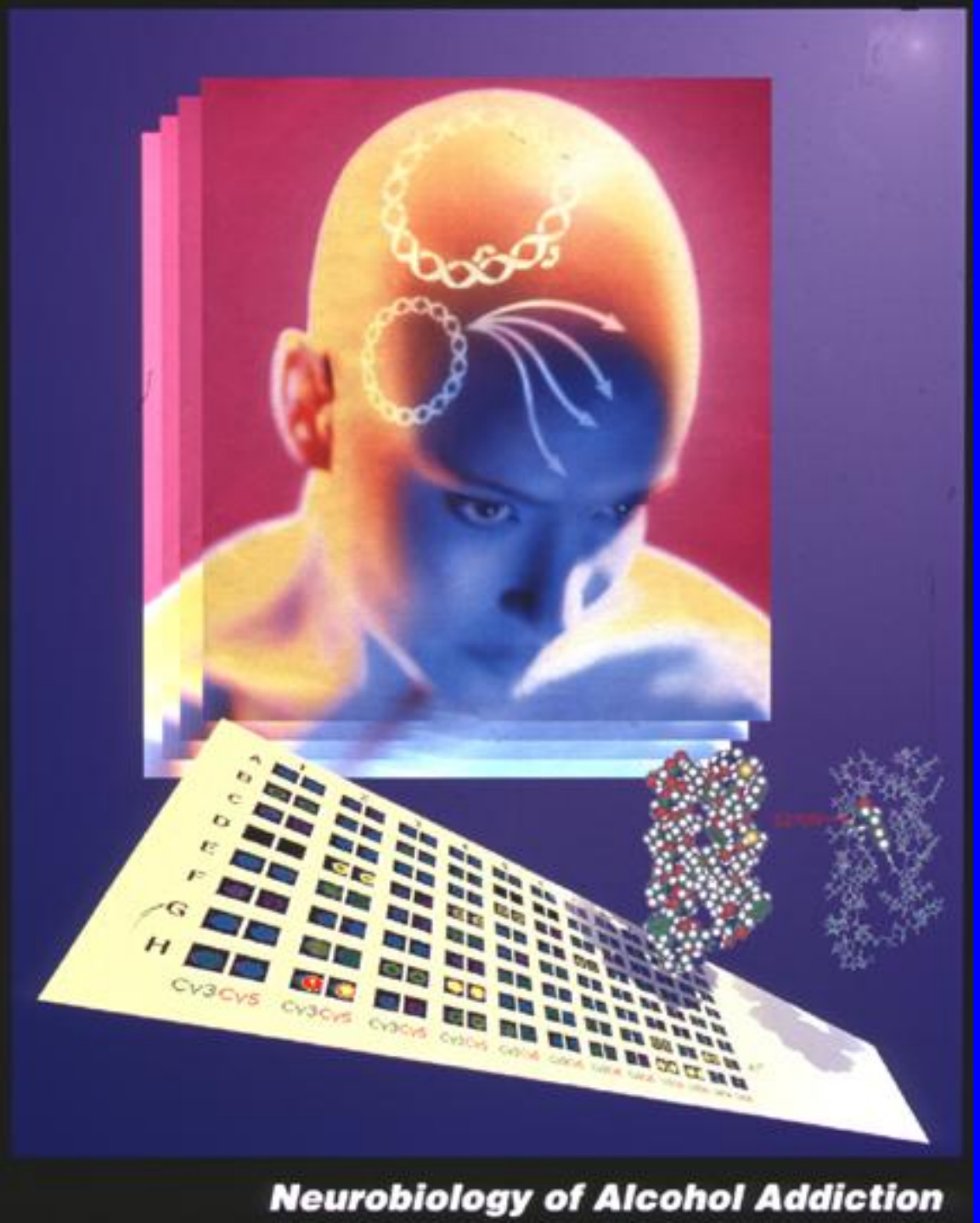


Waggoner Center for Alcohol and Addiction Research

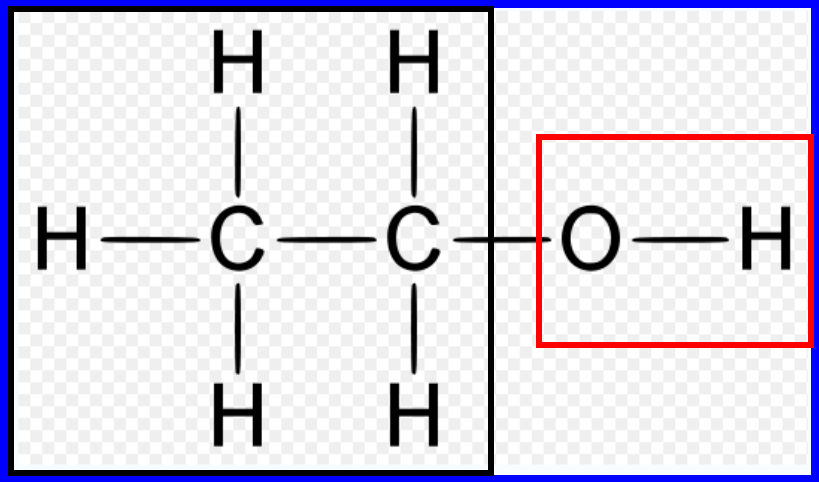
R. Adron Harris, Director

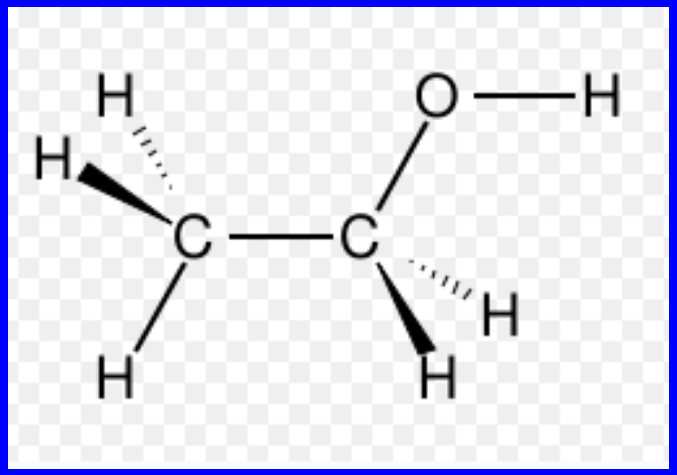
University of Texas Austin

Key Points

- Alcohol requires far higher blood levels than other drugs. As a result, it has more diverse molecular and cellular targets than other drugs
- The alcohol field has made excellent progress in molecular, behavioral and population genetics
- This work absolutely requires the integrated, multi-organ, systems approach which has successfully evolved within NIAAA

