Význam opioidného systému v rozvoji a liečbe závislosti od alkoholu

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Psychiatrické oddelenie, NsP Sv. Jakuba, n.o., Bardejov

Dni prof. Vladimíra Novotného v Bojniciach
(9. bojnická AT konferencia)
2.-4. október 2015, Bojnice

Obsah

I. Opioidný systém – história a definícia

II. Význam opioidného systému pri závislosti od alkoholu

Opioidný systém – história a definícia

„Opioidy“ *(Acheson, 1957)*



George Hawkins Acheson
(1912 – 2000)

- opium (lat.) – latinská verzia slova opion
- opion (gr.) = šťava z makovice
- opos (gr.) = rastlinná šťava všeobecne
- opiáty = prirodzene sa vyskytujúce alkaloidy v P. somniferum
- opioidy = všetky látky s účinkom analogickým morfiu

Peri hylés iatrikés / De materia medica *(Dioskúridés, 70 n.l.)*



Pedanios Dioskúridés
(40 – 90 n.l.)



„mékón agrios / emeros“

1. Mekonion
2. Opion

Kniha IV

Codex Vidobonensis, 512 d. C., Vienna

Panacey s obsahom ópia

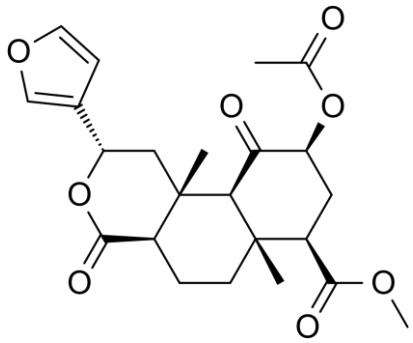


Paracelsus
(1493 –1541)

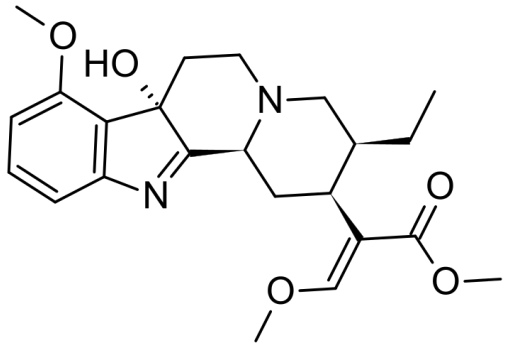
- Mithridatium *(Mithridatés Veľký 133-63 pr. n.l.)*
- Thériaké *(Andromachus, 1. stor. n.l.)*
- Philonium *(Philón z Tarsu, 1. stor. n.l.)*
- Diascordium *(Fracastorius, 1478-1553)*
- Laudanum *(Paracelsus, 1493-1541)*

Terry, C.E. – Pellens, M::The opium problem. New York: Bureau of the Social Hygiene, 1928, xvi+1042s

Ďalšie rastlinné opioidy



Salvinorín A



7-hydroxymitragynín

(mitragynine hydroxyindolenine)



Salvia divinorum

(Epling and Játiva-M, 1962)



Mitragyna speciosa (kratom)

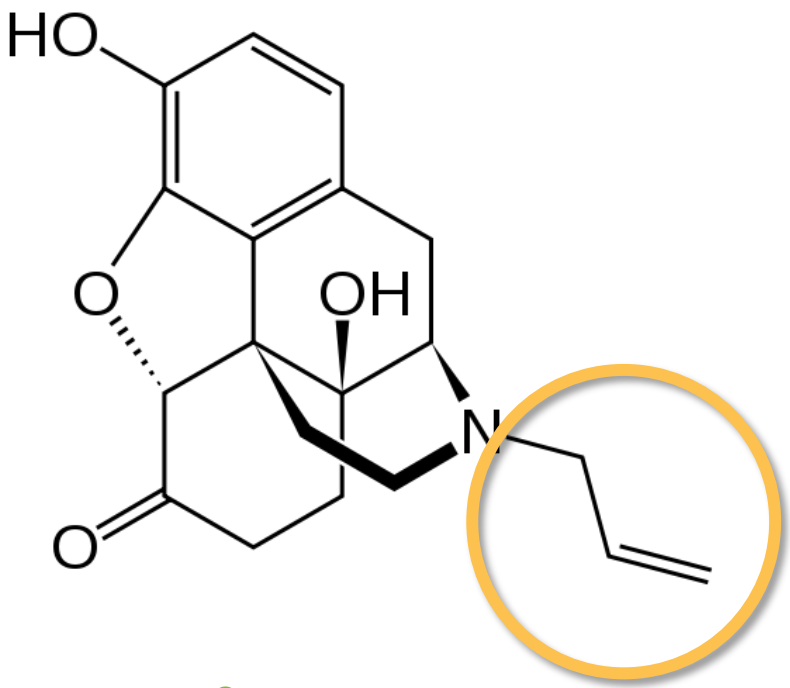
(Korthals (1839); Haviland (1897))

Dôkaz prítomnosti ópioidných receptorov
1973 – Pertová & Snyder



Candance Pert (1946-2013)

Solomon H. Snyder (1938 -)



[^{3}H]naloxon

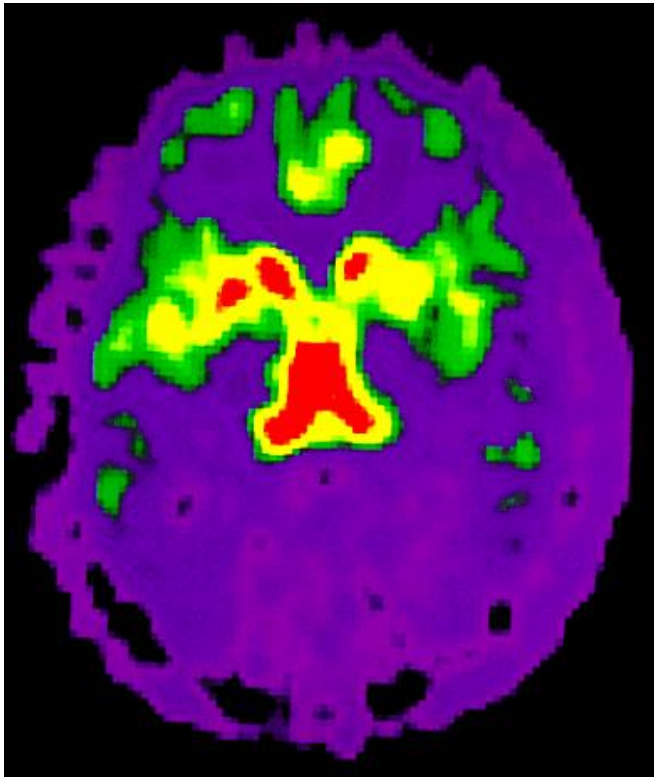
http://articles.latimes.com/2013/sep/24/local/la-me-candace-pert-20130924

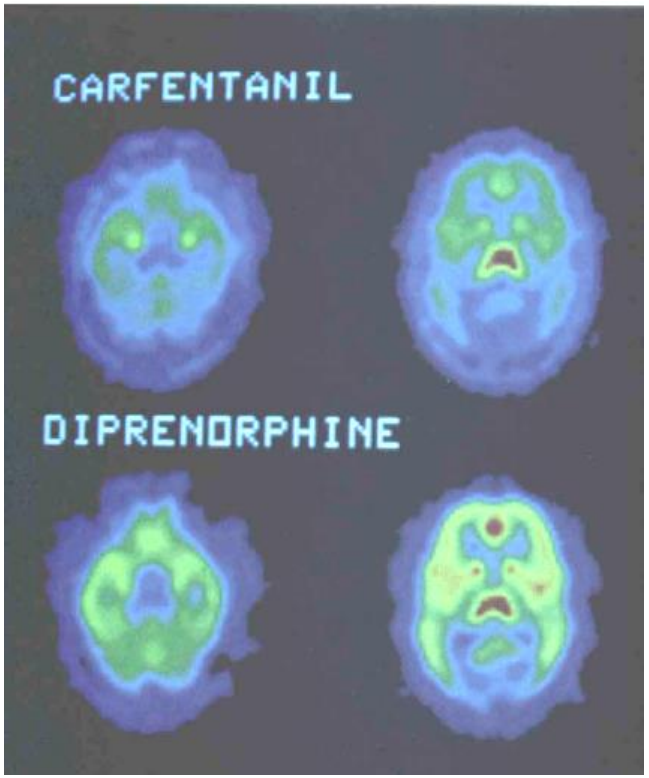
Snyder SH, Matthysse S. Opiate Receptor Mechanisms. Neurosci Res Program Bull. 1975; 13(1): 1–66.

PET μ-receptorov *(Frost et al., 1985)*



James J. Frost





Carfentanil – mí agonista

Diprenorphine – neselektívny opioidný antagonista

Frost et al. (1985). J Comput Assist Tomogr. 1985 Mar-Apr;9(2):231-6.

Frost et al. (1990). J Cereb Blood Flow Metab. 1990 Jul;10(4):484-92

Objav enkefalínov *(Hughes et al., 1973)* - pentapeptidy



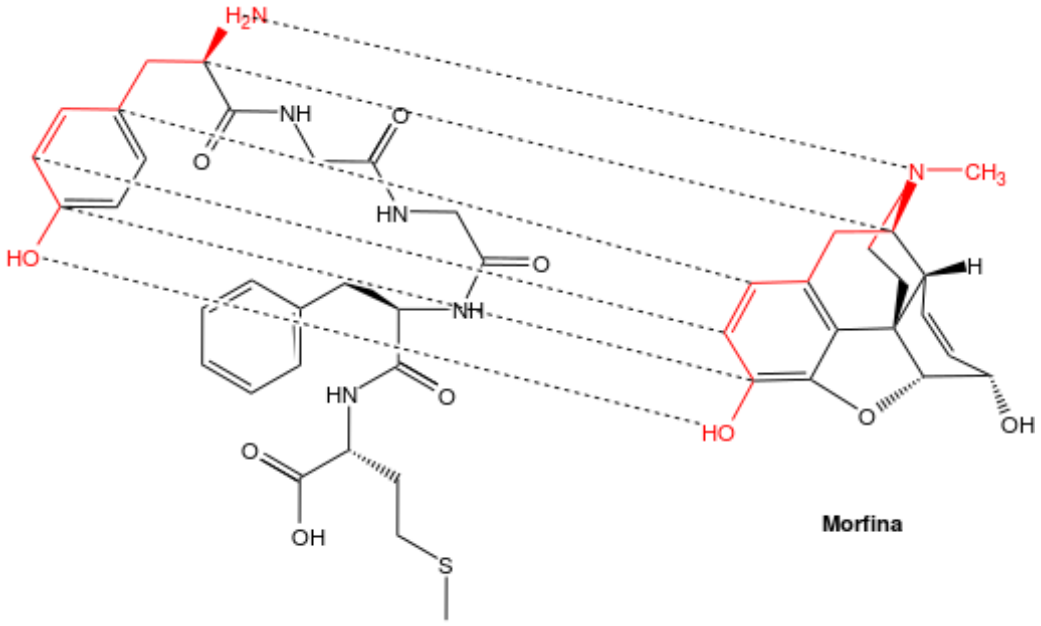
Hans W. Kosterlitz
(1903 – 1996)



John Hughes
(1942 -)

Tyr-Gly-Gly-Phe-**Leu**

Tyr-Gly-Gly-Phe-**Met**



Albert Lasker Basic Medical Research Award
(1978 Winners)

Hughes et al. (1975). Nature. 1975; 258(5536): 577–9.
http://en.wikipedia.org/wiki/File:Correlaci%C3%B3n_estructural_entre_las_encefalinas_y_la_morfina.svg

Objav ďalších endogénnych opioidov *(1976-1979, 1995)*

Opioidný motív

1975	• **(Leu)-enkefalín**	Tyr-Gly-Gly-Phe-**Leu**
	• **(Met)-enkefalín**	Tyr-Gly-Gly-Phe-**Met**
1976	• **β-endorfín**	Tyr-Gly-Gly-Phe-**Met**-Thr-Ser-Glu-Lys-Ser-Gln-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu
1979	• **Dynorfín A**	Tyr-Gly-Gly-Phe-**Leu**-Arg-Arg-Ile-Arg-Pro-Lys-Leu-Lys
	• **Dynorfín B**	Tyr-Gly-Gly-Phe-**Leu**-Arg-Arg-Gln-Phe-Lys-Val-Val-Thr
1995	• **Nociceptín**	Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln

Li et al. (1976) Biochem Biophys Res Commun. 1976; 72(4):1542–7.
Doneen et al. (1977) Biochem Biophys Res Commun. 1977; 74(2):656–62.
Goldstein et al. (1979) Proc Natl Acad Sci USA. 1979; 76(12):6666–70.
Meunier*et al.* (1995) *Nature* 377:532–535.
Reinscheid *et al.* (1995) *Science* 270:792–794.

