Probouzení

z celkové anestezie není opakem úvodu

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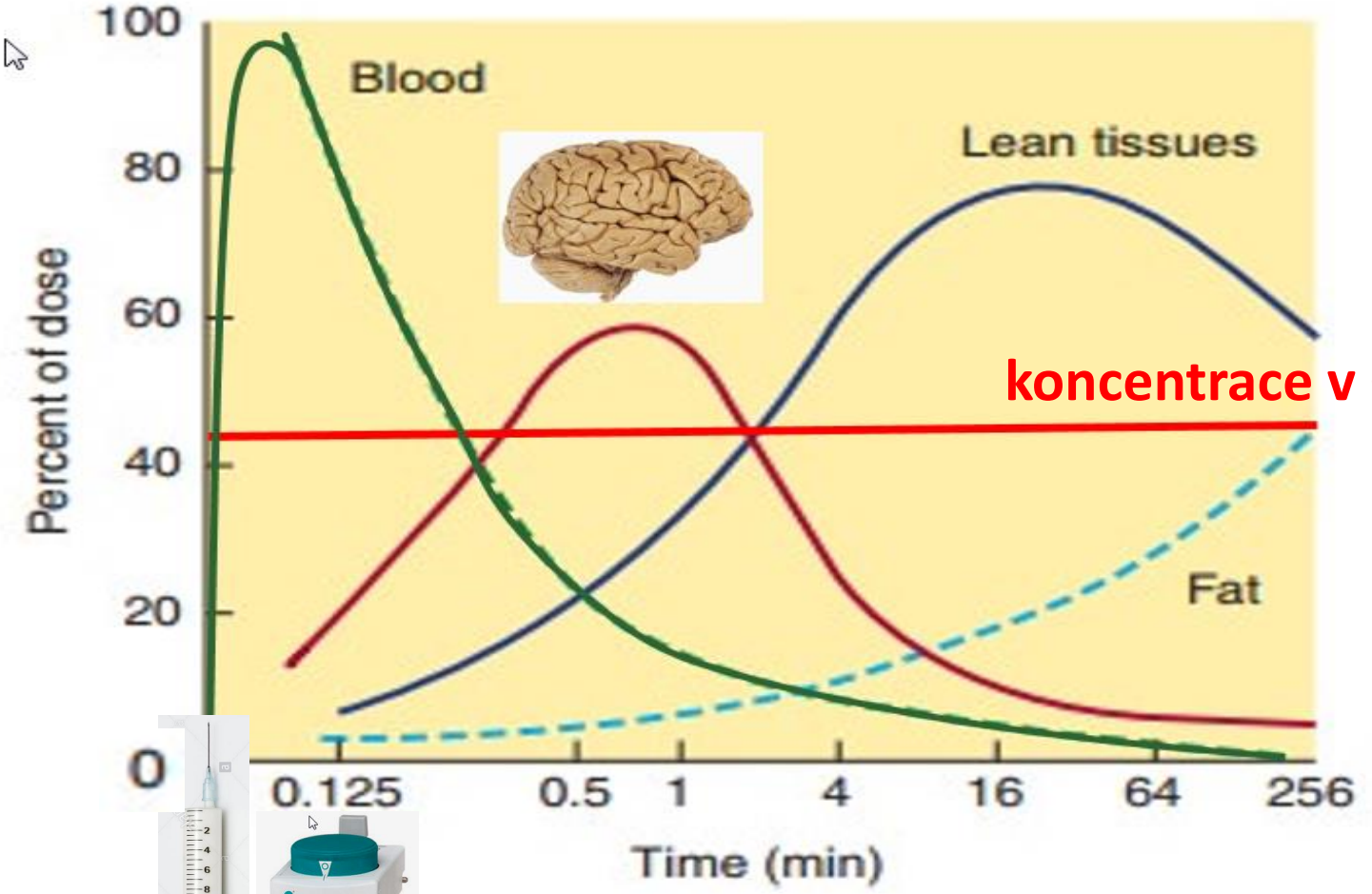
KARIM 2. LF UK ve FN v Motole
a katedra AIM IPVZ

