Nicotine Receptors in the Brain: Implications for Addiction and Depression

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The problem:

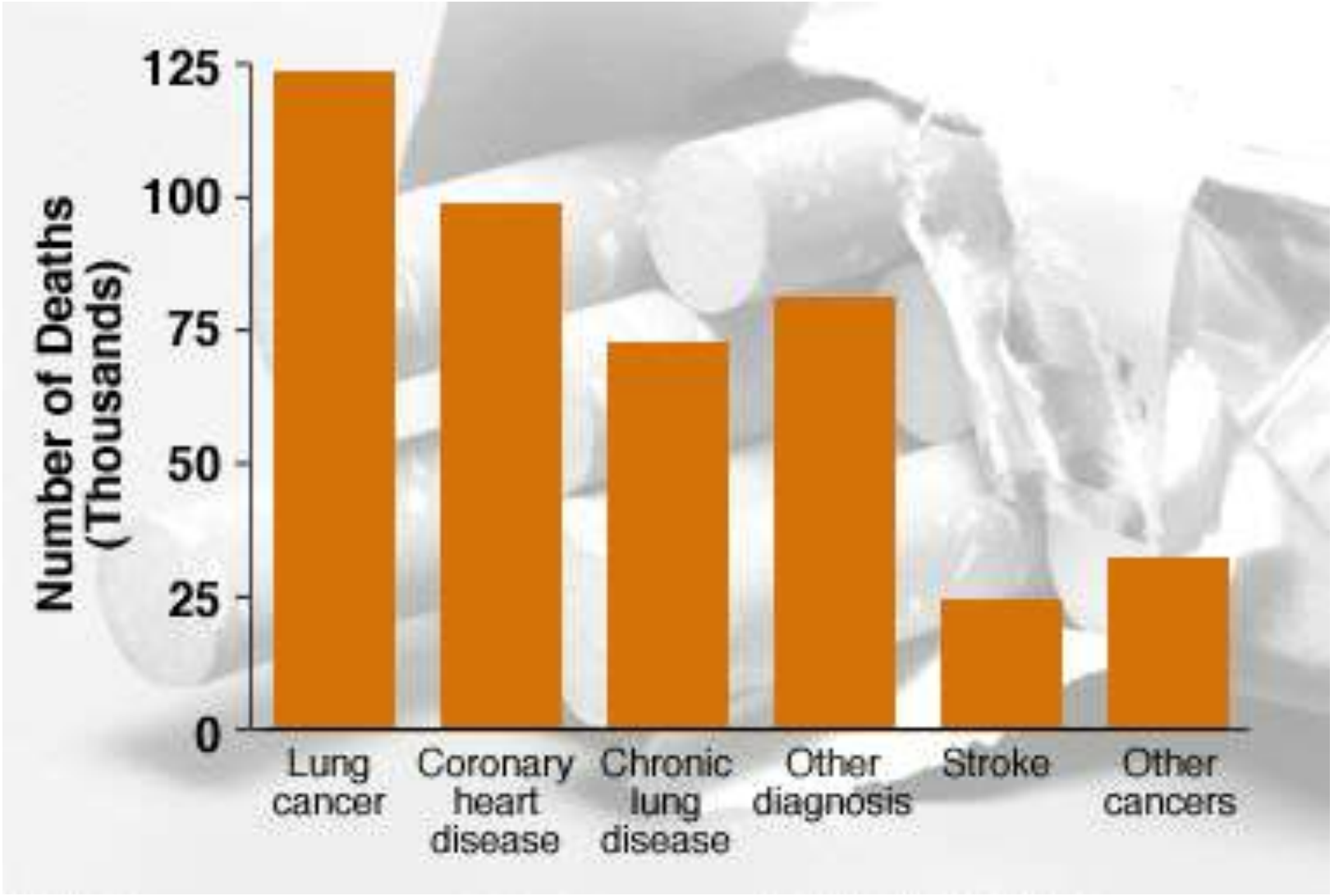
There are more than 350,000 smoking-related deaths every year.

Smoking remains the major cause of preventable death in the United States.

