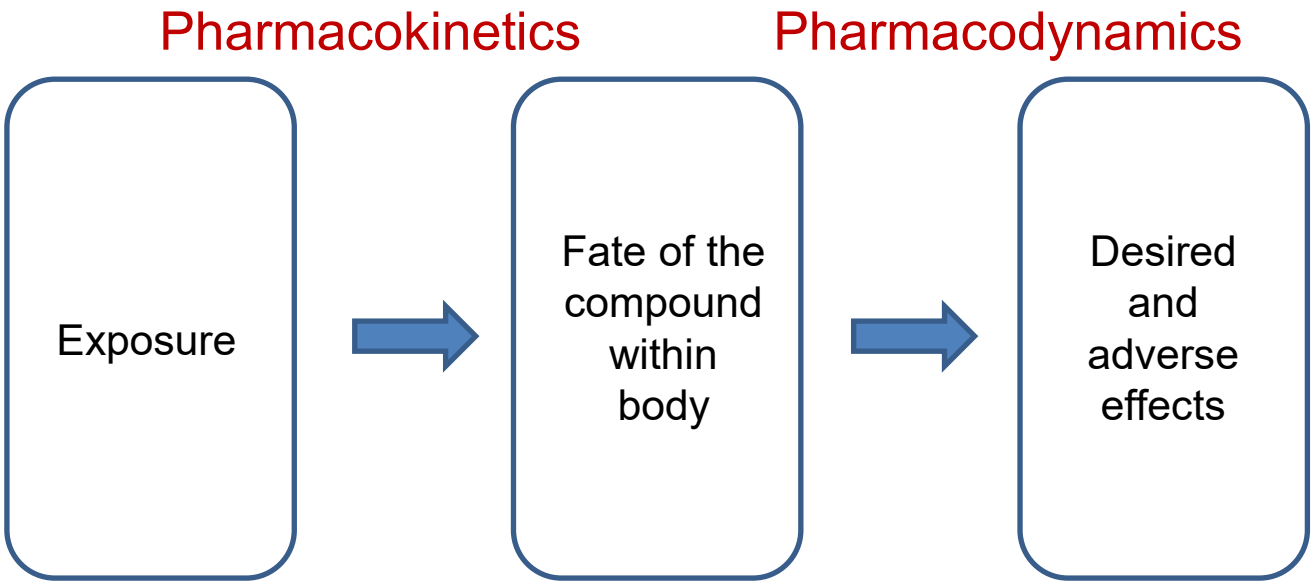
Effetti e meccanismo d’azione dell’ Ecstasy

Marco Gobbi

Laboratorio di
FARMACODINAMICAE FARMACOCINETICA (PD/PK)

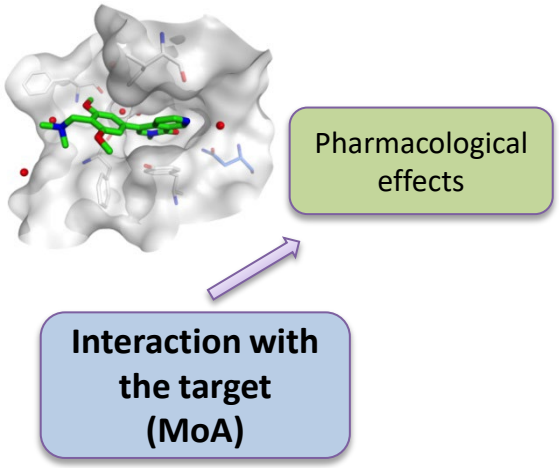
lunedì 5 giugno 2023

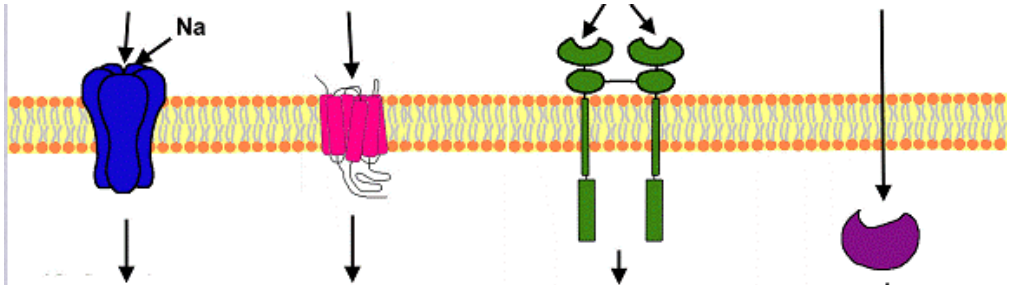
ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS


Pharmacokinetics
Pharmacodynamics
Exposure
Fate of the compound within body
Desired and adverse effects

Pharmacodynamics

describes the biochemical and molecular effects of drugs on the body
Mechanism of Action (MoA)
(receptor binding and post-receptor effects)



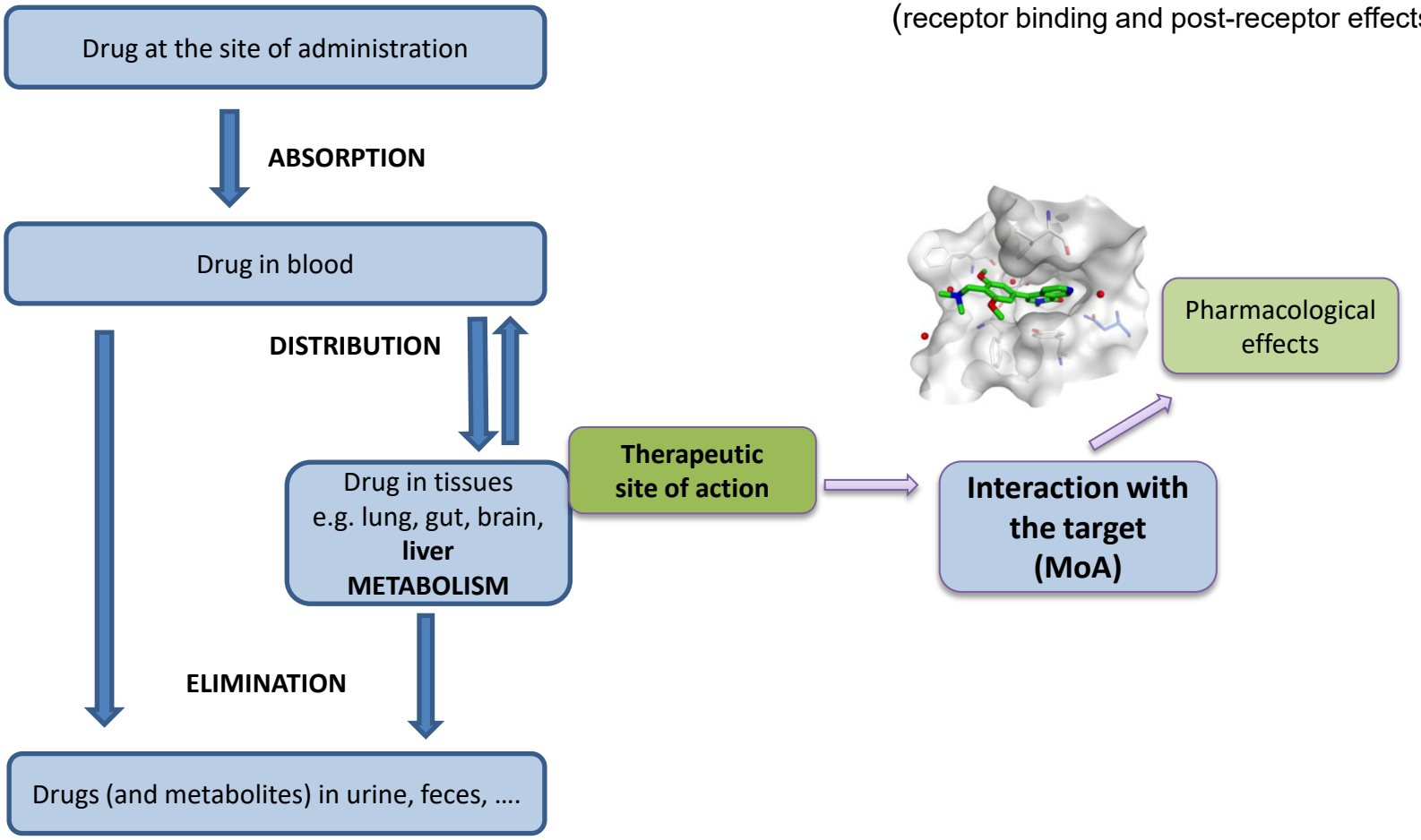


Pharmacokinetics

quantitatively describes the processes controlling the time-course of drug concentrations in the organism : Absorption, Distribution, Metabolism and Elimination (ADME)

Pharmacodynamics

describes the biochemical and molecular effects of drugs on the body
Mechanism of Action (MoA)
(receptor binding and post-receptor effects)

