Histoire des antagonistes NMDA et perspectives

Congrès de la SFAR 22 septembre 2022

Georges Mion

Hôpital Cochin

Paris

1956 la PCP

The Synthesis of Phencyclidine and Other 1-Arylcyclohexylamines

V Harold Maddox, Erik F. Godefroi, and Robert F. Parcell

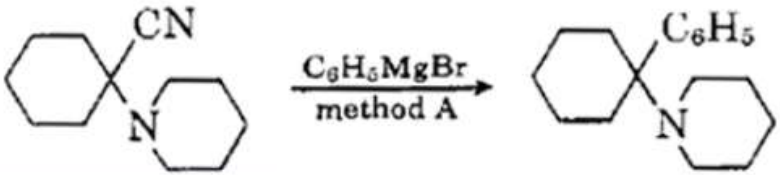
J Med Chem. 1965 Mar;8:230-5.

Detroit Michigan

Harold Maddox

chimiste de Parke-Davies

synthétise la phencyclidine

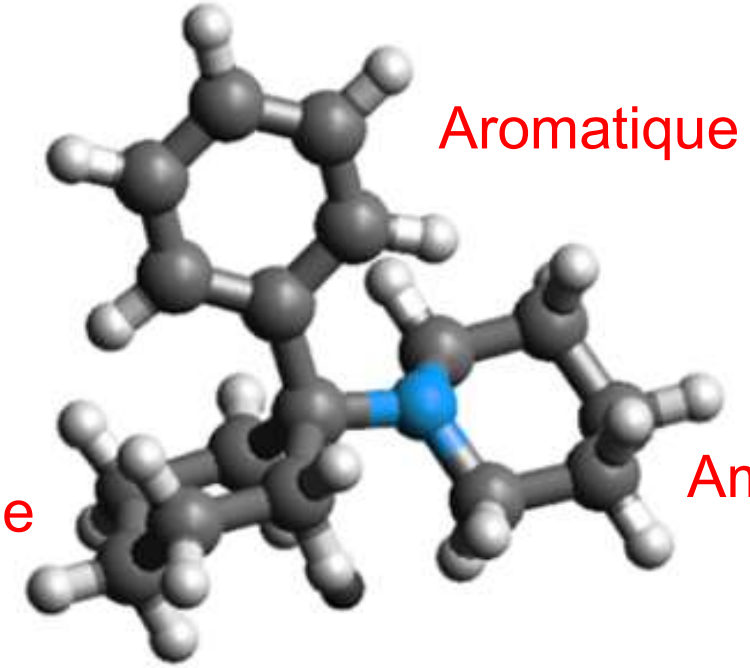


1-piperidinocyclo-hexanecarbonitrile

Zur Kenntnis hydroaromatischer Alkamine

A. Kötz und Paul Merkel

(Eingegangen am 8. März 1926)



1958 Le Sernyl

Ferdinand Greifenstein

étudie la **PCP** chez l'homme

VOLUME 37, NUMBER 5 — SEPTEMBER-OCTOBER, 1958 283

A STUDY OF A 1-ARYL CYCLO HEXYL AMINE FOR ANESTHESIA*

F. E. GREIFENSTEIN, M.D.†
MARION DeVAULT, M.D.
JUNICHI YOSHITAKE, M.D.
J. E. GAJEWSKI, M.D.
Detroit, Michigan

Catalepsie
Conservation des réflexes
Préservation cardio-respiratoire
Analgésie

L’anesthésique idéal ?

Effets Psychomimétiques !!!