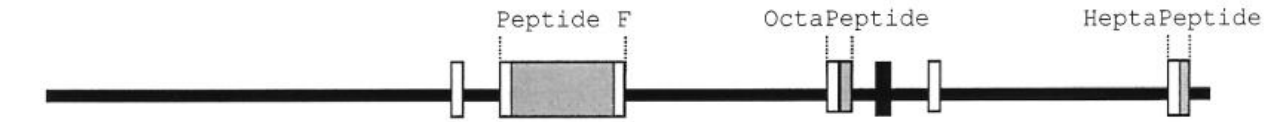
1979-1982 identifikované prekurzory a klonovaná ich DNA

PDYN



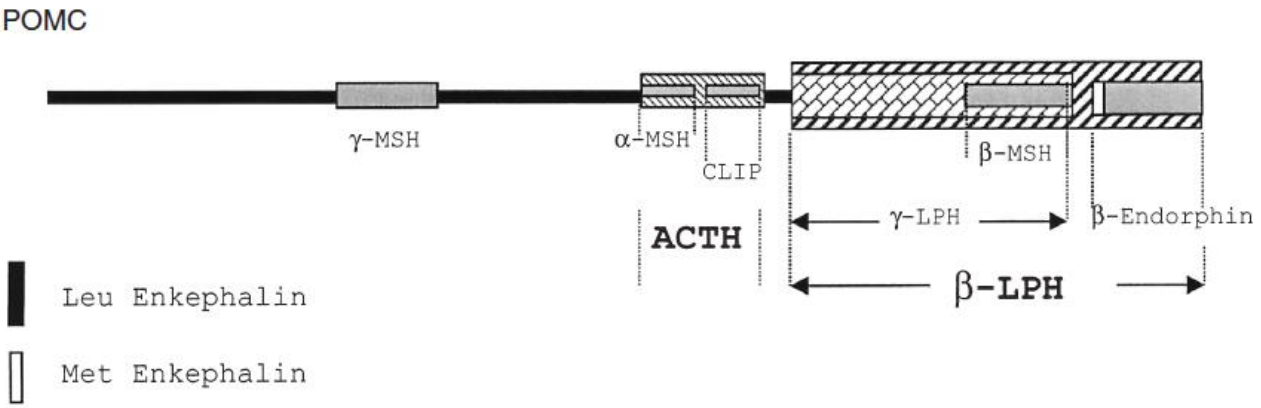
20p13

PENK



8q23-q24

POMC



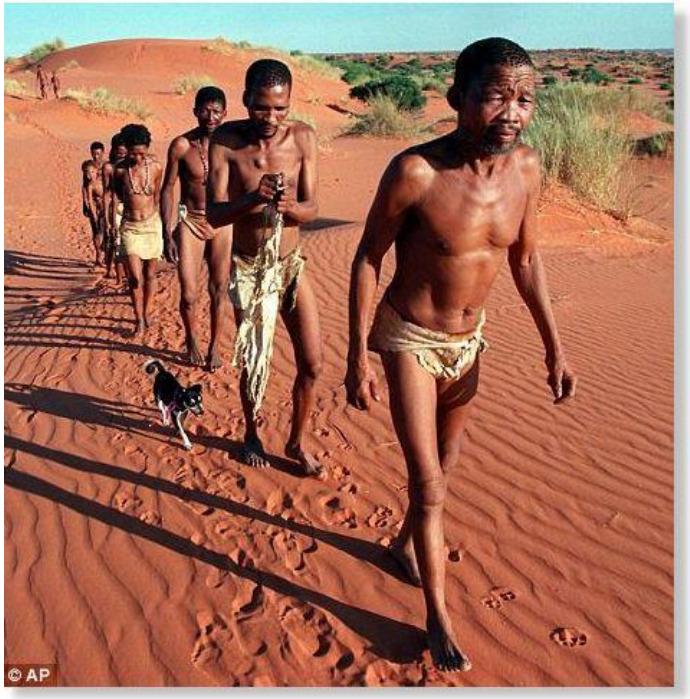
2p23.3

Literatúra:

1. Nakanishi et al. Nature. 1979 Mar 29;278(5703):423-7.
2. Noda et al. Nature. 1982 Jan 21;295(5846):202-6.
3. Kakidani et al. Nature. 1982 Jul 15;298(5871):245-9.

Prevzaté z: Akil et al. (1998)
Drug Alcohol Depend. 1998 Jun-Jul;51(1-2):127-40.

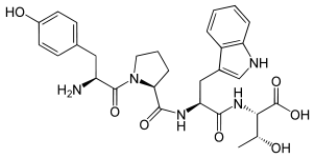
Alimentárne opioidy (exorfíny) *(Zioudrou et al., 1979)*



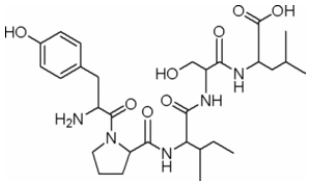




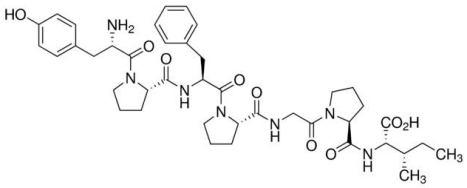




Tyr-Pro-Trp-Thr
hemorfín-4



Tyr-Pro-Ile-Ser-Leu
exorfín C



Tyr-Pro-Phe-Pro-Gly-Pro-Ile
(hovädzí) **β-kazomorfín 7**

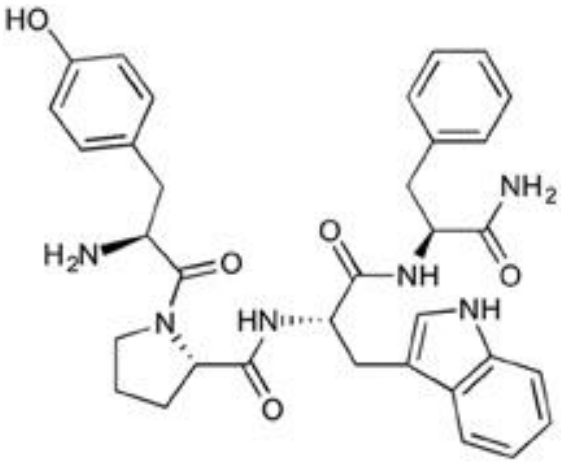
- Beta-kazeín pozícia 60-68
- Fragment 34-37 beta-reťazca hovädzieho hemoglobínu

Zioudrou et al. (1979). J Biol Chem. 1979 Apr 10;254(7):2446-9.
Brantl et al. (1979) Hoppe Seylers Z Physiol Chem. 1979 Sep;360(9):1211-6
Brantl et al. (1986) Eur J Pharmacol. 1986 Jun 17;125(2):309-10

Endomorfíny-1 a -2 (selektívne MOP agonisty) *(Zadina et al., 1997)*

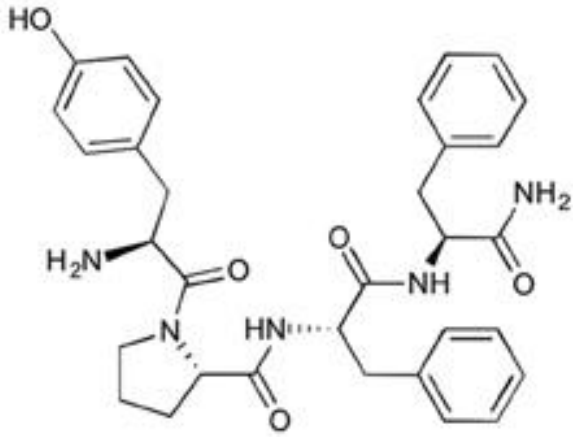


James E. Zadina



Endomorphin-1

Tyr-Pro-Trp-**Phe**



Endomorphin-2

Tyr-Pro-Phe-**Phe**

Tyr-Gly-Gly-Phe-Leu

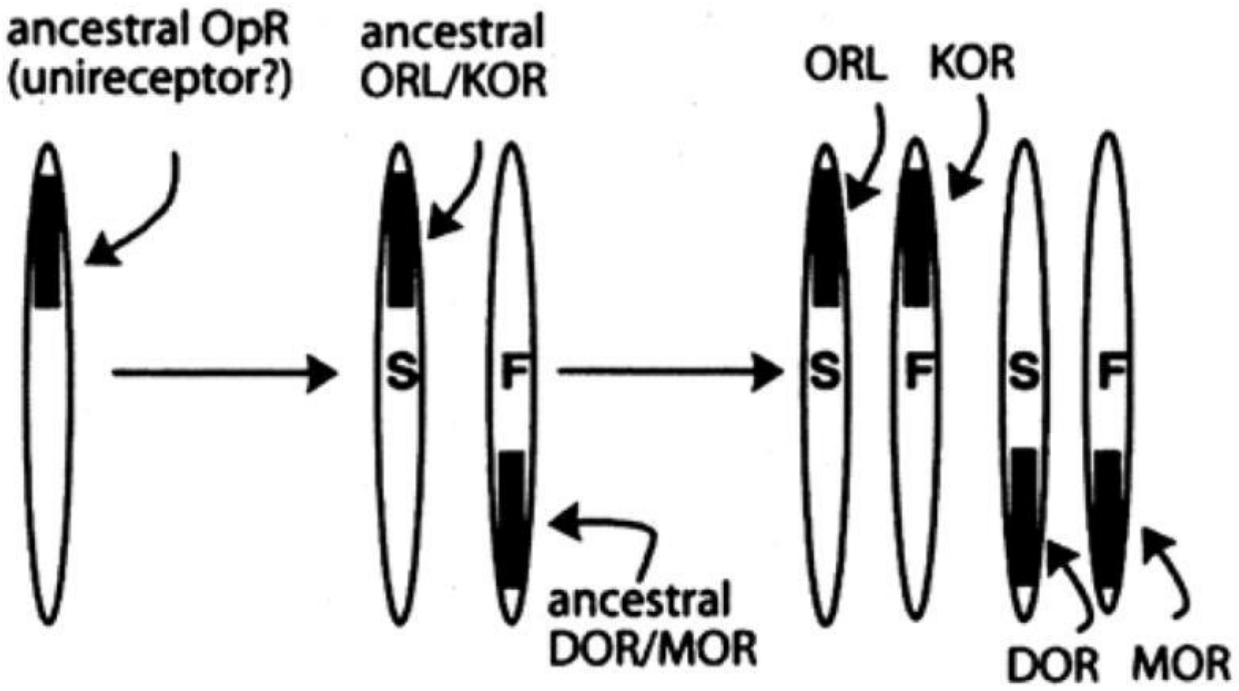
1. Erchegyi et a. (1992). Peptides. 1992 Jul-Aug;13(4):623-31.
2. Zadina et al. (1997): Nature. 1997; 386(6624):499–502.
3. Hackler et al. (1997). Peptides. 1997; 18(10):1635–9.

Terskiy et al. (2007) Life Sci. 2007 Nov 30;81(23-24):1593-601.
Varamini & Toth (2013). Front Pharmacol. 2013 Dec 13;4:155.

Systém endogénnych opioidov v skratke

?	**Endomorfíny**	**μ-receptory (MOP)**	OPRM1 *(6q24-q25)*
POMC *(2p23.3)*	**Beta-endorfín**		
PENK *(8q23-q24)*	**Enkefalíny**	**δ-receptory (DOP)**	OPRD1 *(1p36.1-p34.3)*
PDYN *(20p13)*	**Dynorfíny**	**κ-receptory (KOP)**	OPRK1 *(8q11.2)*
PNOC *(8p21)*	**Nociceptín**	**NOP**	OPRL1 *(20q13.33)*

450 miliónov rokov (quadruplikácia)

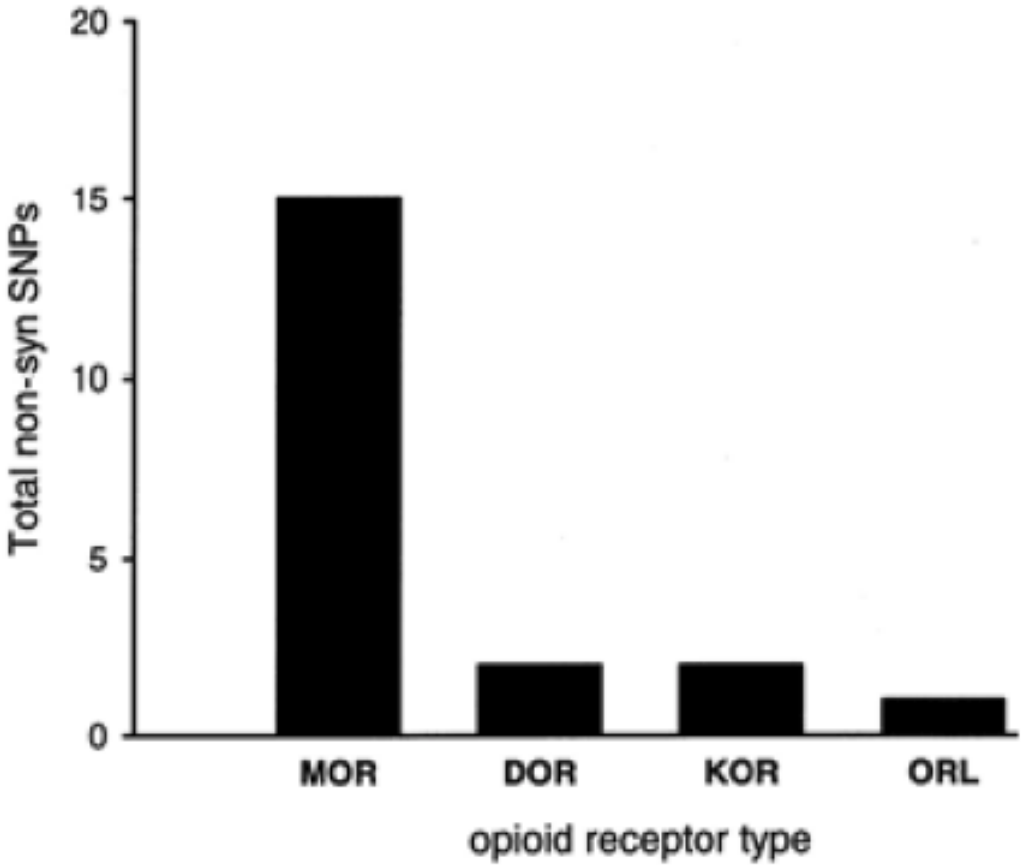


R1 **R2**

Stevens. Front Biosci. 2009 Jan 1; 14: 1247–1269.

Larhammar D et al. 2009

>4000 tisíc synonymných a 15 nesynonymných jednonukletidových polymorfizmov (SNP) pre OPRM1



Pasternak & Pan (2013). Pharmacol Rev. 2013 Sep 27;65(4):1257-317.

Stevens. Front Biosci. 2009 Jan 1; 14: 1247–1269.