Ethanol



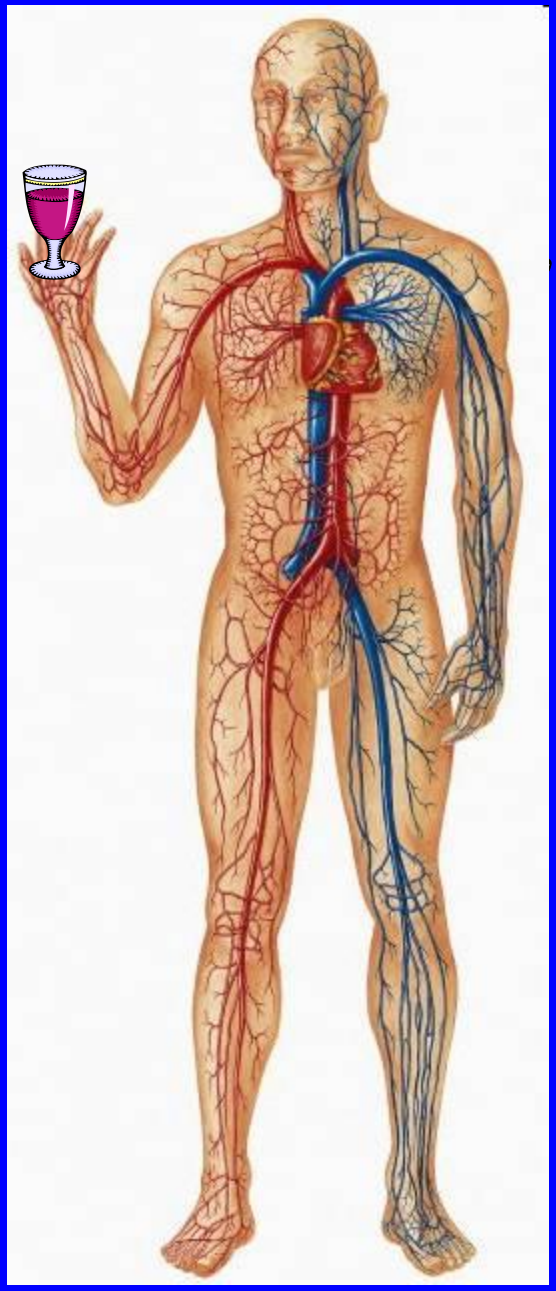


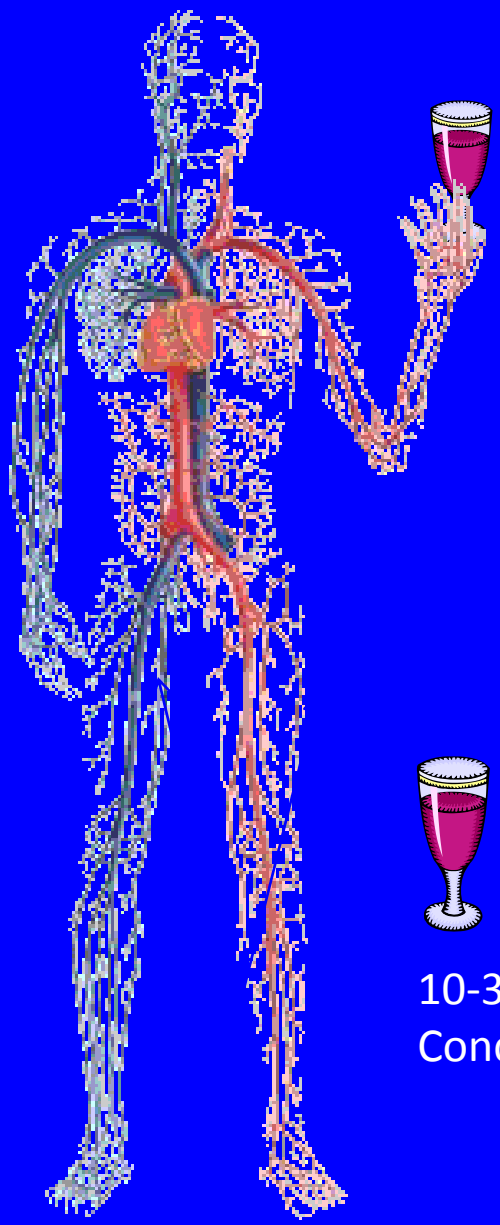
1. Small hydrophilic molecule. Low binding energy. Readily passes through biological membranes (timescale sec-min)
2. Interactions with biological targets
   a. Hydrogen bonding at –OH group
   b. Very weak hydrophobic interactions (-CH3 end of molecule)
   c. Results in low affinity (~mM) interactions with biomolecules

Driver's blood alcohol: 7.27

VILNIUS — Police were astonished by a breath test that registered 18 times Lithuania's legal alcohol limit for drivers. Police said Vidmantas Sungaila, 41, registered 7.27 grams per liter of alcohol in his blood repeatedly on different devices after he was pulled over Saturday for driving his truck down the center of a two-lane highway. Experts say anything above 3.5 grams per liter of alcohol in the blood is lethal for most people.

(A blood ethanol of 7.27 g/l is 158 mM)