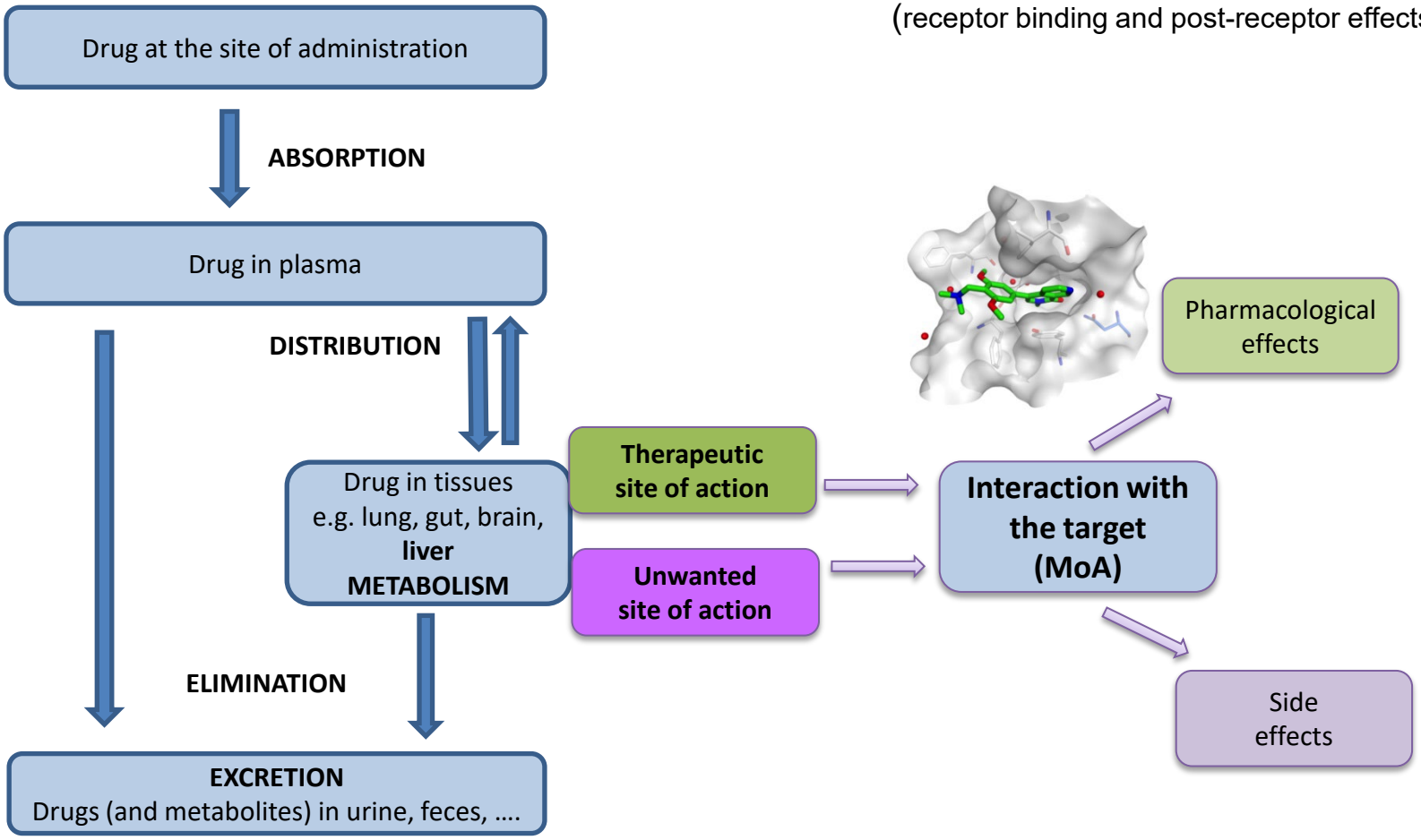


Pharmacokinetics

quantitatively describes the processes controlling the time-course of drug concentrations in the organism : Absorption, Distribution, Metabolism and Elimination (ADME)

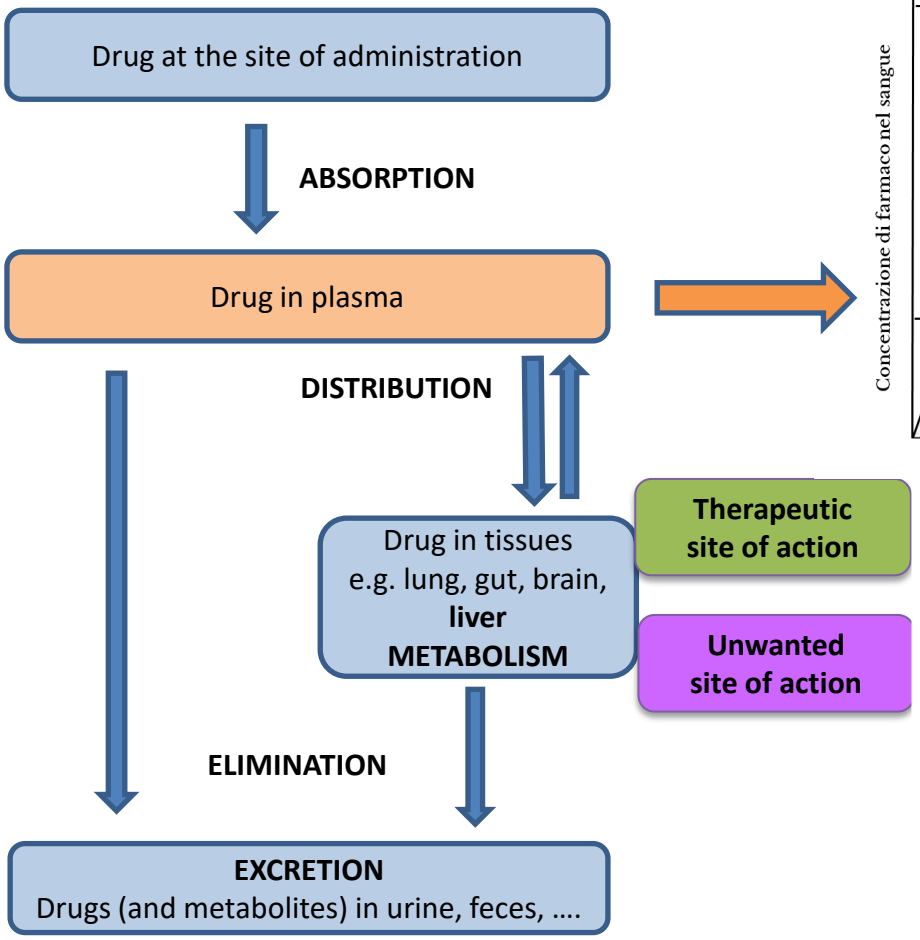
Pharmacodynamics

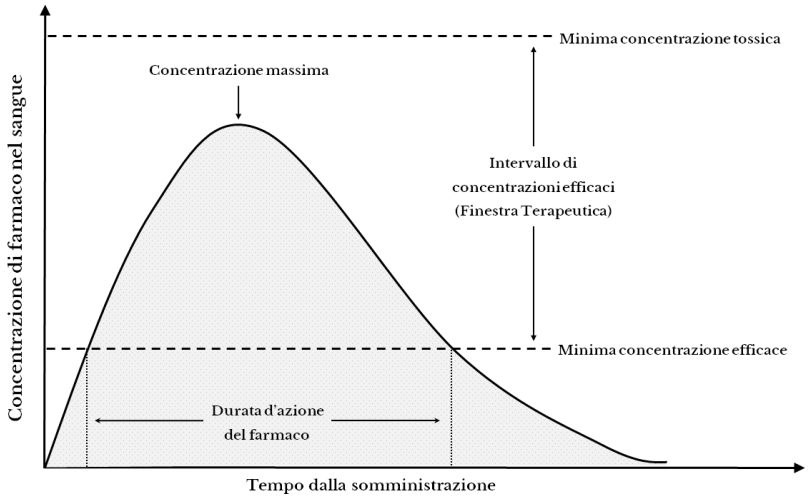
describes the biochemical and molecular effects of drugs on the body
Mechanism of Action (MoA)
(receptor binding and post-receptor effects)