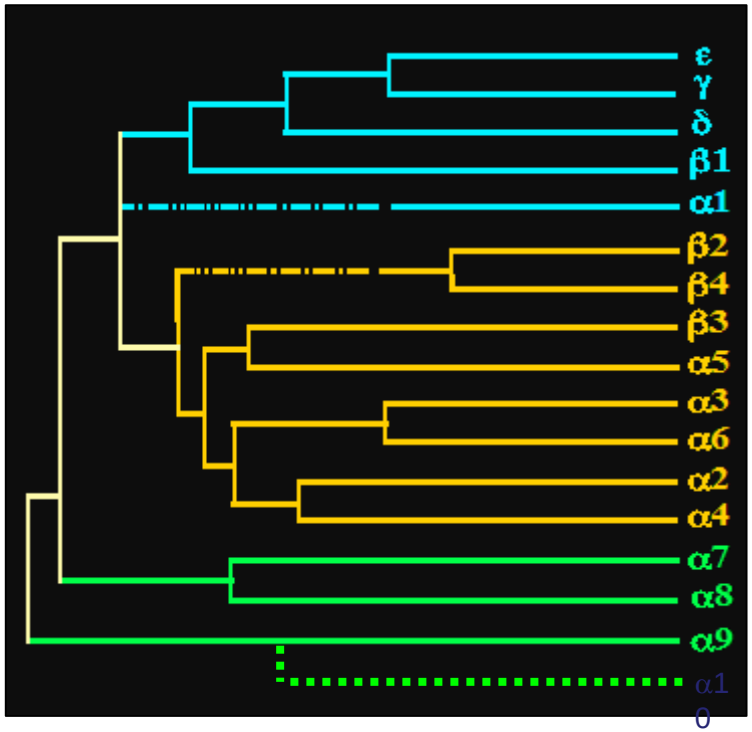
The majority of smokers would like to quit, but have relapsed repeatedly.

Only a small percentage of unaided quit attempts result in cessation one year later.

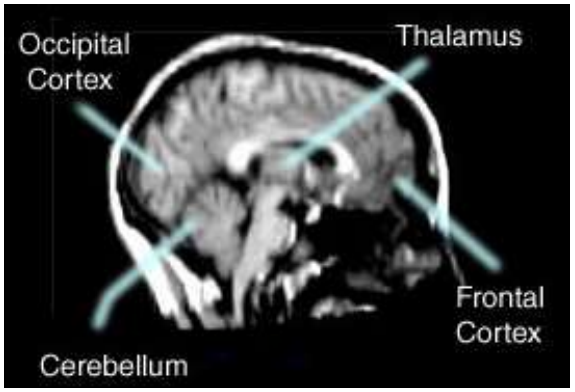
The problem:

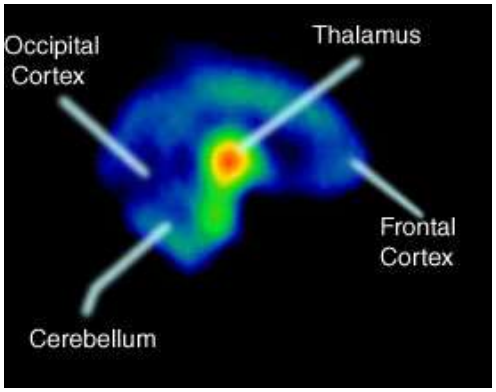

Number of Deaths (Thousands)
125
100
75
50
25
0
Lung cancer
Coronary heart disease
Chronic lung disease
Other diagnosis
Stroke
Other cancers

The problem:



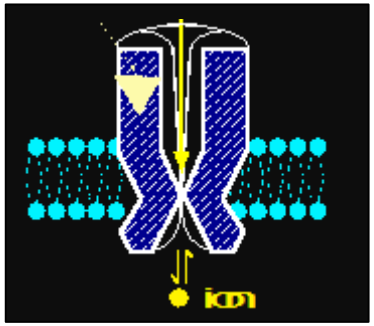
Many nicotine receptors (nAChRs)