Praha

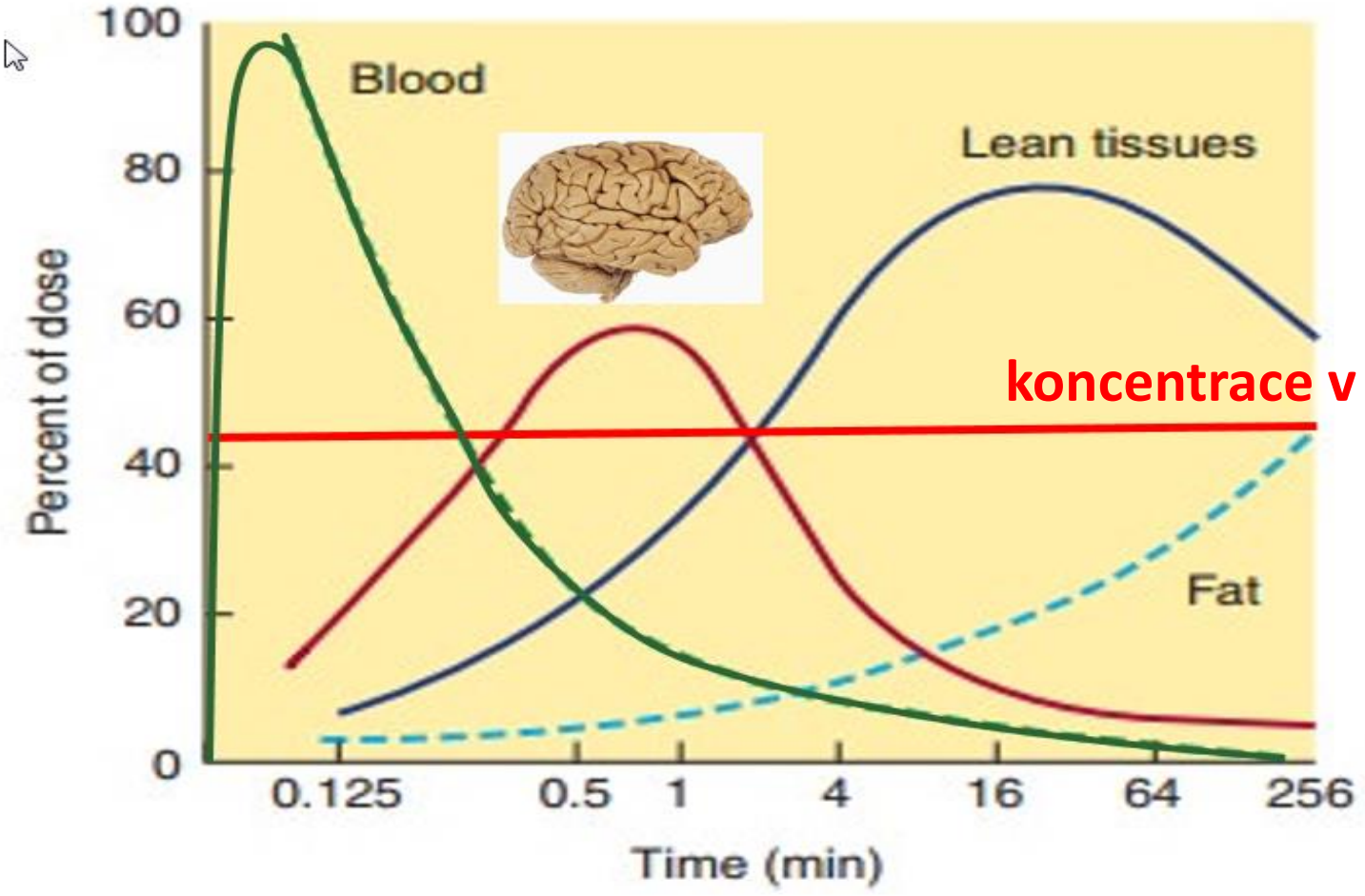
3.10.2019

Úvod do anestezie



koncentrace v CNS > práh
= anestezie

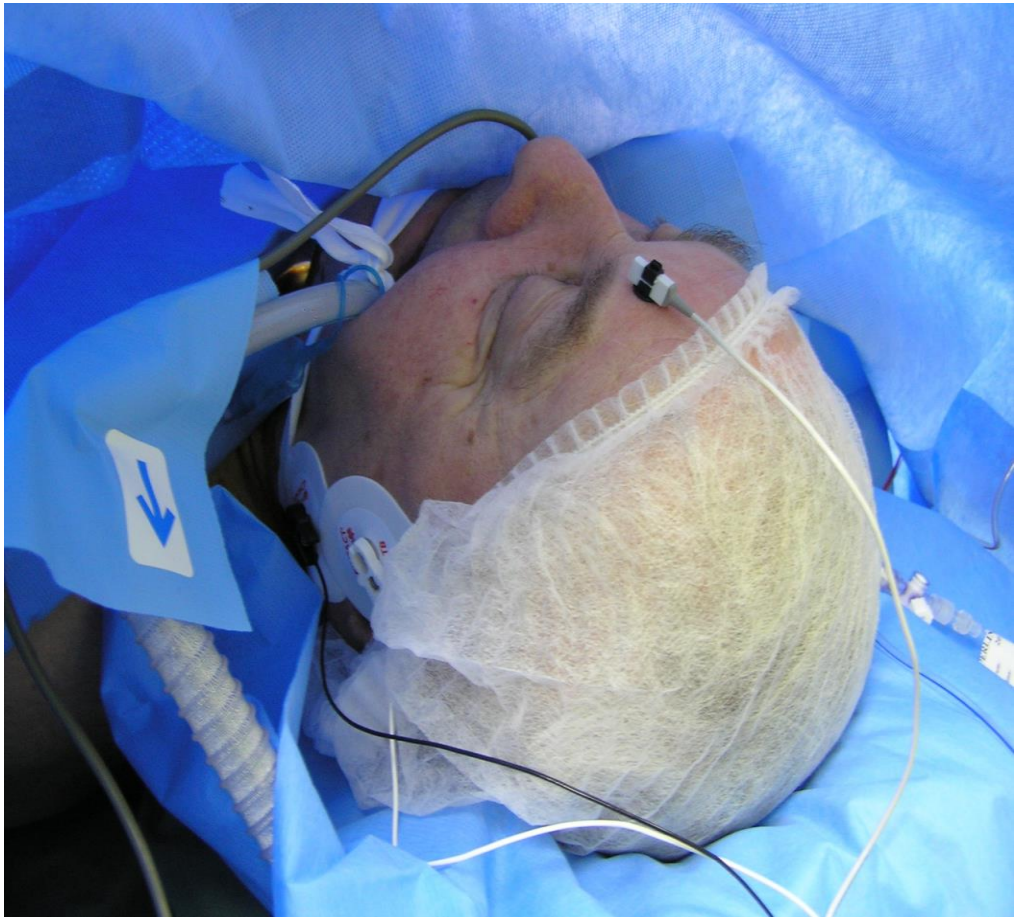
Probouzení z anestezie jako pasivní proces



koncentrace v CNS < práh
= probouzení

Probouzení z anestezie jako pasivní proces?

- poslední sufentanil dávno
- relaxace antagonizována
- $ETAC_{sevo}$ 0,3 MAC_{age}
- ale pacient se nebudí



Program

- Jak fungují anestetika?
- Jak probíhá úvod do anestezie?
- Jak probíhá probolouzení?

Robert Hinckley: První operace s éterem 16.10.**1846**

Neuron

A Common Neuroendocrine Substrate for Diverse General Anesthetics and Sleep

Li-Feng Jiang-Xie, Luping Yin, Shengli Zhao, Vincent Prevosto, Bao-Xia Han, Kafui Dzirasa and **Fan Wang**

2019 (June 5); 102(5):1053-1065

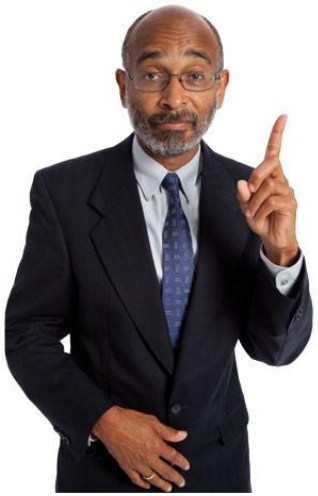
- How general anesthesia (GA) induces loss of consciousness

remains unclear

- and whether diverse anesthetic drugs and sleep share a common neural pathway

is unknown.

Definice anestezie



Celková anestezie je
léky navozený, reverzibilní stav mozku a těla charakterizovaný:

- bezvědomím,
- amnezií,
- analgezií
- nehybností
- stabilitou životních funkcí.

Celková anestezie je vlastně reverzibilní,
léky navozené kóma.

Emery N. Brown

- Warren M. Zapol **Professor of Anesthesia**
  at Harvard Medical School and at Massachusetts General Hosp.
- Edward Hood Taplin **Professor of Medical Engineering**
  at Massachusetts Institute of Technology

MECHANISMS OF DISEASE
Robert S. Schwartz, M.D., *Editor*

General Anesthesia, Sleep, and Coma

Emery N. Brown, M.D., Ph.D., Ralph Lydic, Ph.D., and Nicholas D. Schiff, M.D.

IN THE UNITED STATES, NEARLY 60,000 PATIENTS PER DAY RECEIVE GENERAL anesthesia for surgery.[1] General anesthesia is a drug-induced, reversible condition that includes specific behavioral and physiological traits — unconsciousness, amnesia, analgesia, and akinesia — with concomitant stability of the autonomic, cardiovascular, respiratory, and thermoregulatory systems.[2] General anesthesia produces distinct patterns on the electroencephalogram (EEG), the most common of which is a progressive increase in low-frequency, high-amplitude activity as the level of general anesthesia deepens[3,4] (Fig. 1). How anesthetic drugs induce and maintain the behavioral states of general anesthesia is an important question in medicine and neuroscience.[6] Substantial insights can be gained by considering the relationship of general anesthesia to sleep and to coma.

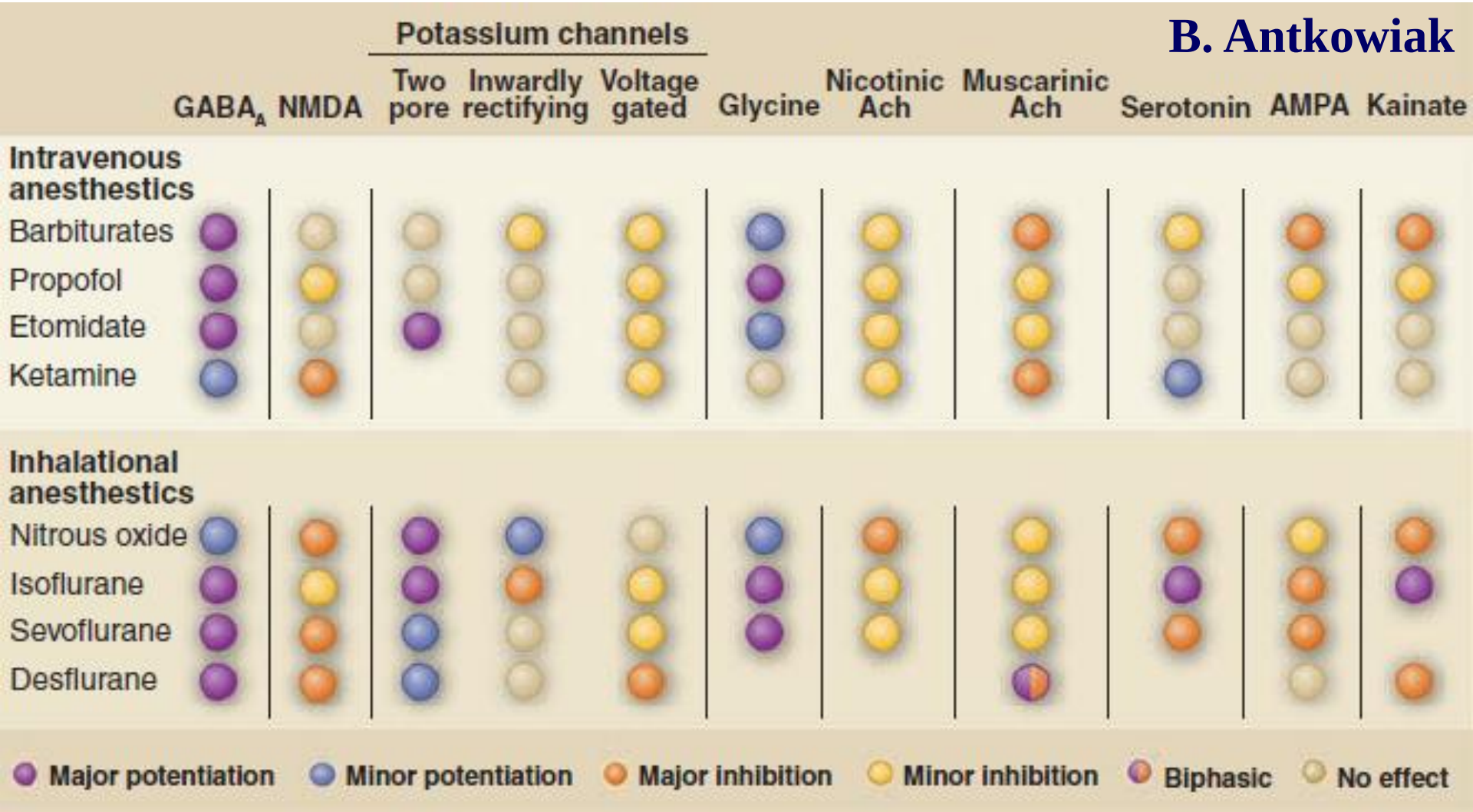
Humans spend approximately one third of their lives asleep. Sleep, a state of decreased arousal that is actively generated by nuclei in the hypothalamus, brain stem, and basal forebrain, is crucial for the maintenance of health.[7,8] Normal human sleep cycles between two states — rapid-eye-movement (REM) sleep and non-REM sleep — at approximately 90-minute intervals. REM sleep is characterized by rapid eye movements, dreaming, irregularities of respiration and heart rate, penile and clitoral erection, and airway and skeletal-muscle hypotonia.[7] In REM sleep, the EEG shows active high-frequency, low-amplitude rhythms (Fig. 1). Non-REM sleep has three distinct EEG stages, with higher-amplitude, lower-frequency rhythms accompanied by waxing and waning muscle tone, decreased body temperature, and decreased heart rate.