OPRM1 *(6q24-q25)*
Hyperfunkčná mutácia A118G (Asn40 → Asp40)

β-endorfín sa viaže 3x silnejšie na μ-receptor s mutáciou A118G

Table 1. SNPs in the [illegible]

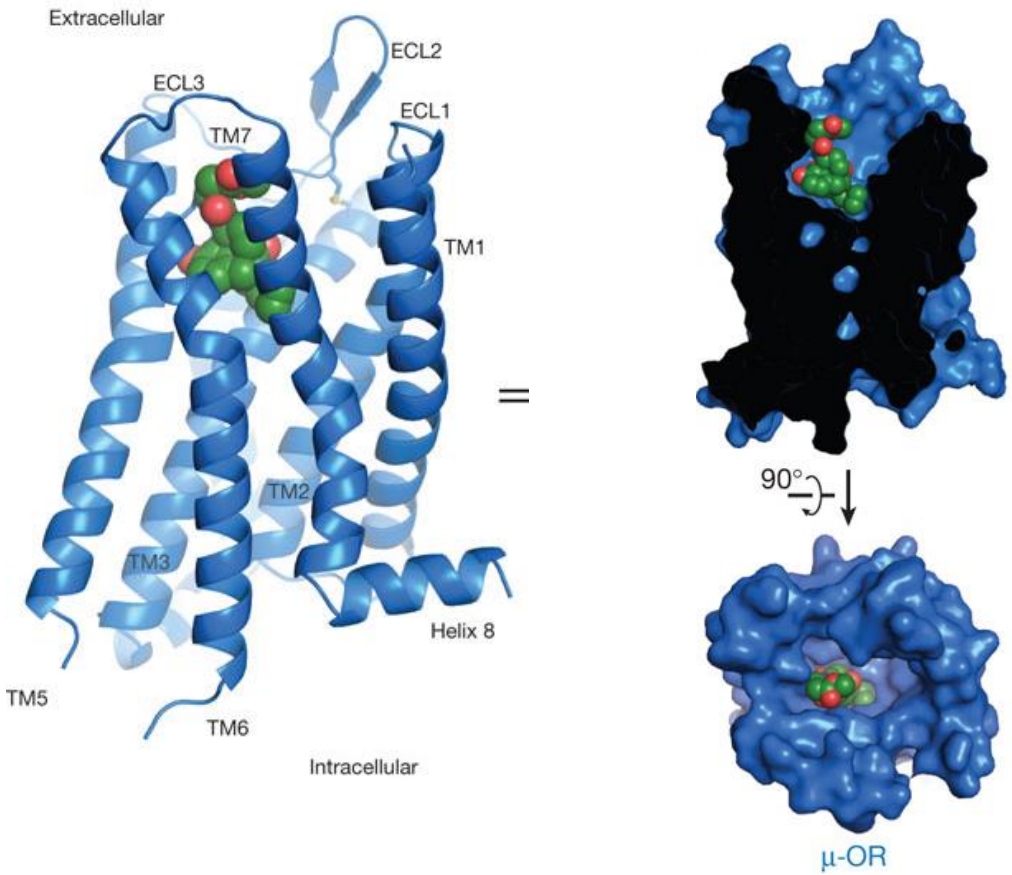
Variant name	Nucleotide position	Exon location	Corresponding amino acid change	Protein domain	Allele frequency
A118G	118	1	Asn-40 → Asp (N40D)	N terminal	10.5% (26 heterozygous individual and 3 homozygous individuals, n = 152)
C17T	17	1	Ala-6 → Val (A6V)	N terminal	6.6% (14 heterozygous individuals and 3 homozygous individuals, n = 152)
G24A	24	1	Silent mutation	N terminal	2% (six heterozygous individuals, n = 152)
G779A	779	3	Arg-260 → His (R260H)	CL3	One heterozygous individual
G942A	942	3	Silent mutation	EL3	One heterozygous individual

Nucleotide position 1 is the first base of the start codon. Protein domains are based on the seven-transmembrane model for opioid receptors. EL, extracellular loop; CL, cytoplasmic loop.

A = adenozín
G = guanozín
Asn = asparagín
Asp = aspartát

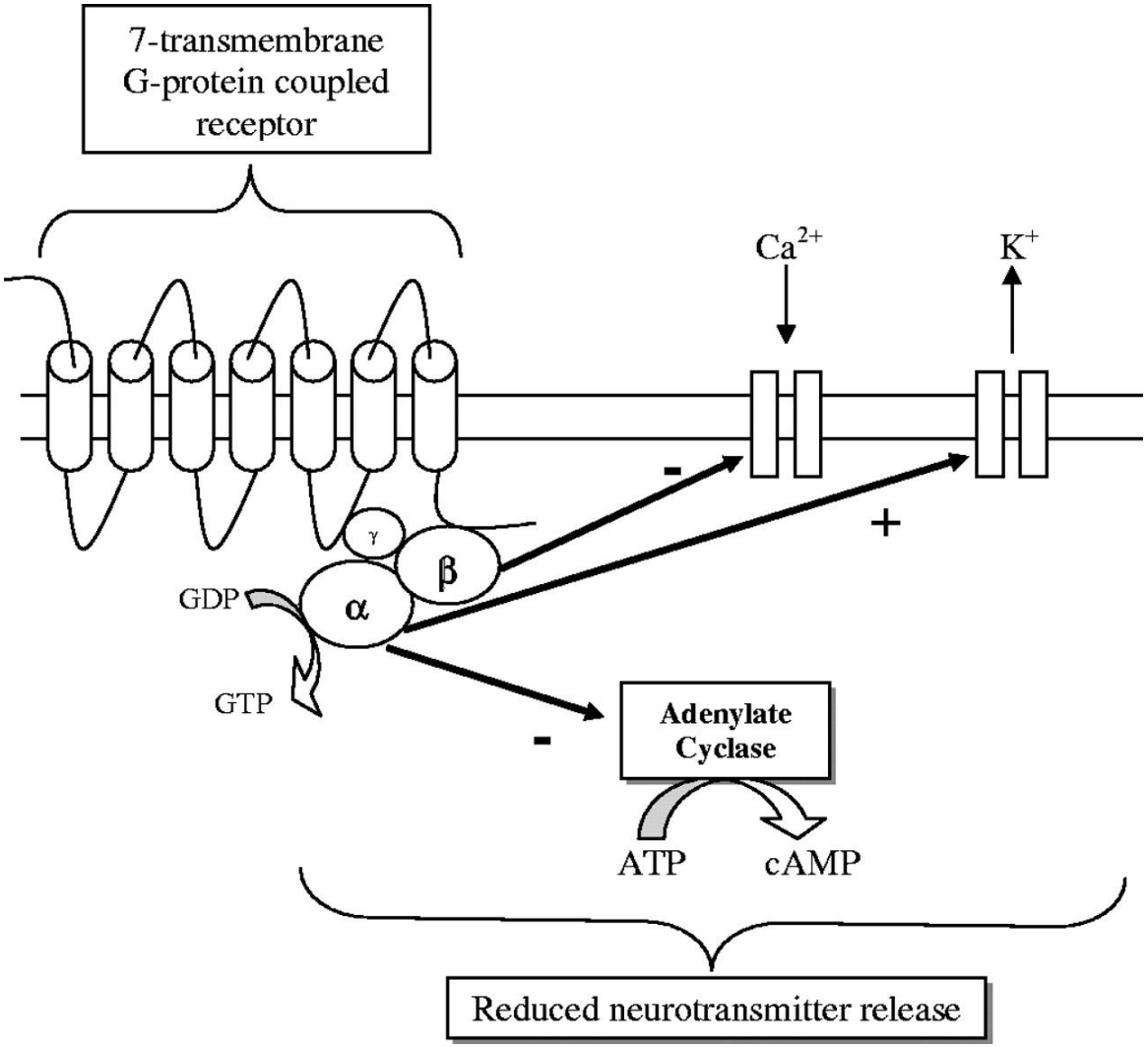
Bergen et al. (1997) Mol Psychiatry. 1997 Oct-Nov;2(6):490-4.
Bond et al. (1998) Proc Natl Acad Sci U S A. 1998 Aug 4;95(16):9608-13

μ-opioidné receptory (MOP)



Manglik et al. (2012)
Nature. 2012 Mar 21; 485(7398): 321–326.

G protein–coupled receptor (GPCR) - všetky spojené s $G\alpha_i$



http://ceaccp.oxfordjournals.org

McDonald (2005). Contin Educ Anaesth Crit Care Pain (2005) 5 (1): 22-25.

G protein–coupled receptor (GPCR) - všetky spojené s $G\alpha_i$

Všetky opioidné receptory sú inhibičné

http://ceaccp.oxfordjournals.org

McDonald (2005). Contin Educ Anaesth Crit Care Pain (2005) 5 (1): 22-25.

Runner´s high



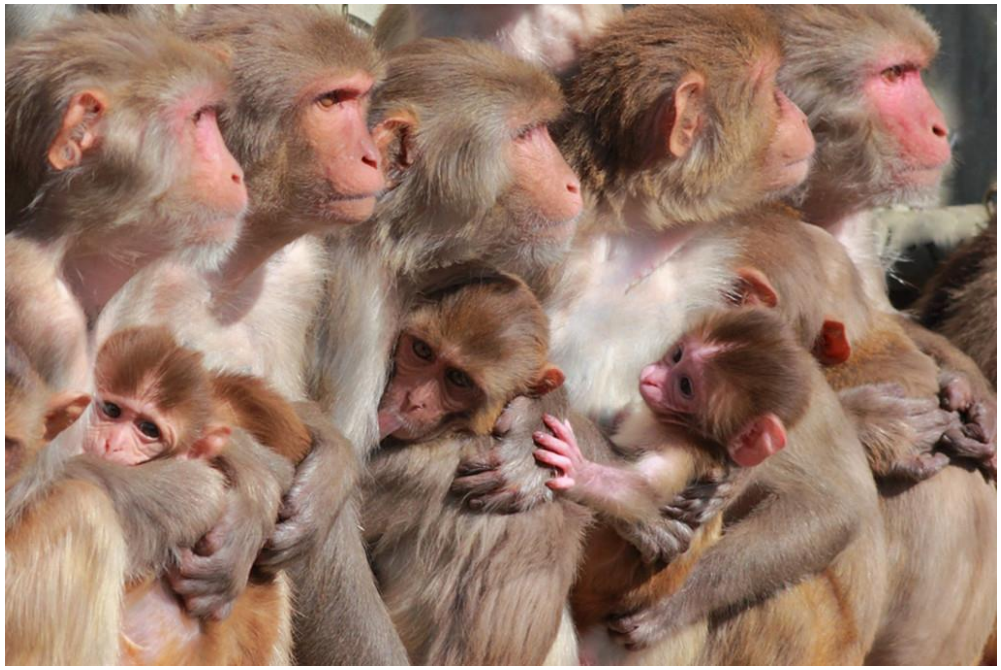
Fraioli et al. (1980).

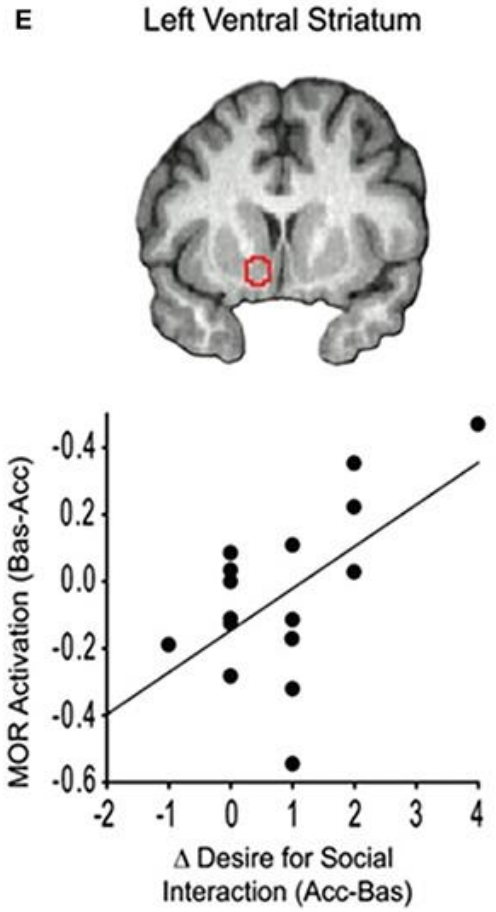
Physical exercise stimulates marked concomitant release of beta-endorphin and adrenocorticotropic hormone (ACTH) in peripheral blood in man.

Experientia. 1980 Aug 15;36(8):987-9.

Attachment

Response of the μ-opioid system to social rejection and acceptance.





Herman & Panksepp (1978). Pharmacol Biochem Behav. 1978 Aug;9(2):213-20.

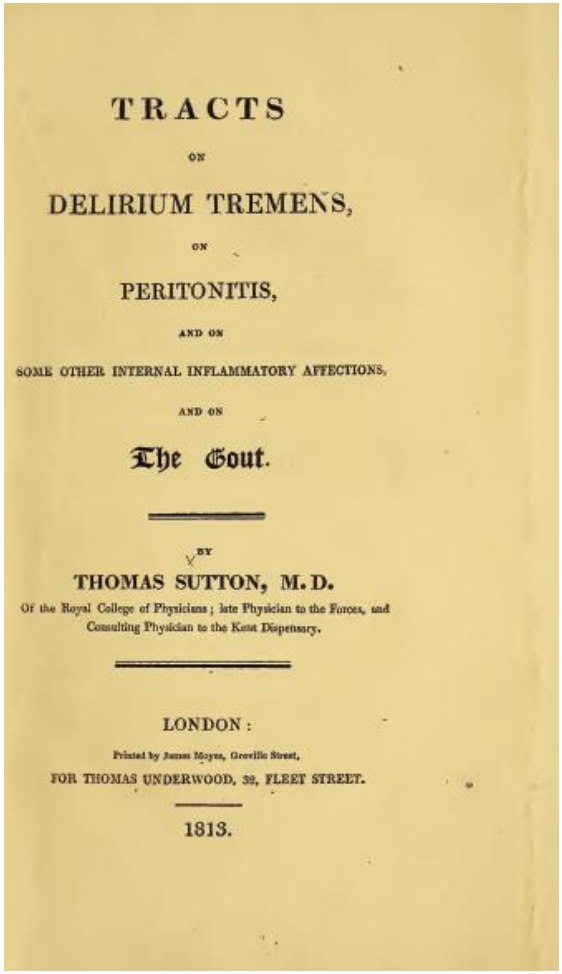
Moles et al. (2004). Science. 2004 Jun 25;304(5679):1983-6

Barr et al. (2008). Proc Natl Acad Sci U S A. 2008 Apr 1;105(13):5277-81.

Hsu et al. (2013). Mol Psychiatry. 2013 Nov; 18(11): 10.1038/mp.2013.96.

Význam opioidného systému pri závislosti od alkoholu

Delirium tremens *(Sutton, 1813)*



TRACTS

ON

DELIRIUM TREMENS,

ON

PERITONITIS,

AND ON

SOME OTHER INTERNAL INFLAMMATORY AFFECTIONS,

AND ON

The Gout.

BY

THOMAS SUTTON, M.D.