Many brain areas expressing nAChRs

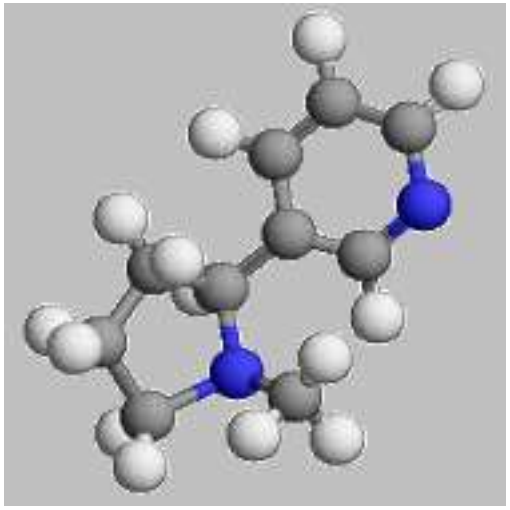
Many reasons people smoke

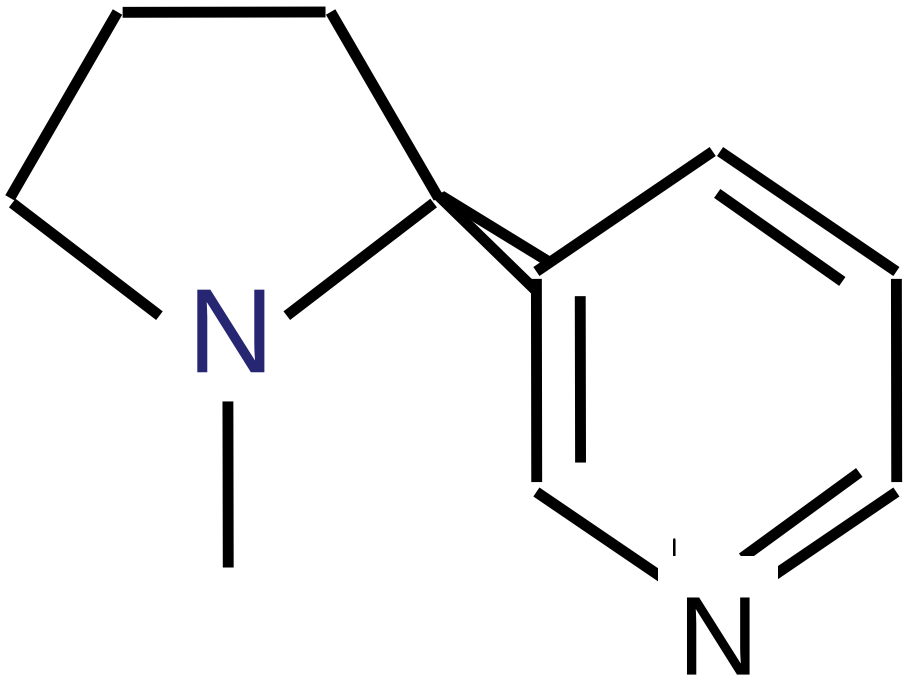


Why do people smoke despite negative effects on health?

Nicotine in tobacco is reinforcing, like other addictive drugs, and drives ongoing smoking.