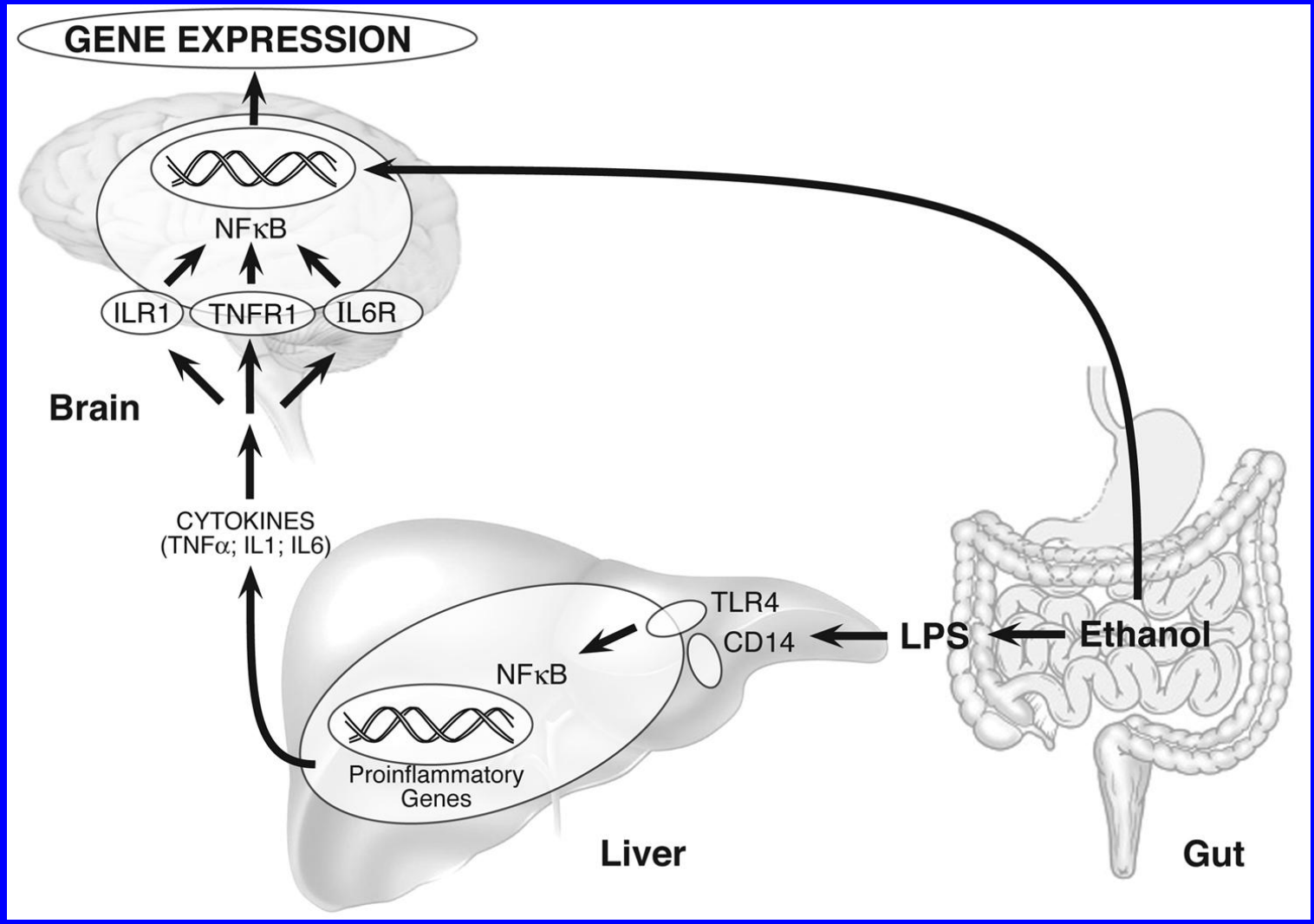


Wine has 2500 mM Ethanol

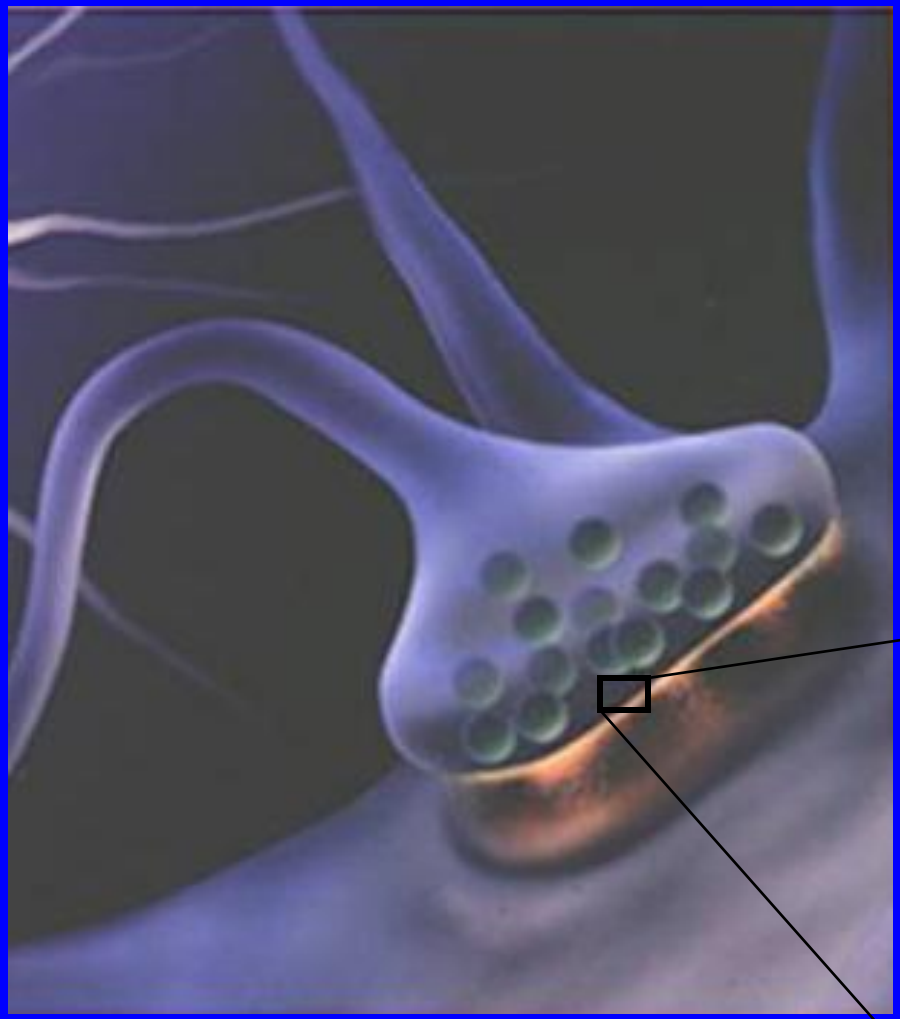
10-30 mM Blood Ethanol Concentration

The human gut contains an abundant bacterial flora. The inset shows a scanning electron micrograph of part of the small intestine, with bacteria shown in green. (Bajzer and Seeley)

Alcohol abuse causes bacterial toxins (LPS) to leak from gut and damage the liver and change gene expression in brain