Coma is a state of profound unresponsiveness, usually the result of a severe brain injury.[9] Comatose patients typically lie with eyes closed and cannot be roused to respond appropriately to vigorous stimulation. A comatose patient may grimace, move limbs, and have stereotypical withdrawal responses to painful stimuli yet make no localizing responses or discrete defensive movements. As the coma deepens, the patient's responsiveness even to painful stimuli may diminish or disappear. Although the patterns of EEG activity observed in comatose patients depend on the extent of the brain injury, they frequently resemble the high–amplitude, low-frequency activity seen in patients under general anesthesia[10] (Fig. 1). General anesthesia is, in fact, a reversible drug-induced coma. Nevertheless, anesthesiologists refer to it as "sleep" to avoid disquieting patients. Unfortunately, anesthesiologists also use the word "sleep" in technical descriptions to refer to unconsciousness induced by anesthetic drugs.[11] (For a glossary of terms commonly used in the field of anesthesiology, see the Supplementary Appendix, available with the full text of this article at NEJM.org.)

This review discusses the clinical and neurophysiological features of general anesthesia and their relationships to sleep and coma, focusing on the neural mechanisms of unconsciousness induced by selected intravenous anesthetic drugs.

„Každé anestetikum má specifické spektrum účinků.“

B. Antkowiak

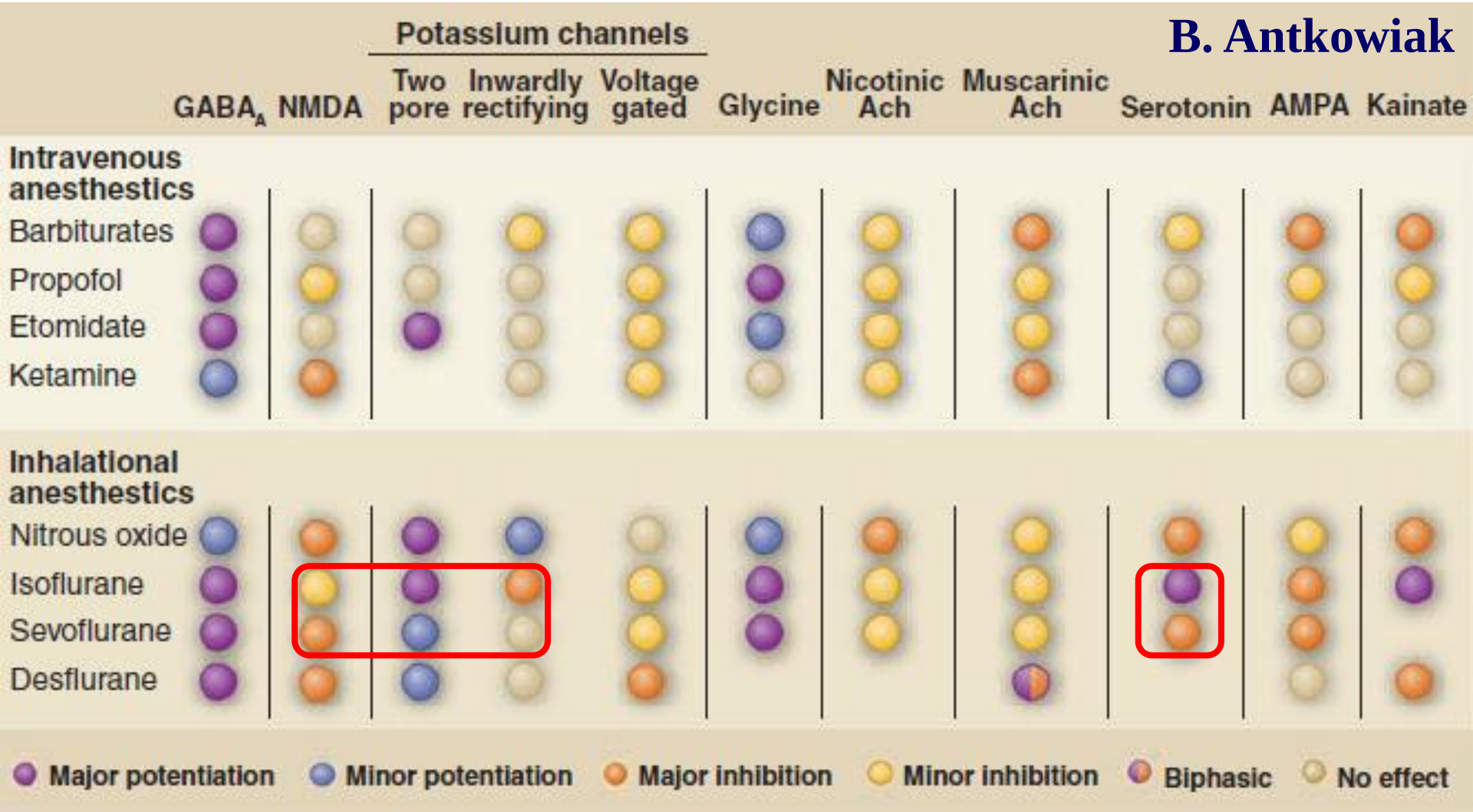


Naturwissenschaften 2001; 88: 201-13

Alkire MT: Science 322, 876 (2008)