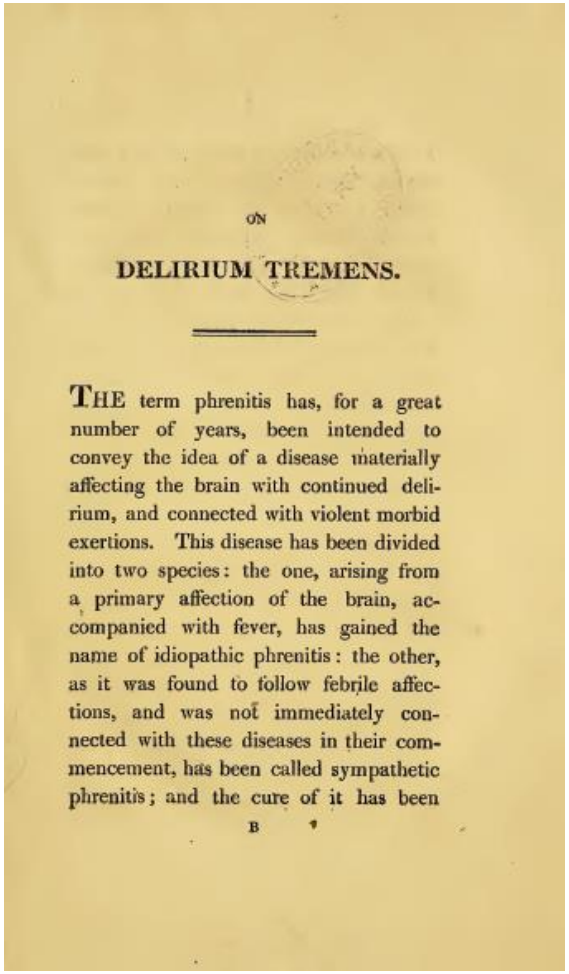
Of the Royal College of Physicians; late Physician to the Forces, and Consulting Physician to the Kent Dispensary.

LONDON:

Printed by James Moyes, Greville Street,

FOR THOMAS UNDERWOOD, 32, FLEET STREET.

1813.



ON

DELIRIUM TREMENS.

THE term phrenitis has, for a great number of years, been intended to convey the idea of a disease materially affecting the brain with continued delirium, and connected with violent morbid exertions. This disease has been divided into two species: the one, arising from a primary affection of the brain, accompanied with fever, has gained the name of idiopathic phrenitis: the other, as it was found to follow febrile affections, and was not immediately connected with these diseases in their commencement, has been called sympathetic phrenitis; and the cure of it has been

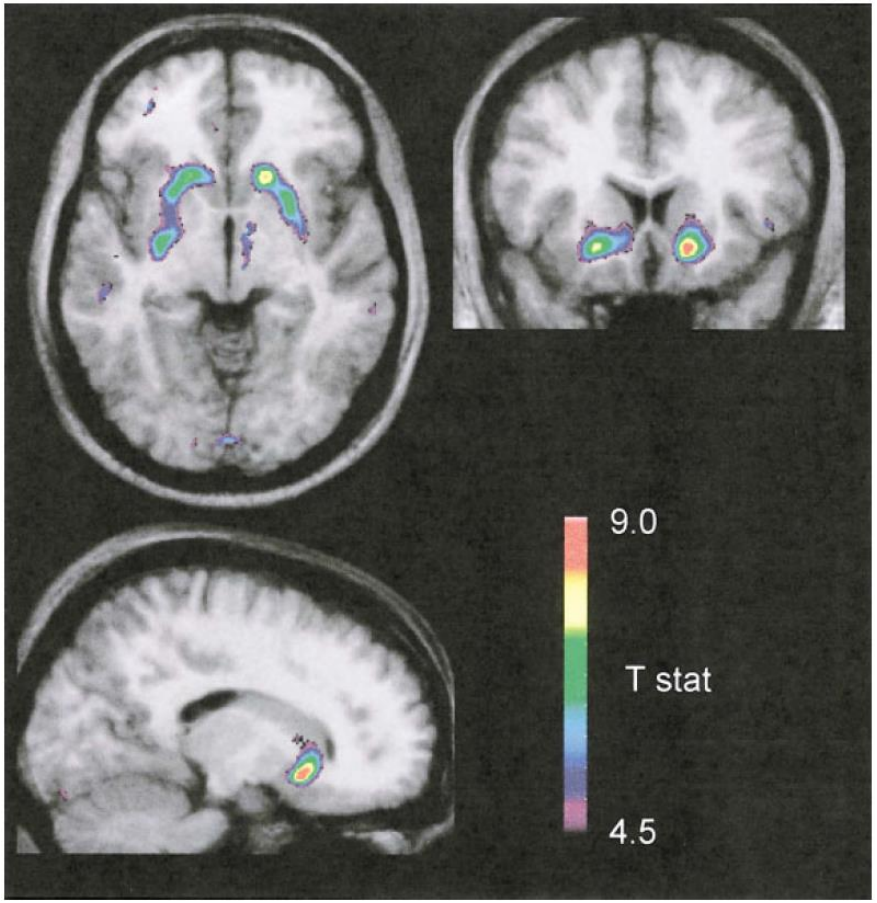
B

Sutton Thomas (1813). Tracts on Delirium tremens, on peritonitis... London: Thomas Underwood, 1813, s. 1-77

Alkohol spôsobuje uvoľnenie dopamínu v Nac



Isabelle Boileauová



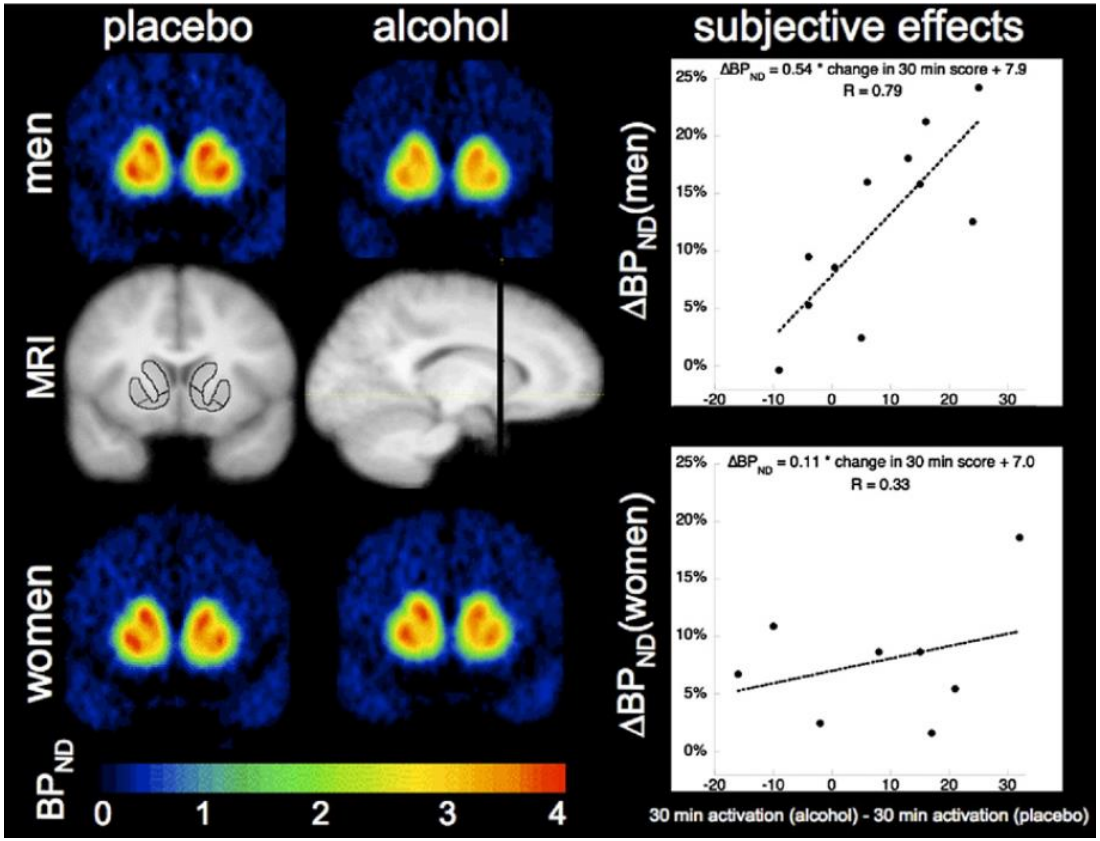
[11C]rakloprid

Boileau et al. (2003)
Alcohol promotes dopamine release in the human nucleus accumbens.
Synapse. 2003 Sep 15;49(4):226-31.

Etanol stimuluje uvoľnenie dopamínu viac u mužov



Nina Urbanová



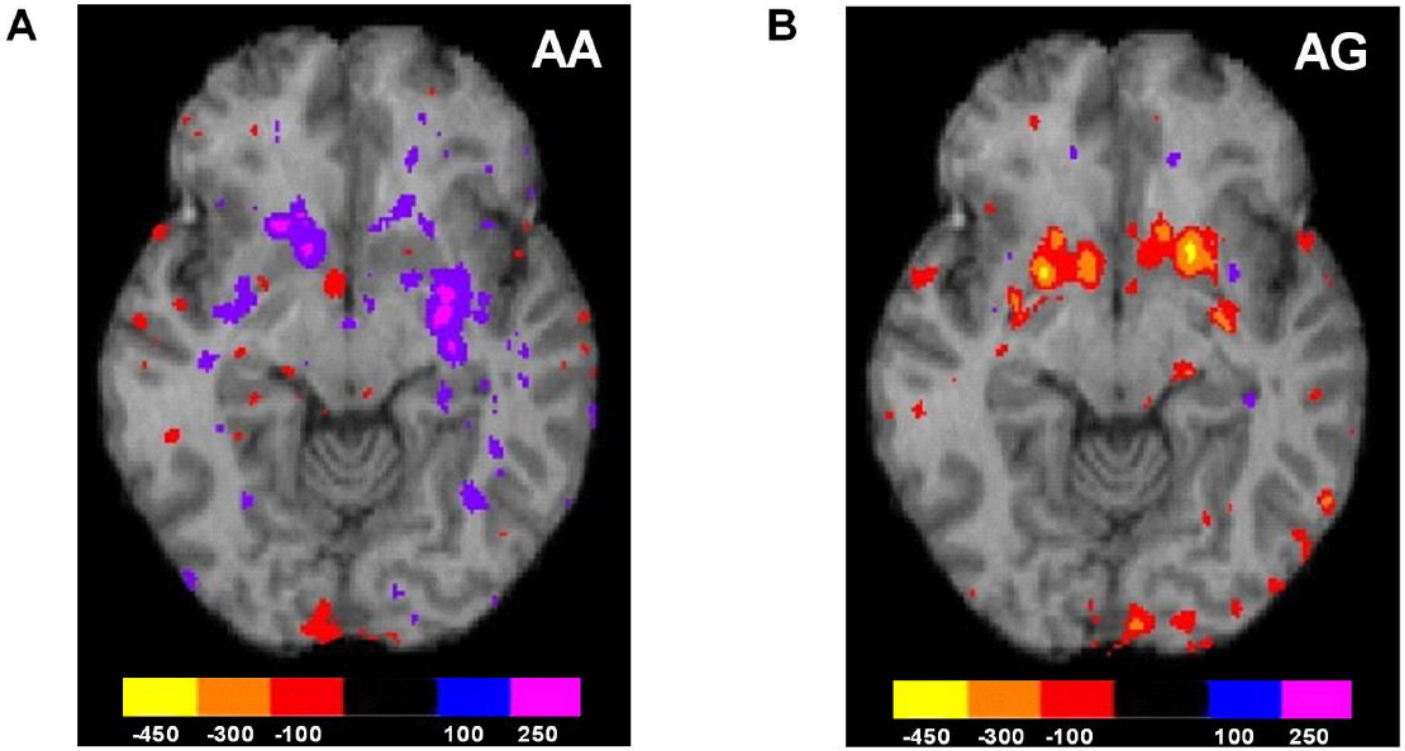
PET štúdia s [^{11}c]raclopridom

Urban et al. (2010)

Sex differences in striatal dopamine release in young adults after oral alcohol challenge: a positron emission tomography imaging study with [^{11}C]raclopride.

Biol Psychiatry.2010 Oct 15;68(8):689-96.

Zvýšené uvoľňovanie dopamínu u nositeľov G-alely



Placebo vs. Alkohol
u „social drinkers“

PET štúdia - rozdiel väzobného potenciálu [^{11}C]-raklopridu

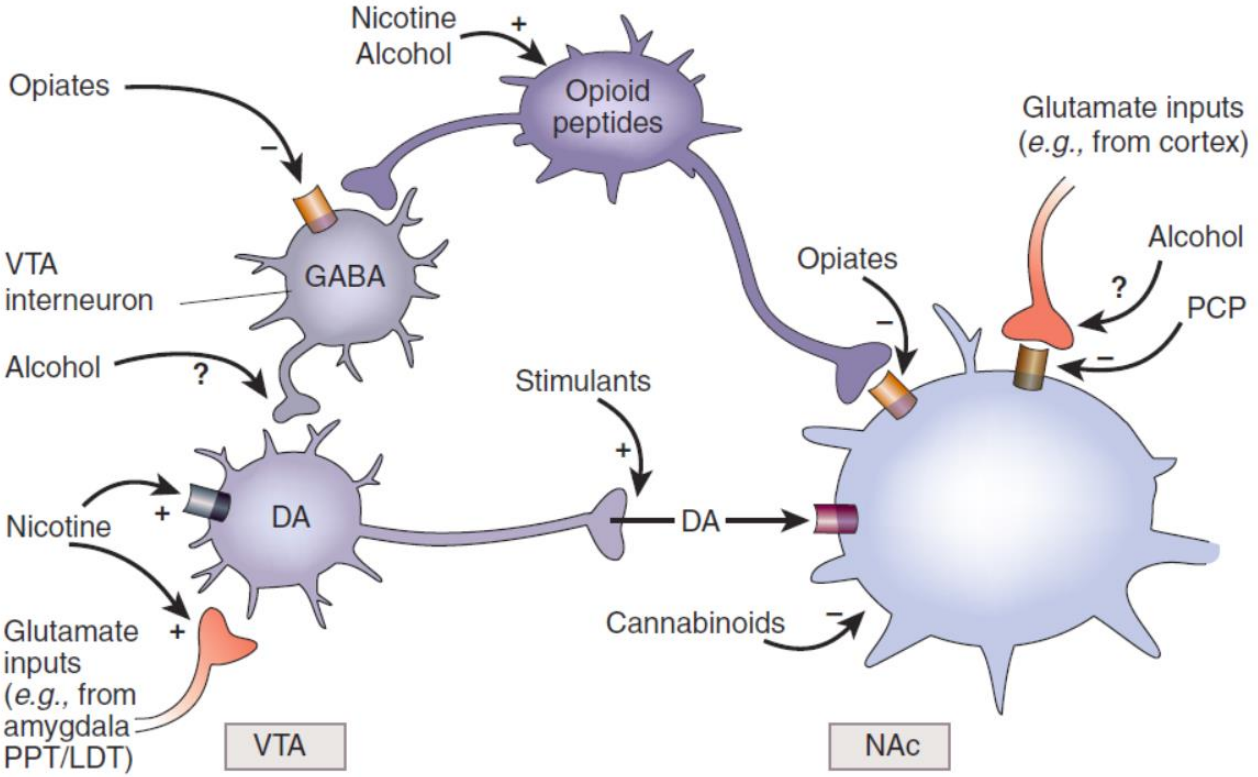
Ramchandani et al. (2011). Mol Psychiatry. 2011 August ; 16(8): 809–817