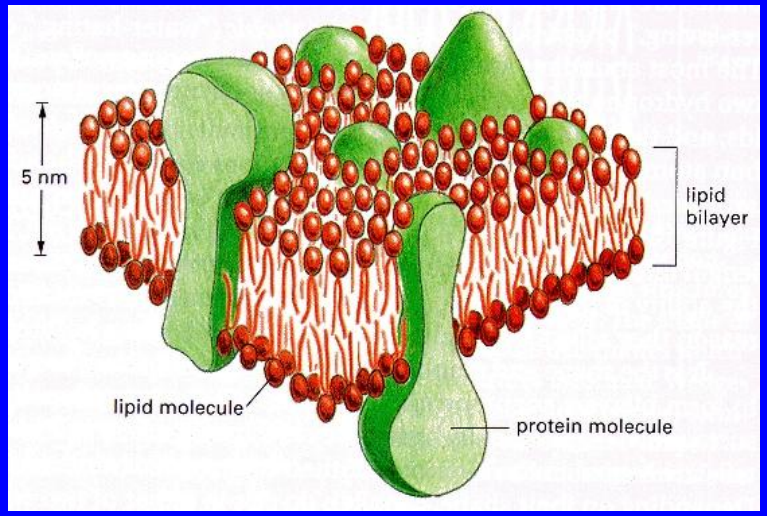


Synaptic Transmission: The Way Drugs Change Brain and Behavior

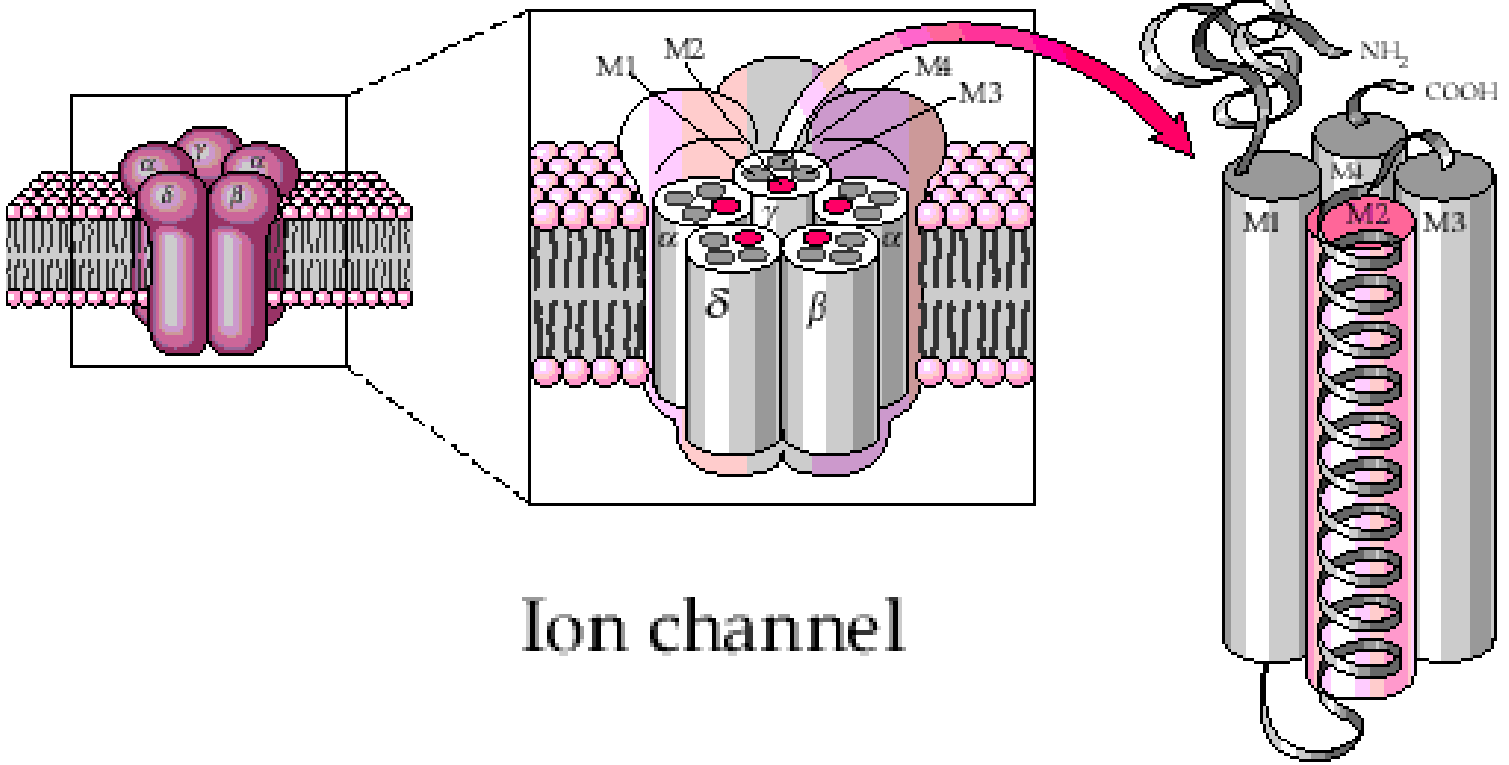


Chemical communication between neurons:

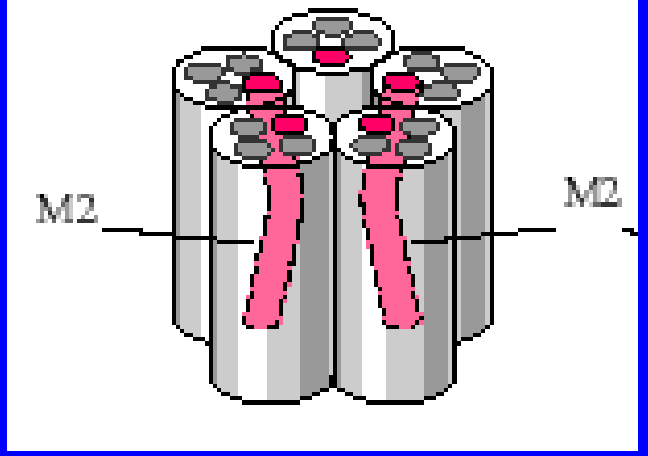
- Release of chemical messengers from one neuron
- Activation of specific proteins in the another neuron
- Excitation or inhibition of the neuron