„Lze skutečně jedno anestetikum nahradit jiným?“

B. Antkowiak



Naturwissenschaften 2001; 88: 201-13

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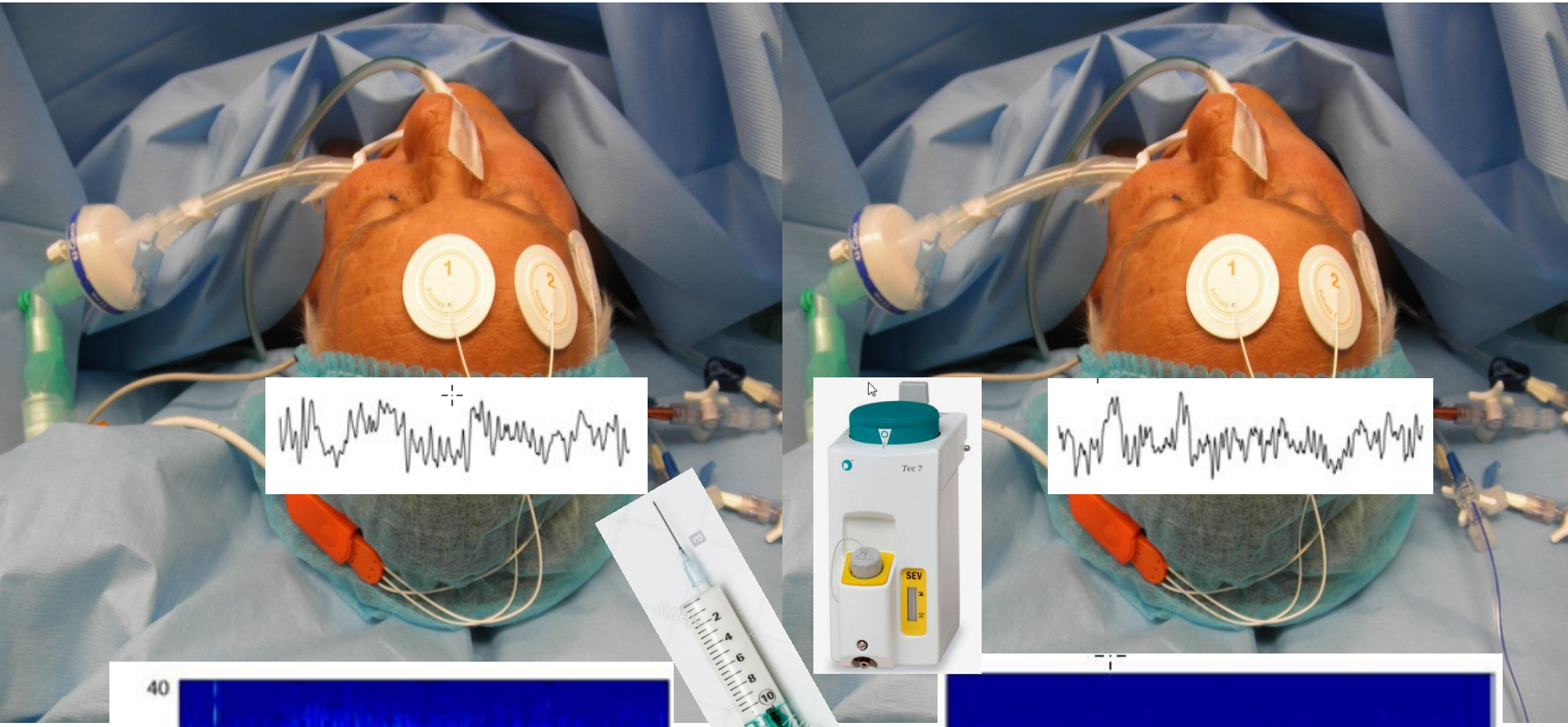
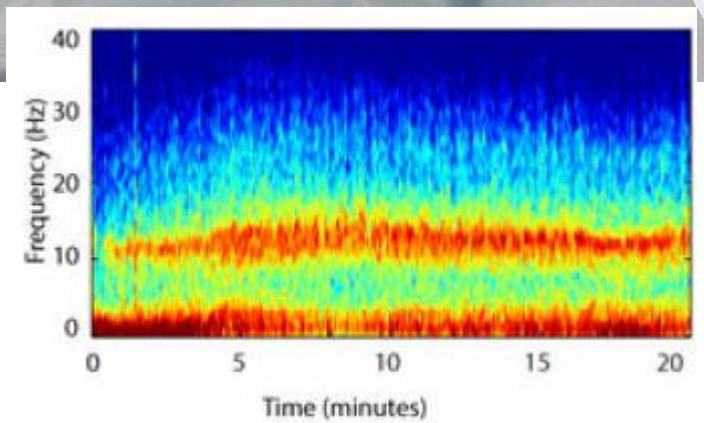
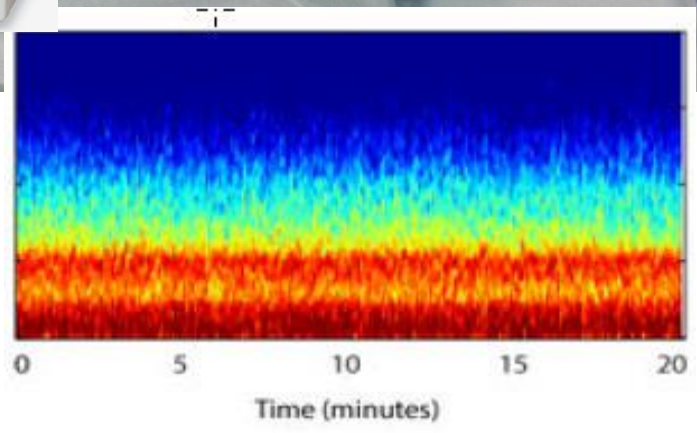
propofol ← EEG → sevofluran



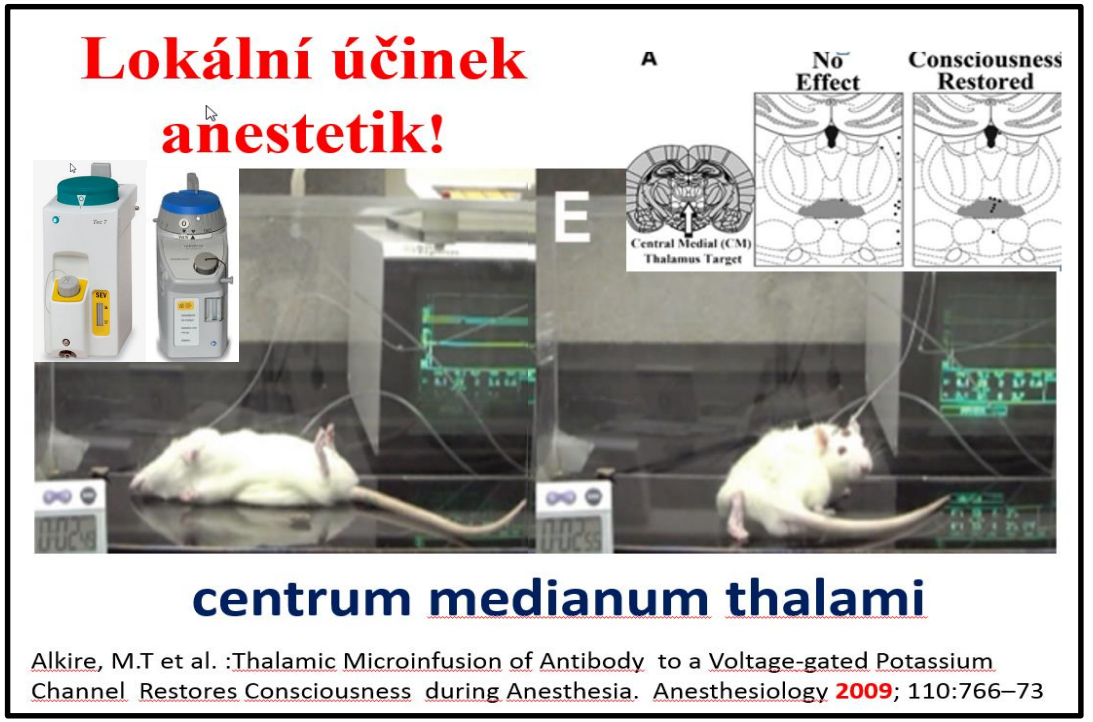




Mechanismus anestezie

účinek anestetik není globální, ale **multilokulární!**

- mikroinjekce agonisty, antagonisty, protilátky
- chemogenetická aktivace/inhibice
  - Designer Receptor Exclusively Activated by Designer Drugs (DREADD) Receptor Activated Solely by a Synthetic Ligand (RASSL)
- optogenetická aktivace/inhibice opsiny