Agitation, délire, cauchemars, symptômes schizoïdes

Il y a 60 ANS

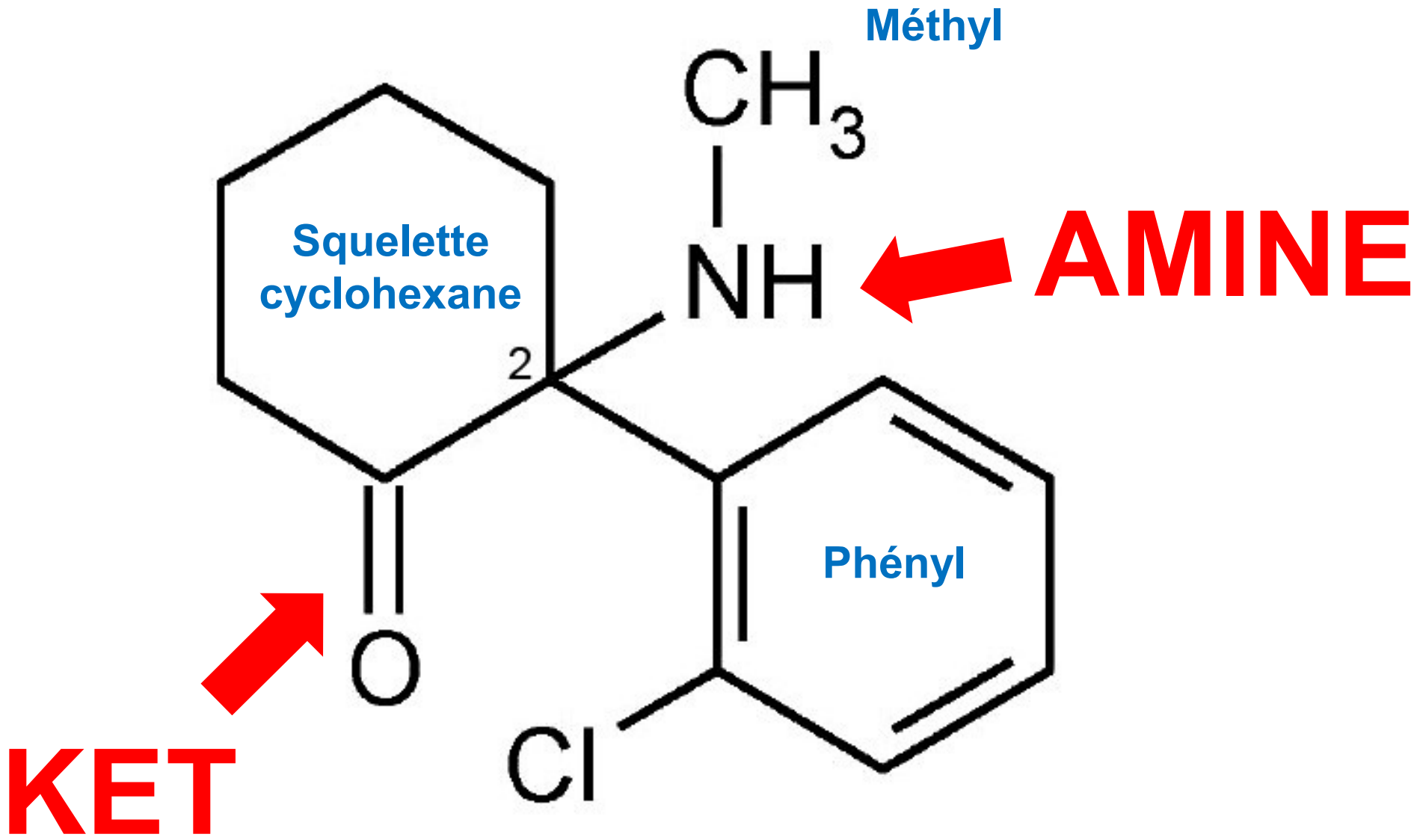
en 1962

Calvin Stevens (1923-2014)

Chimiste des laboratoires Parke-Devis

synthétise le CI-581

2 - ortho-chlorophényl - 2 – méthyl-amino - cyclohexanone



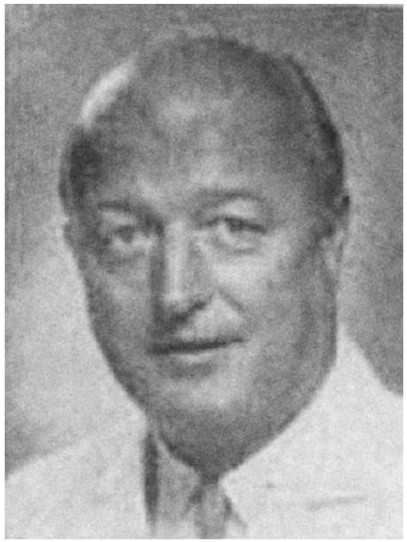
3 aout 1964

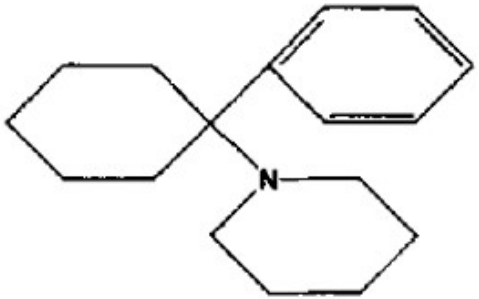
Pharmacologic effects of CI-581, a new dissociative anesthetic, in man

Edward F. Domino, M.D., Peter Chodoff, M.D., and Guenter Corssen, M.D.
Ann Arbor, Mich.
Departments of Pharmacology and Anesthesiology, The University of Michigan Medical Center

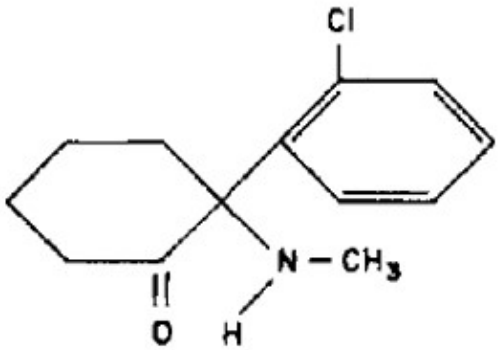
Clinical Pharmacology and Therapeutics

Jan. 4, 1965.