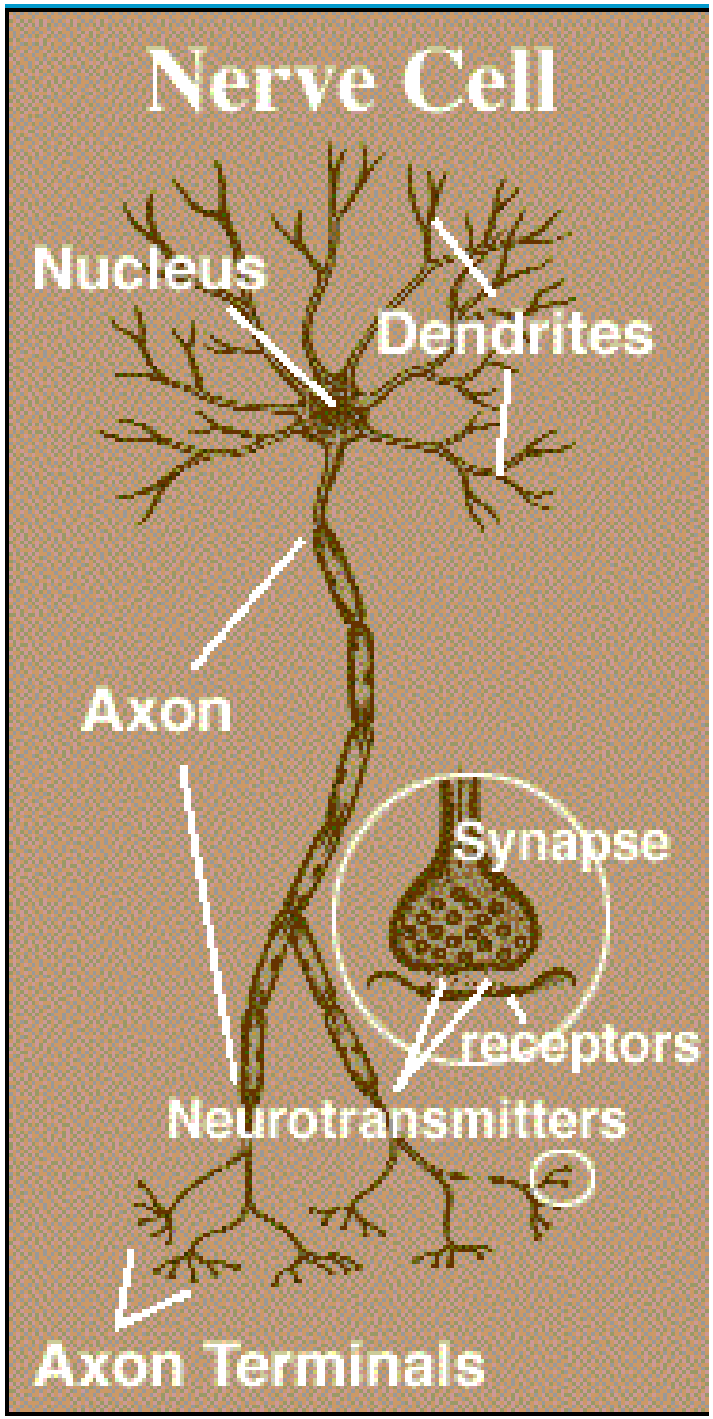


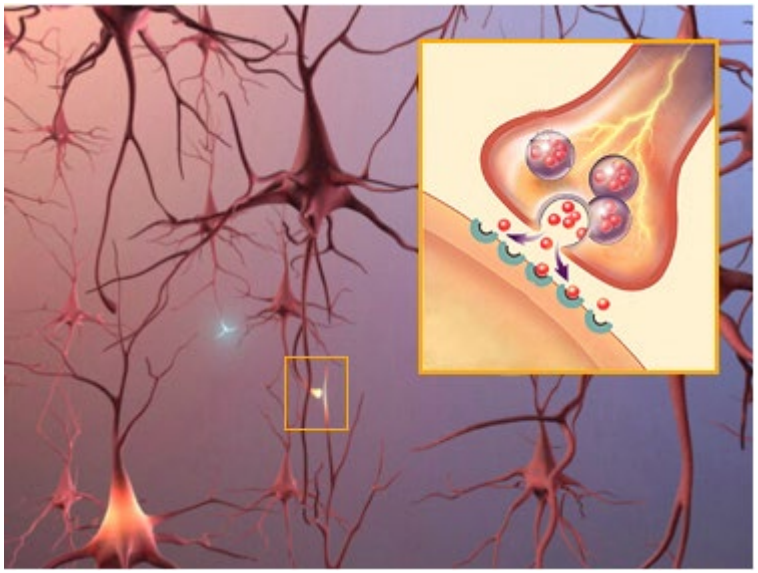
Pharmacokinetics

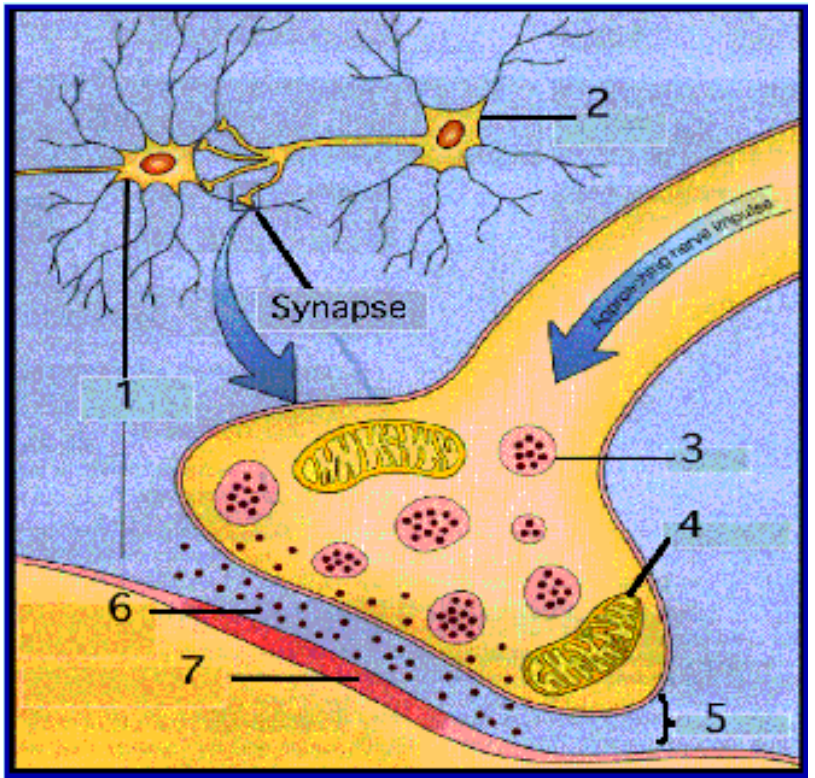
quantitatively describes the processes controlling the time-course of drug concentrations in the organism : Absorption, Distribution, Metabolism and Elimination (ADME)

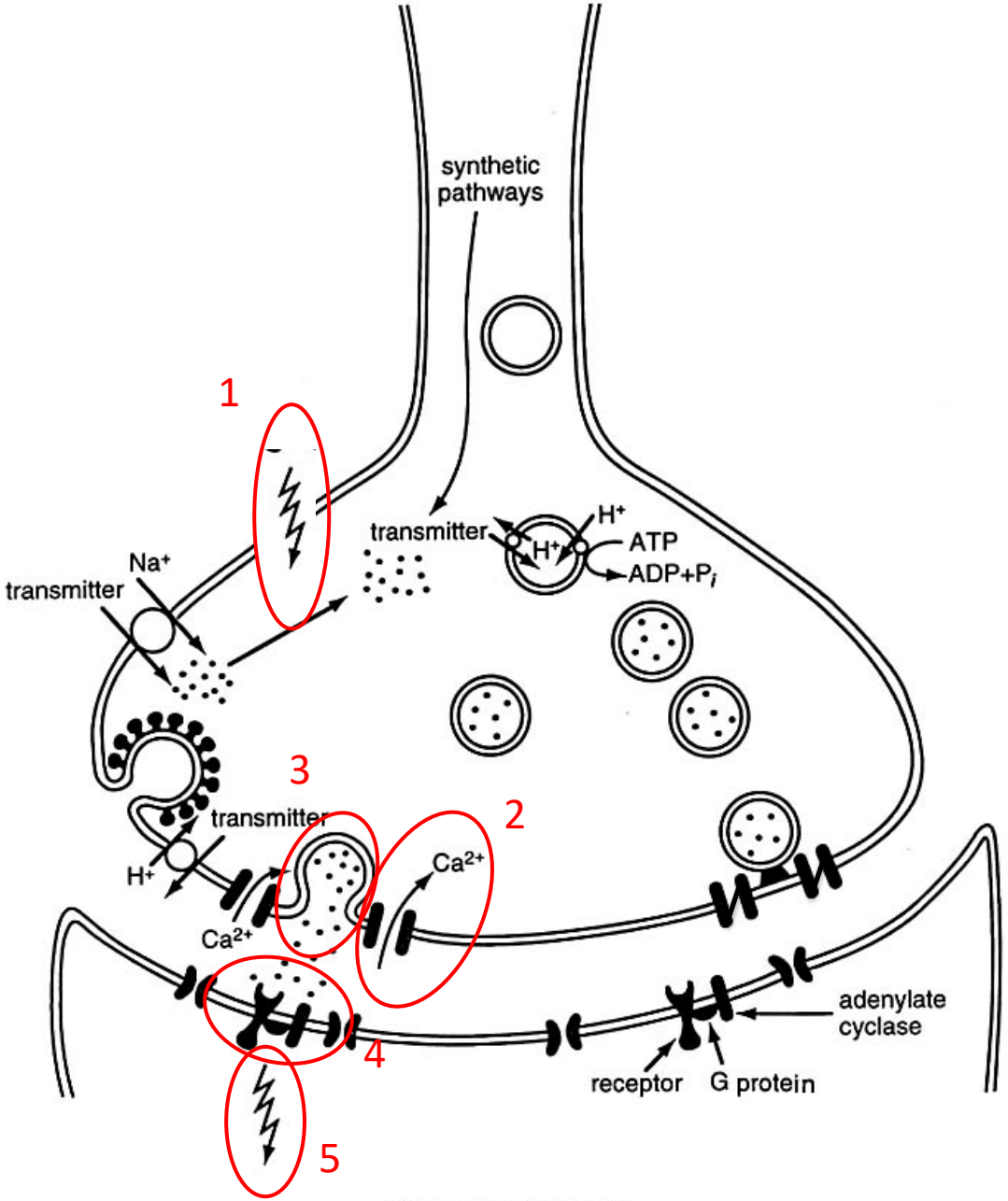





Nerve Cell
Nucleus
Dendrites
Axon
Synapse
receptors
Neurotransmitters
Axon Terminals




2
Synapse
1
3
4
6
7
5



The neuronal synapse.

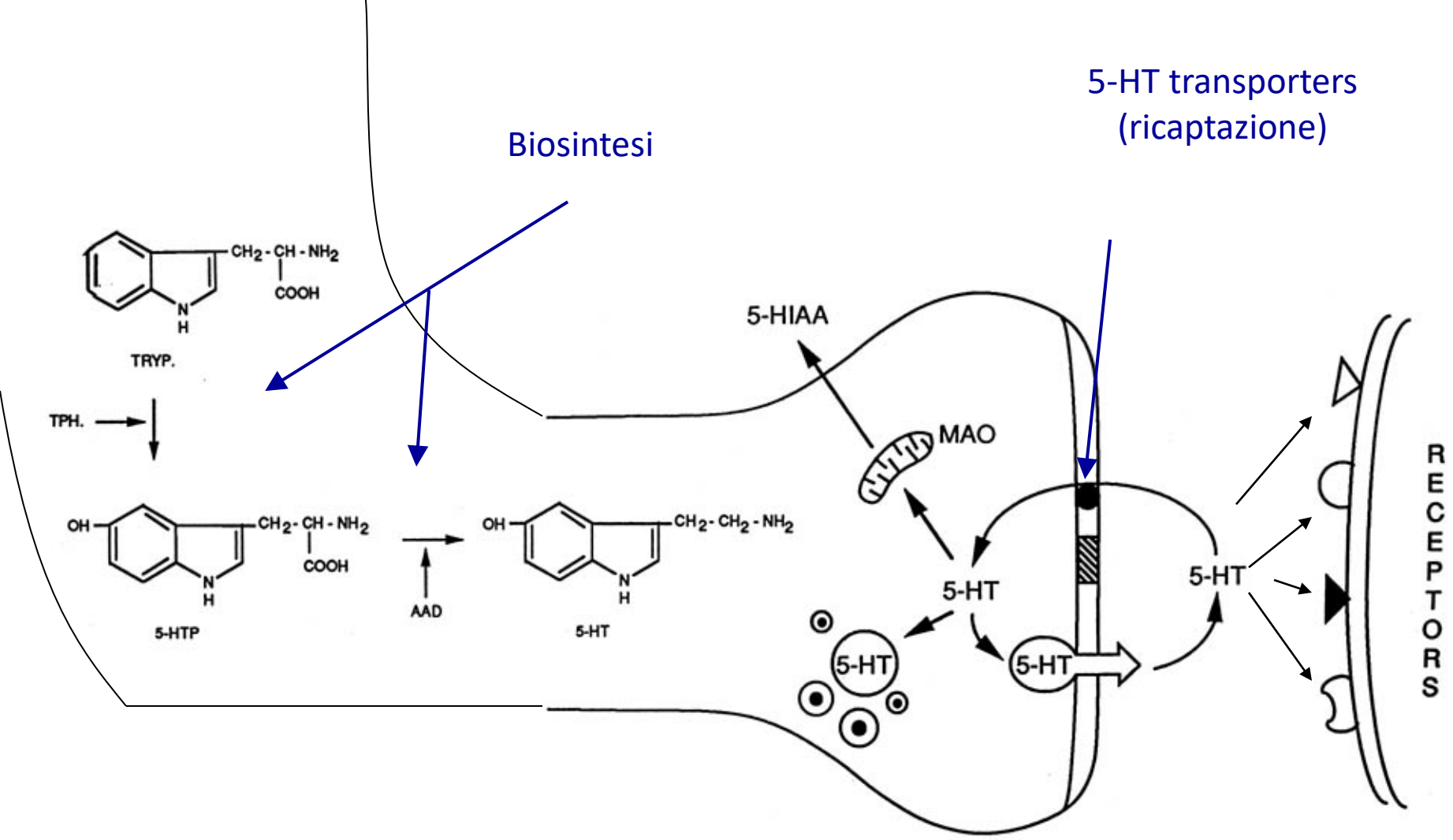
Neurotrasmettitori:

Amino acidi
- Acido glutammico
- Acido γ-amino-butirrico
- Glicina

Acetilcolina

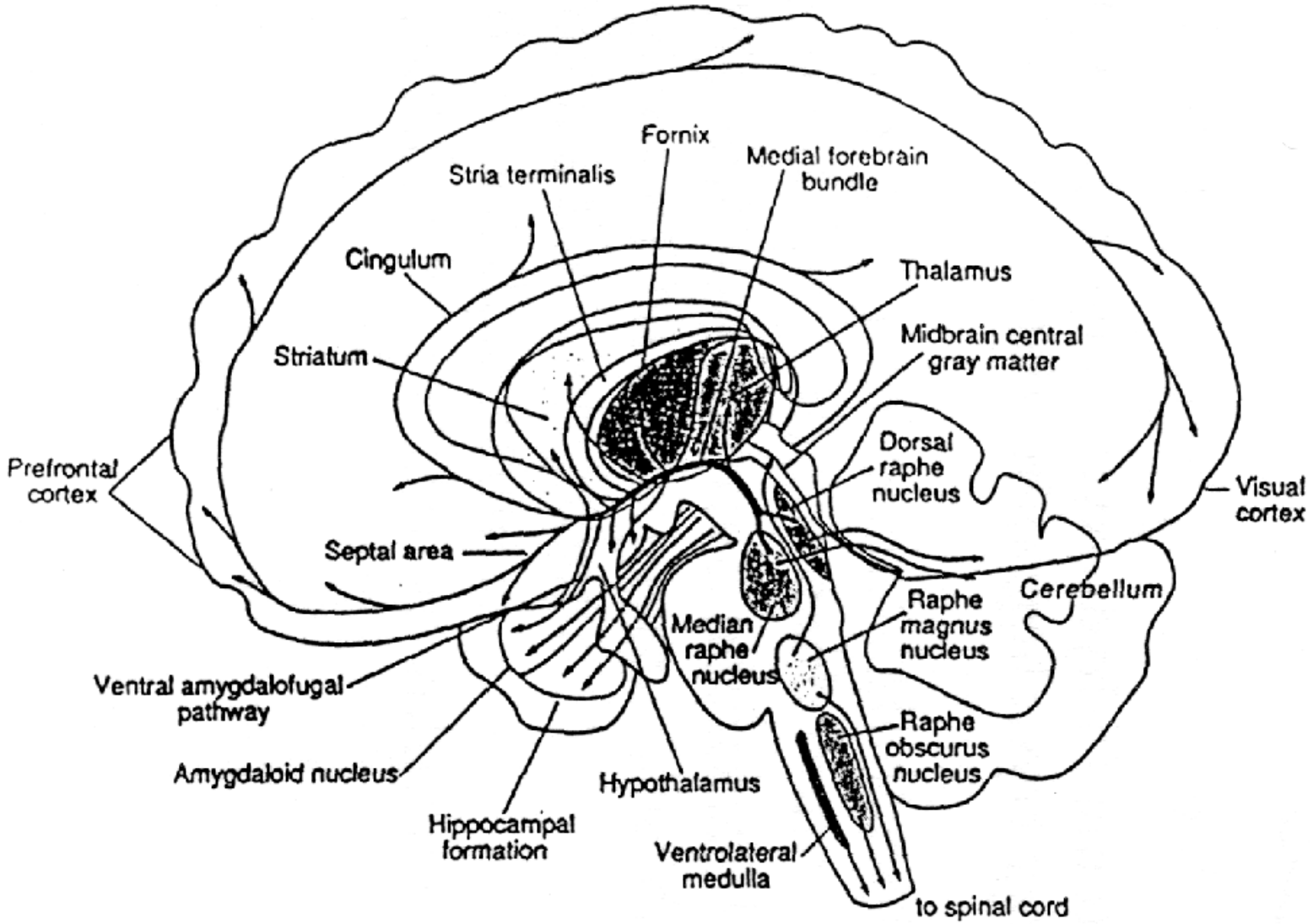
Monoamine
- Serotonina
- Dopamina
- Noradrenalina
- Istamina

Peptidi
- Somatostatina
- Neurotensina
- Neuropeptide Y



Il Neurone Serotoninergico

INNERVAZIONE SEROTONINERGICA



Nel S.N.C. la serotonina è coinvolta in:

- Assunzione di cibo
- Attività sessuale
- Dolore
- Sonno
- Funzioni cognitive e memoria
- Comportamento

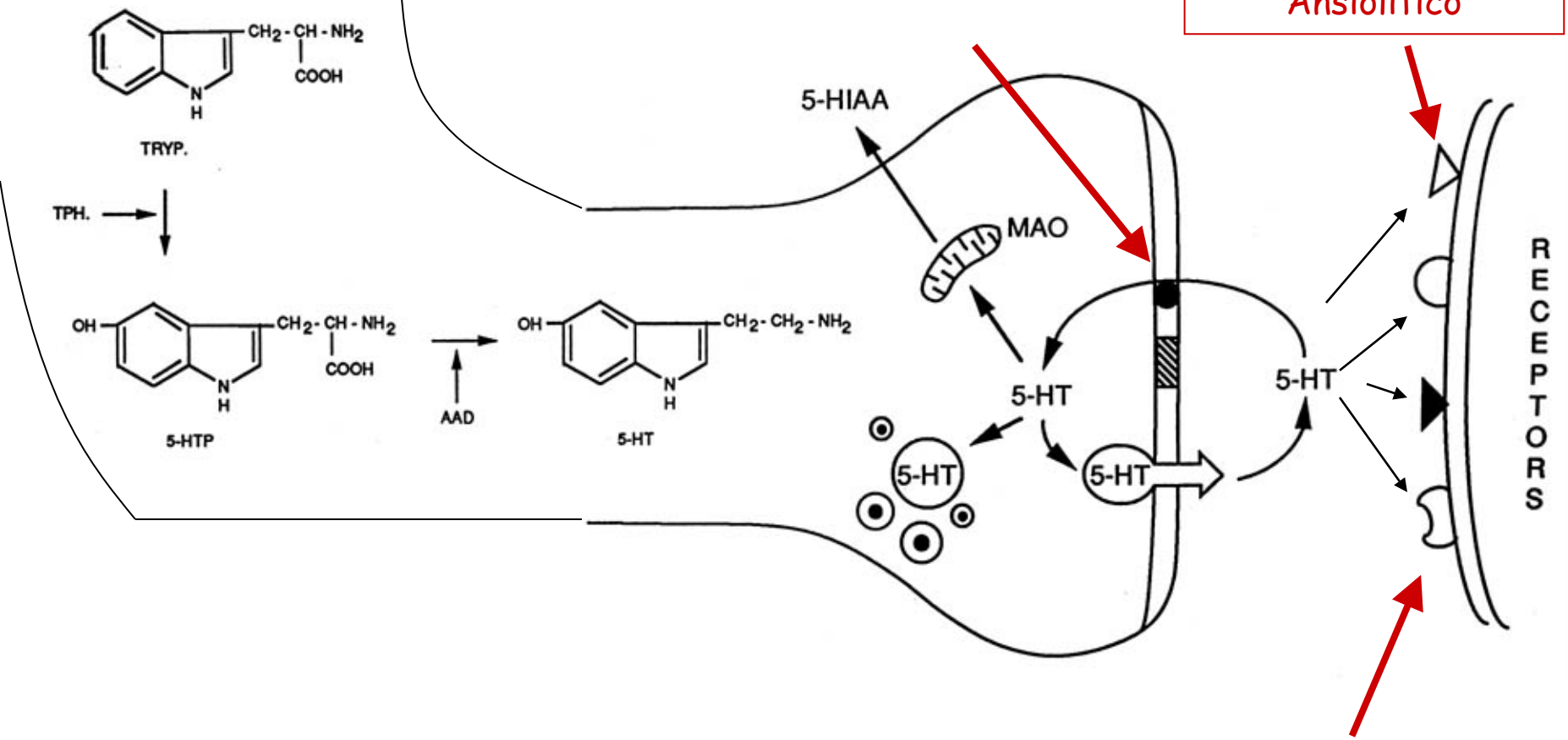
Alterazioni del sistema serotoninergico sono coinvolte in

- Disturbi dell'alimentazione
- Disturbi del comportamento
- Depressione
- Ansia
- Stress
- schizofrenia

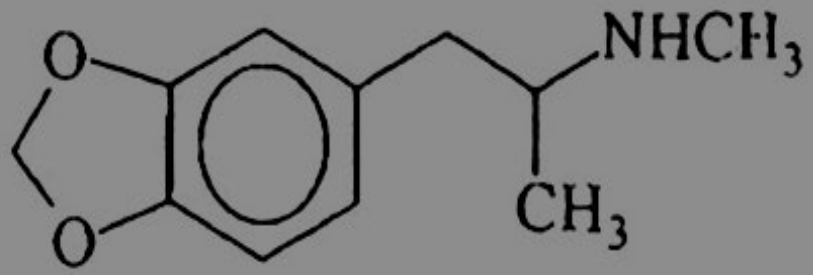
Principali farmaci che agiscono sul sistema serotoninergico

fluoxetine
(inibitore ricaptazione 5-HT)
Antidepressivo

buspirone
(agonista recettori
5-HT 1A)
Ansiolitico



odansetron
(antagonista recettori 5-HT3)
Antiemetico



3,4-methylenedioxymethamphetamine
(MDMA)
Ecstasy

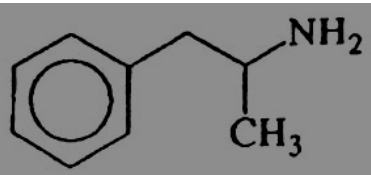
- Brevettata nel 1912

- Effetti sulla psiche
  - Sensazione di energia
  - Aumentata intensità delle emozioni
  - Aumentata capacità di interazione/apertura con gli altri
  - Diminuzione delle barriere difensive
  - Maggiore capacità introspettiva

- Utilizzo sperimentale in psicoterapia ('75-85)

- Utilizzo come sostanza d'abuso
  - inizialmente come droga "new-age"
  - poi ('87 ->) come droga "da party"

Interazione con le sinapsi serotoninergiche

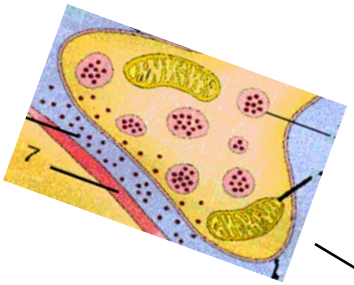


Amphetamine

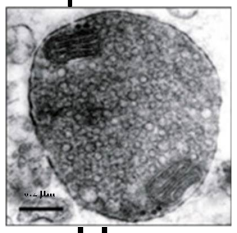
- 1986 : Divieto internazionale (sostanze stupefacenti)