Oblasti mozku spojené s účinky anestetik

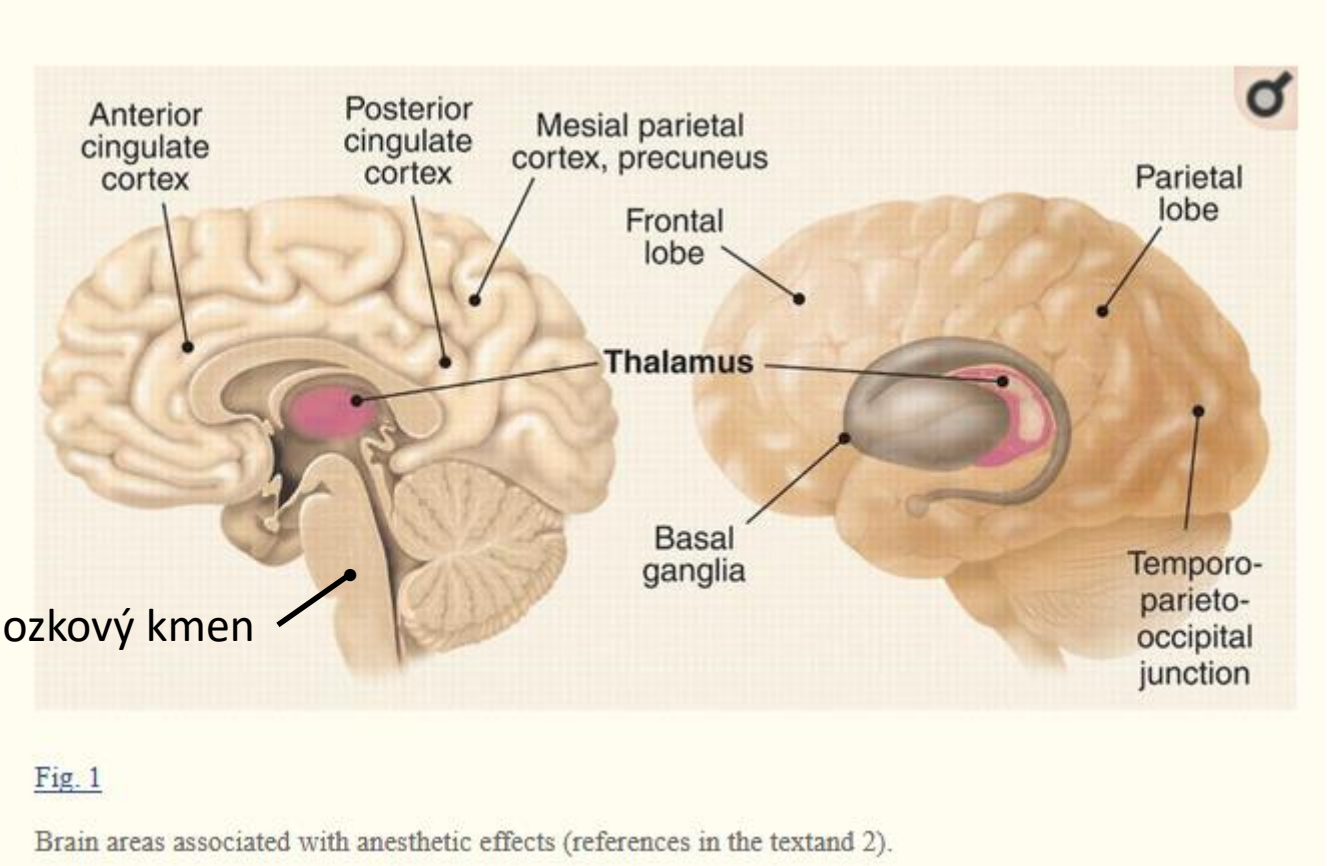


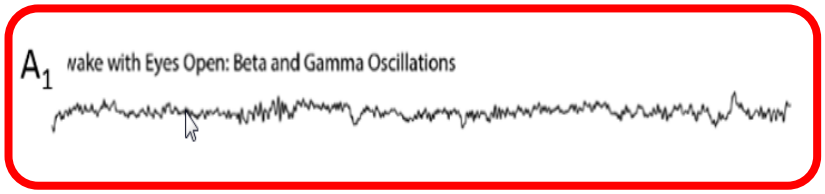
Fig. 1

Brain areas associated with anesthetic effects (references in the textand 2).

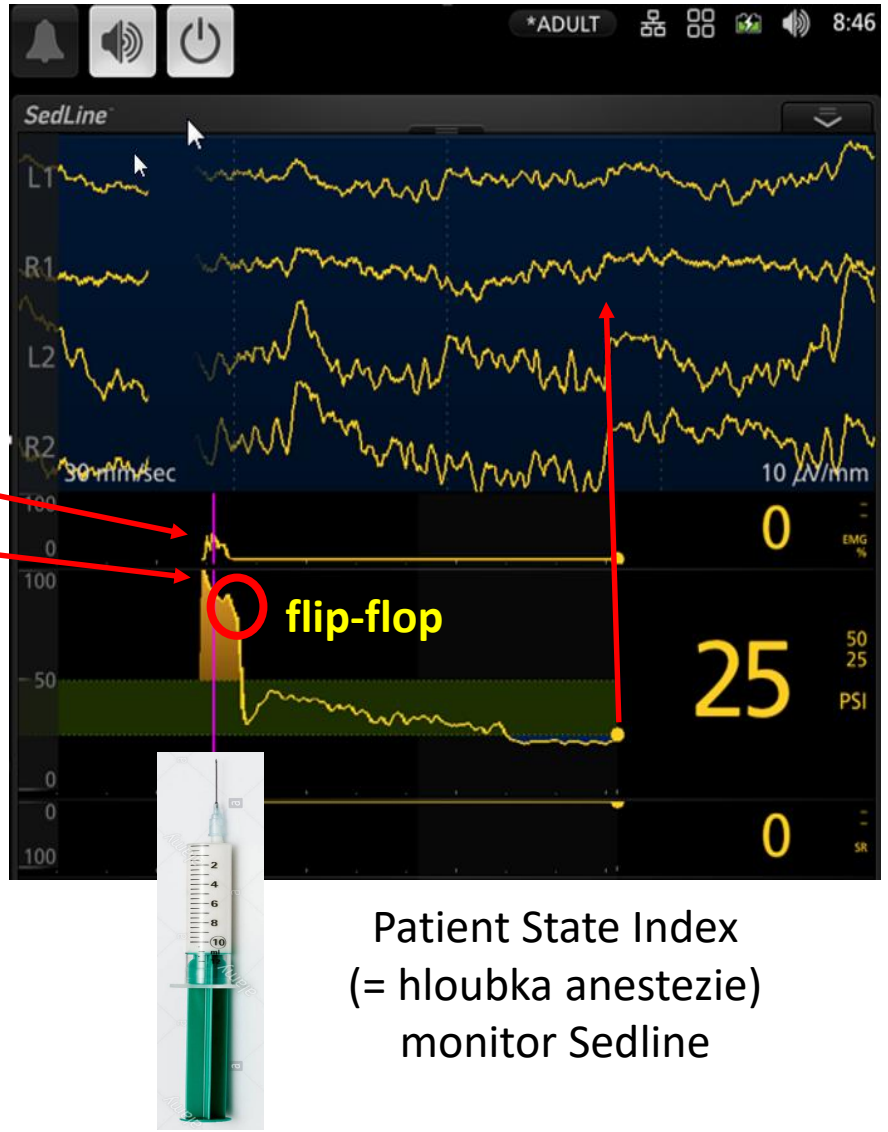
Alkire MT, Hudetz AG, Tononi G.: **Consciousness and anesthesia.** Science. 2008 Nov 7;322(5903):876-80. doi: 10.1126/science.1149213.

Jak probíhá úvod do anestezie?

- muž, 60 let, 83 kg, k CABG



- sufentanil 25 ug i. v.
  - zvýšení rigidity svalů
  - sedace
- propofol 100 mg i. v.
  - další sedace
  - nástup anestezie
- sevofluran, MAC_{age} 0,7



Patient State Index
(= hloubka anestezie)
monitor Sedline

Jak probíhá úvod do anestezie?