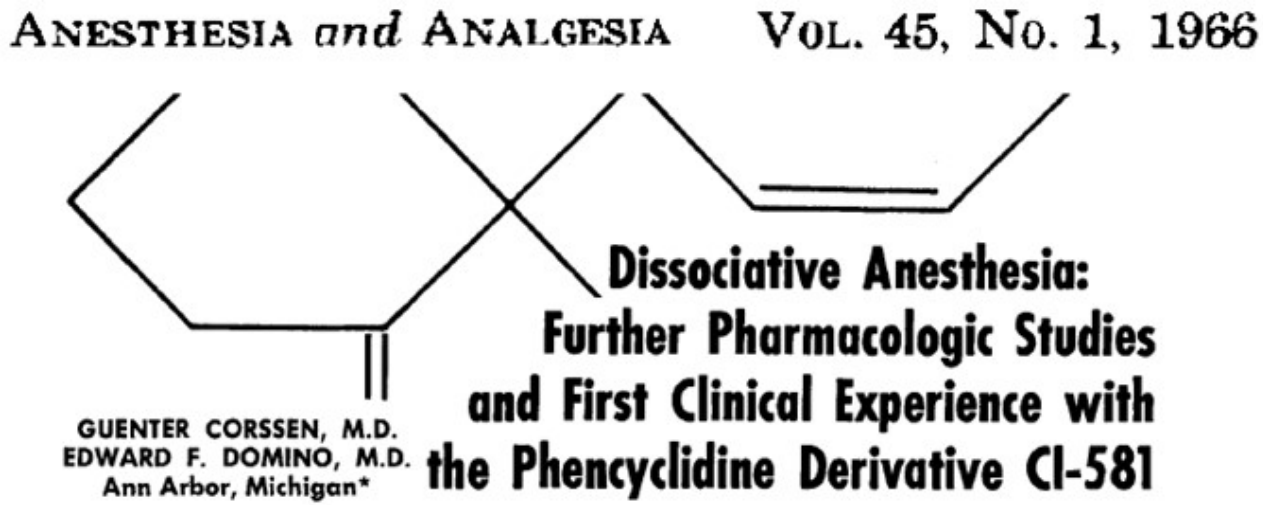


PHENCYCLIDINE



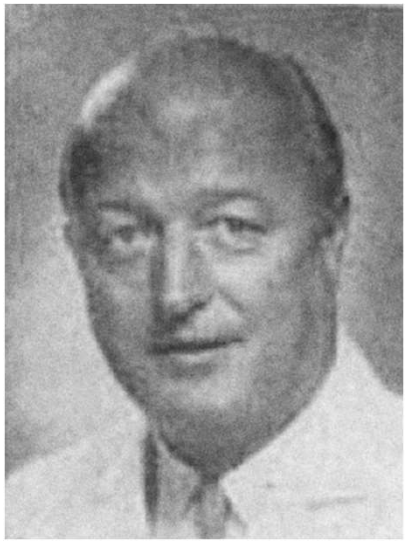
CI-581

Anesthésie dissociative


ANESTHESIA and ANALGESIA VOL. 45, NO. 1, 1966

Dissociative Anesthesia: Further Pharmacologic Studies and First Clinical Experience with the Phencyclidine Derivative CI-581

GUENTER CORSSEN, M.D.
EDWARD F. DOMINO, M.D.
Ann Arbor, Michigan*



L'information sensorielle parvient à rejoindre le cortex mais les aires associatives nécessaires à la sensation douloureuse sont déconnectées

1965

Sernyl abandonné en 1965
la PCP devient une « *street-drug* »

Seventies

BRITISH MEDICAL JOURNAL 19 JUNE 1971

Ketamine—A New Anaesthetic

Ketamine hydrochloride is a new, non-barbiturate, general anaesthetic. Administered intravenously the patient is ready for surgery within a minute; by intramuscular injection induction takes only a little longer. Cardiovascular and respiratory depression are said to be rare; the airway re-

Mais…

BRITISH MEDICAL JOURNAL 25 MARCH 1972

Psychosis and Ketamine

D. L. COPPEL

The Royal Victoria Hospital, Belfast

J. W. DUNDEE

The Queen's University of Belfast

The overall incidence of 21% delirium and 17% unpleasant or terrifying dreams in the absence of depressant pre-medication is quite unacceptable.

« benzo »

The taming of ketamine

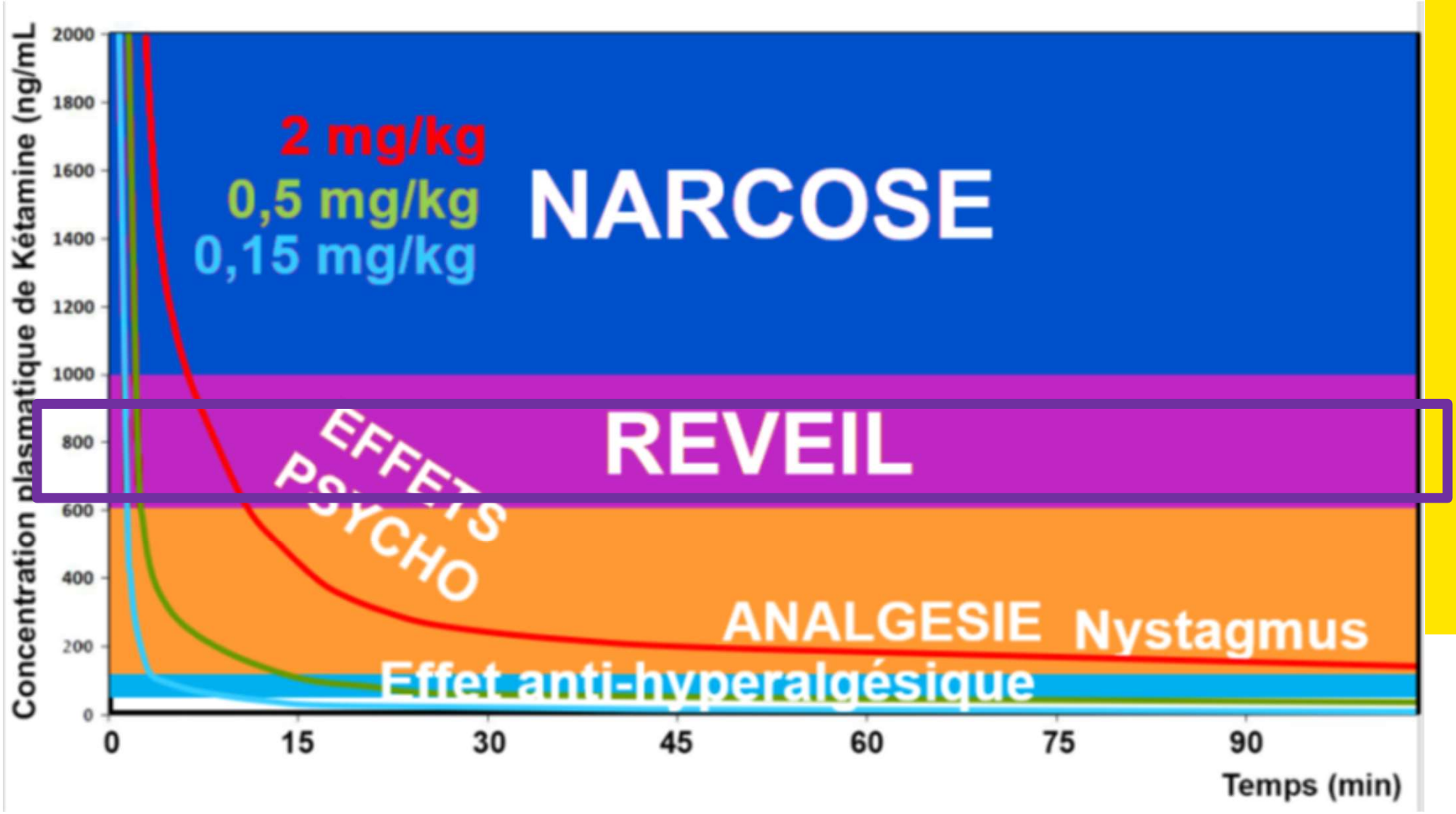
D. L. COPPEL, J. G. BOVILL AND J. W. DUNDEE