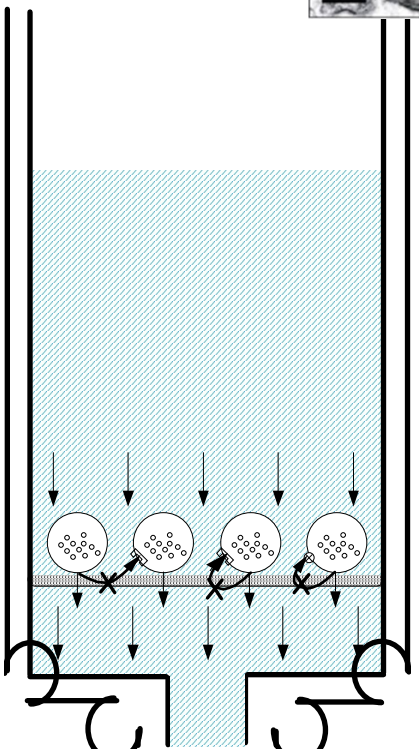
Interazione con le sinapsi dopaminergiche

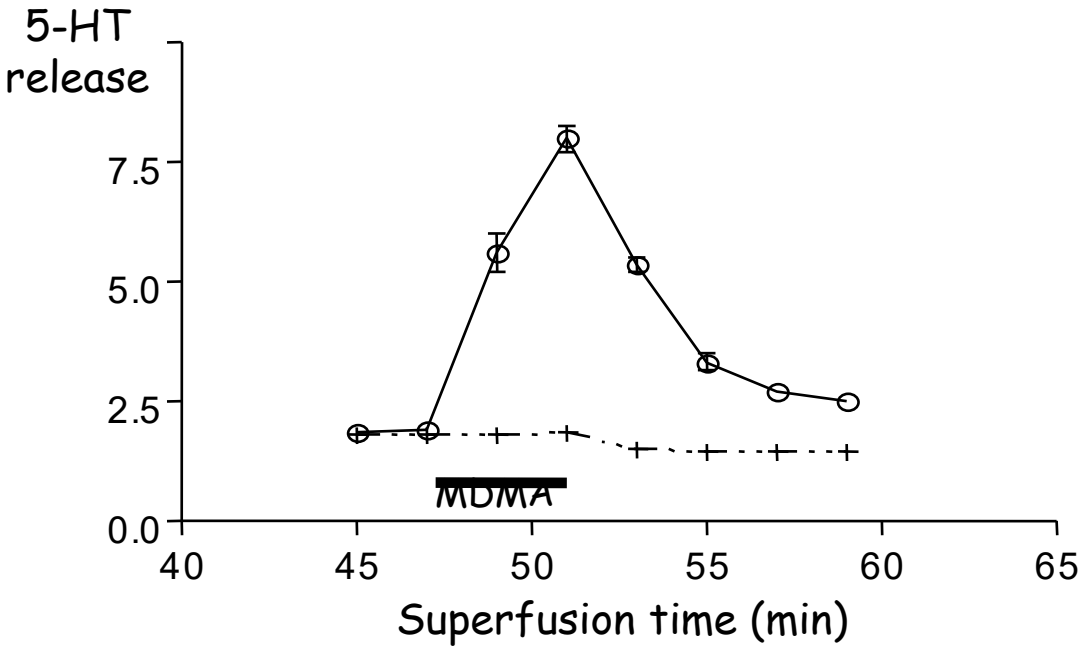
L'MDMA INDUCE RILASCIO DI SEROTONINA DALLE TERMINAZIONI NERVOSE (SINAPSI) (prova sperimentale)



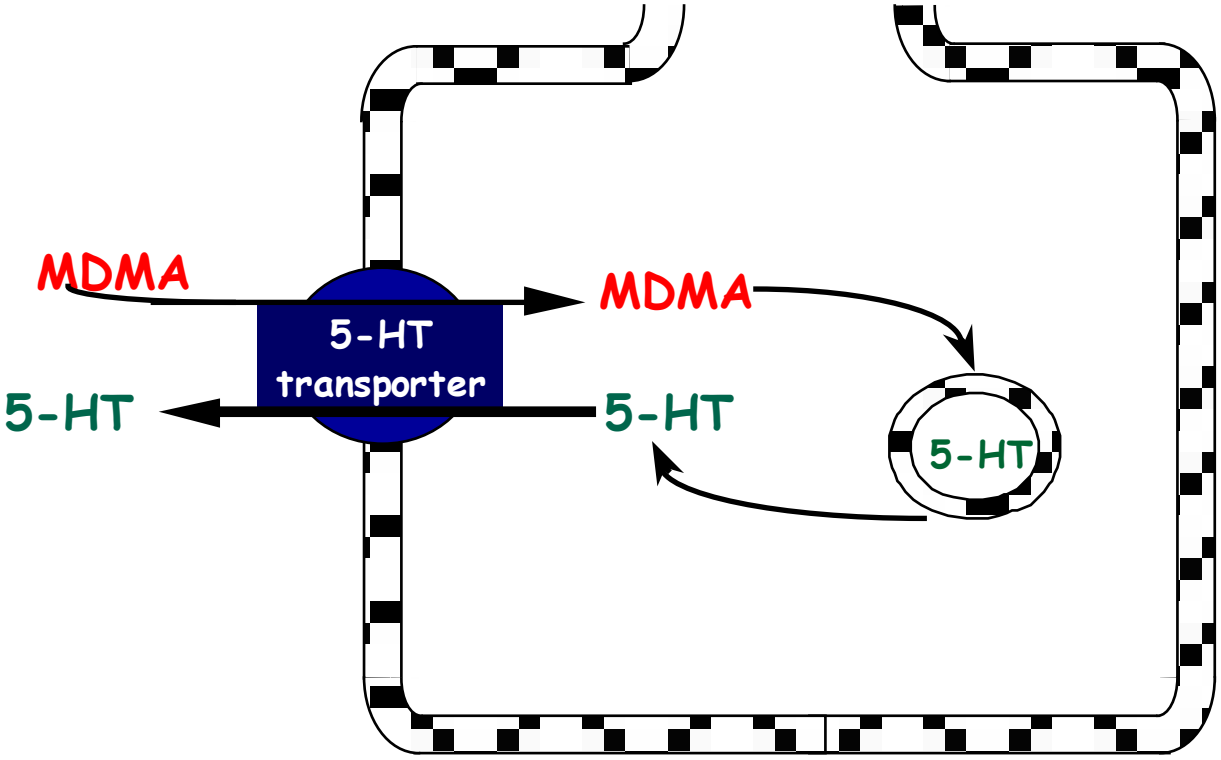
sinaptosoma







L'MDMA INDUCE RILASCIO DI SEROTONINA DALLE TERMINAZIONI NERVOSE (meccanismo)

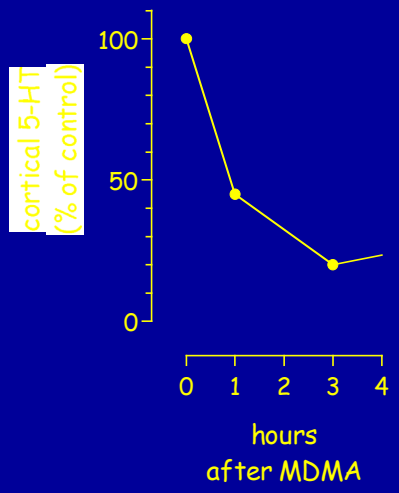


L'MDMA INDUCE RILASCIO DI SEROTONINA DALLE TERMINAZIONI NERVOSE
EFFETTI ACUTI

Animale da esperimento:

- Ipertermia
- "Sindrome serotoninergica"
  - diaforesi
  - tremori
  - atassia

- Marcata riduzione dei livelli cerebrali di serotonina (-> 80%)



Uomo:

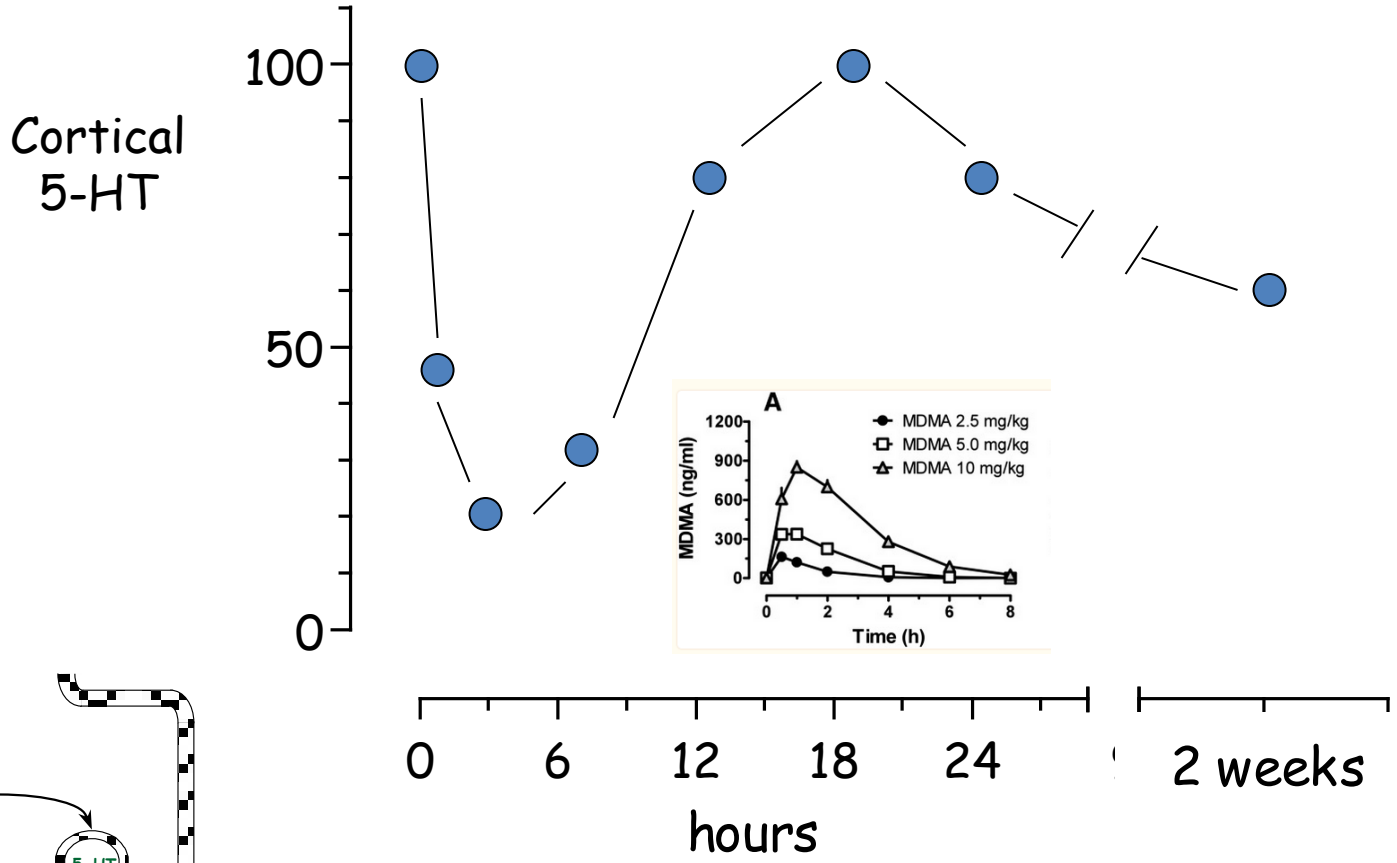
- "Sindrome serotoninergica"
  - Ipertermia (--> 43°C)
    - (T ambientale, attività fisica)
  - alterazioni neuromuscolari
    - Tremori/incoordinazioni
  - alterazioni "vegetative"
    - Sudorazione/tachicardia
    - insonnia
  - alterazioni stato mentale
    - Agitazione/confusione