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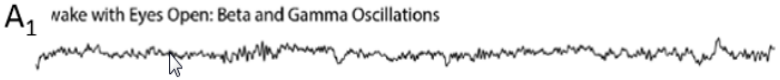
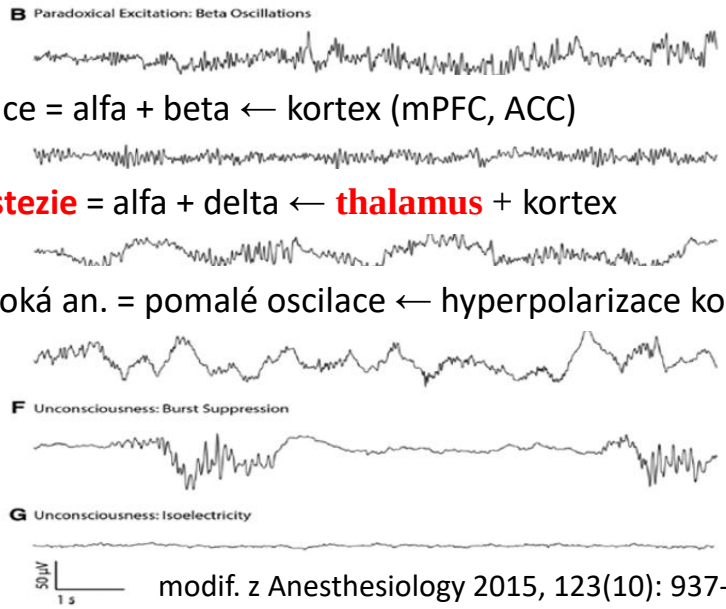


- sufentanil
  - zvýšení rigidity svalů
- propofol



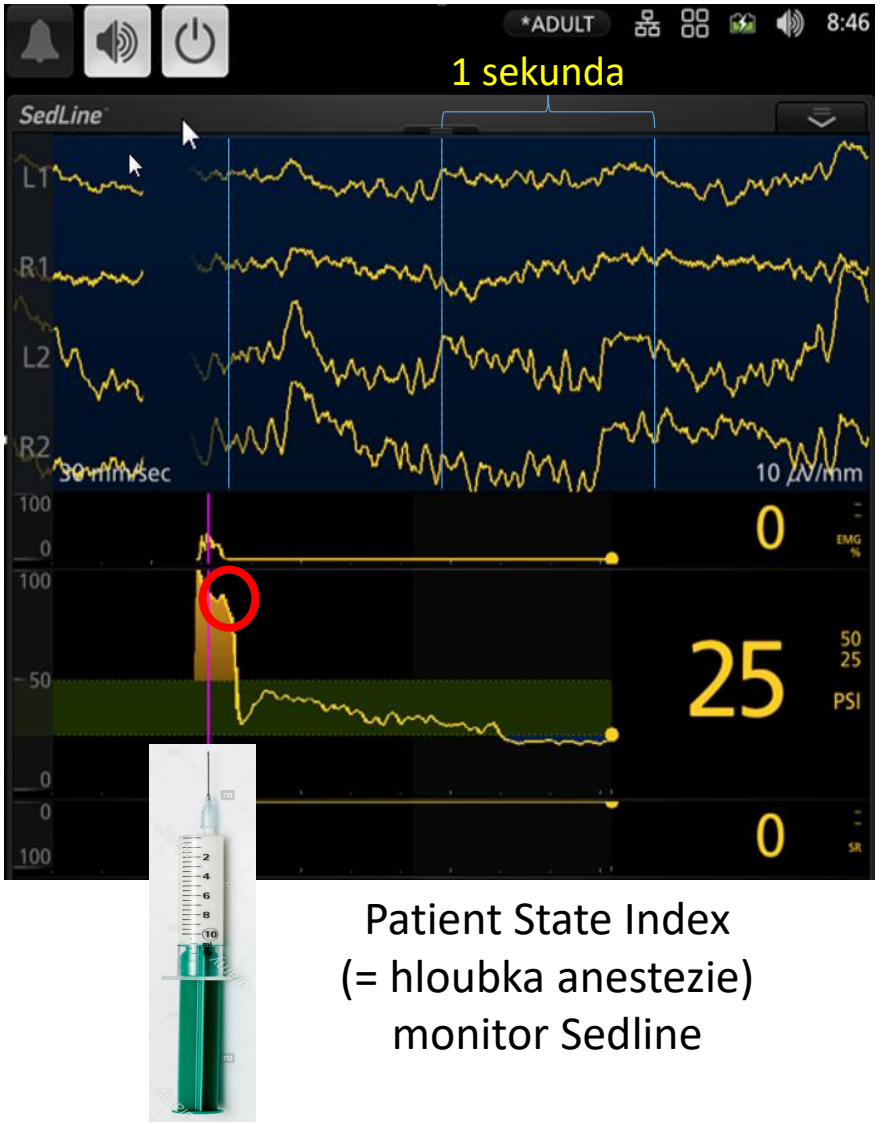
sedace = alfa + beta ← kortex (mPFC, ACC)

anestezie = alfa + delta ← **thalamus** + kortex

hluboká an. = pomalé oscilace ← hyperpolarizace kortexu

BS

modif. z Anesthesiology 2015, 123(10): 937-960



Patient State Index
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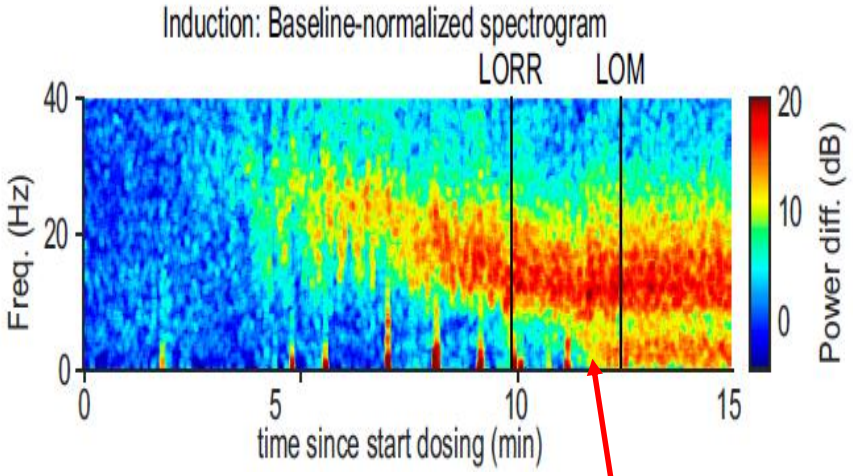
Jak probíhá úvod do anestezie?

- muž, 60 let, 83 kg, CABG
- sufentanil + propofol



LORR = loss of righting reflex
LOM = loss of movement

SWAS = Slow Wave Activity Saturation = ztráta vnímání stimulů, tj. izolace od okolí!

Flores FJ et al.: Thalamocortical synchronization during induction and emergence from propofol-induced unconsciousness. Proc Natl Acad Sci U S A. 2017 Aug 8;114(32):E6660-E6668.

Dva mechanismy úvodu

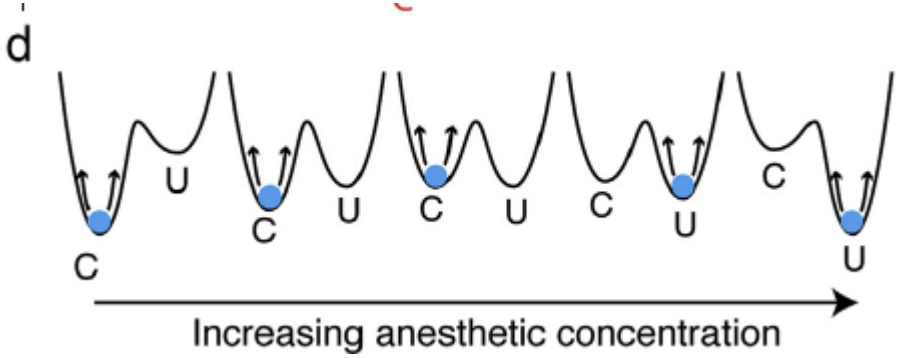
- bottom-up
  - anestetika interagují s neurony v okruzích řídících spánek-bdění (bdělost)
  - anestezie není možná jen selektivní blokádou kmene (Sleigh 2019)
- top-down
  - anestetika narušují přenos informací v kůře a thalamu (obsah vědomí)
    - kortiko-kortikální okruhy
    - thalamo-kortikální okruhy
- thalamic switch (vypínač)?
- **thalamic readout (ukazatel)?**