Anaesthesia, 1973, Volume 28, pages 293–296

diazepam at the end of the operation
to block the delirium and unpleasant dreams

Les **benzodiazépines**
permettent de « dompter »
la kétamine

Relation dose-effet



1981

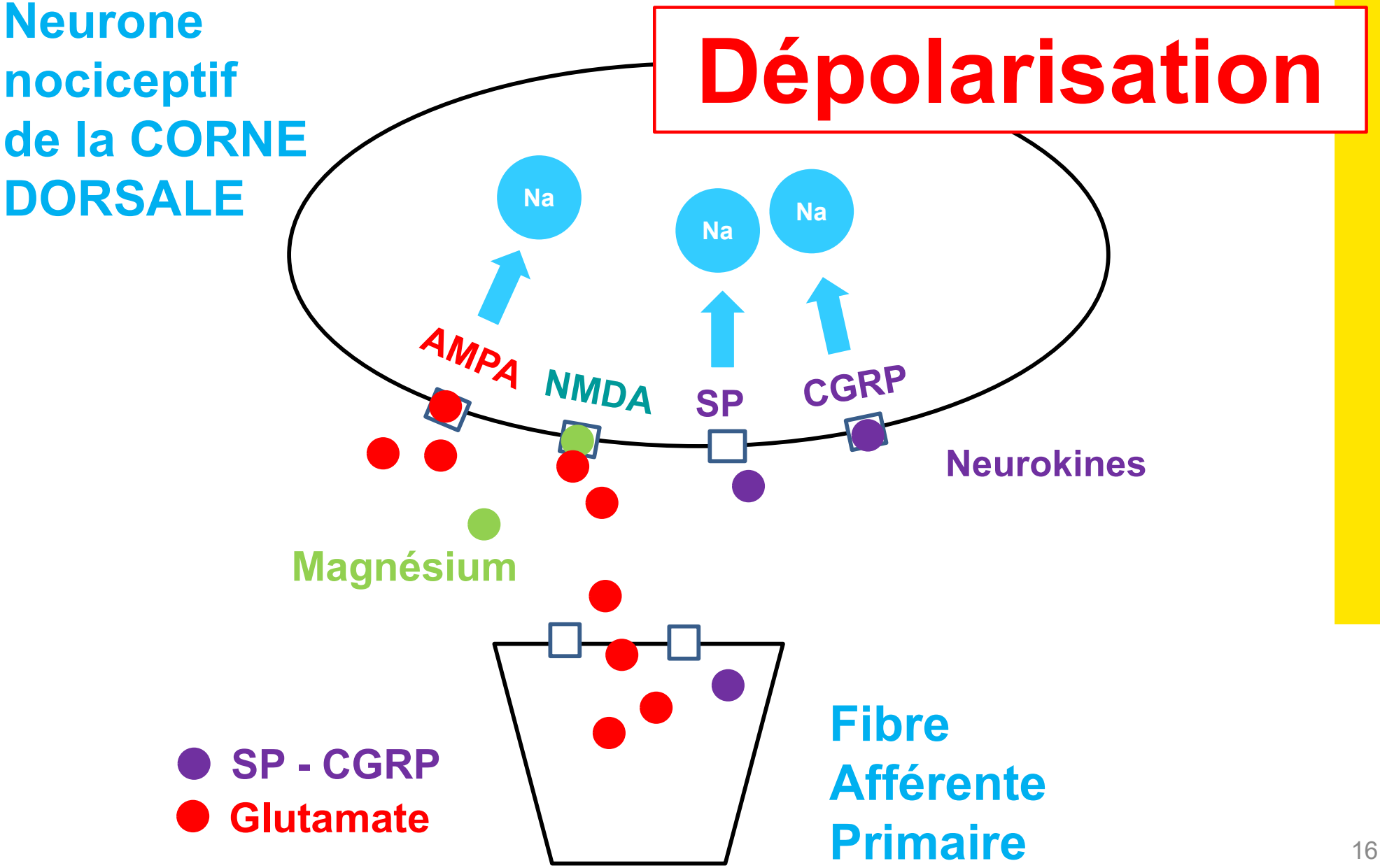
Br. J. Pharmac. (1983), **79,** 565–575

The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate

N.A. Anis, S.C. Berry, N.R. Burton & D. Lodge

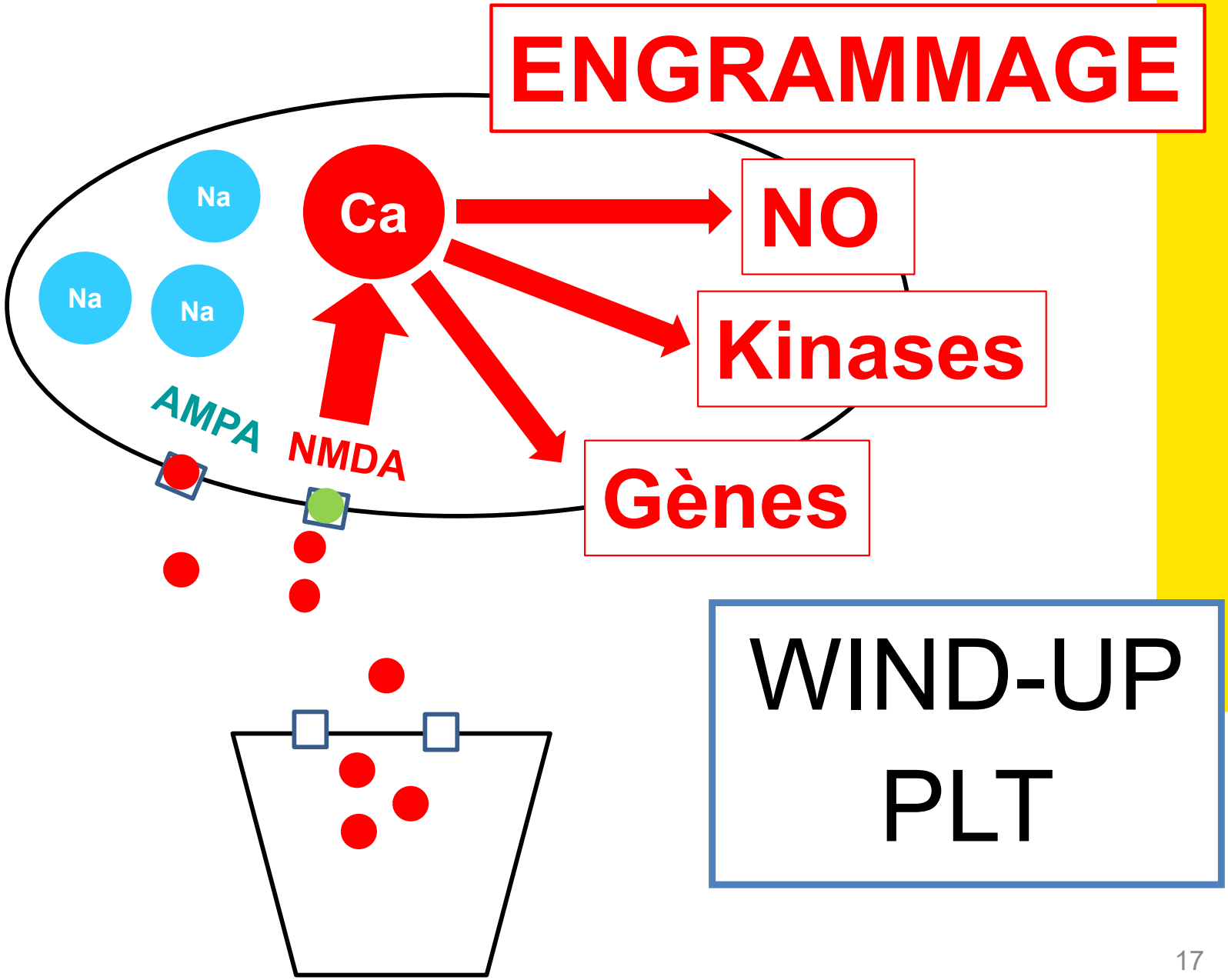
Antagoniste des récepteurs NMDA

Glutamate : AMPA et NMDA



HYPERALGESIE

Neurone nociceptif de la CORNE DORSALE



WIND-UP PLT

2000 R-NMDA et HIO

Long-lasting Hyperalgesia Induced by Fentanyl in Rats

Preventive Effect of Ketamine

Evelyne Célèrier, Ph.D., Cyril Rivat, B.S.,* Yan Jun, M.D.,† Jean-Paul Laulin, Ph.D.,‡ Agnès Larcher, Ph.D.,§ Patrick Reynier, M.D.,‖ Guy Simonnet, Ph.D.#*

Anesthesiology 2000; 92:465–72

les morphiniques aussi provoquent une hyperalgésie !

ANTIHYPERALGESIQUE

‘Balanced analgesia’ in the perioperative period: is there a place for ketamine?

PAIN

Marc De Kock*, Patricia Lavand’homme, Hilde Waterloos

Department of Anesthesiology, University of Louvain, St. Luc Hospital, Avenue Hippocrate 10-1821, 1200 Brussels, Belgium

Received 27 November 2000; received in revised form 16 January 2001; accepted 18 January 2001

