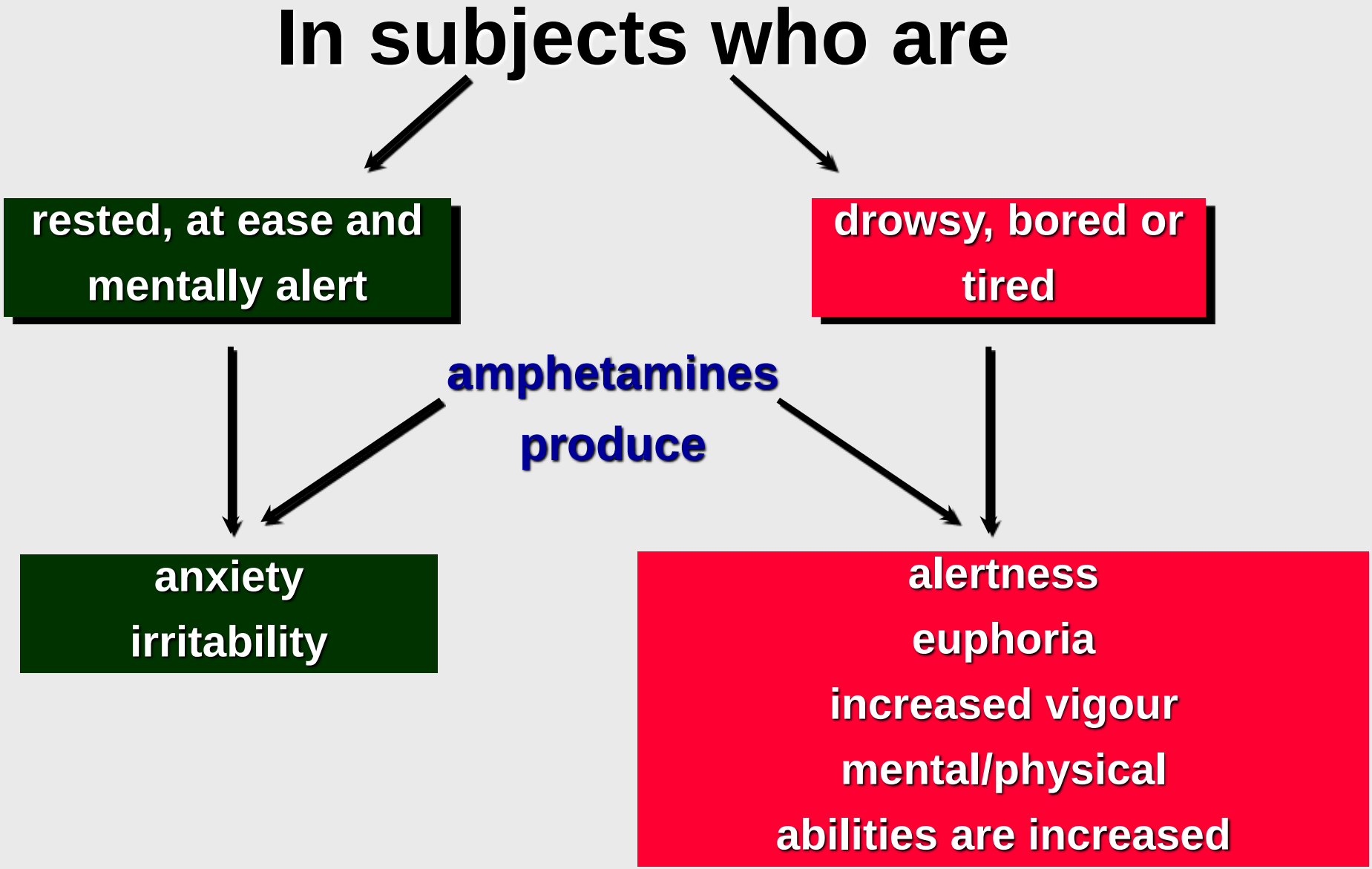
EFFECT of AMPHETAMINES

- Increased motor activity
- Euphoria and excitement

} lasts for a few hours, and is followed by depression and anxiety

- Anorexia
- With prolonged administration psychotic behaviour

- **Tolerance to the stimulant effects develops rapidly, though peripheral sympathomimetic effects may persist**


In subjects who are
rested, at ease and mentally alert
drowsy, bored or tired
amphetamines produce
anxiety
irritability
alertness
euphoria
increased vigour
mental/physical
abilities are increased

THERAPEUTICAL APPLY of ATS

- narcolepsy
- attention deficit hyperkinetic syndrome (methylphenidate)
- they used to be used (e.g. dexfenfluramine) as appetite-suppressants

Therapeutically used amphetamine derivative is METHYLPFENIDATE (low abuse potential)

Clinical aspects induced by ATS:

- acute intoxication
- withdrawal

TOXIC EFFECTS of ATS I

Central nervous system

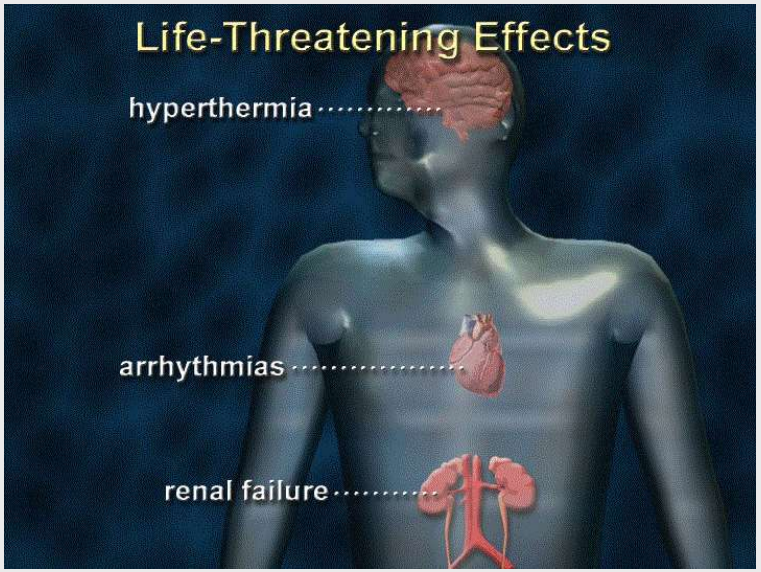
agitation
convulsions
muscle rigidity
hyperthermia
sweating
dehydration/or water poisoning (hyponatremia)
hallucinations
panic
dilated pupils
coma

Cardiovascular system

tachycardia
ventricular arrhythmias
hypertension
followed by hypotension
spontaneous bleeding
stroke

Renal system

oliguria; myoglobinuria
kidney failure



TOXIC EFFECTS of ATS II

Gastrointestinal system	**jaundice; hepatomegaly**
Laboratory tests	**metabolic acidosis; hyperkalemia; raised creatinine, creatine phosphokinase, impaired liver function tests; hypoglycemia**
Hematology	**disseminated intravascular coagulation (DIC) (thrombocytopenia, abnormal coagulation profile, low fibrinogen)**

TREATMENT of MDMA INTOXICATION

supportive therapy

ventilation, gastric lavage with charcoal

agitation /convulsions: *diazepam*

hypotension: fluid therapy, inotropic support

temperature control: over 42^{o} C no survival !!!!

cooling **blankets, ice packs, infusion of cold saline etc.**

neuromuscular blockade: *dantrolene*

(inhibits Ca^{++} release from SR)