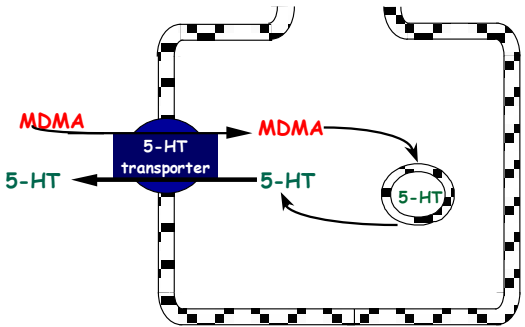
- Coagulazione intravascol. dissem.
- Insufficienza renale acuta
- Epatite fulminante

EFFETTI A LUNGO TERMINE DELL' MDMA

NEUROTOSSICITA'

Effetto di una singola somministrazione di MDMA nel ratto



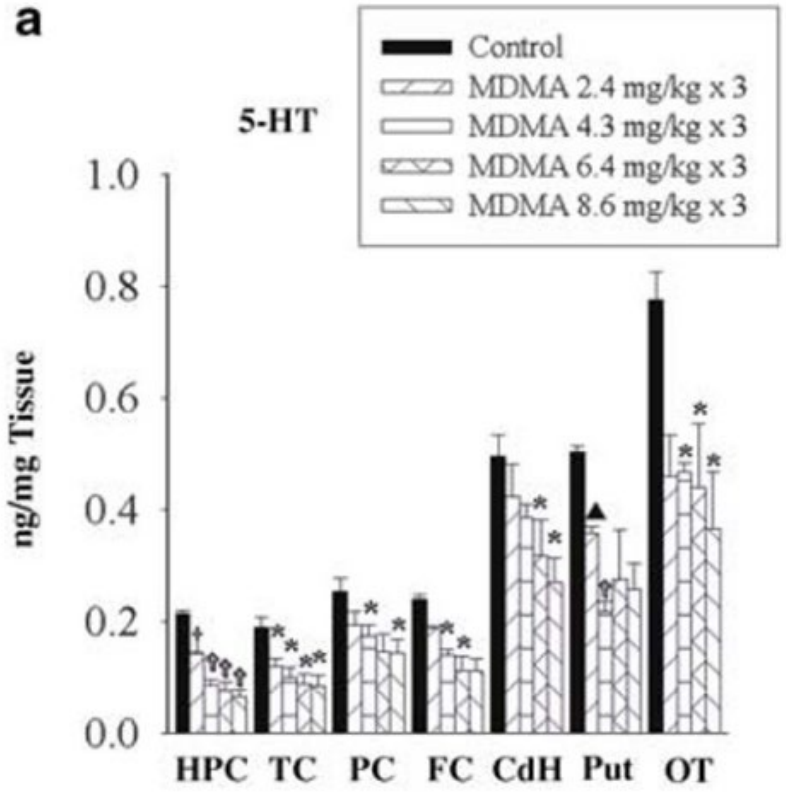


time after MDMA injection

Neuropsychopharmacology (2006) 31, 339–350

www.neuropsychopharmacology.org

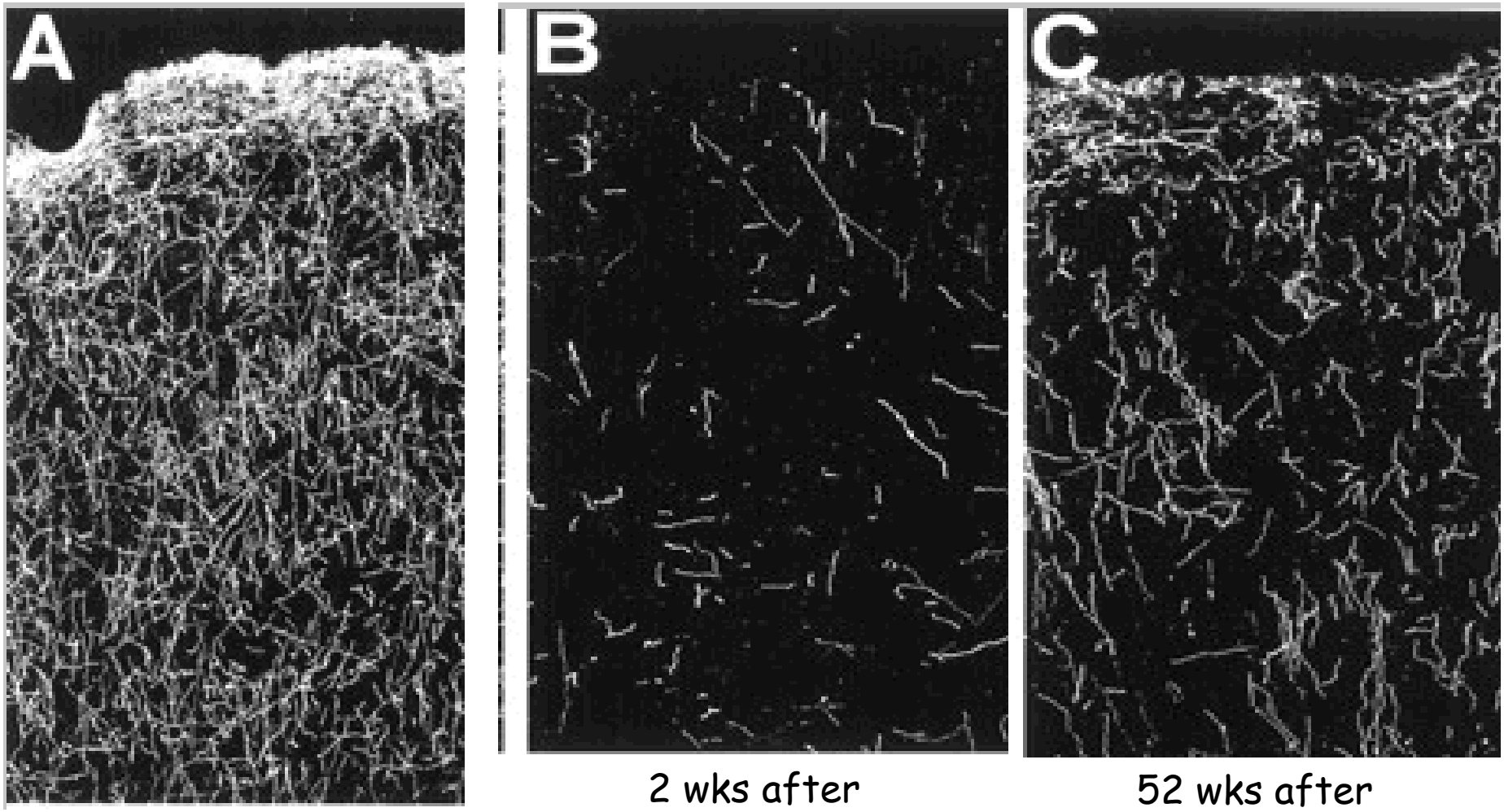
Pharmacokinetic Profile of Single and Repeated Oral Doses of MDMA in Squirrel Monkeys: Relationship to Lasting Effects on Brain Serotonin Neurons



2 weeks after drug treatment

NEUROTOSSICITA' INDOTTA DA MDMA

Serotonin-immunoreactive axons in the frontal cortex



Control

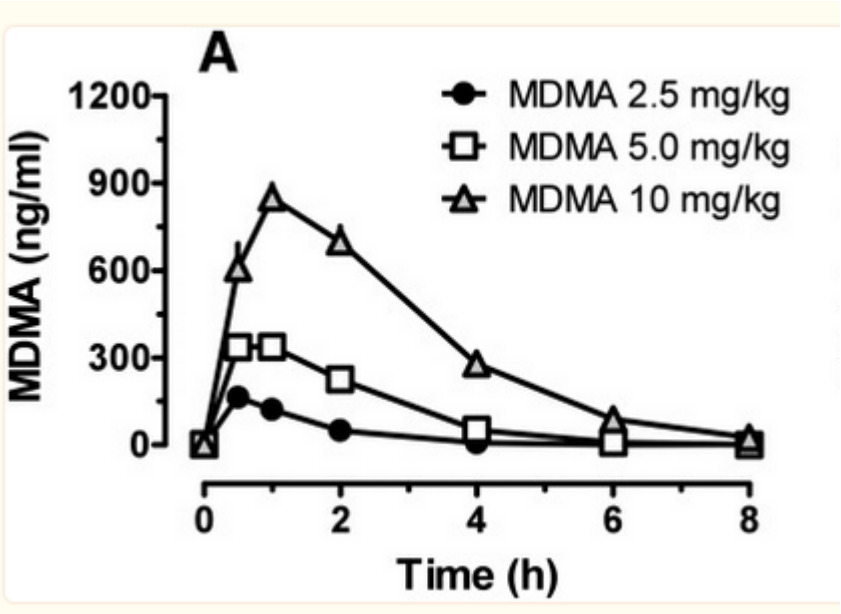
2 wks after MDMA

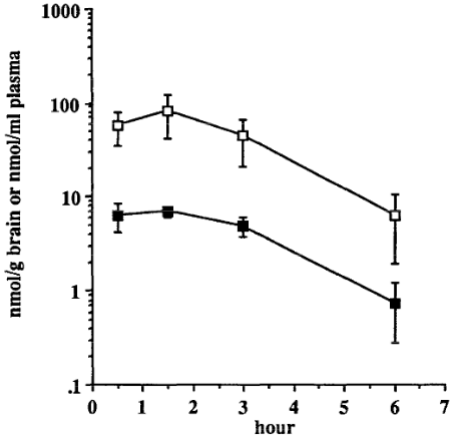
52 wks after MDMA

NEUROTOSSICITA' INDOTTA DA MDMA:

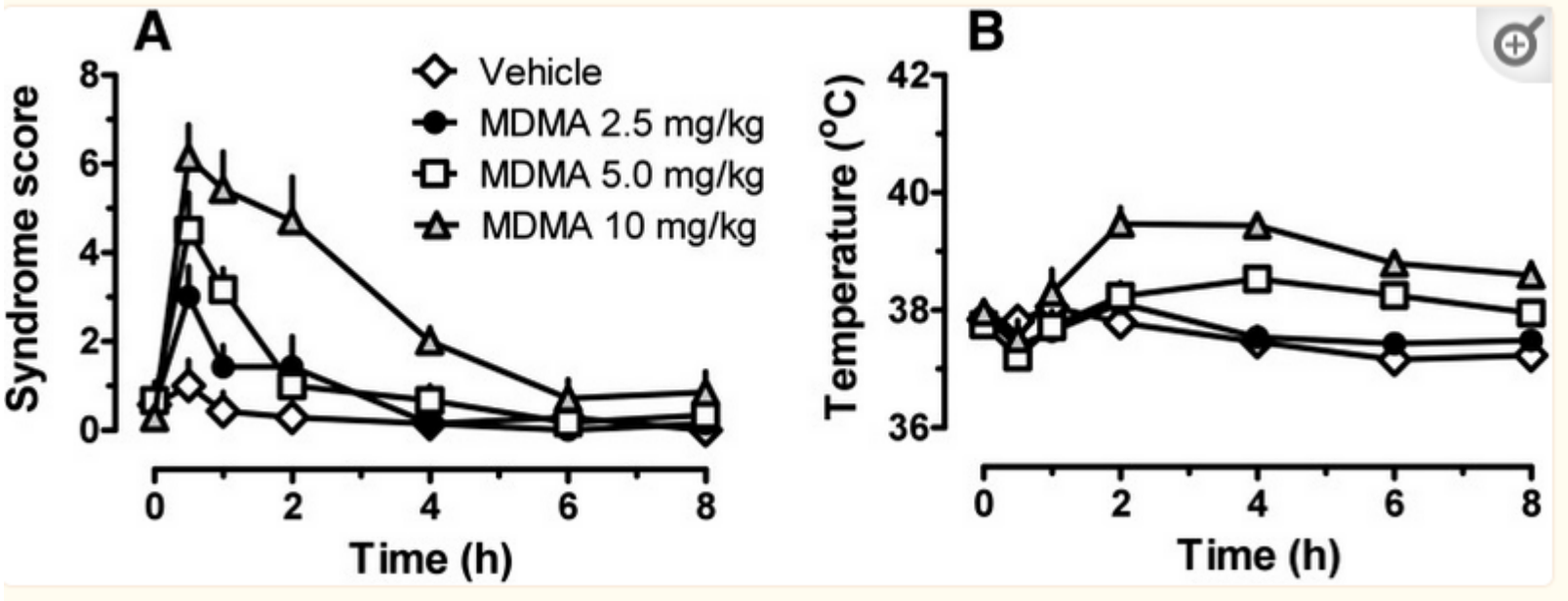
DALL' ANIMALE ALL' UOMO ?????

- Dosi





https://doi.org/10.1016/0006-2952(95)02397-6



doi: 10.1124/dmd.113.053678

NEUROTOSSICITA' INDOTTA DA MDMA NELL' UOMO ?
Dosi

Typical human MDMA doses (1–2 mg/kg) (tablets ~100 mg)

Toxic doses in rats ~ 20 mg/kg (10-20x)

After using standard interspecies dose-scaling equation
(smaller animals require higher dosages of drug, on a mg/kg basis, to achieve the same effect)

20 mg/kg in rats equivalent to 4 mg/kg in humans (5x)

Pharmacokinetic Profile of Single and Repeated Oral Doses of MDMA in Squirrel Monkeys: Relationship to Lasting Effects on Brain Serotonin Neurons

Annis Mechan[1], Jie Yuan[1], George Hatzidimitriou[1], Rodney J Irvine[2], Una D McCann[3] and George A Ricaurte*,[1]

[1]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Clinical and Experimental Pharmacology, University of Adelaide, Adelaide, SA, Australia; [3]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

A large body of data indicates that (±)3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') can damage brain serotonin neurons in animals. However, the relevance of these preclinical data to humans is uncertain, because doses and routes of administration used in animals have generally differed from those used by humans. Here, we examined the pharmacokinetic profile of MDMA in squirrel monkeys after different routes of administration, and explored the relationship between acute plasma MDMA concentrations after repeated oral dosing and subsequent brain serotonin deficits. Oral MDMA administration engendered a plasma profile of MDMA in squirrel monkeys resembling that seen in humans, although the half-life of MDMA in monkeys is shorter (3 *vs* 6–9 h). MDMA was biotransformed into MDA, and the plasma ratio of MDA to MDMA was 3–5/100, similar to that in humans. MDMA accumulation in squirrel monkeys was nonlinear, and plasma levels were highly correlated with regional brain serotonin deficits observed 2 weeks later. The present results indicate that plasma concentrations of MDMA shown here to produce lasting serotonergic deficits in squirrel monkeys overlap those reported by other laboratories in some recreational 'ecstasy' consumers, and are two to three times higher than those found in humans administered a single 100–150 mg dose of MDMA in a controlled setting. Additional studies are needed on the relative sensitivity of brain serotonin neurons to MDMA toxicity in humans and non-human primates, the pharmacokinetic parameter(s) of MDMA most closely linked to the neurotoxic process, and metabolites other than MDA that may play a role.

Neuropsychopharmacology (2006) **31,** 339–350. doi:10.1038/sj.npp.1300808; published online 6 July 2005

NEUROTOSSICITA' INDOTTA DA MDMA NELL' UOMO ?
Studi "comportamentali"

Reported Undesirable Effects
(up to 1 week post-MDMA, or longer):

- Anxiety
- Restlessness
- Irritability
- Sadness
- Impulsiveness
- Aggression
- Sleep disturbances
- Lack of appetite
- Thirst
- Reduced interest in and pleasure from sex
- Significant reductions in mental abilities

Potential Adverse Health Effects:

- Nausea
- Chills
- Sweating
- Involuntary jaw clenching and teeth grinding
- Muscle cramping
- Blurred vision
- Marked rise in body temperature (hyperthermia)
- Dehydration
- High blood pressure
- Heart failure
- Kidney failure
- Arrhythmia

Symptoms of MDMA Overdose:

- High blood pressure
- Faintness
- Panic attacks
- Loss of consciousness
- Seizures

- L'MDMA (Ecstasy) interagisce selettivamente con i neuroni serotoninergici, inducendo rilascio di 5-HT

- L'aumento di 5-HT extracellulare è responsabile degli effetti acuti dell'MDMA (effetti sulla "psiche" ed effetti "collaterali", anche gravi).

- Nell'animale da esperimento è chiara l'indicazione di una neurotossicità selettiva e a lungo termine dei neuroni 5-HT,

indotta anche da poche somministrazioni di MDMA.

- Anche nell'uomo, ci sono dati che suggeriscono che l' assunzione di MDMA, possa indurre neurotossicità serotoninergica.

Alterazioni del sistema serotoninergico possono avere conseguenze comportamentali, cognitive e psichiatriche.

- Sia gli effetti collaterali acuti

che gli effetti neurotossici

sono potenziati (aggravati) in caso di sovradosaggio e se l'assunzione avviene in

  - ambienti surriscaldati,
  - e/o con intensa attività fisica,
  - e/o con ridotta idratazione,
- e/o con contemporanea assunzione di altre droghe (incluso l'alcol).

Neuroscience 145 (2007) 764–774

HIGH AMBIENT TEMPERATURE INCREASES 3,4-METHYLENEDIOXYMETHAMPHETAMINE (MDMA, "ECSTASY")-INDUCED Fos EXPRESSION IN A REGION-SPECIFIC MANNER

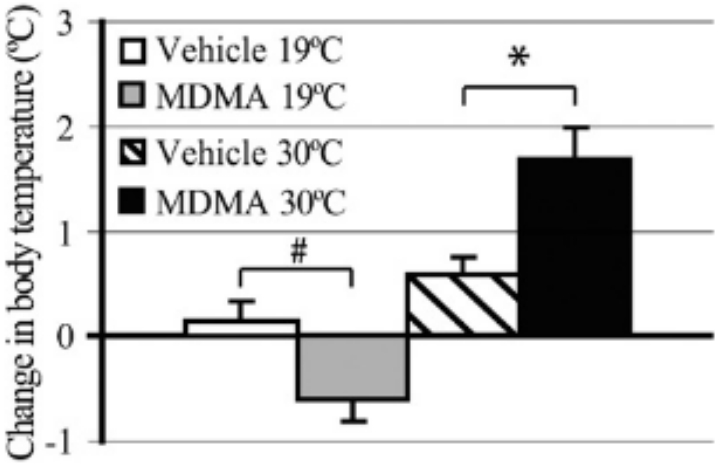
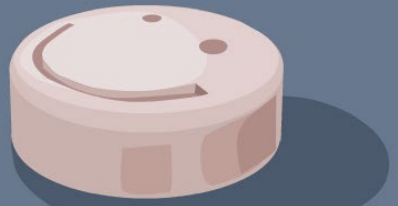


Fig. 3. Changes in body temperature in the four treatment groups over the 2 h test period (mean±S.E.M.). # $P<0.05$, * $P<0.01$ (ANOVA with pair-wise contrasts).

MDMA

(ecstasy, E, X, XTC, Adam, hug, love drug, roll)

Many so-called ecstasy tablets contain not only MDMA, but also other drugs, such as methamphetamine, caffeine, the cough suppressant dextromethorphan, or the diet drug ephedrine.