Nicotine is one of more than 4,000 chemicals in tobacco smoke

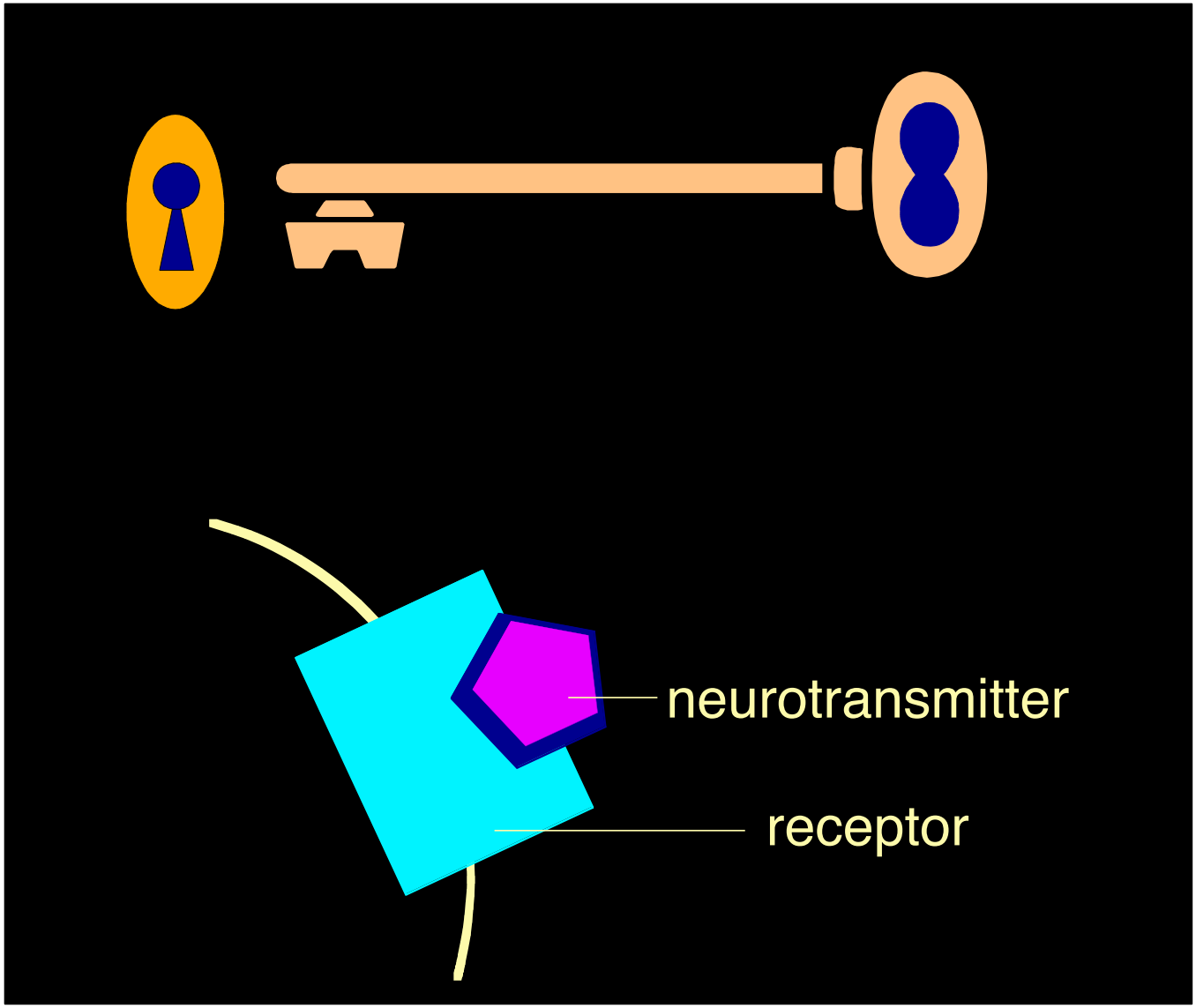




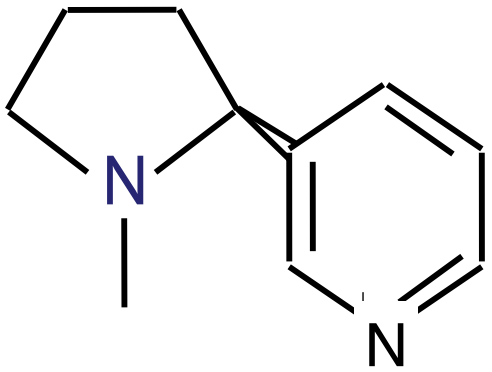
Nicotine is the primary addictive substance in cigarettes.

Cigarette companies have found that changing nicotine levels is the best way to make people smoke more.

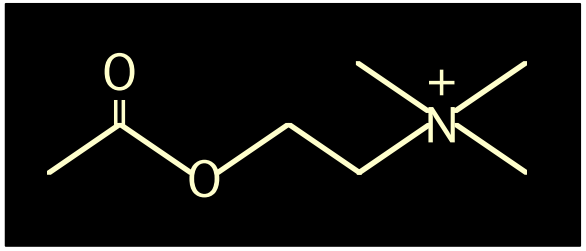
Lock and key model of nicotine receptor function



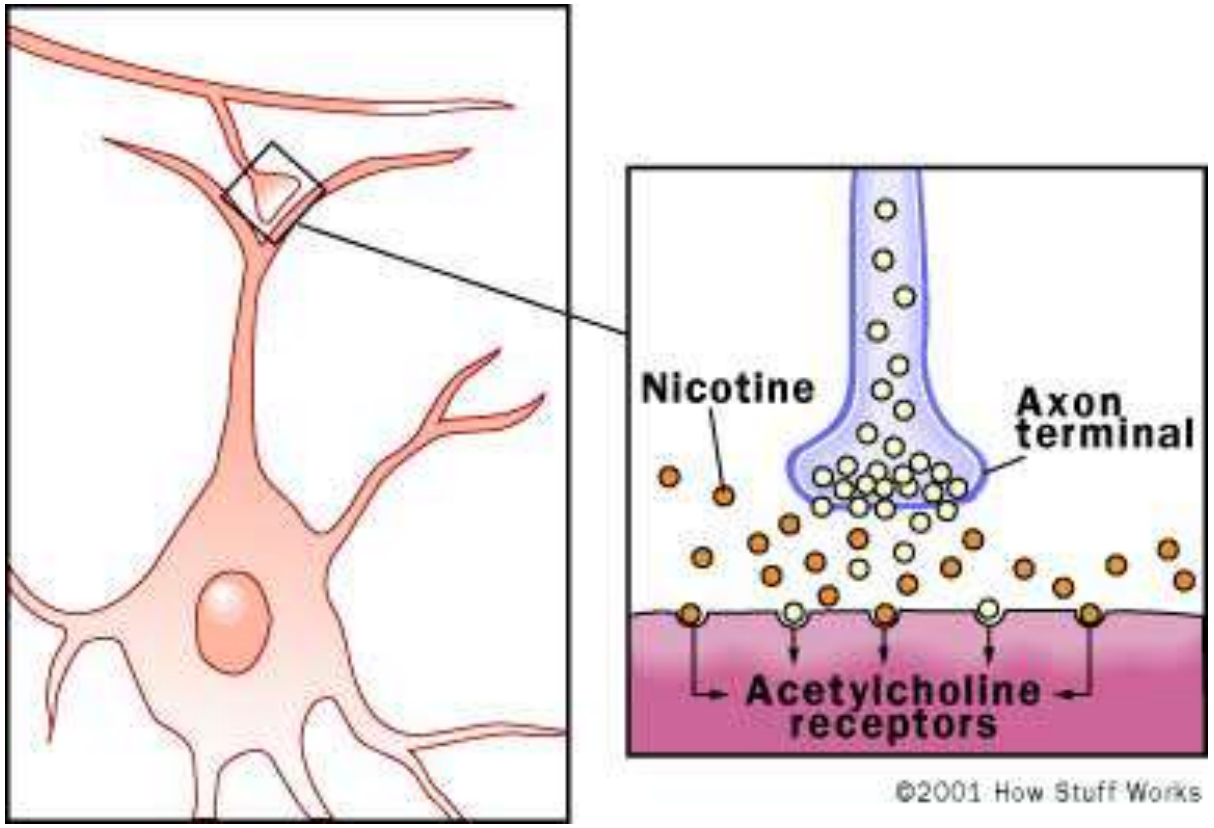
Nicotine binds to receptors for the neurotransmitter acetylcholine in the brain