TREATMENT of MDMA INTOXICATION

supportive therapy (cont.):

metabolic acidosis – precipitating cardiac arrhythmias

sodium bicarbonate

DIC: with severe bleeding – replacement of clotting factors

specific therapy ???

selective 5-HT_2 receptor antagonist: ketanserin

chlormethiazole: attenuates thermogenesis given before MDMA (rat)

REPEATED ATS

Tolerance can develop to

euphoria

anorexia

hyperthermia

acute lethal effects

anorexia → ketosis → acidic urine → increased elimination

Sensitization can develop to

amphetamine psychosis can develop even after one dose

↓

(high individual differences)

CHARACTERISTIC USES of ATS

Instrumental usage – usage in order to attain something (e.g. improve the concentration, overcome some fatigue)

Recreational (subcultural) usage

Chronic usage

MOUTH and SKIN LESIONS in REPEATED MA USERS

„Meth mouth”

Enhanced dental decay,
dry mouth – gingival disorders

Skin symptoms

- unnaturally grey and leathery skin (melanin content changes)
- acne sores – obsessive picking of the skin (hallucination – feeling of bugs)
- weeping sores and open wounds (debilitated immune system)

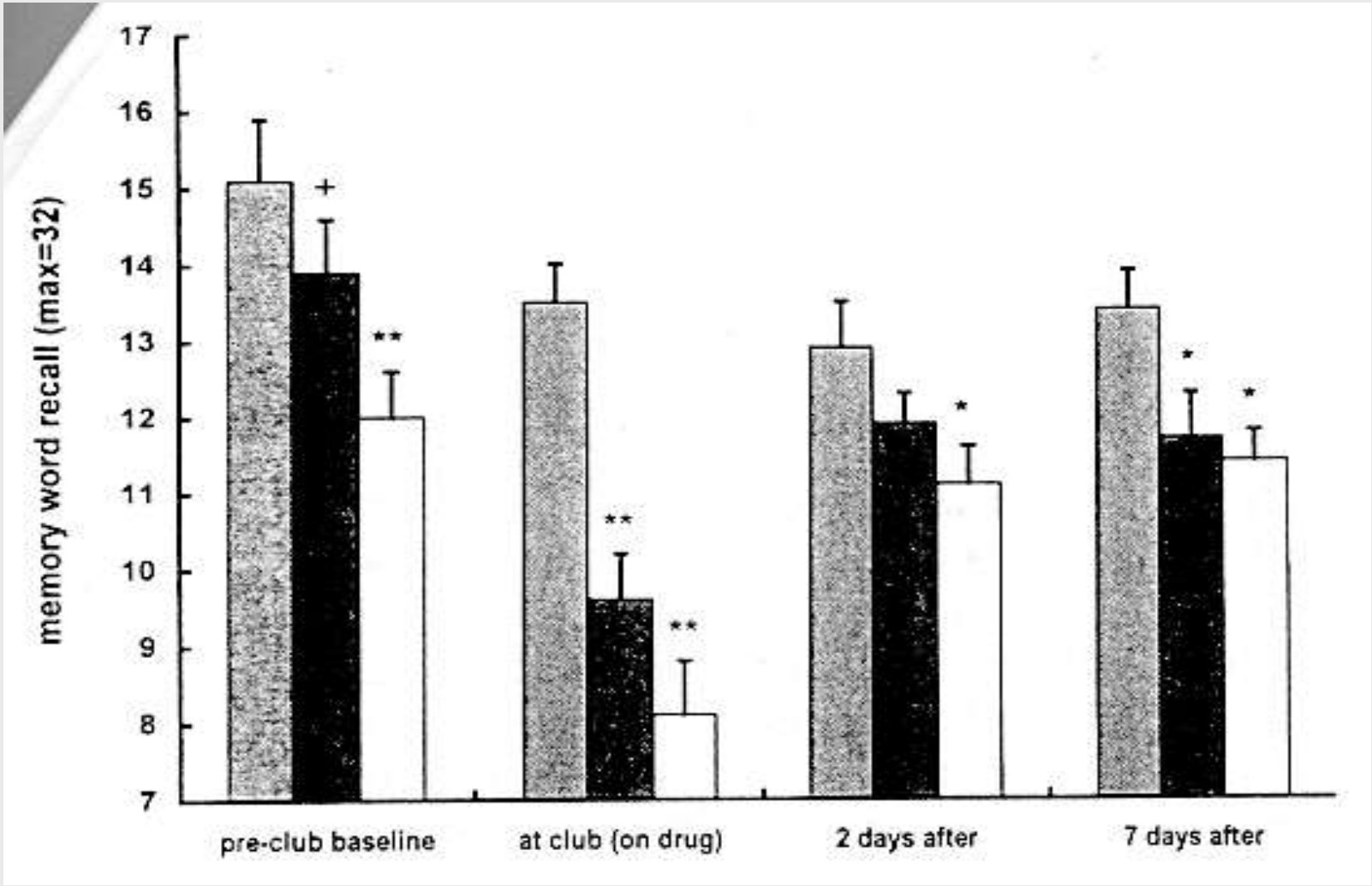
WITHDRAWAL SYMPTOMS

- long, restless sleeping
- extreme fatigues
- insomnia/hypersomnia
- marked appetite
- psychomotor hindrance/agitation
- drug seeking behaviour
- depression

FOLLOWING REPEATED METHAMPHETAMINE or MDMA ABUSE

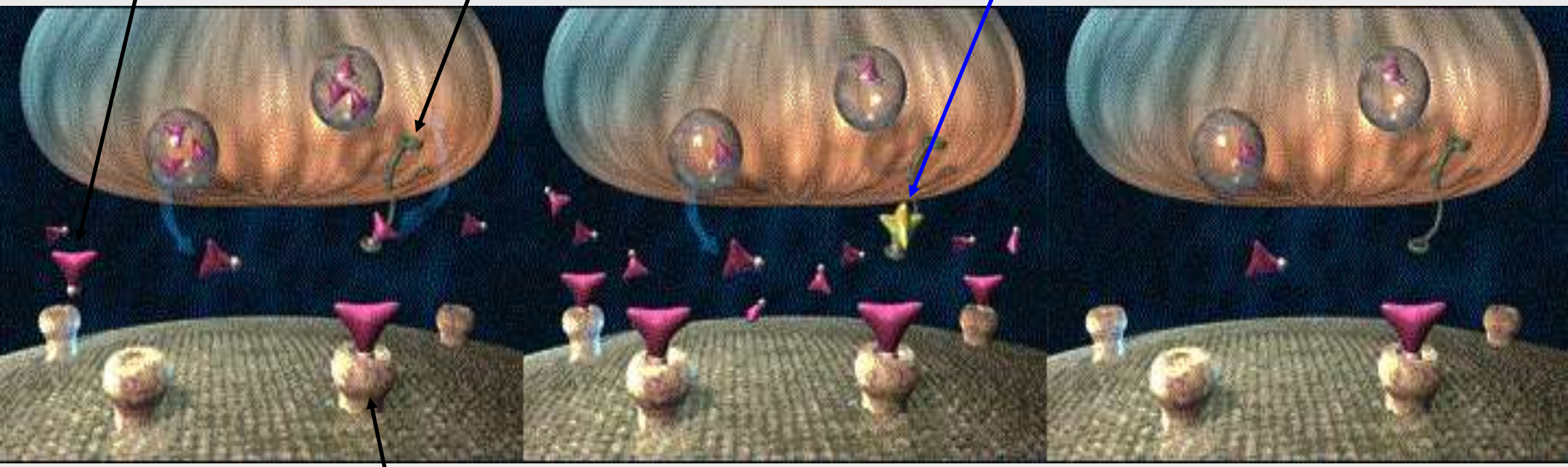
- depression
- risk of committing suicide
- aggressive behaviour
- impairment of cognitive function

is more marked than with amphetamine (5-HT-erg effect?)