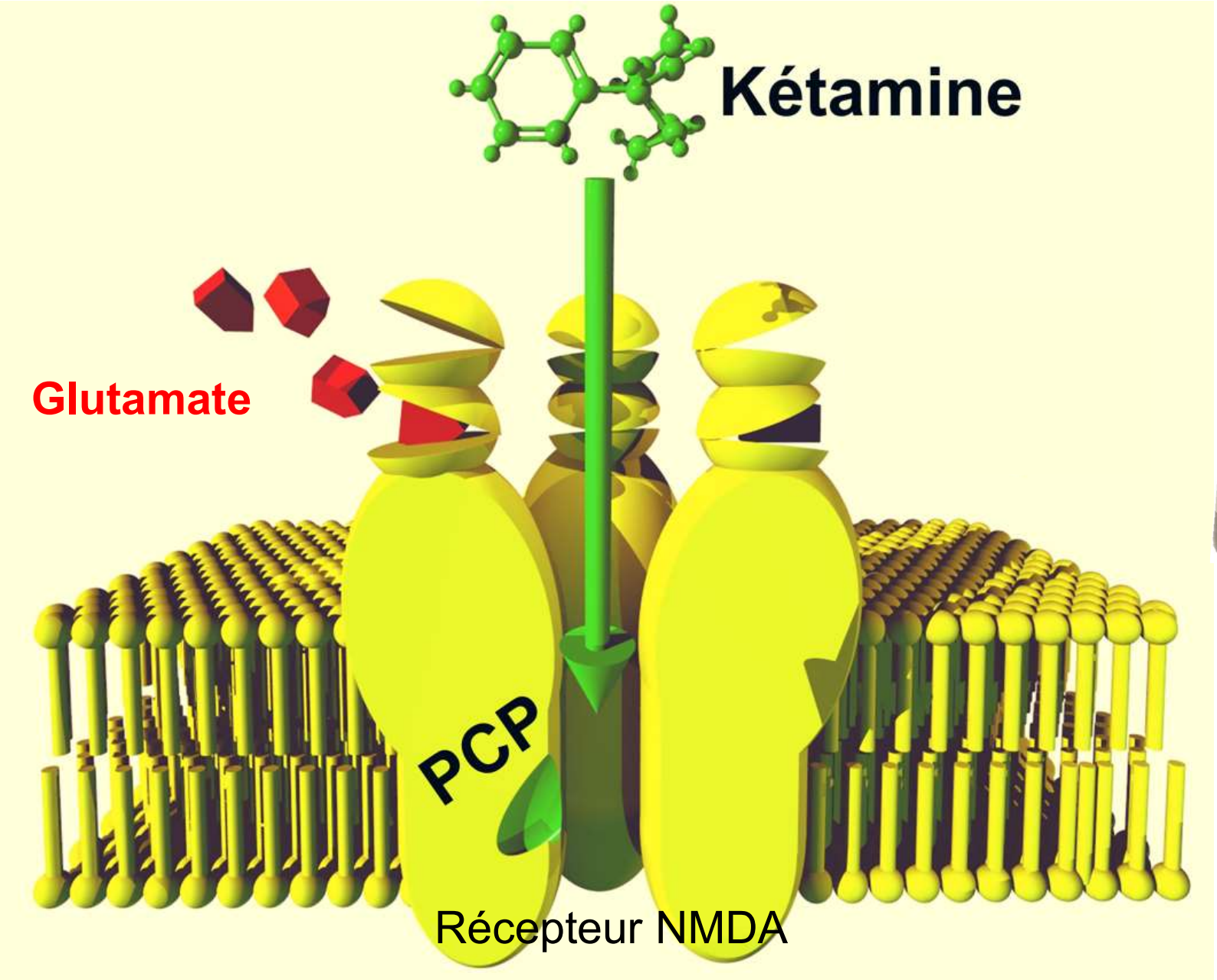
Abstract

We investigated whether intraoperative ‘subanesthetic doses’ of ketamine have a postoperative anti-hyperalgesic and an analgesic effect and which is the preferential route of administration, either systemic (intravenous, i.v.) or epidural. One hundred patients scheduled for rectal adenocarcinoma surgery under combined epidural/general anesthesia were included. Before skin incision all the patients received an epidural bolus followed by an infusion of continuous bupivacaine/sufentanil/clonidine mixture. They were randomly assigned to receive no ketamine (group 1), i.v. ketamine at the bolus dose of 0.25 mg/kg followed by an infusion of 0.125 mg/kg per h (group 2), 0.5 mg/kg and 0.25 mg/kg per h (group 3), epidural ketamine 0.25 mg/kg and 0.125 mg/kg per h (group 4), or 0.5 mg/kg and 0.25 mg/kg per h (group 5). All i.v. and epidural analgesics were supplied in the ward of surgery and patients were connected to an i.v. morphine patient-controlled analgesia (PCA) device. Postoperative analgesia (72 h) was assessed by pain visual analog scale scores at rest, cough, and movements, as well as by PCA requirements. Wound mechanical hyperalgesia was evaluated and residual pain was assessed by asking the patients at 2 weeks, and 1, 6, and 12 months. The area of hyperalgesia and morphine PCA requirements were significantly reduced in group 3. These patients reported significantly less residual pain until the sixth postoperative month. These observations support the theory that subanesthetic doses of i.v. ketamine (0.5 mg/kg bolus followed by 0.25 mg/kg per h) given during anesthesia reduce wound hyperalgesia and are a useful adjuvant in perioperative balanced analgesia. Moreover, they show that the systemic route clearly is the preferential route. © 2001 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

Analgésie préventive

Pain 92 (2001) 373–380

Use-dependence



2000 Effet antidépresseur

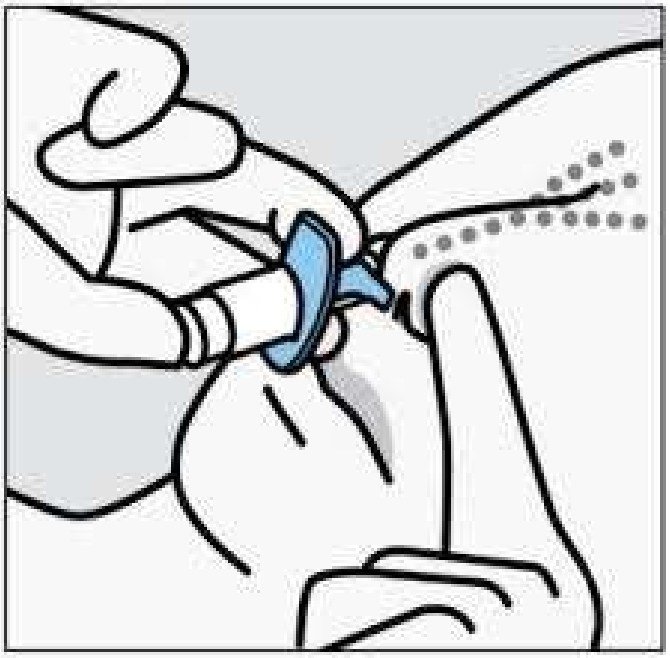
Antidepressant Effects of Ketamine in Depressed Patients

Robert M. Berman, Angela Cappiello, Amit Anand, Dan A. Oren, George R. Heninger, Dennis S. Charney, and John H. Krystal

BIOL PSYCHIATRY
2000;47:351–354

5 mars 2019

La FDA approuve un spray nasal de kétamine pour la dépression résistante au traitement