2 mechanizmy pôsobenia opioidov cez MOP v štrukúrach odmeny:

– inhibícia GABA-brzdy
– priame pôsobenie v NAc



Eric J. Nestler

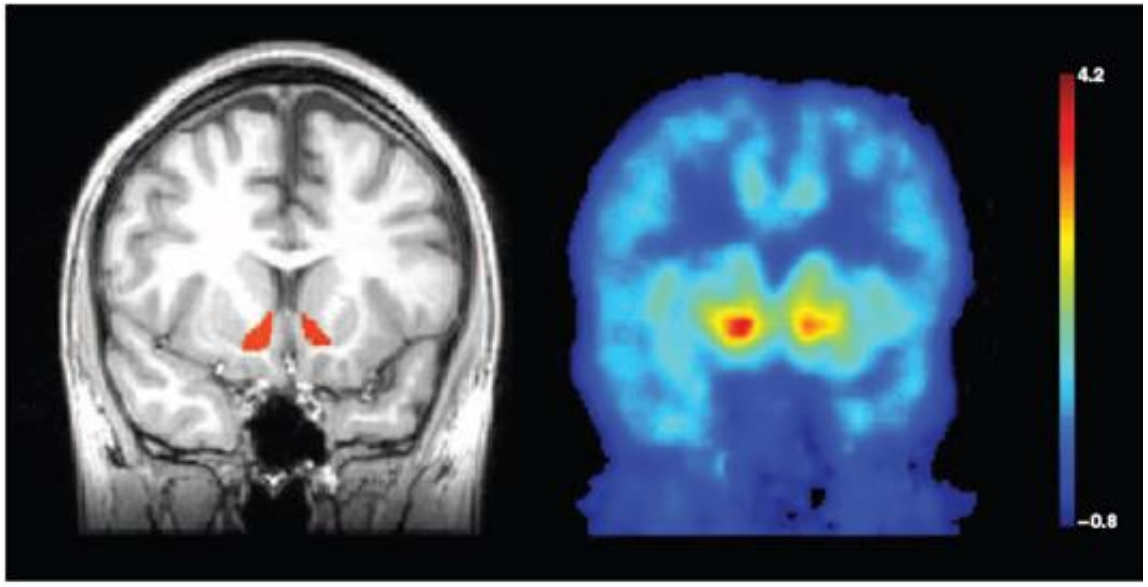


Nestler EJ (2005)
Is there a common molecular pathway for addiction?
Nat Neurosci. 2005 Nov;8(11):1445-9.

Alkohol spôsobuje uvoľňovanie endogénnych opioidov (mOFC a Nac)



Jennifer Mitchellová



Nucleus accumbens

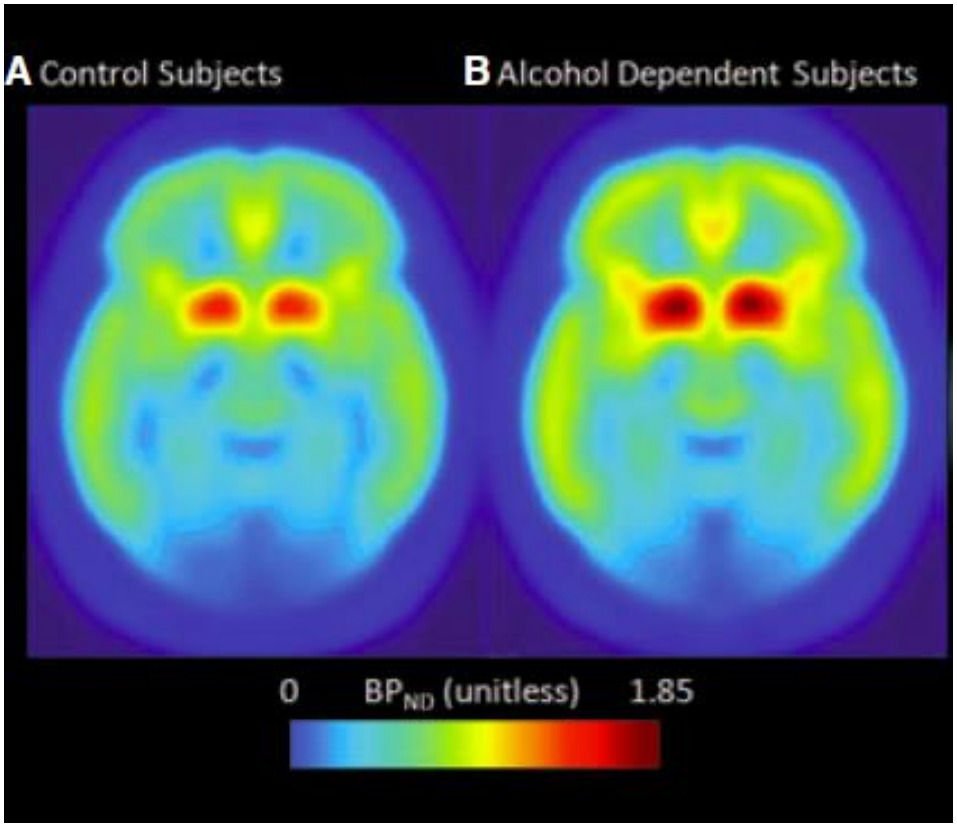
Zmena väzby [^{11}C] carfentanilu (agonista MOR)

PET - 13 ťažkých pijanov vs. 12 kontrol

Obr.: na obrázku je jeden reprezentatívny prípad. Väzobný potenciál koreloval so závažnosťou pitia.

Mitchell et al. (2012) Sci Transl Med. 2012;4(116): 116ra6.

Zvýšený väzobný potenciál (BP) MOP u závislých od alkoholu



Mean [11C]CFN BPND images in control (a) and alcohol-dependent subjects (b). Colored legend depicts [11C]CFN BPND from 0 (light blue) to 1.85

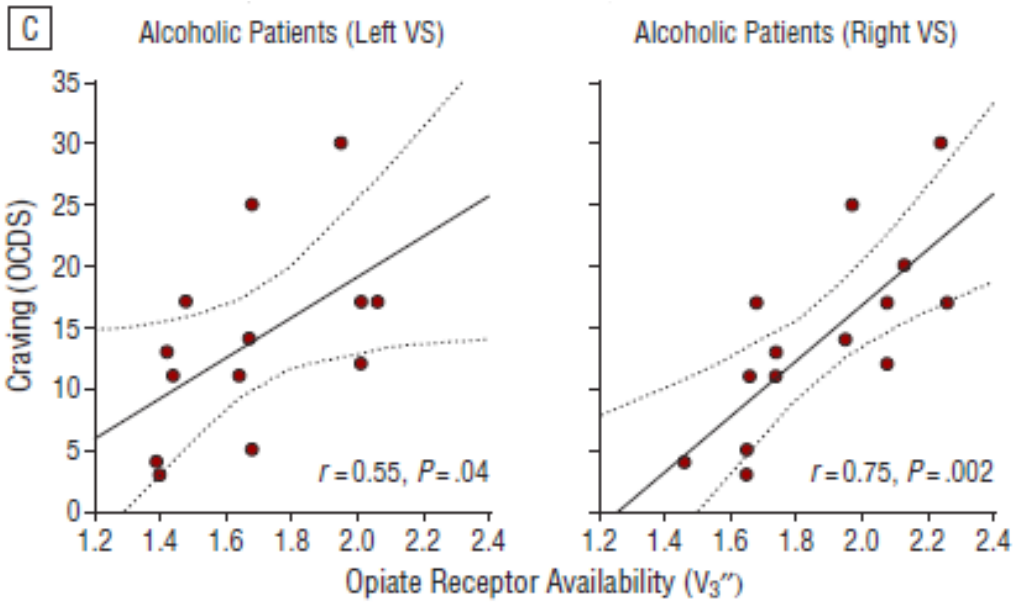
(red). Mean magnetic resonance imaging image of all subjects is shown (c). Images are taken at the level of ventral striatum.

Weerts et al. Alcohol Clin Exp Res. 2011 Dec; 35(12): 2162–2173.

Dostupnosť MOP vo VS koreluje s cravingom



Andreas Heinz



Heinz et al. (2005) Arch Gen Psychiatry. 2005;62:57-64

Naltrexone in the treatment of alcohol dependence

(Volpicelli et al., 1992)



Joseph R. Volpicelli

NTX vs. PLB

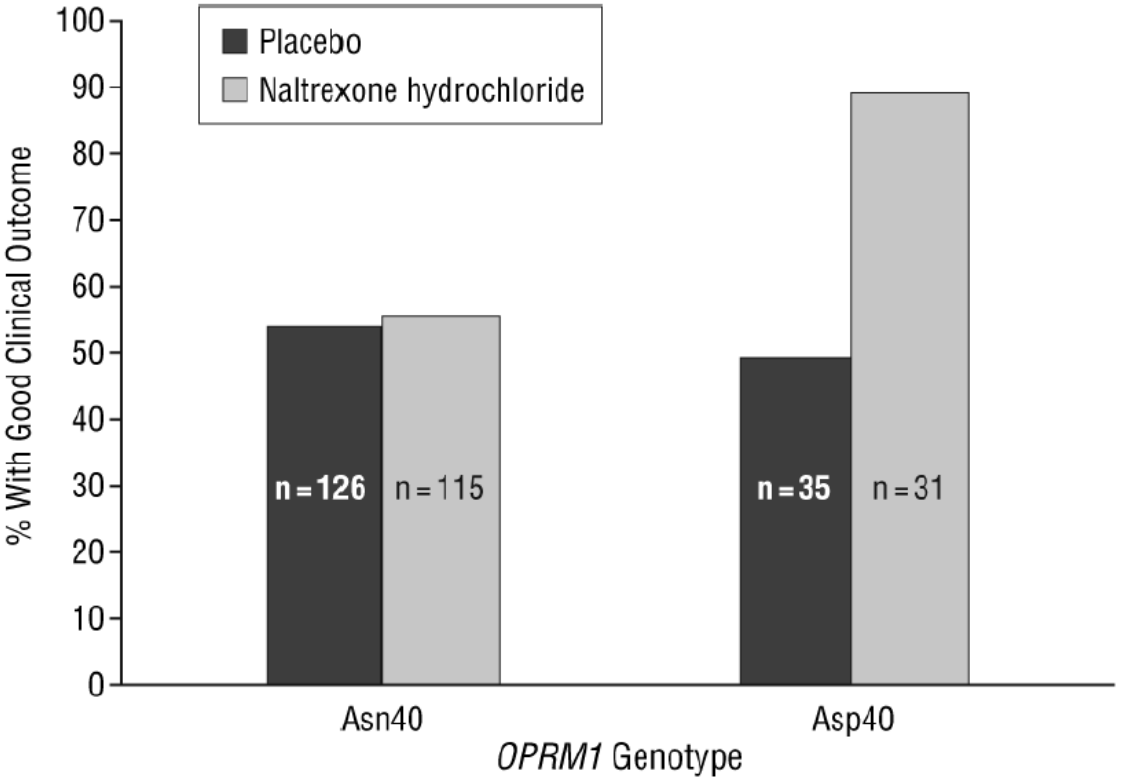
- 23% vs. 54% relabujúcich
- z tých, čo ochutnali alkohol, relaps u 50% vs. 95%
- u relabujúcich blokáda potešenia („high“)

Volpicelli JR et al. (1992) Arch Gen Psychiatry. 1992 Nov;49(11):876-80.
Volpicelli JR et al. Am J Psychiatry.1995 Apr;152(4):613-5.

Efekt naltrexónu je viazaný na nositeľov G-alely



Raymond F. Anton



AA	**:**	**AG/GG**
241	:	66 (20%)

Asn40 = homozygóti Asn40/Asn40

Asp40 = aspoň jedna alela Asp40

Asp40 je výsledok A118G mutácie v exóne 1 génu OPRM1 (6q24-q25)

Anton et al. (2008)
Arch Gen Psychiatry. 2008 Feb;65(2):135-44.

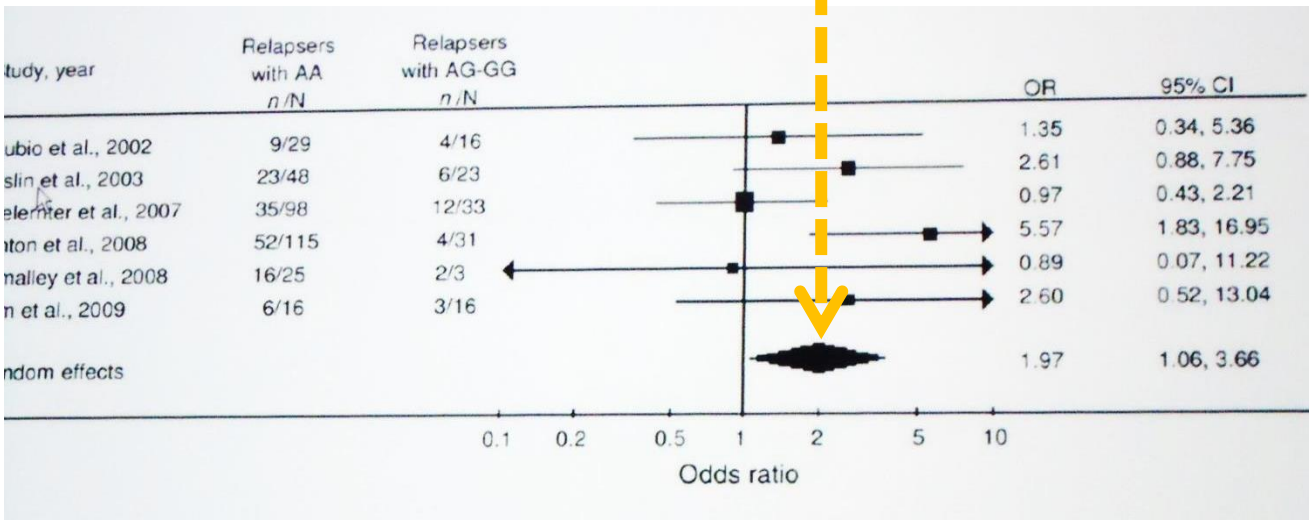
Meta-analýza (relaps AA vs. AG/GG)



Antonio-Javier Chamorro

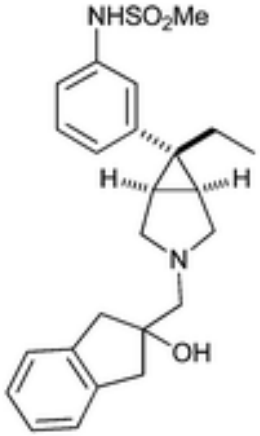
(Hospital of Ourense, Spain)

OR = 2,02



Chamorro et al. (2012)
Addict Biol. 2012 May;17(3):505-12

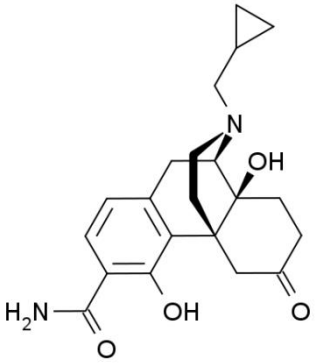
μ - antagonizmus



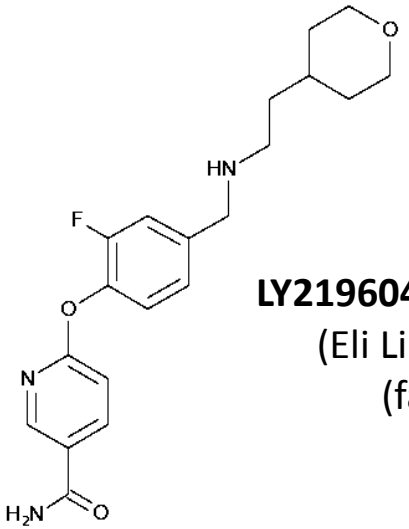
CP-866,087
(compound 15)
(Pfizer)
(fáza 2)



GSK-1521498
(Glaxo Smith Kline)
(fáza 1)



ALKS-33 (RDC-0313)
(samidorphan)
(Alkermes Inc.)
(fáza 2)



LY2196044 (odelepran)
(Eli Lilly and Co.)
(fáza 2) [1]

[1] Wong et al. Alcohol Clin Exp Res. 2014 Feb;38(2):511-20

Skrýva sa za účinkom naltrexónu iba mí-antagonizmus?