Parrott AC, Lasky J (1998) Psychopharmacology, 139, 261

ROLE of 5-HT in THE EFFECT of MDMA



NORMAL

UNDER ECSTASY
stimulated mood
euphoria

AFTER ECSTASY
depression
anxiety

ROUTES of ADMINISTRATIONS

Amphetamine	**i.v.; orally**
Methamphetamine	**i.v.; orally; inhaled**

MDMA	**orally (generally)**
Methamphetamine	**initial dose 20-40 mg**
MDMA	**initial dose 50-100 mg**

oral MDMA usage **onset 20-60 min;**
peak 60-90 min

$t_{1/2}$ **amphetamine ~ 10^h**

methamphetamine, MDMA ~ 5^h

METABOLISM of MDMA

demethylation by CYP2D6

poor metabolizers (7-8%)

↓

risk of toxicity increases

CYP2D6 enzyme function is inhibited by SSRI-s (fluoxetine, paroxitene etc.) and antipsychotics

PERINATAL OUTCOME in INFANTS WHOSE MOTHERS USED AMPHETAMINE DURING PREGNANCY

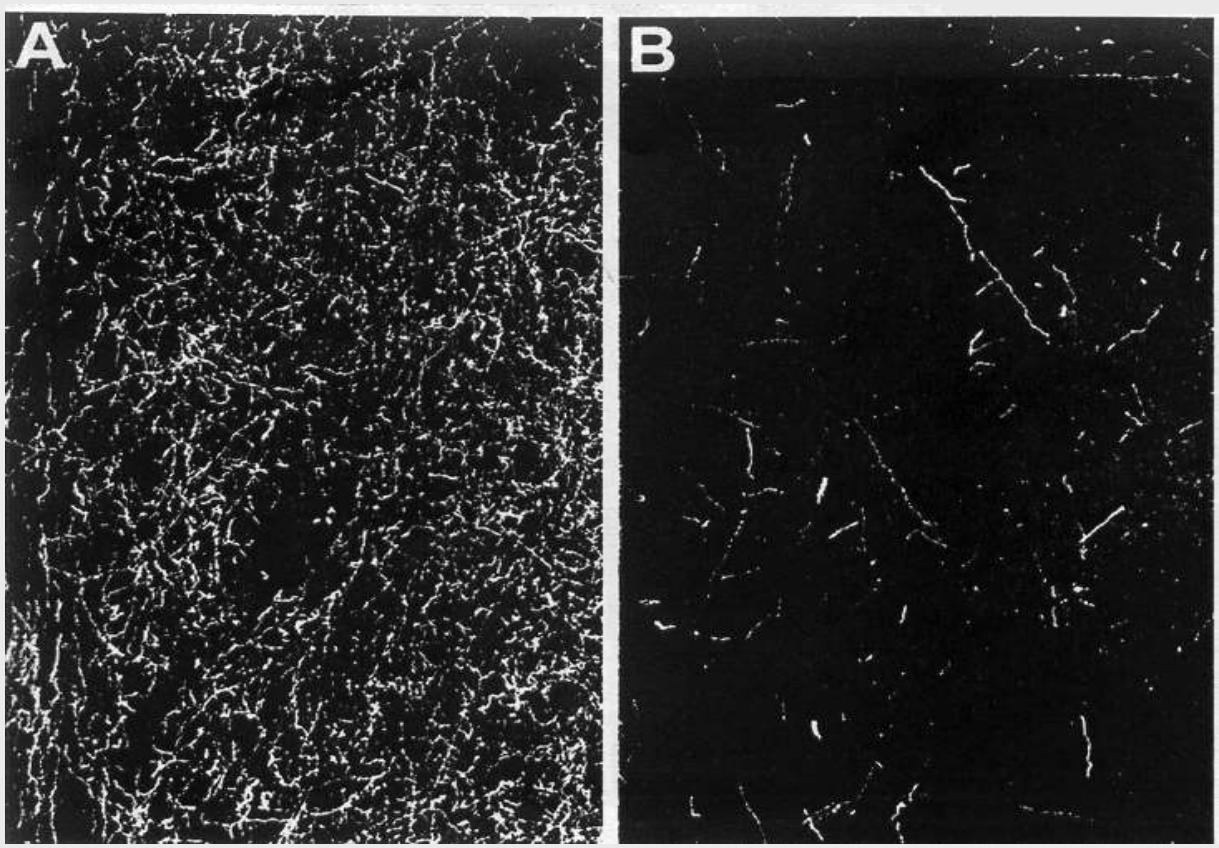
	Study group	Control group
Perinatal mortality	5.6	1.04
Infant mortality	5.8	0.83
Major malformations	3	1.64
Birth weight < 2500 g	18	4.6
Gestational age < 37 weeks	20	5.65
Transfer to neonatal unit	38	10

(Sweden)

Methamphetamine, MDMA abuse

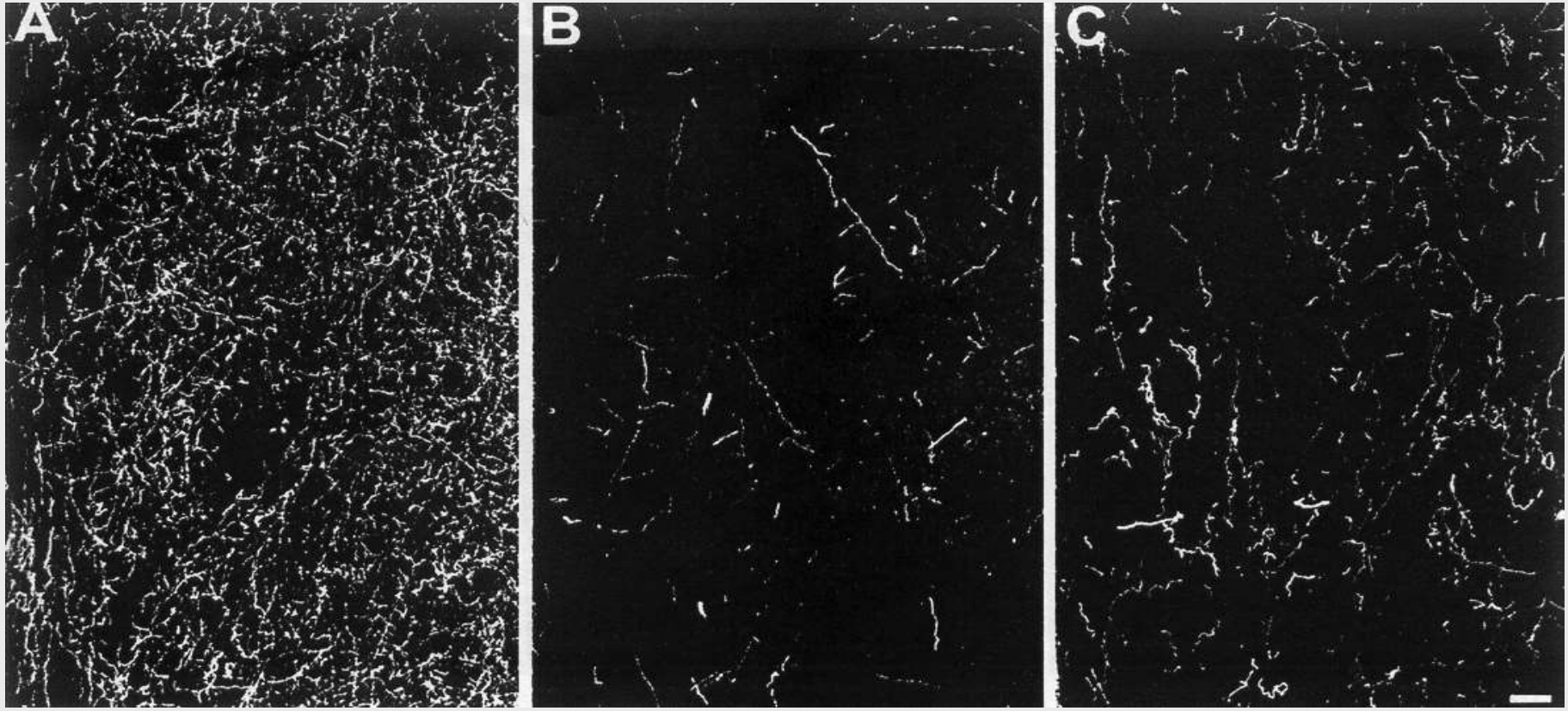
is frequent together with
- cannabis (70-80%?)
- benzodiazepines (40-50%)