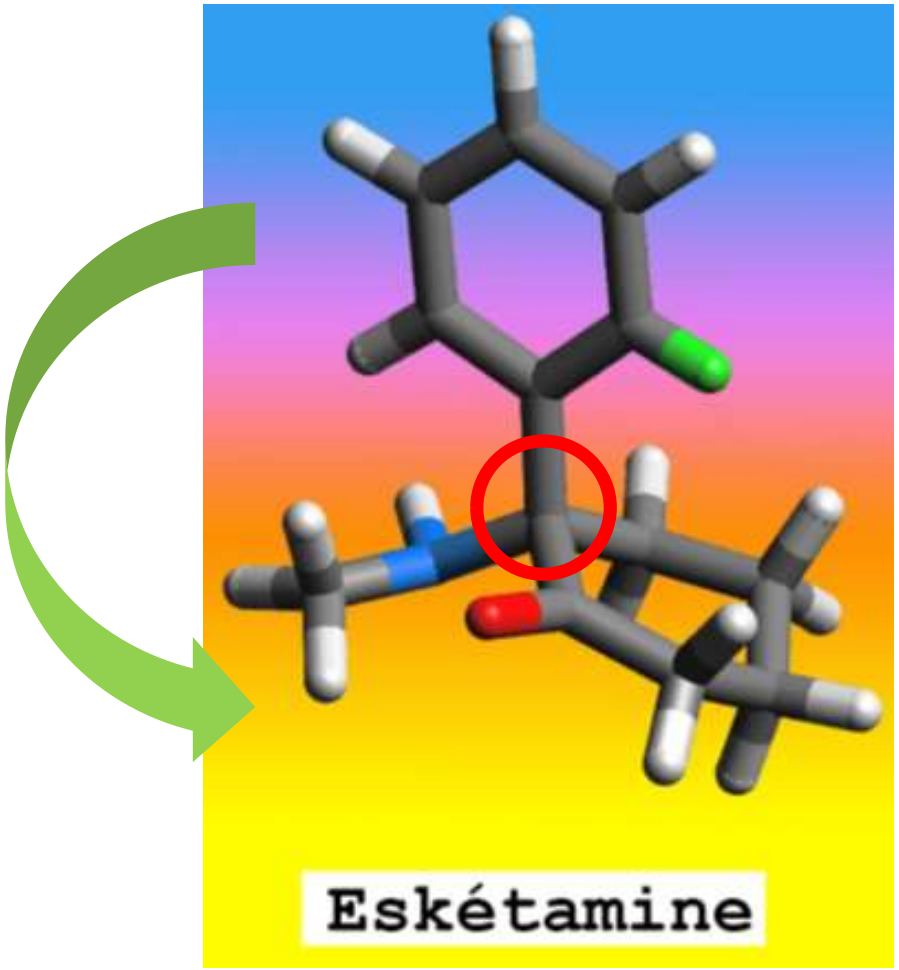


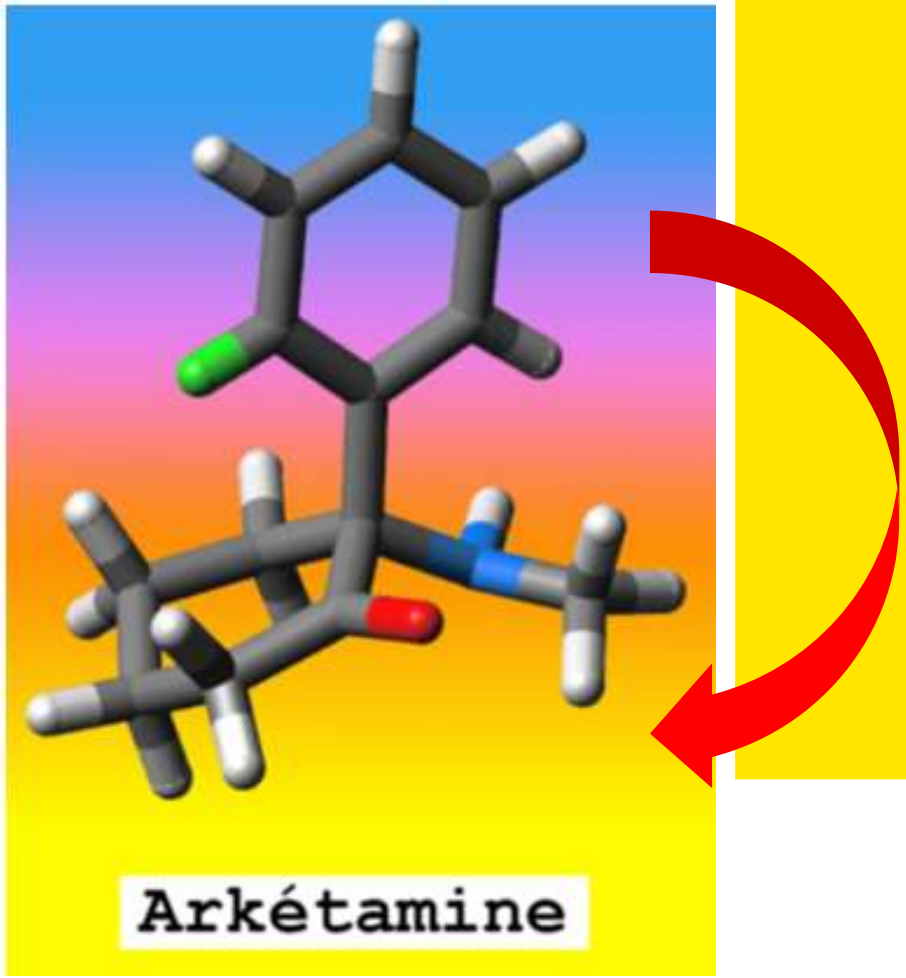
Eskétamine

Eskétamine ???