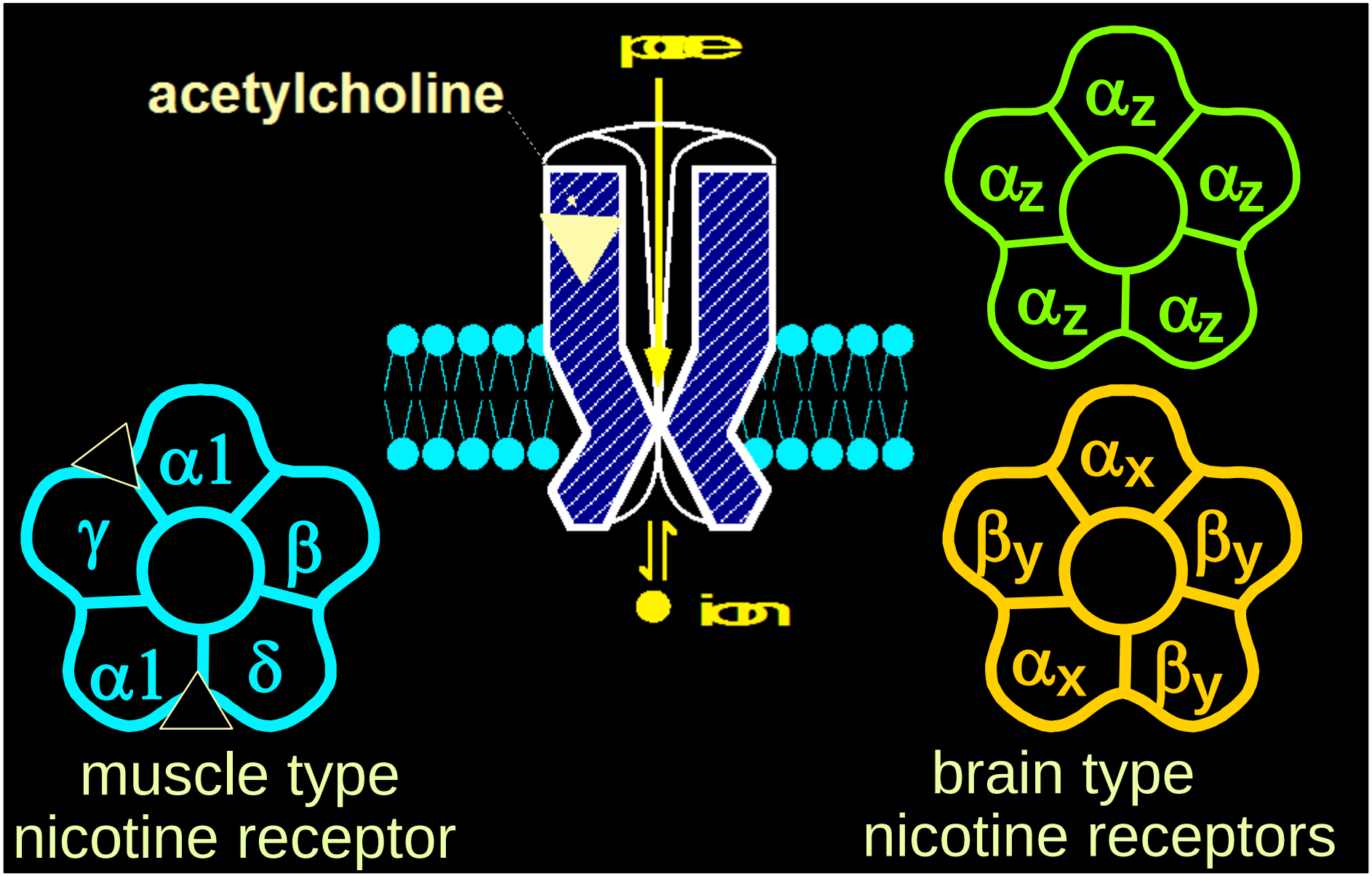
Nicotine



Acetylcholine

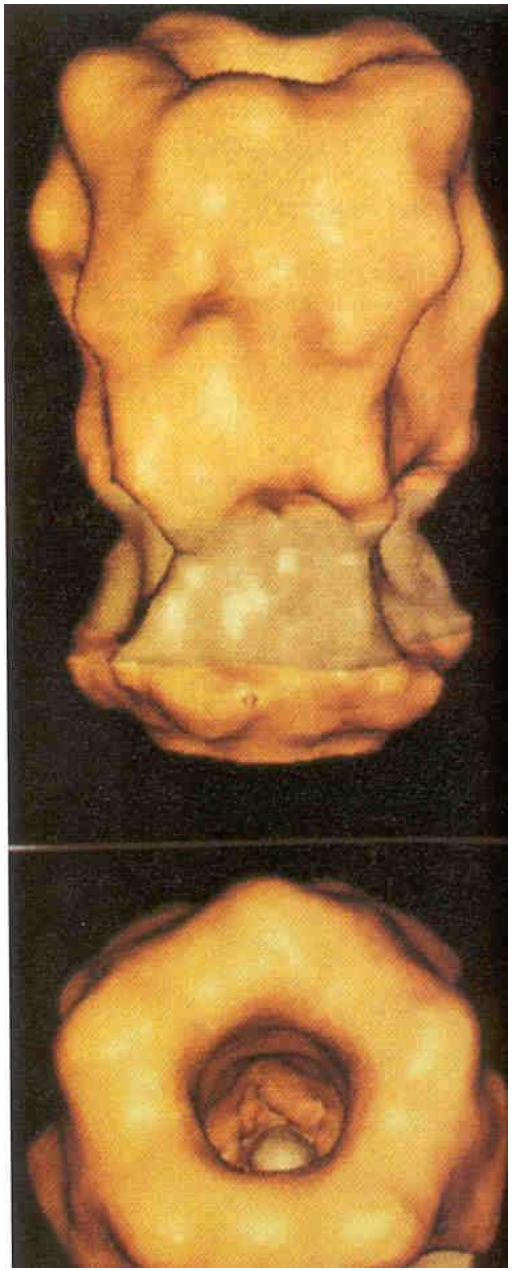