is rare together with heroin



Dark-field photomicrograph, sagittal plane, of 5-HT immunoreactive axons in the caudate nucleus of a control monkey (A), a 2 week MDMA-treated monkey (B). Scale bar, 100 µm.

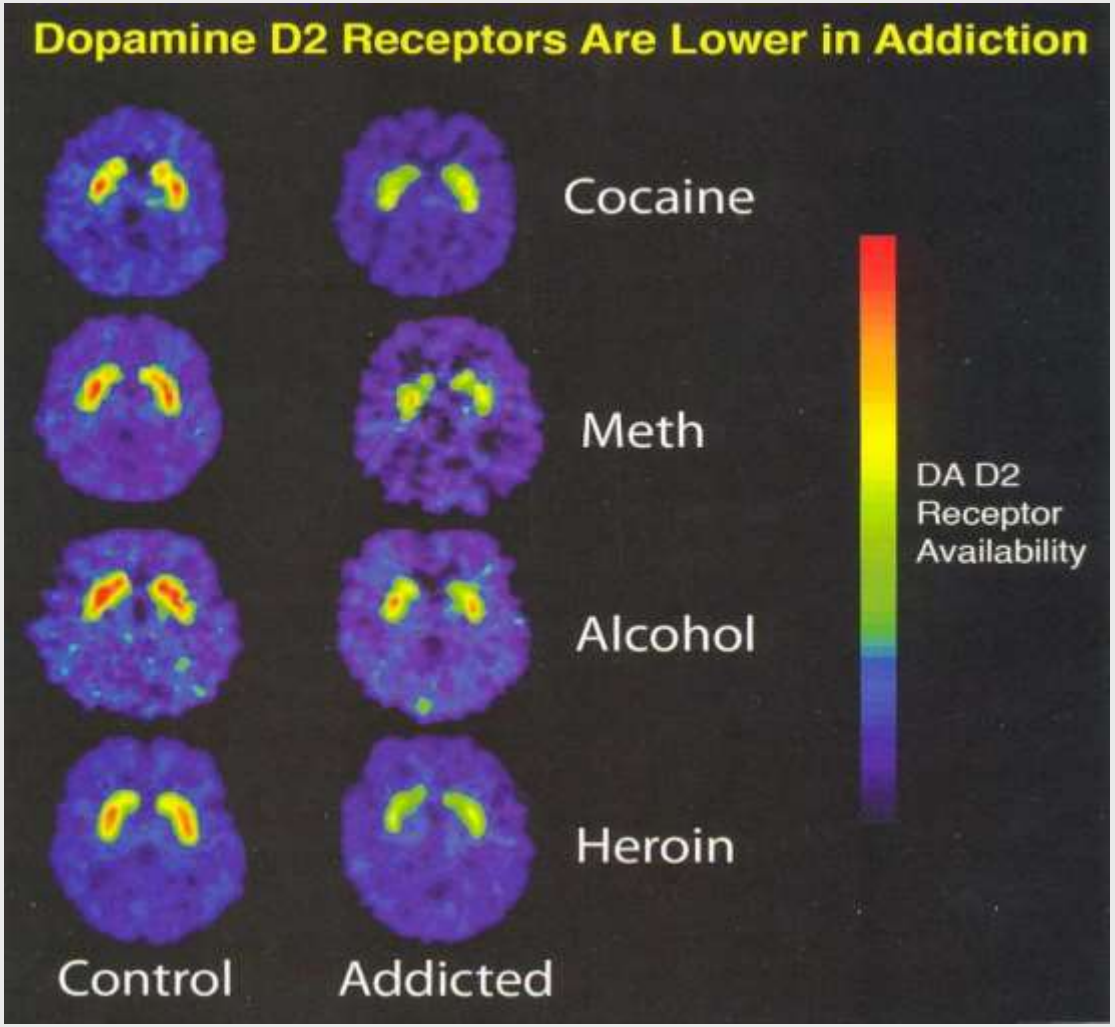
(Hatzidimitriou G et al, (1992)

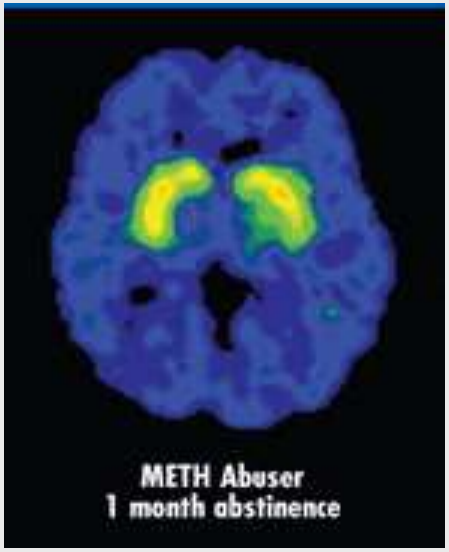


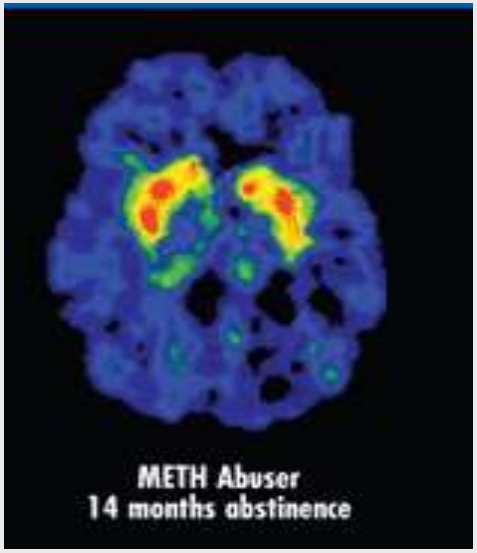
Dark-field photomicrograph, sagittal plane, of 5-HT immunoreactive axons in the caudate nucleus of a control monkey (A), a 2 week MDMA-treated monkey (B), and a 7 year MDMA-treated monkey (C). Scale bar, 100 µm.