Overall structure



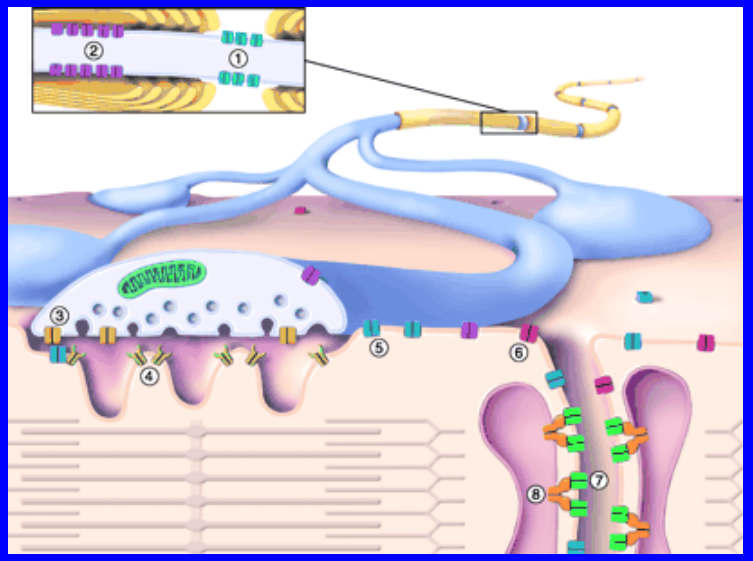
Ion channel



Nicotinic ion channel superfamily

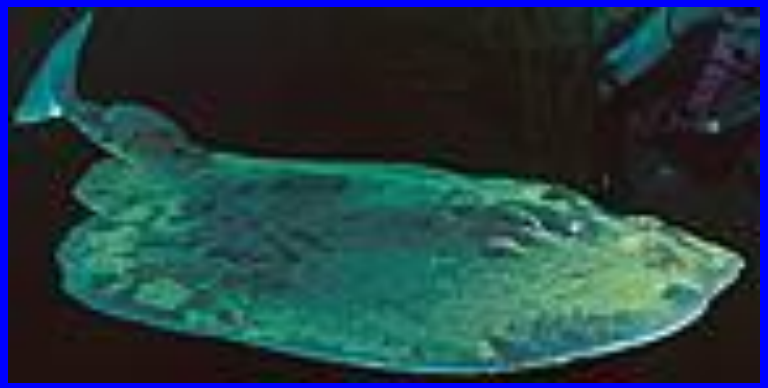
Cationic

- **Nicotinic Acetylcholine receptor (nAChR)**
- **5-HT_3 receptor**



Anionic

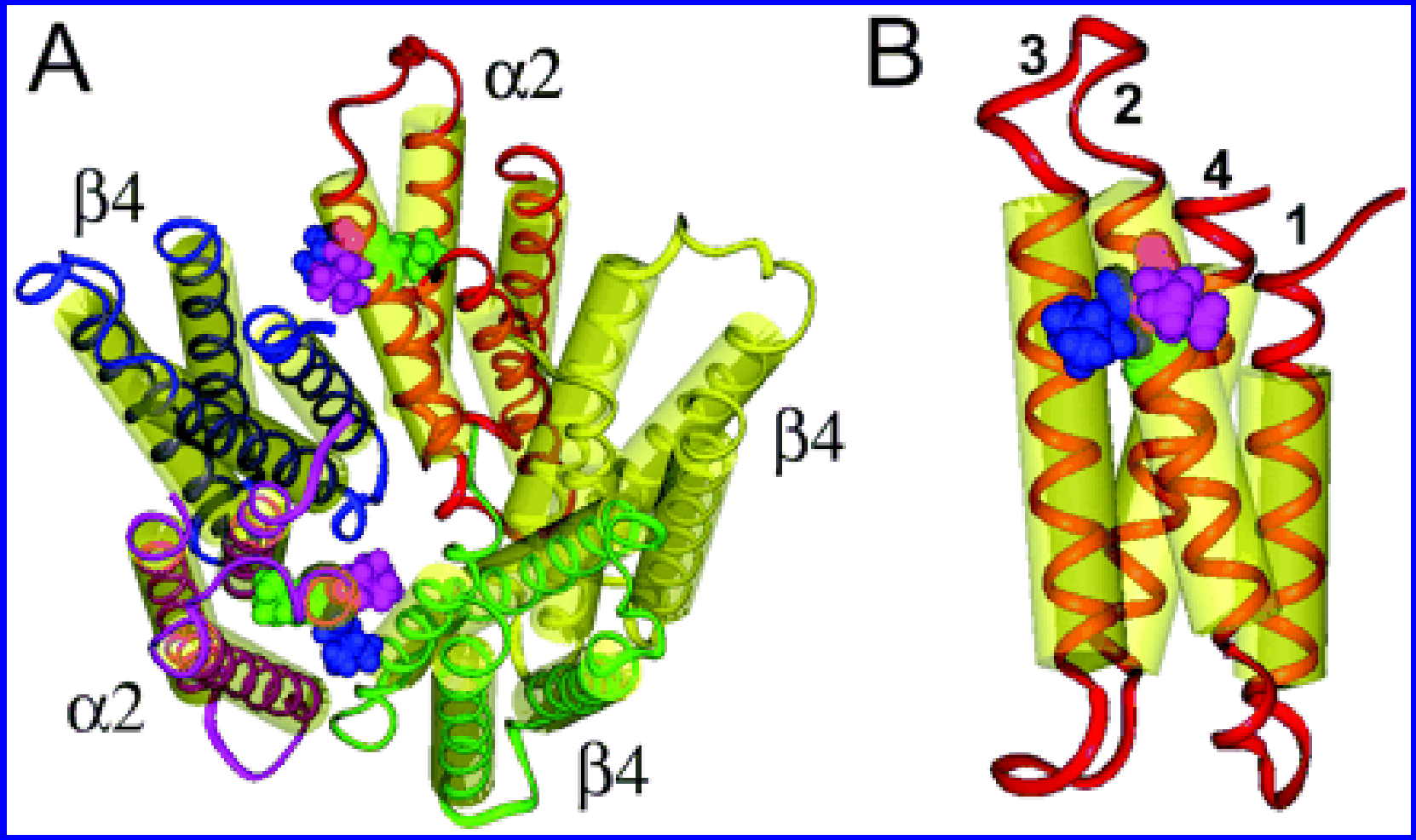
- **$GABA_A$ receptor**
- **$GABA_C$ receptor**
- **Glycine receptor**