Evan D. Morris [1]

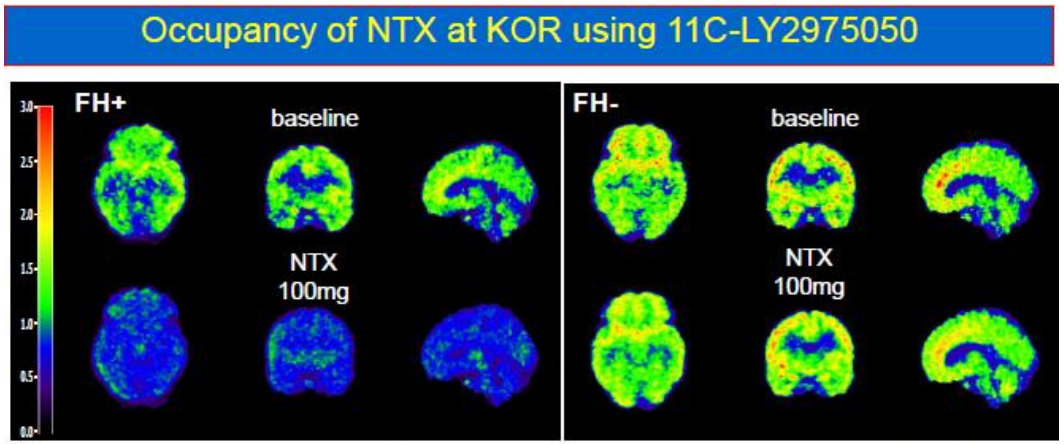


Figure 3. Pre- and post-NTX SUV 0-120 min. emission images in one FH+ and one FH- subject. Note greater occupancy of NTX in FH+ subject as determined by lower uptake of tracer post-drug.

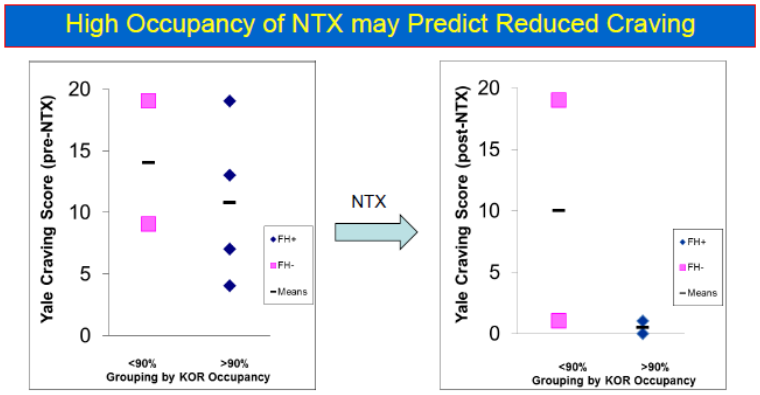


Figure 4. Grouping of subjects by NTX occupancy (<90% vs >90%). High Occupancy group cravings reduced more than Low Occupancy group after week of NTX treatment. (Note overlap of points in High Occupancy group post-NTX)

Morris et al. (Poster)

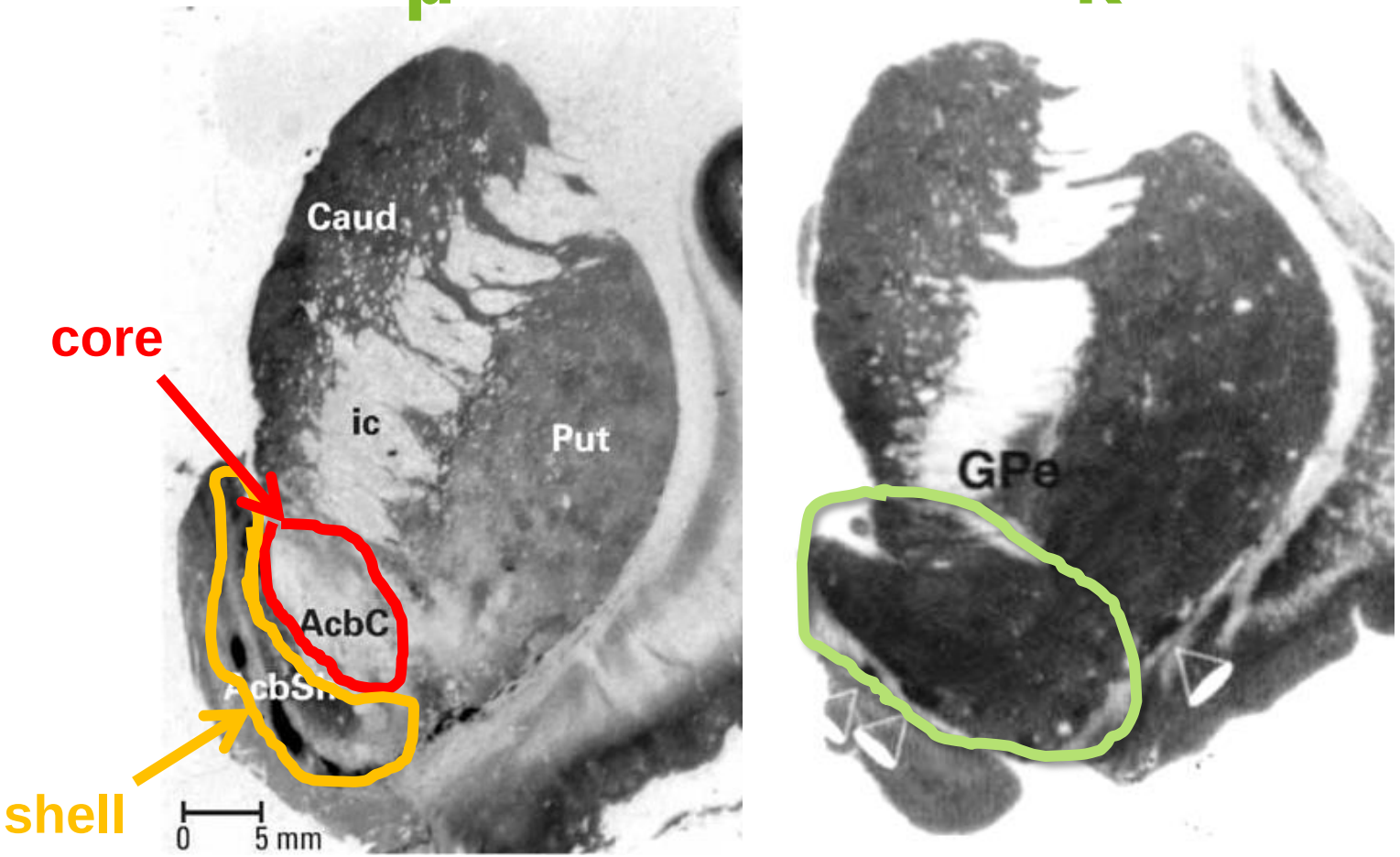
Morris et al. (2014) Yale J Biol Med. 2014 Mar; 87(1): 33–54.

[1] Yale School of Engeneering and Applied Science

Nucleus accumbens MOP vs. KOP

μ

κ



[^{3}H]DAMGO

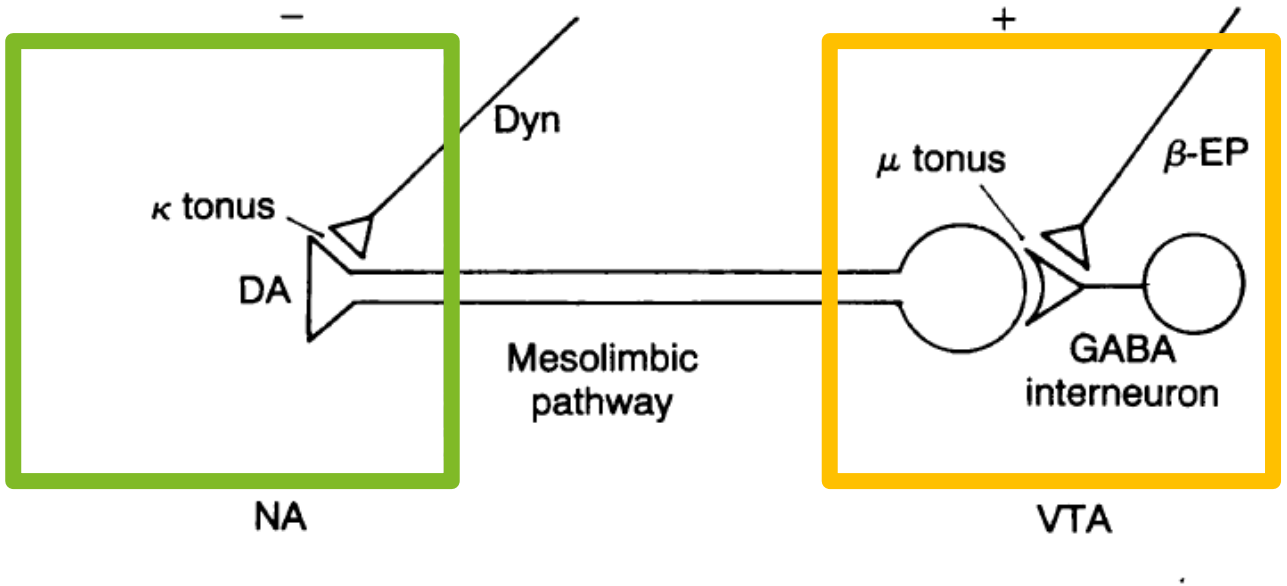
[^{3}H]bremazocine

Voorn et al. (1996) Neuroscience. 1996 Dec;75(3):777-92
Vonkeman et al. (1996). J Comp Neurol. 1996 Oct 14;374(2):223-9.

KOP znižujú a MOP zvyšujú výdaj dopamínu v NAc



Rainer Spanagel [1]
(1961 -)



[1] Institute of Psychopharmacology
Central Institute of Mental Health , University of Heidelberg

Spanagel et al. Proc Natl Acad Sci U S A. 1992 Mar 15;89(6):2046-50
Margolisová et al. (2006) Proc Natl Acad Sci U S A. 2006 Feb 21; 103(8): 2938–2942

Endogénne opioidy a dopamín

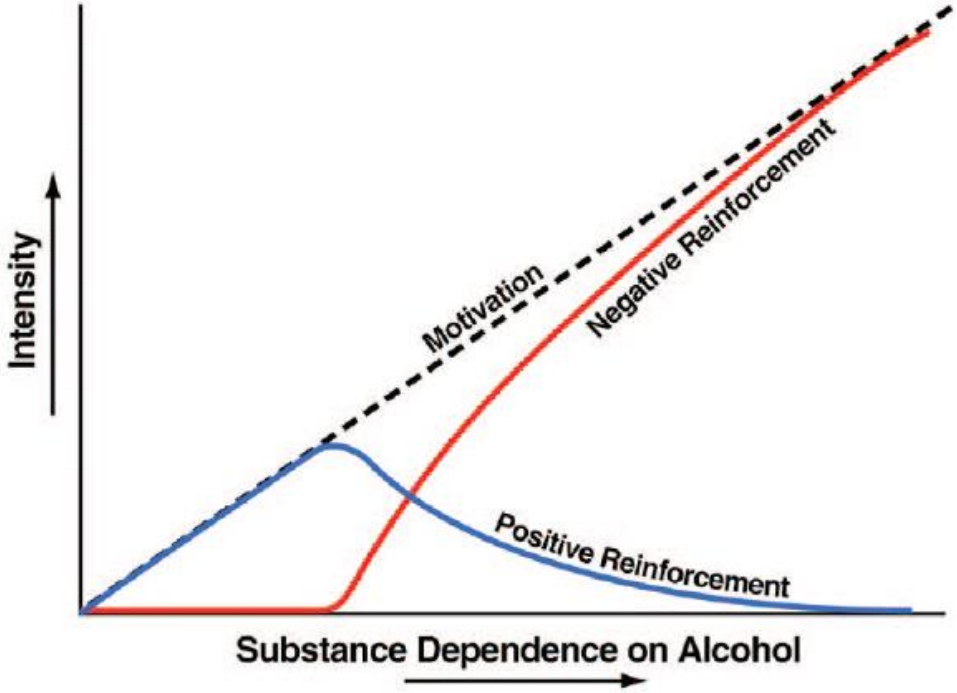
	μ	κ
Hlavný endogénny ligand	β-endorfín	dynorfíny
Vplyv na uvoľňovanie dopamínu v NAc	+	-
Behaviorálny vplyv	Odmena „špička“	Dysfória „pľúšť“

Upravené podľa:
Herz (1997) Psychopharmacology (Bel.). 1997 Jan;129(2):99-111

Motivácia v adiktívnom cykle *(Koob, 2013)*



George F. Koob

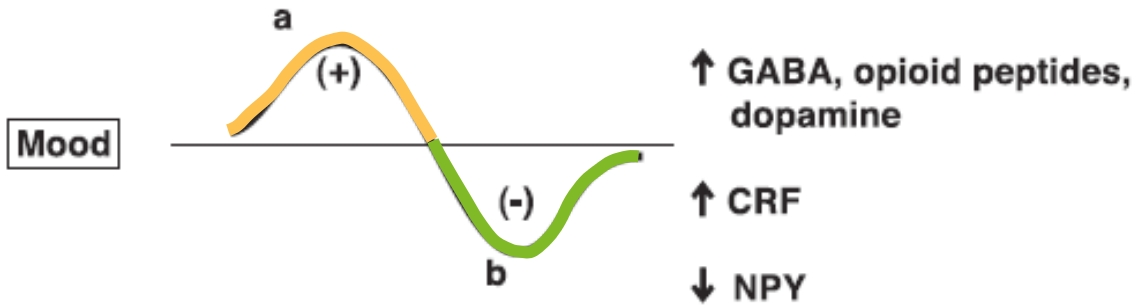


Koob GF (2013). Theoretical frameworks and mechanistic aspects of alcohol addiction: alcohol addiction: alcohol addiction as a reward deficit disorder. In: Sommer WH, Spanagel R editors. *Behavioral Neurobiology of Alcohol Addiction (Series Title: Current Topics in Behavioral Neuroscience* (Vol. **13**), Berlin: Springer-Verlag (2013). p. 3–30.