(Hatzidimitriou G et al, (1999) J. of Neurosci. 19, 5096)

DECREASED DA ACTIVITY





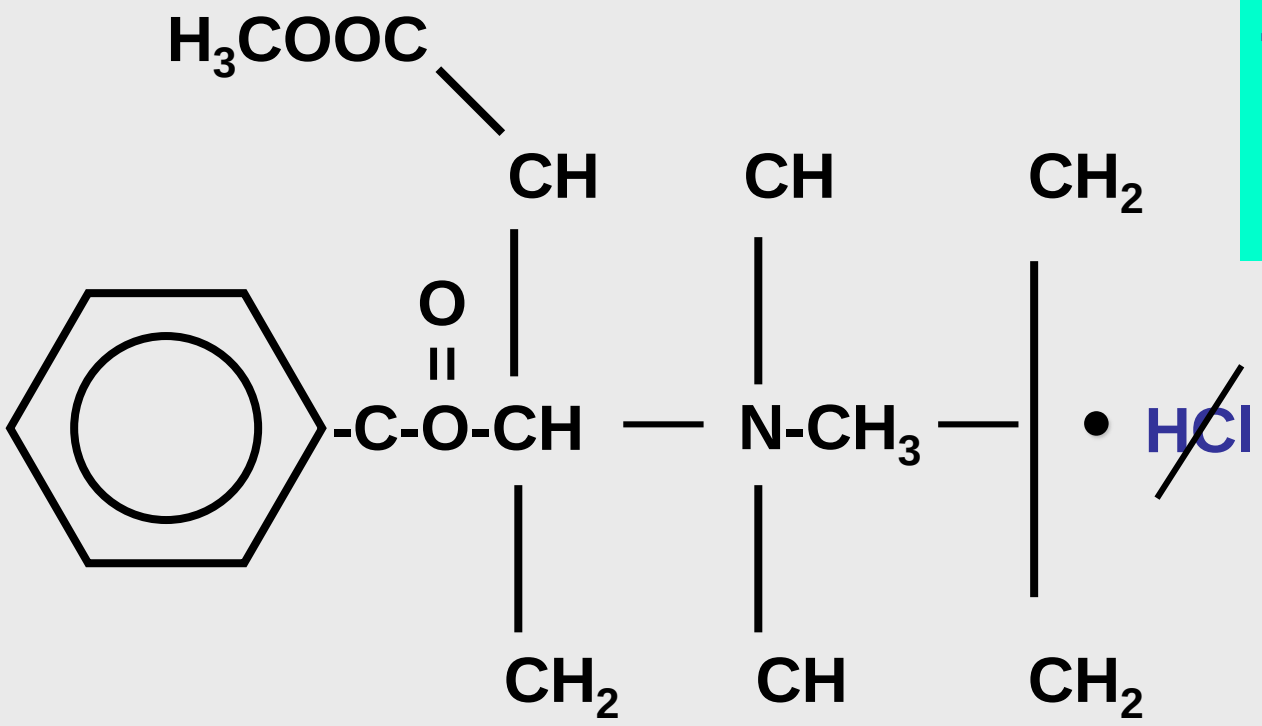


red - high DA receptor level
yellow – low DA receptor level

PSYCHOSTIMULANTS II

COCA plant

COCAINE

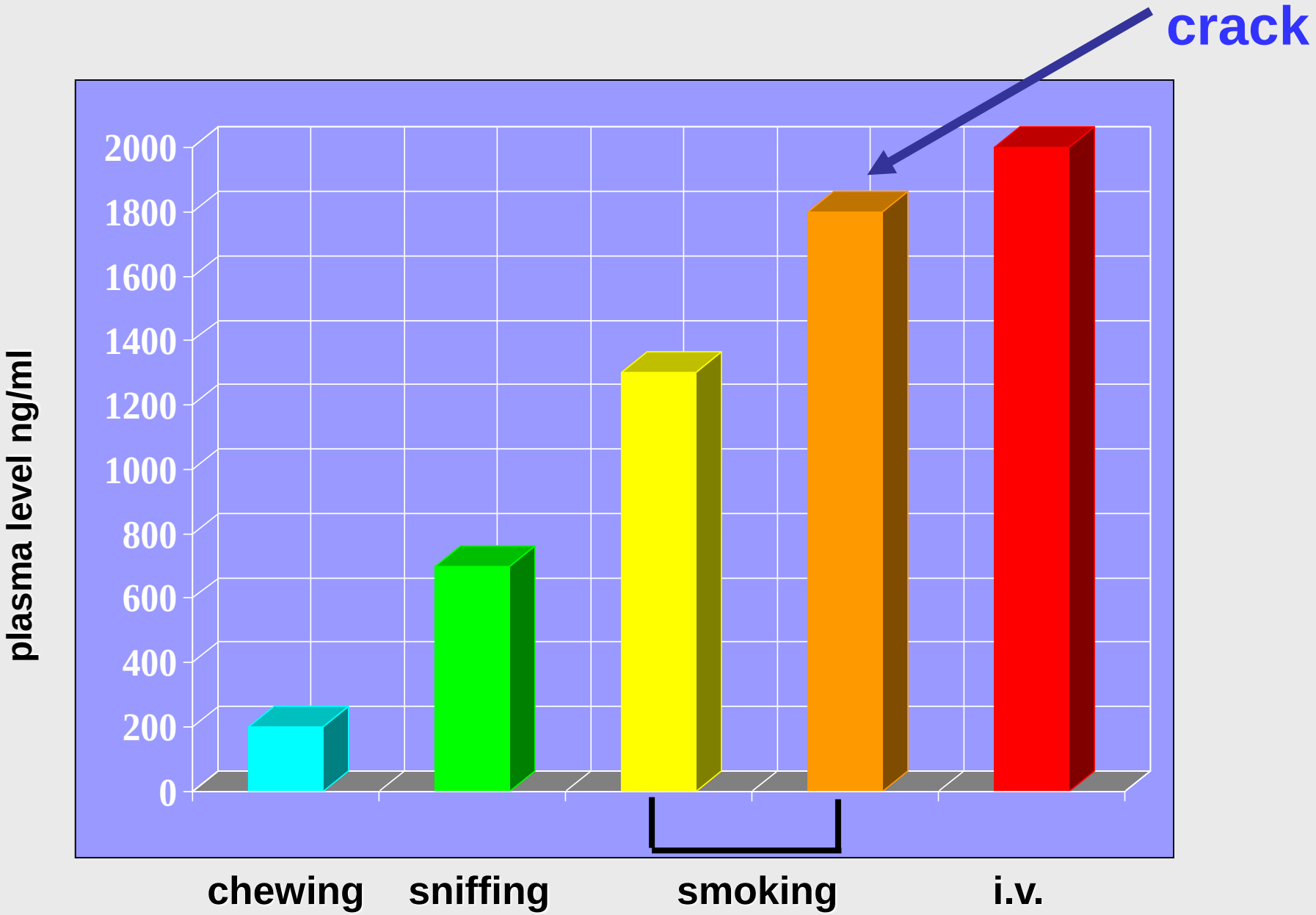


free base „*crack*”