Structure of nicotine receptors

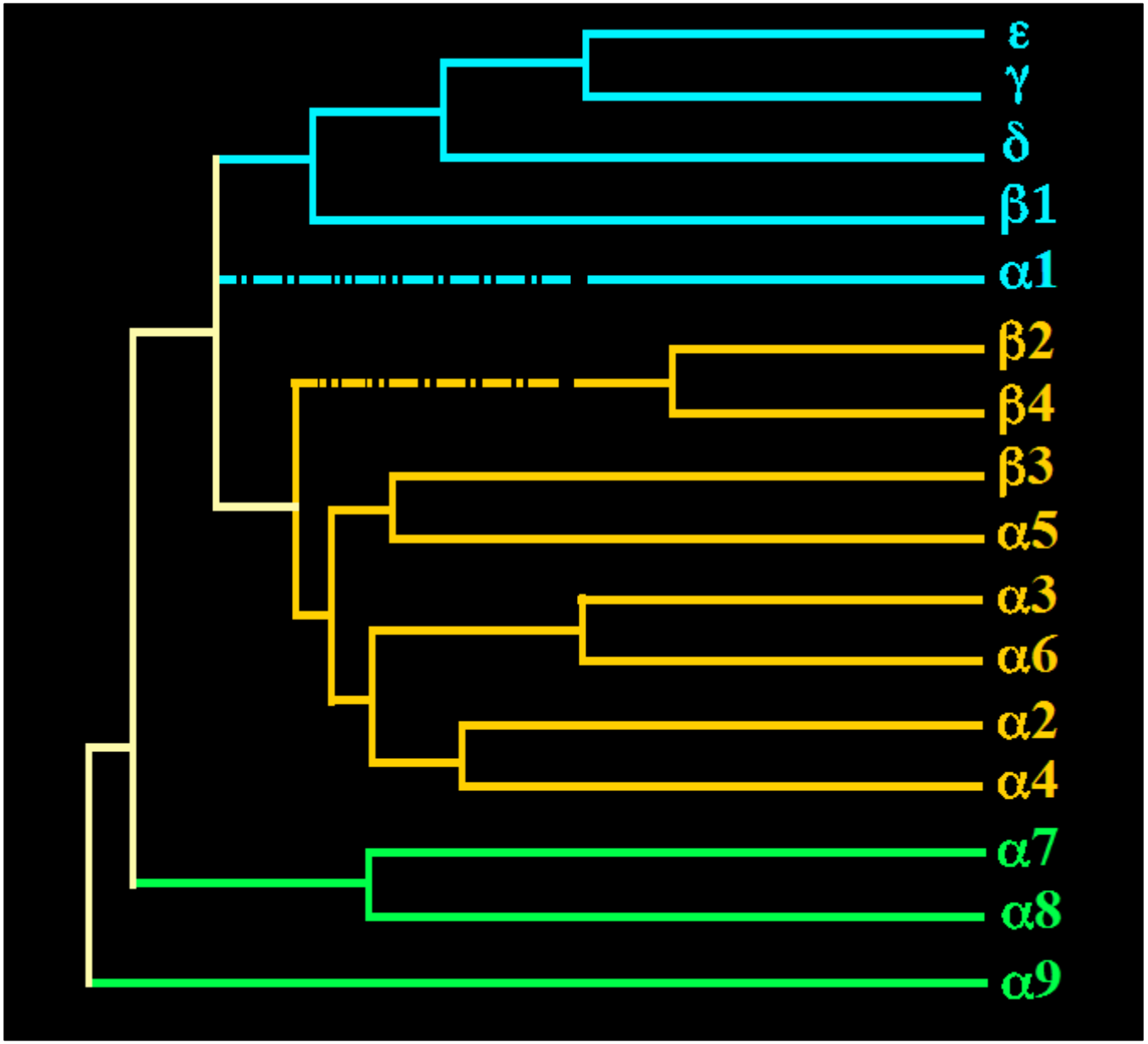


Structure of nicotine receptors