Sites of Excitatory and Inhibitory Actions of Alcohols on Neuronal α2β4 Nicotinic Acetylcholine Receptors

C. M. Borghese, L. A. Henderson, V. Bleck, J. R. Trudell, and R. A. Harris

J Pharmacol Exp Ther. 2003 Oct;307:42-52.



Biol Psychiatry. 2009 July

Varenicline reduces alcohol self-administration in heavy-drinking smokers.

McKee SA, **Harrison EL**, **O'Malley SS**, **Krishnan-Sarin S**, **Shi J**, **Tetrault JM**, **Picciotto MR**, **Petrakis IL**, **Estevez N**, **Balchunas E**

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THE GENETIC BASIS OF ALCOHOL AND DRUG ACTIONS

EDITED BY
JOHN C. CRABBE, JR.
AND
R. ADRON HARRIS

Nicotinic ion channel superfamily
A role in genetics of human alcoholism?

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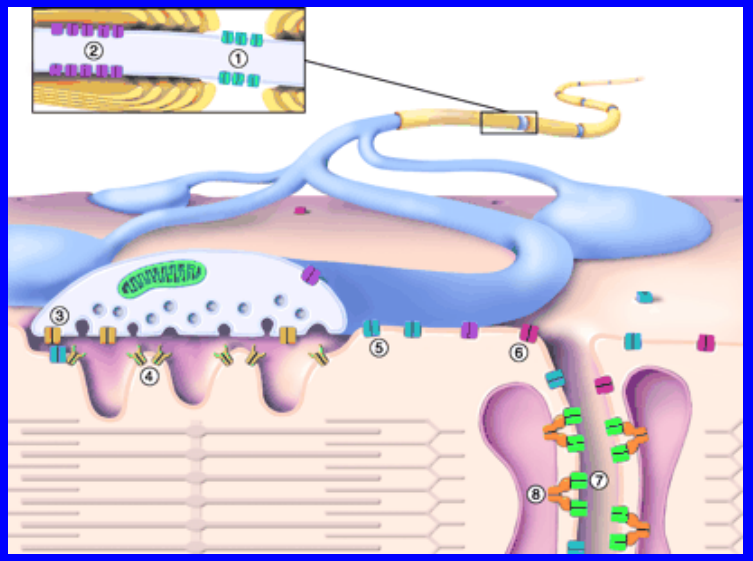

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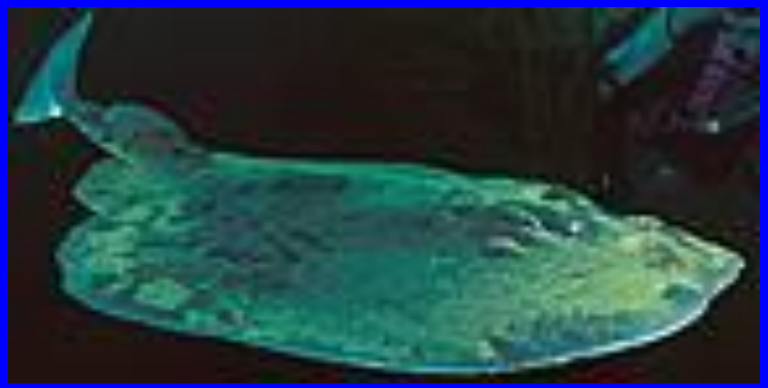

- *Neuropsychopharmacology* (2009)
- **_GABRG1_ and _GABRA2_ as Independent Predictors for Alcoholism in Two Populations**
- Mary-Anne Enoch, Colin A Hodgkinson, Qiaoping Yuan, Bernard Albaugh, Matti Virkkunen and David Goldman
- Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD

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Thanks!