by alkalization and extraction

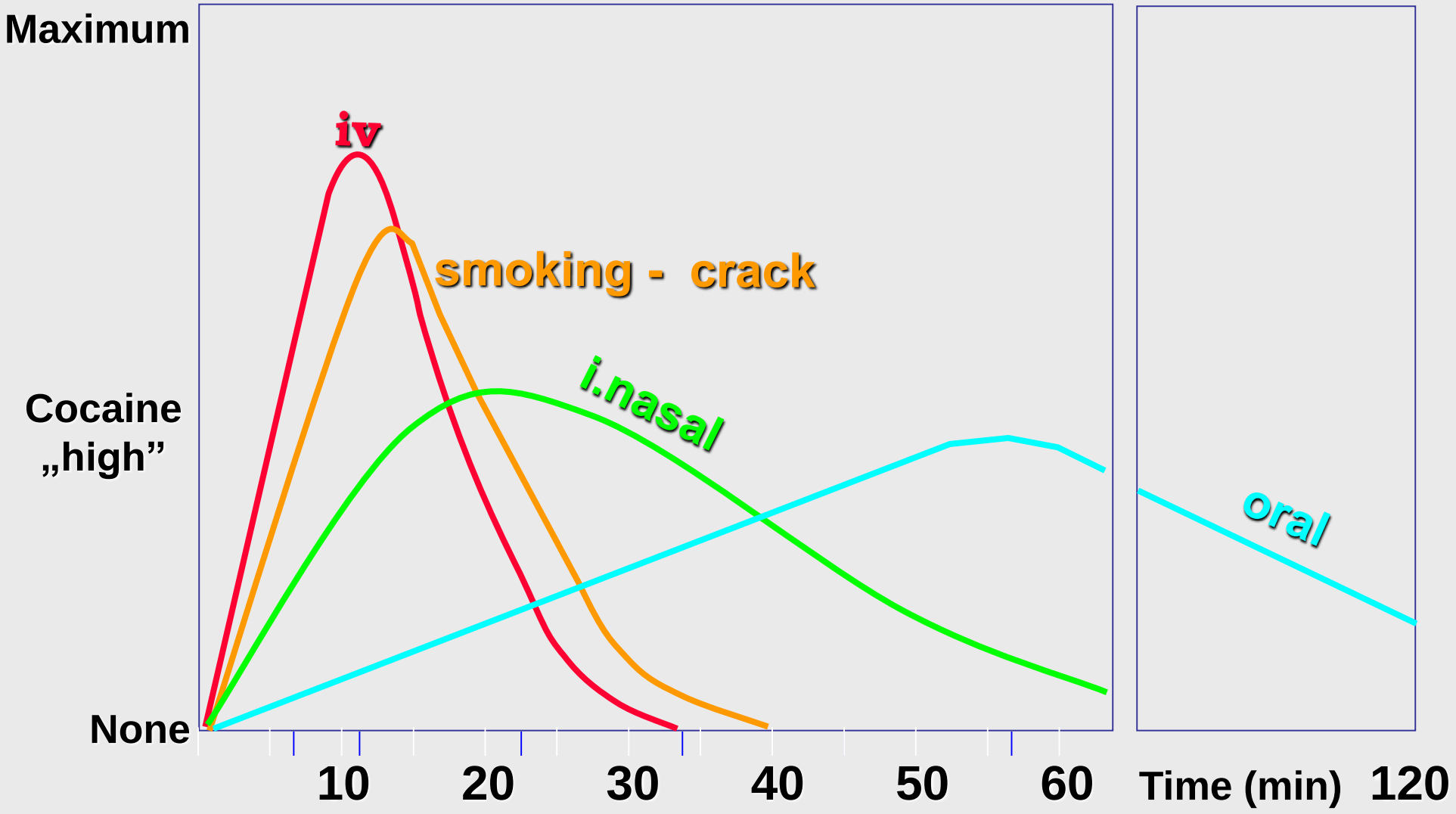
insoluble, very lipophilic

hydrophilic, white powder
„coke”, „gold dust”, „lady”

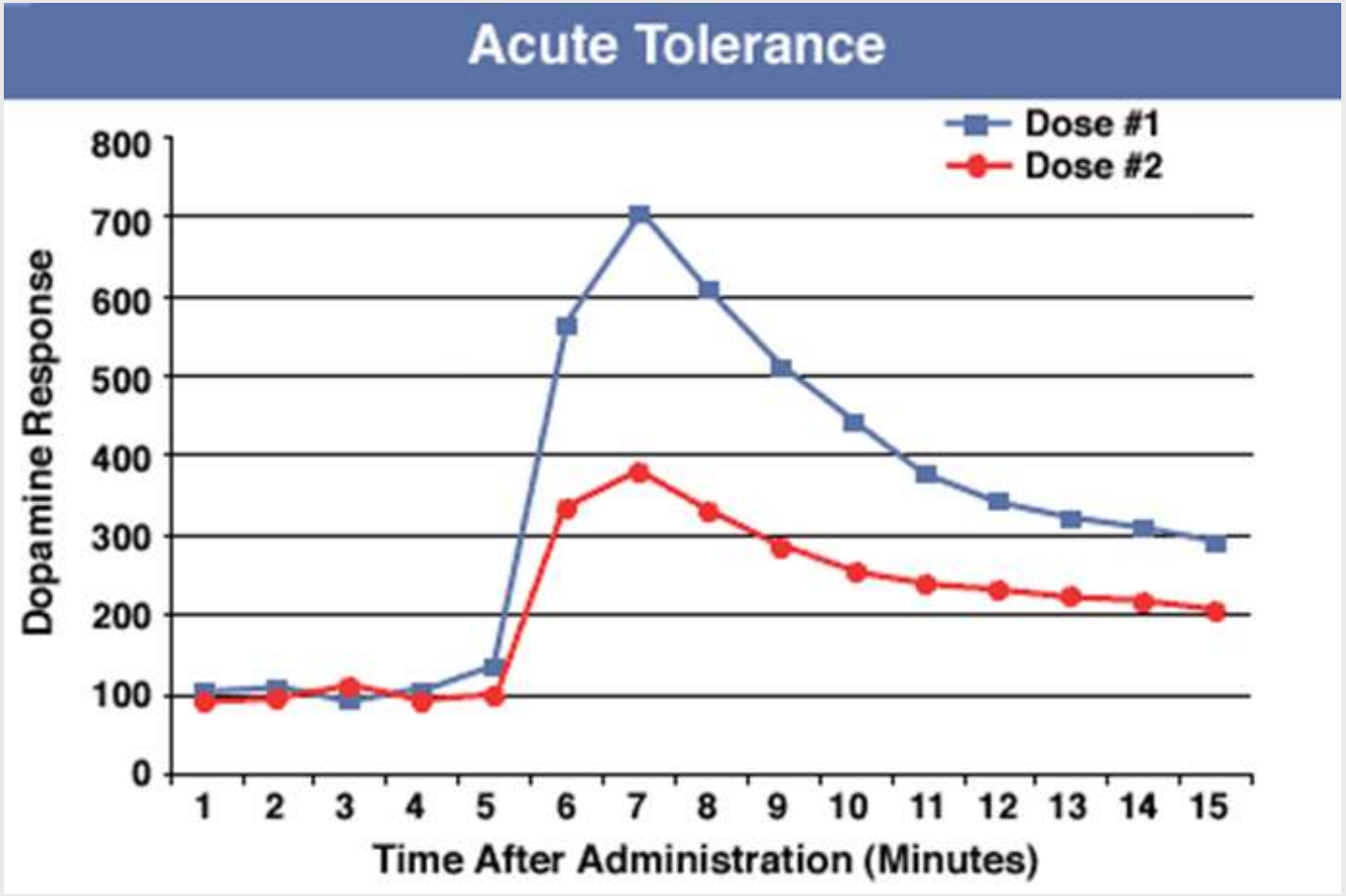
COCAINE – ROUTES of ADMINISTRATION



THE INTENSITY AND TIME COURSE OF COCAINE INTOXICATION



TACHYPHYLAXIS (COCAINE)