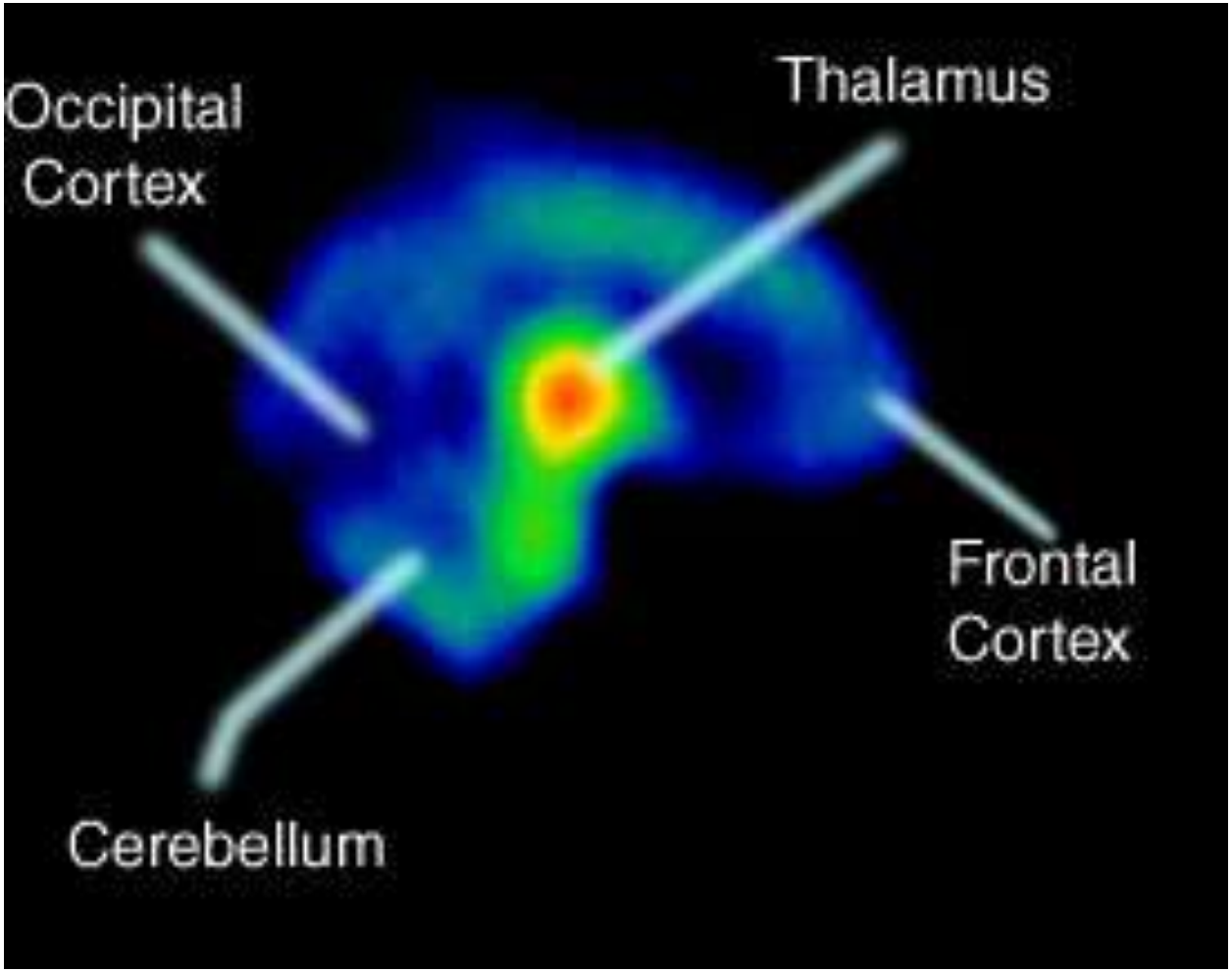
3D computer picture of the nicotine receptor by electron microscopy.