Mashour G 2017

Patient State Index
(= hloubka anestezie)
monitor Sedline

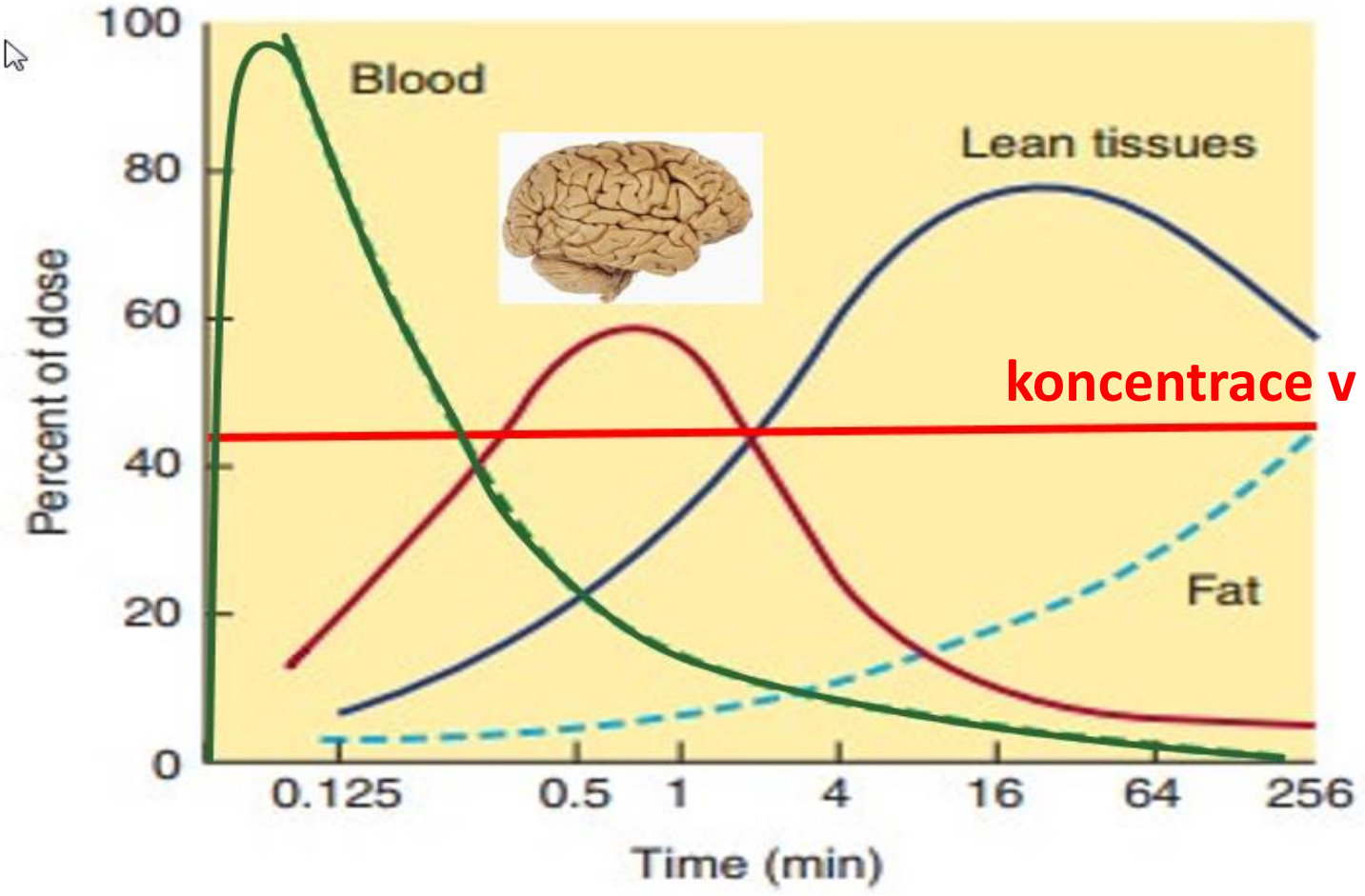
Udržování anestezie

- stav mozku v anestezii je metastabilní (= stabilní vůči slabým vnějším vlivům)
- fluktuace vědomí



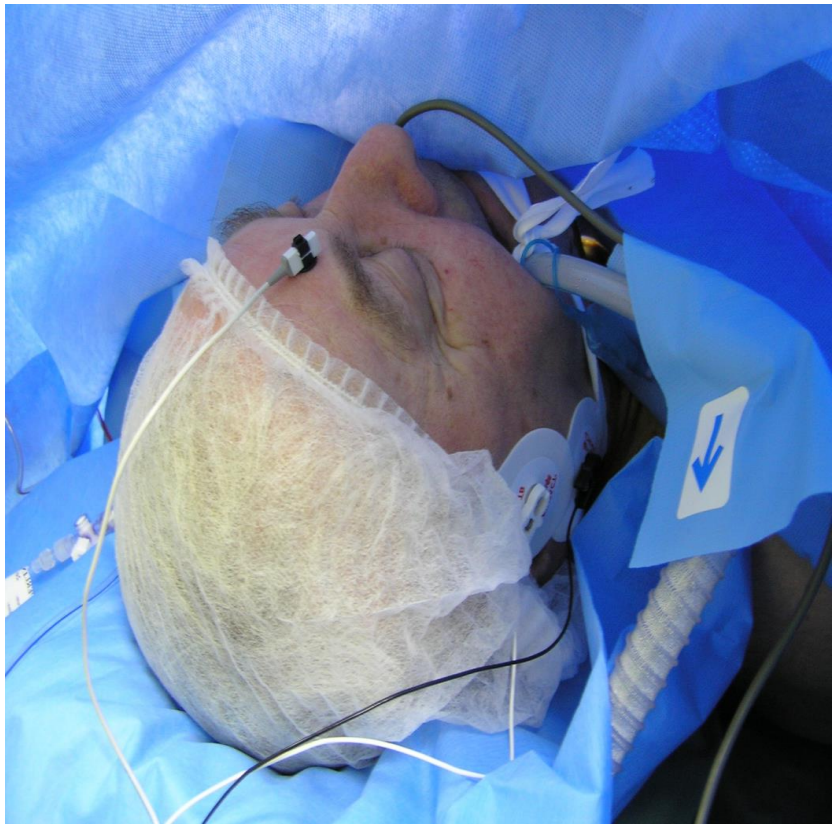
A stochastic basis for neural inertia in emergence from general anaesthesia.
Proekt A, **Hudson** AE.
Br J Anaesth. 2018 Jul;121(1):86-94.

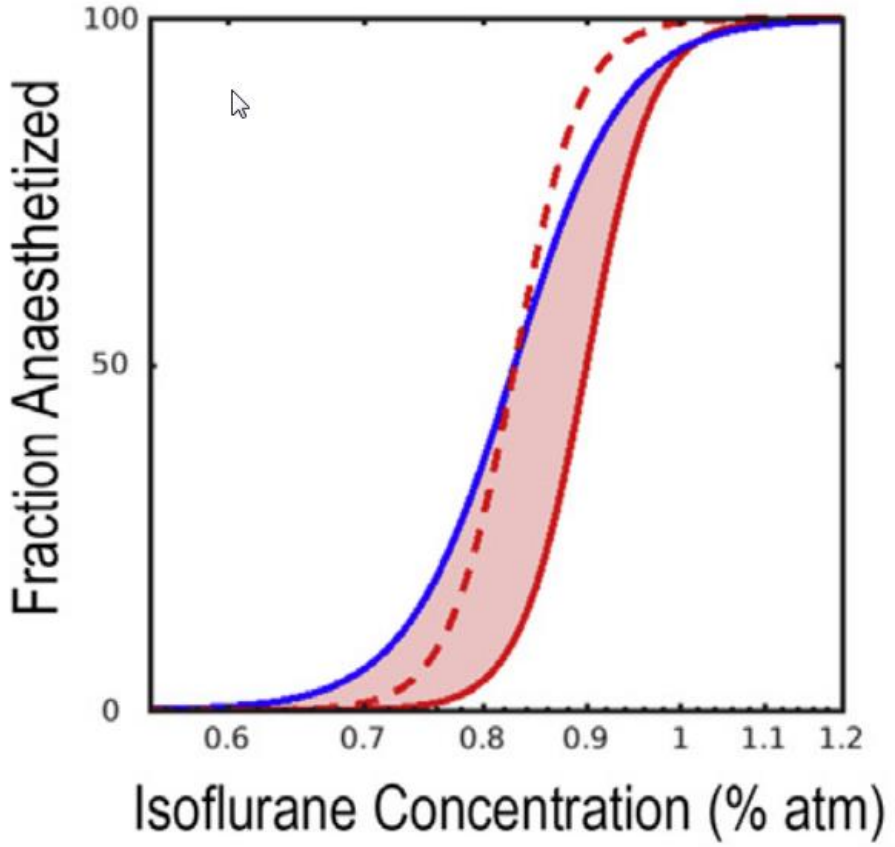
Probouzení z anestezie jako pasivní proces



koncentrace v CNS < práh
= probouzení

Probouzení z anestezie je aktivní proces!