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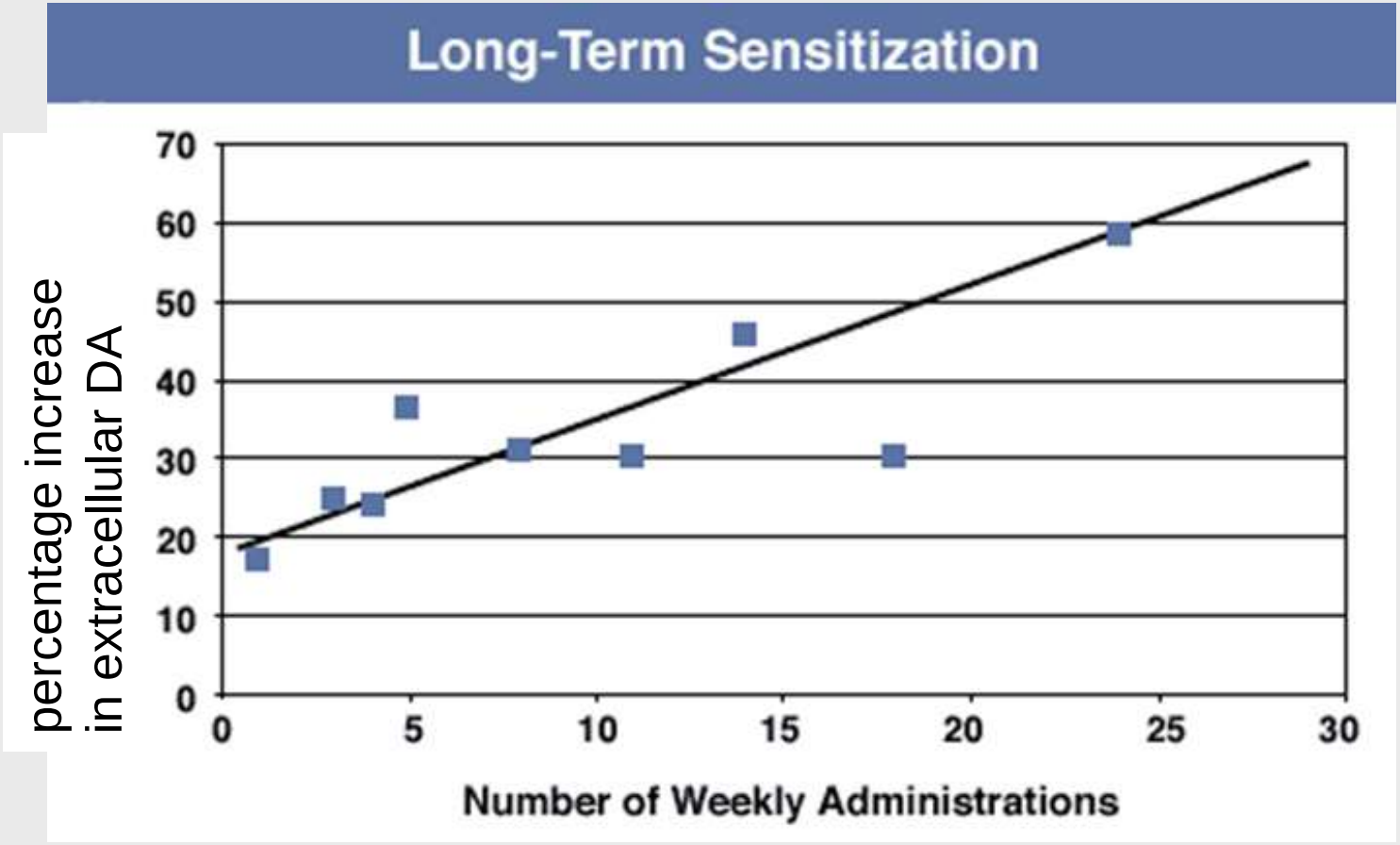
monkey, self-administration

SENSITIZATION (COCAINE)



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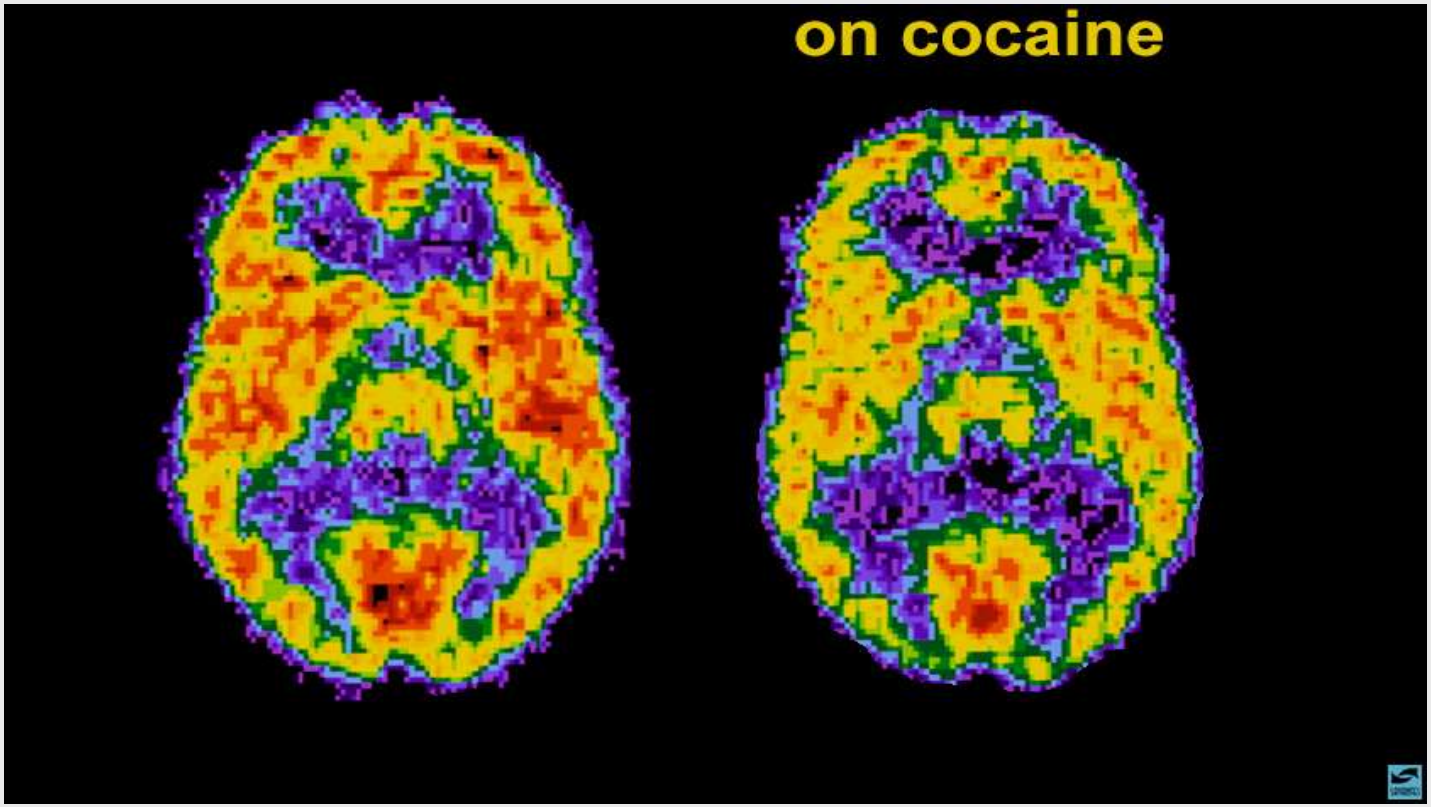
cocaine (0.5 mg/kg), monkey

COCAINE „SUPERAMPHETAMINE”

psychic dependence	**+++**	
physical dependence	**(+)**	
tolerance	**++**	**(in case of repeated apply with short interval)**

cocaine crack is especially dangerous !!!



red - high DA receptor level
yellow – low DA receptor level

PHARMACOKINETICS of COCAINE

$t_{1/2}$ ~ 50 min

route of administration	onset of action
i.v.	1-2 min
intranasal	some min
crack	some min
cocaine HCl	30-40 min
oral	60 min

„rush”

distribution into the brain is very quick

redistribution is also very quick

↓

i.v. cocaine or crack might be repeated after 30-40 min
(quickly developing dependence)

METABOLISM of COCAINE I.