Opponent-process theory of motivation *(Solomon & Corbit, 1974)*
Allostasis *(Sterling & Eyer, 1988)*

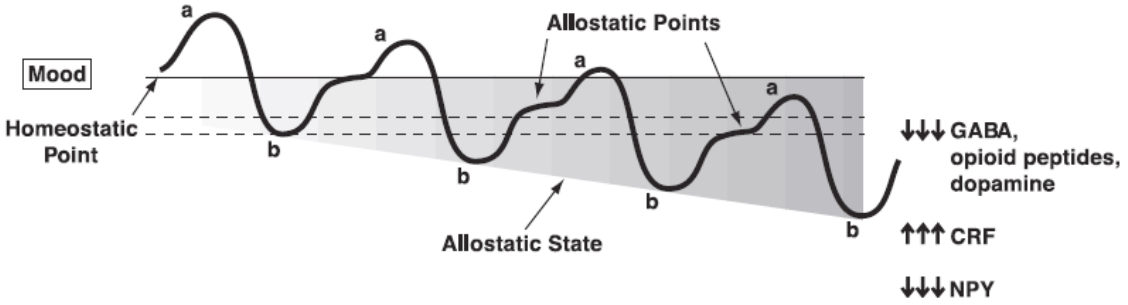


George F. Koob





Michel Le Moal

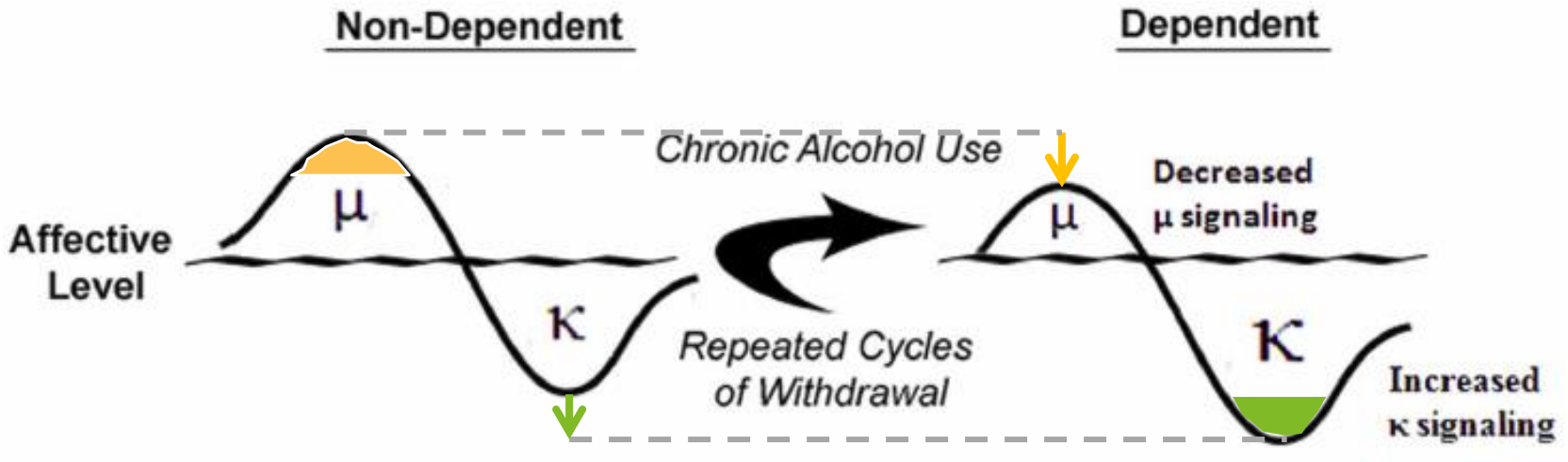


Koob (2003). European Neuropsychopharmacology 13 (2003) 442–452

Solomon & Corbit (1974). Psychol Rev. 1974 Mar;81(2):119-45.

Sterling, P.; Eyer, J. (1988). "Allostasis: A new paradigm to explain arousal pathology". In Fisher, S.; Reason, J. T. *Handbook of life stress, cognition, and health*. Chicester, NY: Wiley.

Pri závislosti je DYN/KOP systém up-regulovaný a naopak MOP systém down-regulovaný



Upravené podľa: Sirohi et al. Front Mol Neurosci. 2012 Sep 27;5:95.
Kissler et al. Biol Psychiatry. 2014 May 15;75(10):774-82.
Shippenberg et al. Pharmacol Ther. 2007 Nov;116(2):306-21.

Genetický výskum svedčí pre úlohu DYN/KOR systému v alkoholizme

- **PPDYN** knock-outované samice myší vykazujú nižšiu preferenciu k alkoholu a majú nižšiu spotrebu.

Blednov et al. (2006)

- **KOR** knock-outované myši majú asi polovičnú spotrebu alkoholu.

Kovacs et al. (2005)

- Variácie v génoch **PDYN** a **OPRK1** sú spojené s rizikom alkoholovej závislosti.

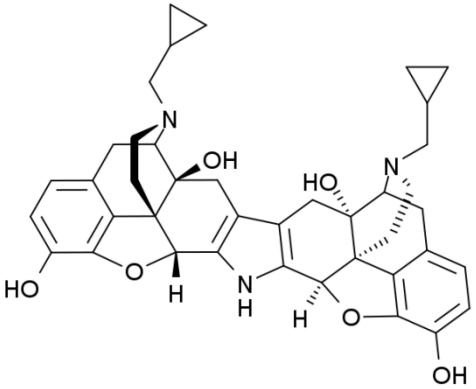
Xuei et al. (2006)

Blednov et al. (2006) Alcohol. 2006 Oct; 40(2):73-86.
Kovacs et al. (2005) Alcohol Clin Exp Res. 2005 May;29(5):730-8X
uei et al. (2006). Mol Psychiatry. 2006 Nov;11(11):1016-24.

Farmakologický výskum na animálnych modeloch svedčí takisto pre úlohu κ-receptorov v závislosti



Brendan Walker



Norbinaltorphimine (nor-BNI)
(selektívny kappa-antagonista)

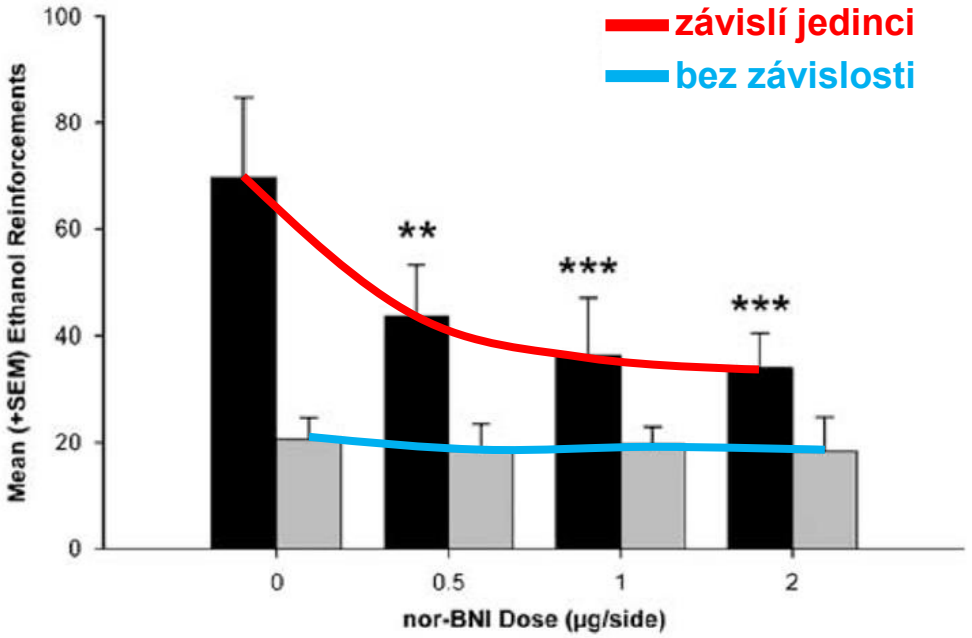
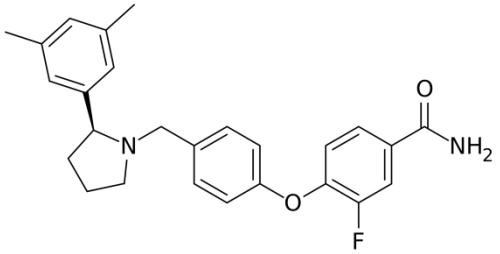


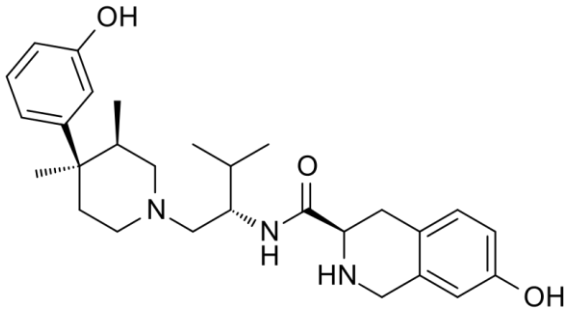
Figure 5.
Mean (+ SEM) responses for ethanol in nondependent and ethanol-dependent animals during acute withdrawal following nor-BNI treatment before self-administration sessions. Nor-BNI selectively attenuated ethanol self-administration in dependent animals (**$p <$ 0.01, ***$p < 0.001$ compared to vapor-exposed vehicle dose).

Walker &Koob (2008)
Neuropsychopharmacology. 2008 Feb;33(3):643-52.

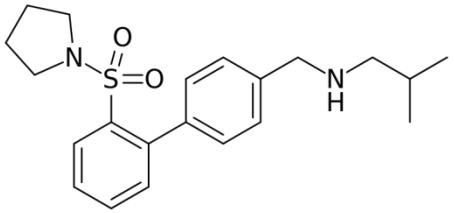
Ďalšie κ-antagonisty – stopnuté vo fáze I



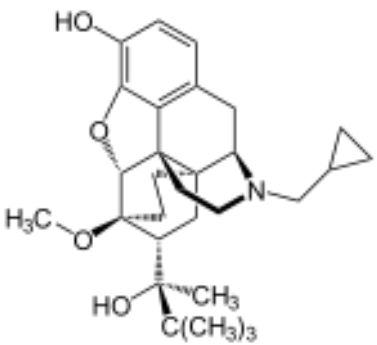
LY2456302 (CERC-501)
(Eli Lilly, Cerecor, Inc.)
11 Jul 2011 Discontinued phase I



JDTic
(komorová tachyarytmia)