S

R





Dextrogyre (+)

Lévogyre (-)

Eskétamine : la clé du NMDAR

Eskétamine

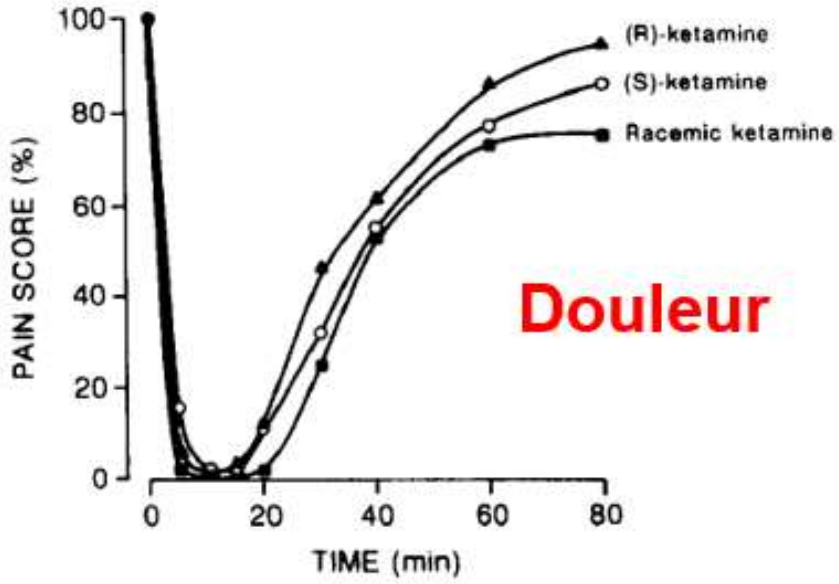
Arkétamine

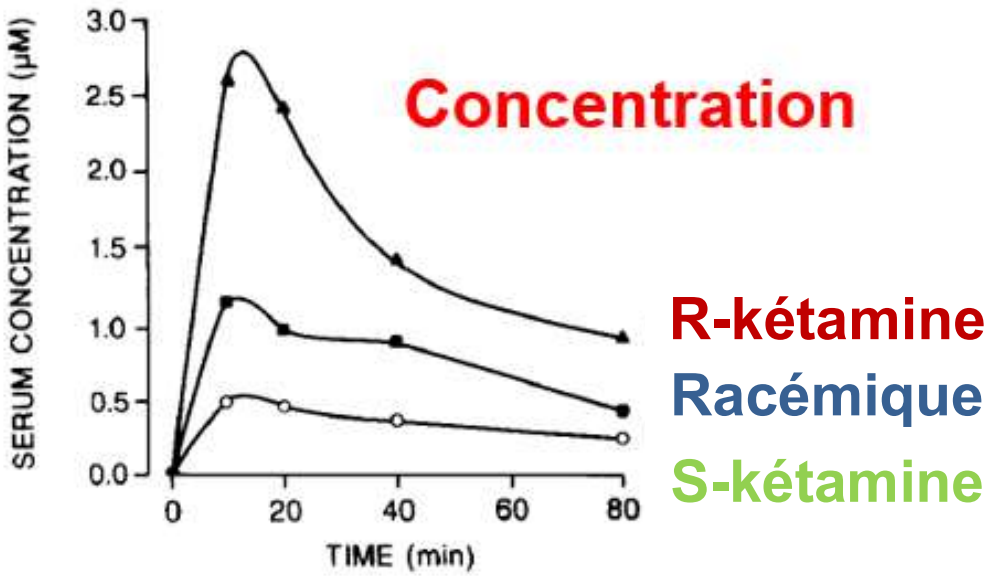
S(+) – kétamine
2 fois plus puissante que le racémique

Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain

Lene Cecilie Mathisen [a,1], Per Skjelbred [b], Lasse A. Skoglund [c] and Ivar Øye [a,*]

Pain, 61 (1995) 215–220





1980

Anesthesiology
52:231–239, 1980

Pharmacology of Ketamine Isomers in Surgical Patients

Paul F. White, M.D., Ph.D.,* Jay Ham, M.D.,† Walter L. Way, M.D.,‡ Anthony J. Trevor, Ph.D.§

equianesthetic doses of
racemic ketamine (RK), 2 mg/kg,
(+)ketamine (PK), 1 mg/kg, randomized,
(−)ketamine (MK), 3 mg/kg,
were administered intravenously to 60 healthy patients

The durations of anesthesia (35 ± 4 min) were the same in all three groups;
drug needed ranged from 2.4 mg/kg in the PK group
to 8.5 mg/kg in the MK group.

At the termination of anesthesia, mean plasma levels of the parent compounds were 0.9 (RK), 0.5 (PK), and 1.7 μg/ml (MK),
consistent with a PK:MK potency ratio of 3.4:1.

PK was judged to produce more effective anesthesia than RK or MK (95 *vs.* 75 *vs.* 68 per cent).

Verbal responses in the postanesthetic period suggested significantly
more psychic emergence reactions after MK than after RK or PK (37 *vs.* 15 *vs.* 5 per cent).
MK produced more agitated behavior than did RK or PK (26 *vs.* 10 *vs.* 0 per cent).
Postoperative pain occurred more commonly in the RK (10 per cent) and MK (16 per cent) groups than in the PK group (0 per cent).

The incidences of dreaming (84 per cent) were the same in all three groups.

The slopes of the plasma decay curves were not significantly different among the three groups.

similarities in the patterns of appearance and excretion of the ketamine metabolites suggest that the differences were due to pharmaco- dynamic factors.

Ratio 1/4

Moins de douleur Avec l'eskétamine

Problèmes d'émergence avec l'arkétamine

Eskétamine

Antagoniste NMDA par excellence

- analgésie x 2
- meilleur profil
- moins toxique
- cinétique plus rapide (clairance plus élevée)
- émergence plus favorable

1997 Eskétamine en Allemagne

Quid de la France ?

2021 AMM

HAS

HAUTE AUTORITÉ DE SANTÉ

COMMISSION DE LA TRANSPARENCE

21 JUILLET 2021

eskétamine

ESKETAMINE **5 mg/ ml et 25 mg/ ml, solution injectable pour perfusion**

Avis favorable au remboursement dans :

- induction et maintien de l'anesthésie générale, comme seul anesthésique ou en association avec des hypnotiques ;
- anesthésie et soulagement de la douleur (analgésie) en médecine d'urgence ;
- contrôle de la douleur liée à la respiration artificielle (intubation).

Arrivée en France de l'eskétamine

La kétamine enfin domptée ?