Main metabolites **benzoilecgonine**
ecgonine methylesther

Metabolizing enzyme - cholinesterase

reduced serum cholinesterase activity in

- **fetus**
- **small children**
- **pregnant women**
- **elder people**
- **hepatic failure**
- **genetic cholinesterase deficiency**

METABOLISM of COCAINE II.

Elimination **via kidney**

detectable for 24-36 hours

via sweat

detectable for weeks

in the hair

detectable for years!

COCAINE OVERDOSE

- **COLLAPSE of CIRCULATION**

  arrhytmia
  ischemia
  myocardial infarct
  seizures
  stroke

- **MIGRAINE**
- **HYPERTHERMIA**
- **RESPIRATORY DEPRESSION**

- **CENTRAL SYMPTOMS**

  anxiety
  paranoia
  fear of death

POSSIBLE LETHAL OUTCOME
within 2-3 hours

COCAINE OVERDOSE

nose - bleeding
headache
exhaustion/depression
hoarseness
cardiovascular problems

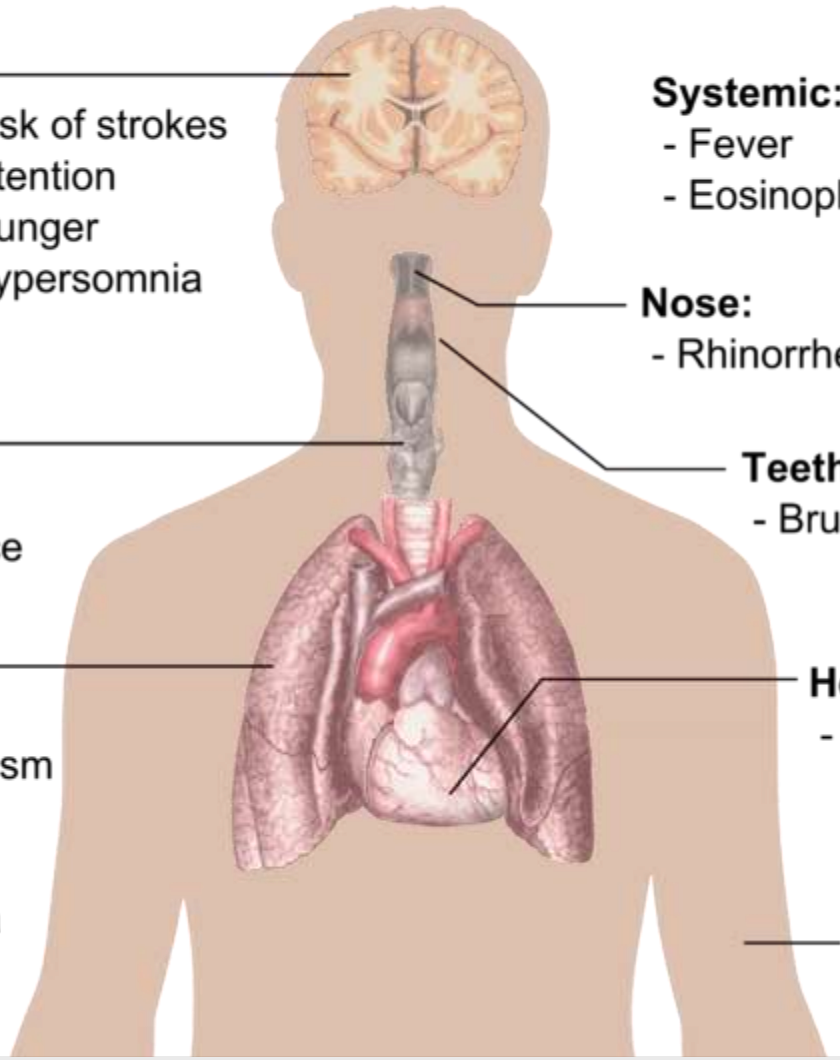
SYNDROME of DIAGNOSTIC VALUE

Treatment: cardiac arrest - epinephrine
arrhytmia – lidocaine
diazepam

Not to give beta-blockers (coronary spasm risk !)

Side effects of chronic use of

Cocaine



Brain:
- Increased risk of strokes
- Reduced attention
- Insatiable hunger
- Insomnia/Hypersomnia
- Lethargy

Throat:
- Soreness
- Hoarse voice

Lungs:
- Hemoptysis
- Bronchospasm
- Dyspnea
- Infiltrates
- Eosinophilia
- Chest pain
- Asthma

Systemic:
- Fever
- Eosinophilia

Nose:
- Rhinorrhea (discharge)

Teeth:
- Bruxism (abrasion)

Heart:
- Increased risk of infarction

Skin:
- Pruritus

SPECIAL TOXIC EFFECTS of COCAINE

- **i.v. usage**
  - **endocarditis, hepatitis, AIDS, thrombophlebitis**
- **intranasal usage**
  - **rhinitis, nasal bleeding, septum perforation, spontaneous pseudomediastinum**
- **oral usage**
  - **GI ischaemia**

Characteristics of cocaine „psychosis”

- **vivid images**
- **acoustic hallucinations**
- **tactile hallucinations**

Characteristic symptoms of cocaine smokers

- **nasal bleeding**
- **chronic hoarseness**
- **inflammation in the septum or rarely perforation**

COCAINE – WITHDRAWAL SYMPTOMS

- very marked craving, which gradually decreases after a couple of day and than ceases
- exhaustion
- sleepiness
- depression
- decrease of heart rate

COCAINE ABUSE and PREGNANCY

- birth weight is smaller
- head circumference is smaller
- CNS developmental disorders because of foetal vasoconstriction

withdrawal symptoms of the newborns

- trembling
- sharp crying voice
- sweating

THERAPY of COCAINE DEPENDENCE

- blockade of DA receptors (neuroleptics e.g. haloperidol)

- replacement therapy ? DA-uptake inhibitors
  (e.g. mazindol)
  DA-agonists (e.g. bromocriptine)
  DA-releasers (e.g. amantadine)

- blockade of cocaine binding site on
  DA - transporter protein

THERAPY of COCAINE DEPENDENCE

- antidepressants (at and after withdrawal)
- on the basis of common DA theory buprenorphine, naltrexone
- symptomatic therapy (e.g. i.v. diazepam; propranolol)

recently studied possibilities

disulfiram
modafinil – stimulant (indicated for narcolepsy)

lorcaserin – 5-HT_{2C} agonist, anorectic

Cocaine abusers usually take the drug in the evening rather than the daytime, and take it continuously over a period of several hours

Cocaine abuse frequent with heroin

Cocaine abuse also frequent with ethanol
which might be especially dangerous

COCAINE + ETHANOL

cocaine plasma cc. ↑ (~ 30%), ethanol plasma cc. ↓ (~ 10%)

coca-ethylene metabolit

its $t_{1/2}$ is about double of cocaine
its effects is similar to that of cocaine,
self-administered by experimental animals

euphoria ↑

paranoia, agitation ↓

withdrawal dysphoria ↓

cardiovascular effects ↑

toxicity ↑