European Journal of Pharmaceutical Sciences 49 (2013) 57–64

Contents lists available at SciVerse ScienceDirect

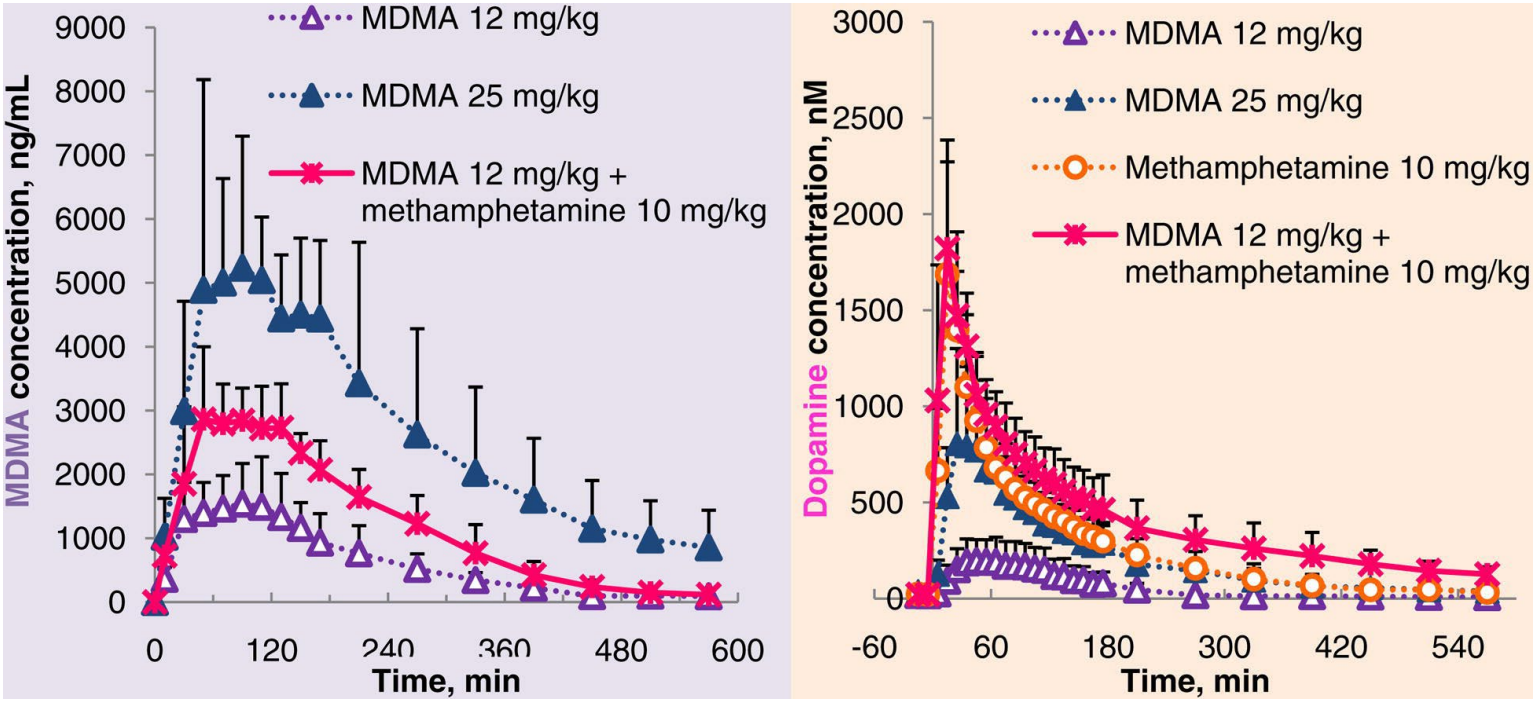
European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Warning against co-administration of 3,4-methylenedioxymethamphetamine (MDMA) with methamphetamine from the perspective of pharmacokinetic and pharmacodynamic evaluations in rat brain

Fuchigami Yuki [a], Ikeda Rie [a], Kuzushima Miki [a], Wada Mitsuhiro [a,*], Kuroda Naotaka [a], Nakashima Kenichiro [a,b]

[a] Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8131, Japan
[b] Faculty of Pharmaceutical Sciences, Nagasaki International University, 2825-7 Huis Ten Bosch Sasebo, Nagasaki 859-3298, Japan



POTENTE AZIONE STIMOLANTE

Sensazione di energia
Prontezza mentale

MARCATA INDUZIONE DI DIPENDENZA
TOLLERANZA
SINDROME DI ASTINENZA
(irrequietezza, depressione, craving)

TOSSICITA' ACUTA

↑ frequenza cardiaca e pressione
sudorazione/tachicardia, insonnia
alterazioni stato mentale; Agitazione/confusione
alterazioni neuromuscolari
tremori/incoordinazioni

Rischio di overdose (T ambientale, attività fisica)
Ipertermia (--> 43°C)
convulsioni

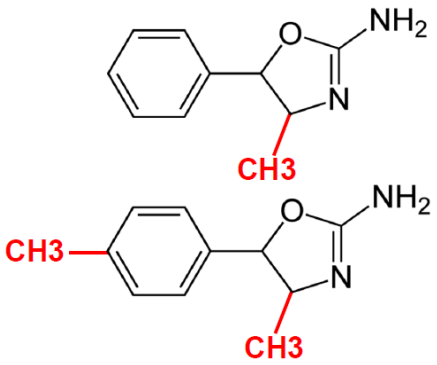
TOSSICITA' DA USO FREQUENTE

Effetti neurotossici ?
Disturbi psichici
Stati confusionali
Comportamenti violenti
Problemi cognitivi e sulla memoria
Patologia cardiovascolare

NUOVE SOSTANZE PSICOATTIVE

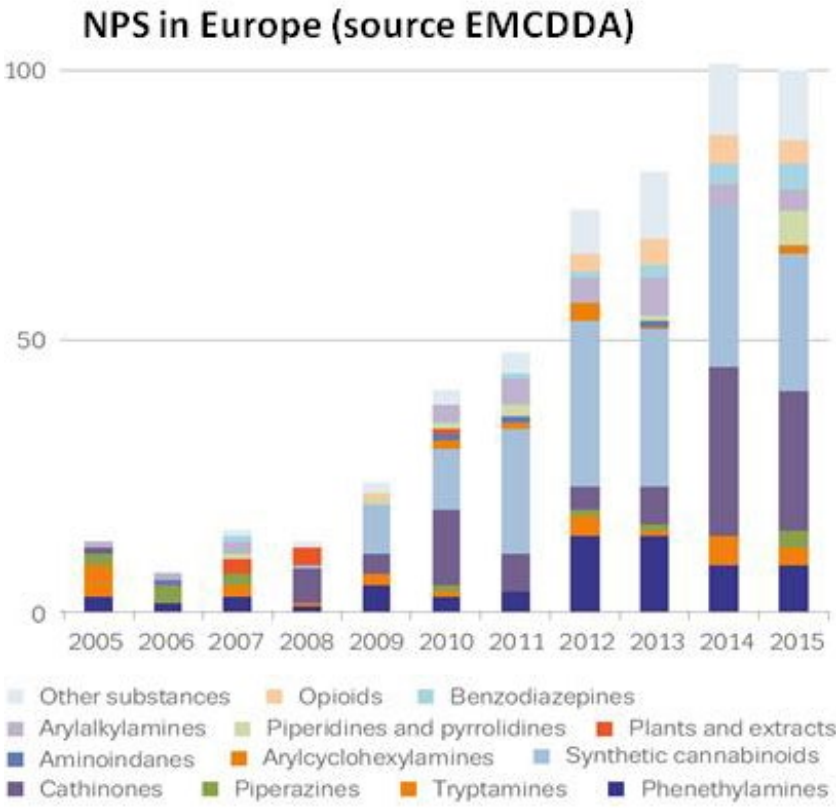
nuova droga stupefacente o psicotropa, non presente nelle convenzioni internazionali sulle sostanze psicotrope,

- LEGALE fino all'identificazione, valutazione del potenziale d'abuso e inserimento nelle tabelle



4-Methylaminorex
a metà degli anni '80 viene "scoperto" il suo utilizzo a scopo "ricreazionale". Sostanza inserita tra quelle vietate

4,4'-Dimethylaminorex (4,4'-DMAR)
Ha fatto la sua comparsa nel dicembre 2012 in Olanda. Si ritiene abbia causato la morte di almeno 30 persone. Sostanza liberamente venduta fino a Settembre 2015



NUOVE SOSTANZE PSICOATTIVE

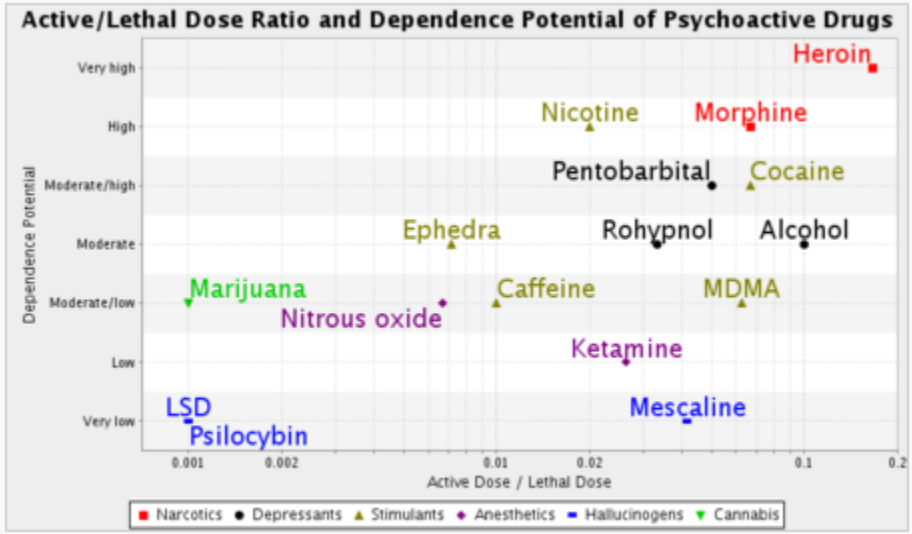
- facilmente reperibili in Internet, in modo anonimo
- vendute “camuffate” (integratori alimentari, sali da bagno, pillole vegetali) e con nomi e confezioni accattivanti

- “Bath salts” is the name given to synthetic cathinones. Cathinone is a stimulant found in the khat plant.

- Sometimes labeled as “plant food”—or as “jewelry cleaner” or “phone screen cleaner”

- Similar to methamphetamine and to MDMA (Ecstasy or Molly).
- They can be much stronger than the natural product and can be very dangerous.

- Incognite sulla composizione : molecola (?), dose (?), tagli (?),
- Interazioni
- Condizioni di utilizzo
- Variabilità inter-individuale



Comparison of physical harm and dependence regarding various drugs.[81]