Max B. Kelz

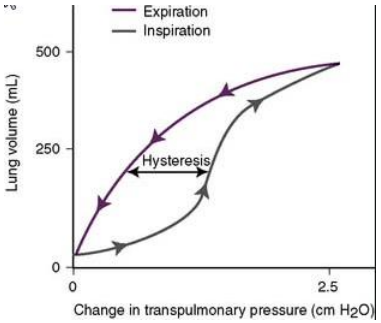
Úloha orexinů při probouzení z celkové anestezie

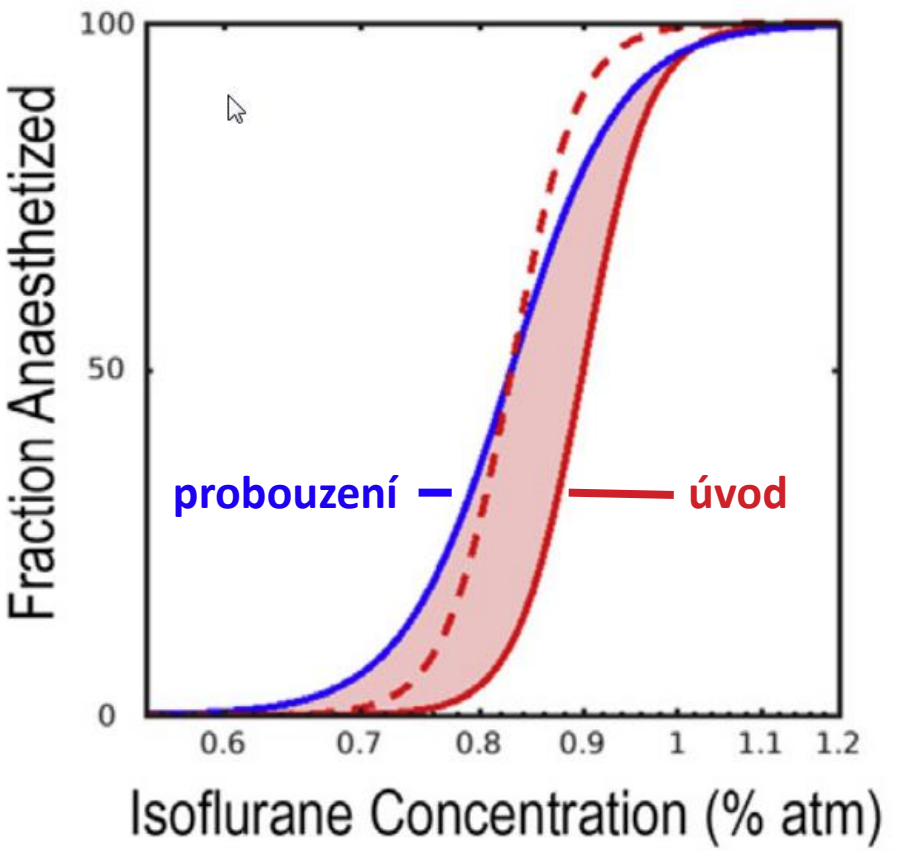
- isofluran a sevofluran inhibují ox. neurony, nepůsobí na sousední MCH (melanin concentrating h.) neurony
  imunohistochemické vyšetření exprese c-Fos
- srovnání divoké myši x myši knock-out orexin/ataxin-3
  - indukce (ztráta vzpřimovacího reflexu) – stejně citlivé
    podání SB-334867 beze změny
  - probouzení u knock-out myší opožděné
    podání SB-334867 ↑ probouzení v závislosti na dávce
- **úvod a probouzení různé okruhy**

Kelz MB et al.: An essential role for orexins in emergence from general anesthesia. PNAS 2008;105(4):1309-1314

Hystereze

- ὑστέρησις = „nedostatek, zaostávání“ (1890)
- obecná vlastnost dynamických systémů
- výstupní veličina záleží na:
  - vstupní veličina
  - předchozí stav systému
- zvyšuje odolnost proti rušení
- fyzika, ekonomie, medicína aj.

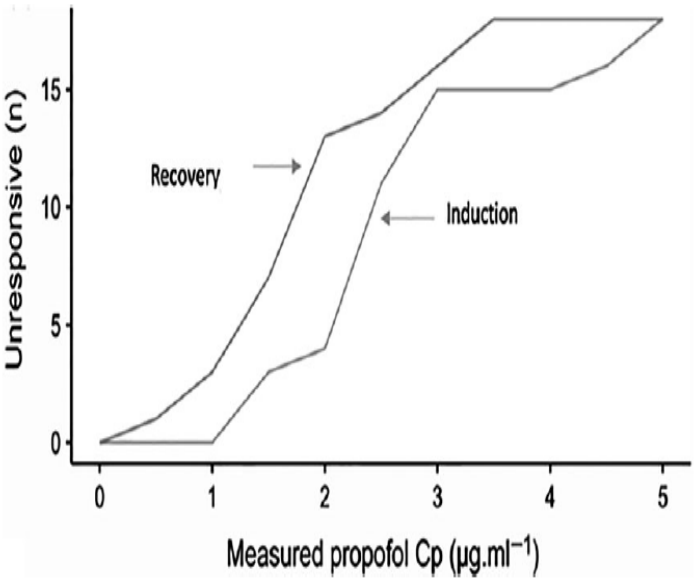




Proekt A, Kelz M.: **Schrödinger's cat**: anaesthetised and not! Br J Anaesth. 2018 Mar;120(3):424-428.

Hystereze

- projevem setrvačnosti (inertnosti) neuronů
- tendence CNS odolávat změně behaviorálních stavů (bdělost x spánek, vědomí x anestezie)
- vysvětlení:
  - PK/PD modely: časová prodleva mezi vyrovnáním koncentrací v krvi a v mozku
  - genetika, resp. mechanismus úvodu a probouzení (Kelz 2008, Friedmann 2010)



Probouzení z anestezie

- fMRI, propofol TCI k hluboké sedaci, aktivace oblastí CNS podle BOLD analýzy
- aktivace LC (right), NR, VTA, MB (části ARAS) a thalamu trvala < 2,5 min, **startér vědomí (consciousness)**
- aktivace kůry (gyrus frontalis inf. a precuneus), dálková korelace - explozivní synchronizace
- stimulace kmene neprobudí z anestezie s MAC > 0,7[2] („cortical veto“), protože kortikální sítě jsou daleko od bodu přechodu („transition point“)
- ideál: **consciousness → connectedness → responsiveness**

1. Nir T, Matot I. et al.: Transient subcortical functional connectivity upon emergence from propofol sedation in human male volunteers: evidence for active emergence. Br J Anaesth. 2019 ;123:298-308.
2. Sleigh J, Warnaby CE.: Finding the starter motor for the engine of consciousness.
Br J Anaesth. 2019 Sep;123(3):259-261

Závěr: Jak vést anestezii?

- obvyklý úvod
- opiody v dávce k vypnutí kmene (compliance, zornice)
- hypnotika možno snížit, MAC_{age} 0,6-0,9, vypne kůru
- dojde-li k aktivaci kmene (pohyb a ↑ TK a SF), hypnotika zabrání probuzení kůry
- na konci vypnout hypnotika při dostatečné analgezii, takže kmen nastartuje vědomí (bdělost), pak vnímání a nakonec reakce

Scheib CM: Brainstem Influence on Thalamocortical Oscillations during Anesthesia Emergence.
Front Syst Neurosci. 2017 Sep 14;11:66