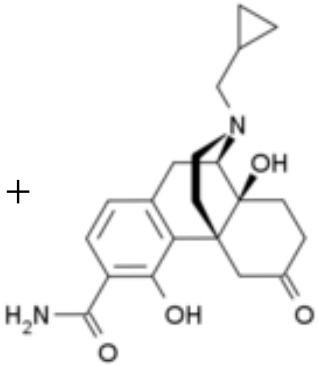


PF-4455242
(Pfizer, Inc.)
9/2010 stopped on BIP



Buprenorphine

\+



Samidorphan

=

ALKS-5461
(Alkermes, Inc.)
Fáza 3 na MDD

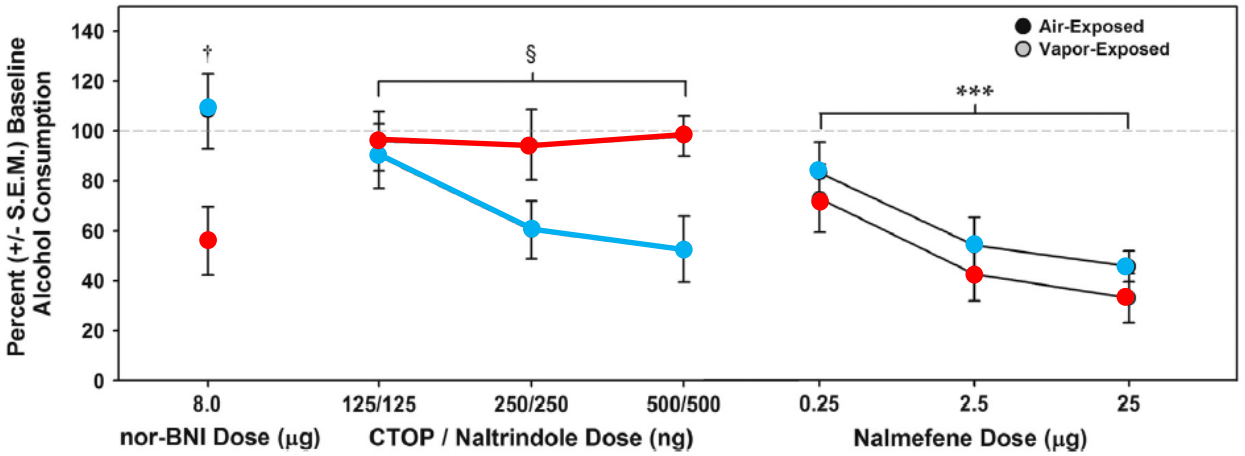
www.clinicaltrials.gov

Antagonizmus κ vs. μ



Jessica L. Kisslerová

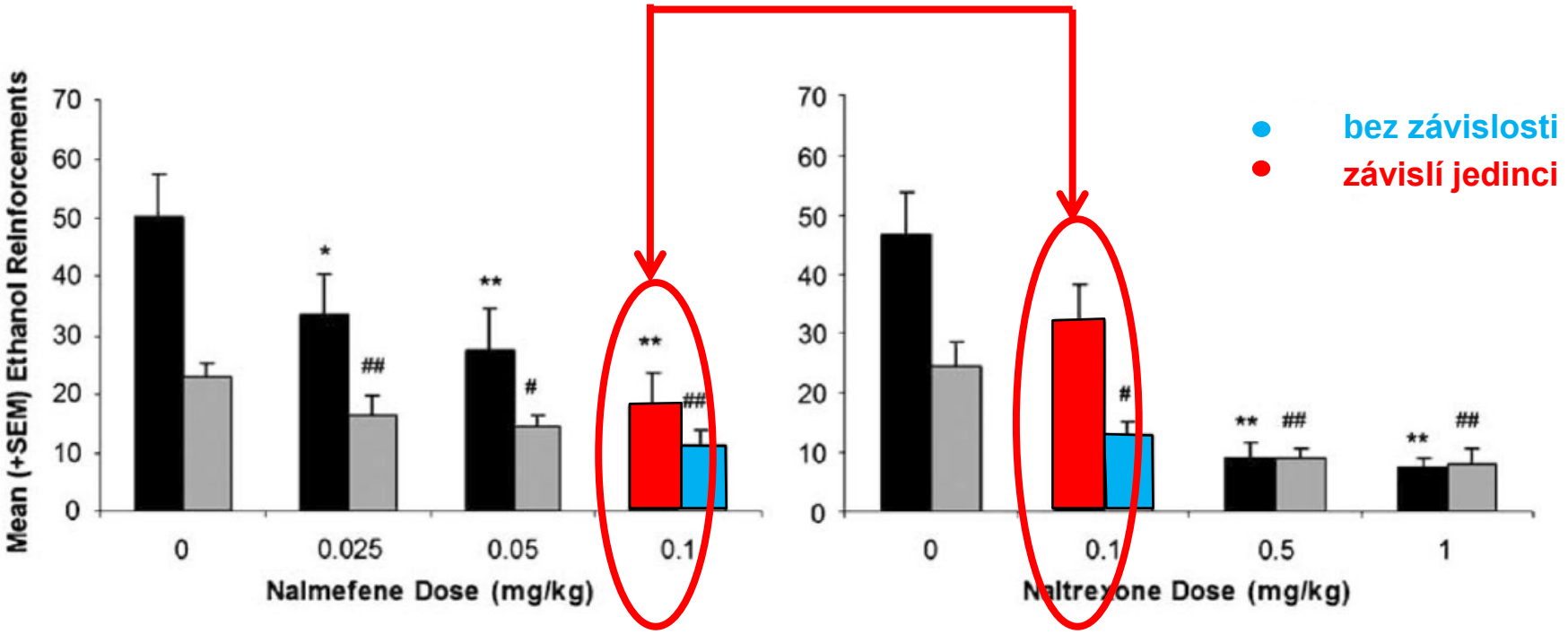
- bez závislosti
- závislí jedinci



κ μδ κμ

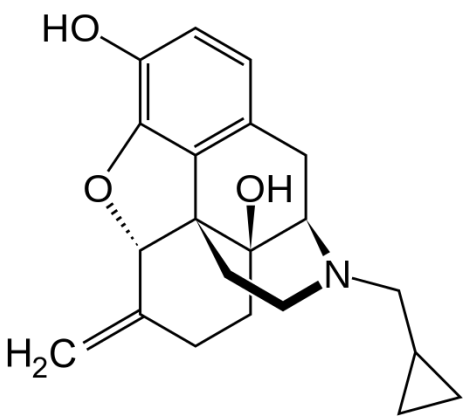
Kissler J.L et al. Biol Psychiatry. 2014 May 15;75(10):774-82

Nalmefén (0,1 mg/kg) účinnejší ako naltrexón (0,1 mg/kg) u závislých podkanov

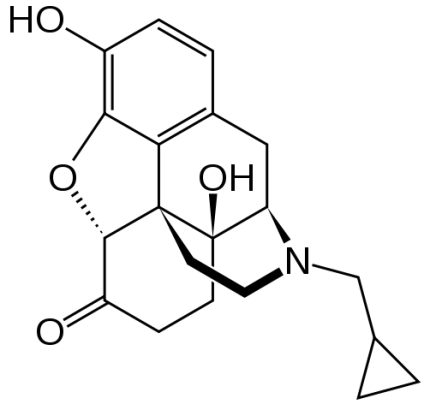


Walker, Koob (2008). Neuropsychopharmacology. 2008 Feb;33(3):643-52.

Afinita k receptorom (K_i)



nalmefén



naltrexón

Ki / EC50 (nM)	μ [^{3}H]DAMGO	κ [^{3}H]Naltrindole	δ [^{3}H]U69,593
nalmefén	1,8	1,6	40
naltrexón	1,7	3,9	58

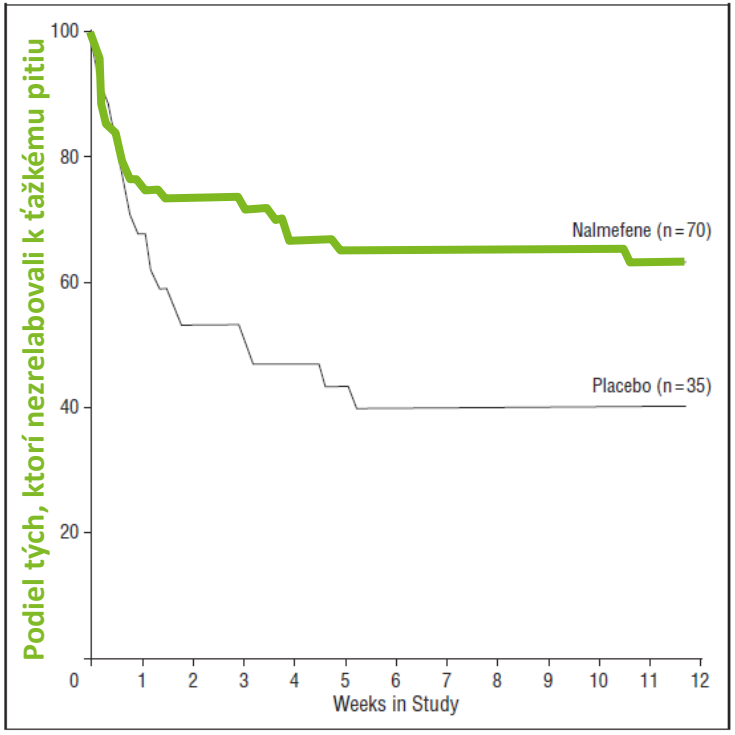
Walker (2014) – prezentácia na ECNP

Nalmefén - fáza II *(Masonová a kol., 1999)*

A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence.



Barbara J. Masonová



Rates of never relapsing to heavy drinking from randomization (week 0) through the end of double-blind treatment (week 12).

Riziko relapsu (PCB vs. NMF)

OR = 2,4

Mason et al. (1999). Arch Gen Psychiatry. 1999 Aug;56(8):719-24.

Mason et al. (1994). Alcohol Clin Exp Res. 1994 Oct;18(5):1162-7

Fáza III – ESENSE 1 *(Mann a kol., 2013)*, ESENSE 2 *(Gual a kol., 2013)*

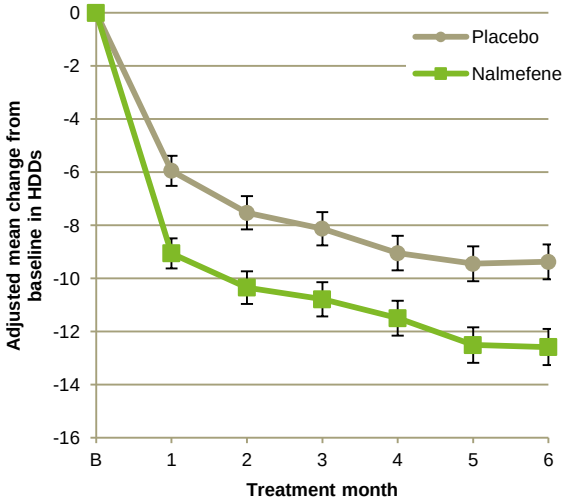


Karl Mann

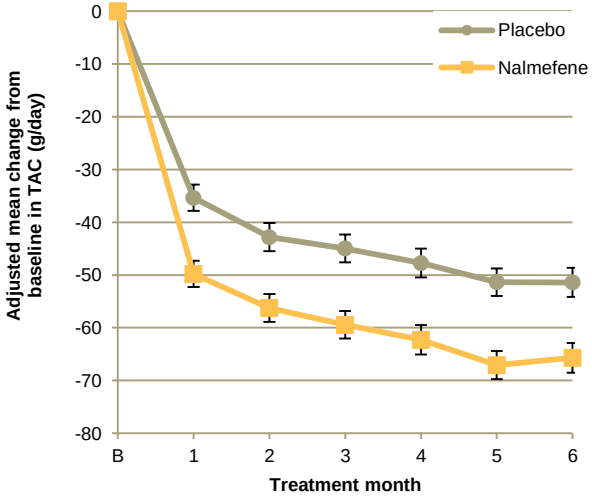


Antoni Gual

Zmena
heavy drinking days
(HDDs)



Zmena
total alcohol consumption
(TAC)



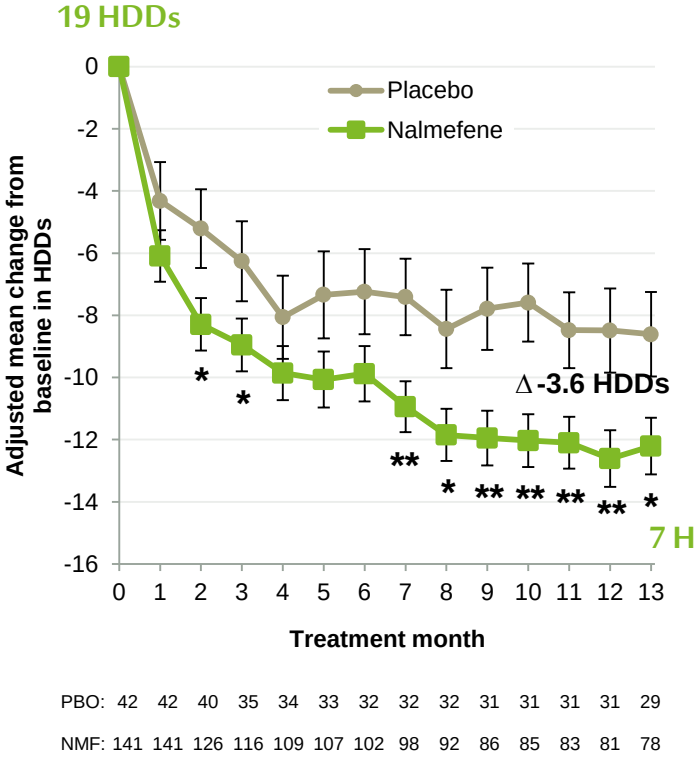
Mann et al. Biol Psychiatry 2013;73(8):706–713;
Gual et al. Eur Neuropsychopharmacol 2013;23(11):1432–1442;
Prevzaté z: van den Brink et al. Alcohol Alcohol 2013;48(5):570–578

Fáza III – SENSE *(van den Brink a kol., 2014)*



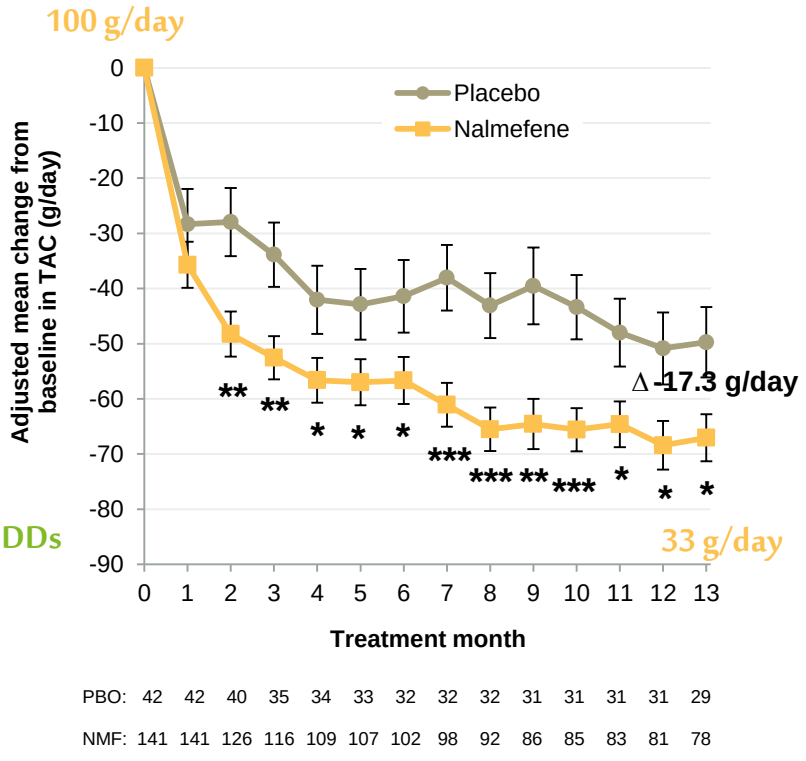
Wim
van den Brink

Zmena
heavy drinking days
(HDDs)



PBO:	42	42	40	35	34	33	32	32	32	31	31	31	31	29
NMF:	141	141	126	116	109	107	102	98	92	86	85	83	81	78

Zmena
total alcohol consumption
(TAC)



PBO:	42	42	40	35	34	33	32	32	32	31	31	31	31	29
NMF:	141	141	126	116	109	107	102	98	92	86	85	83	81	78

MMRM (OC) FAS estimates and SE; *p<0.05, **p<0.01, ***p<0.001 vs placebo; MMRM=mixed-effect model repeated measure; OC=observed cases; FAS=full analysis set; SE=standard error; HDD=heavy drinking day; TAC=total alcohol consumption; PBO=placebo; NMF=nalmefene

Prevzaté z: van den Brink et al. J Psychopharmacol 2014;28(8):733–744

Ďakujem za pozornosť

miro.grohol@gmail.com