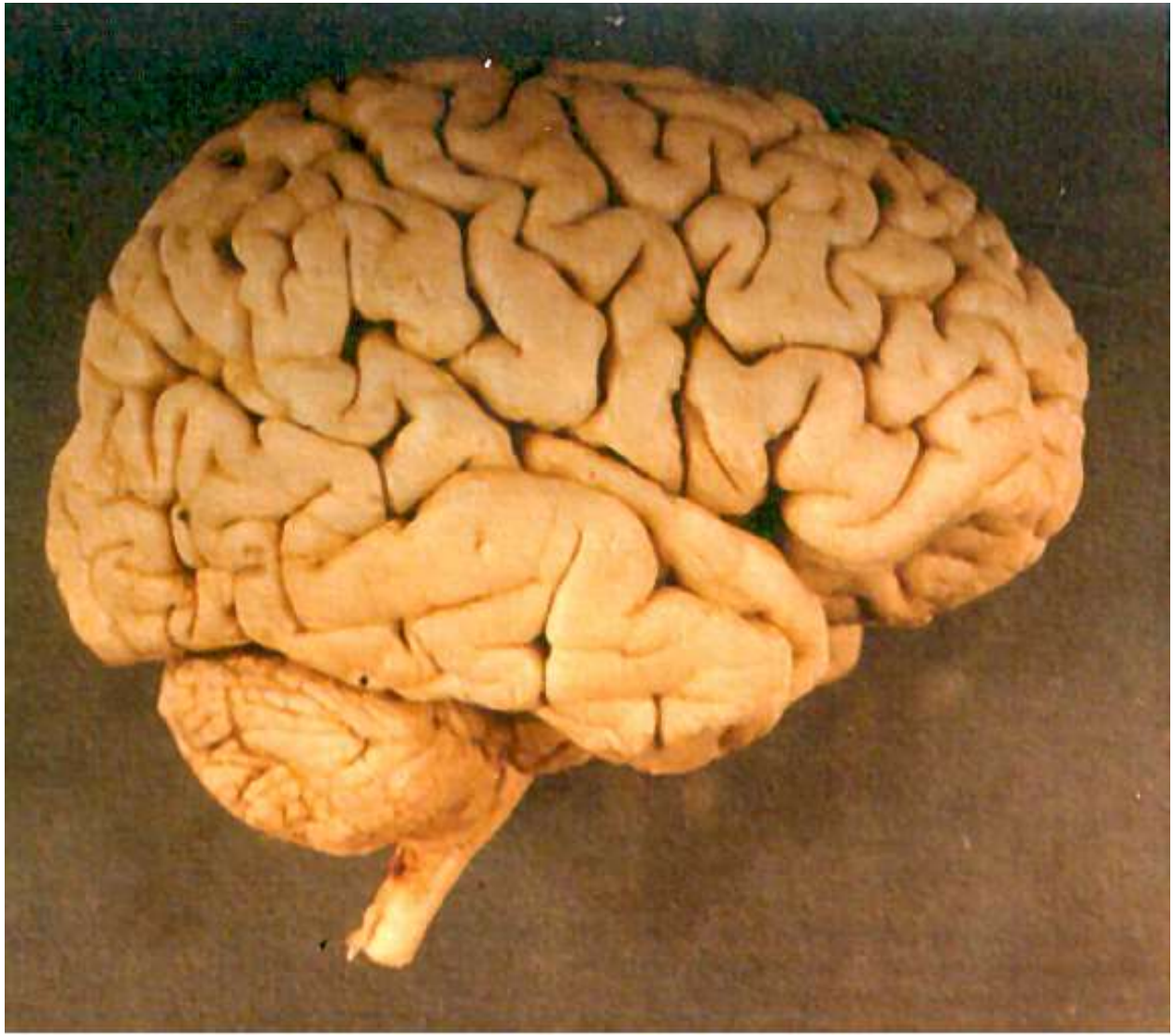
Nicotine receptor family tree



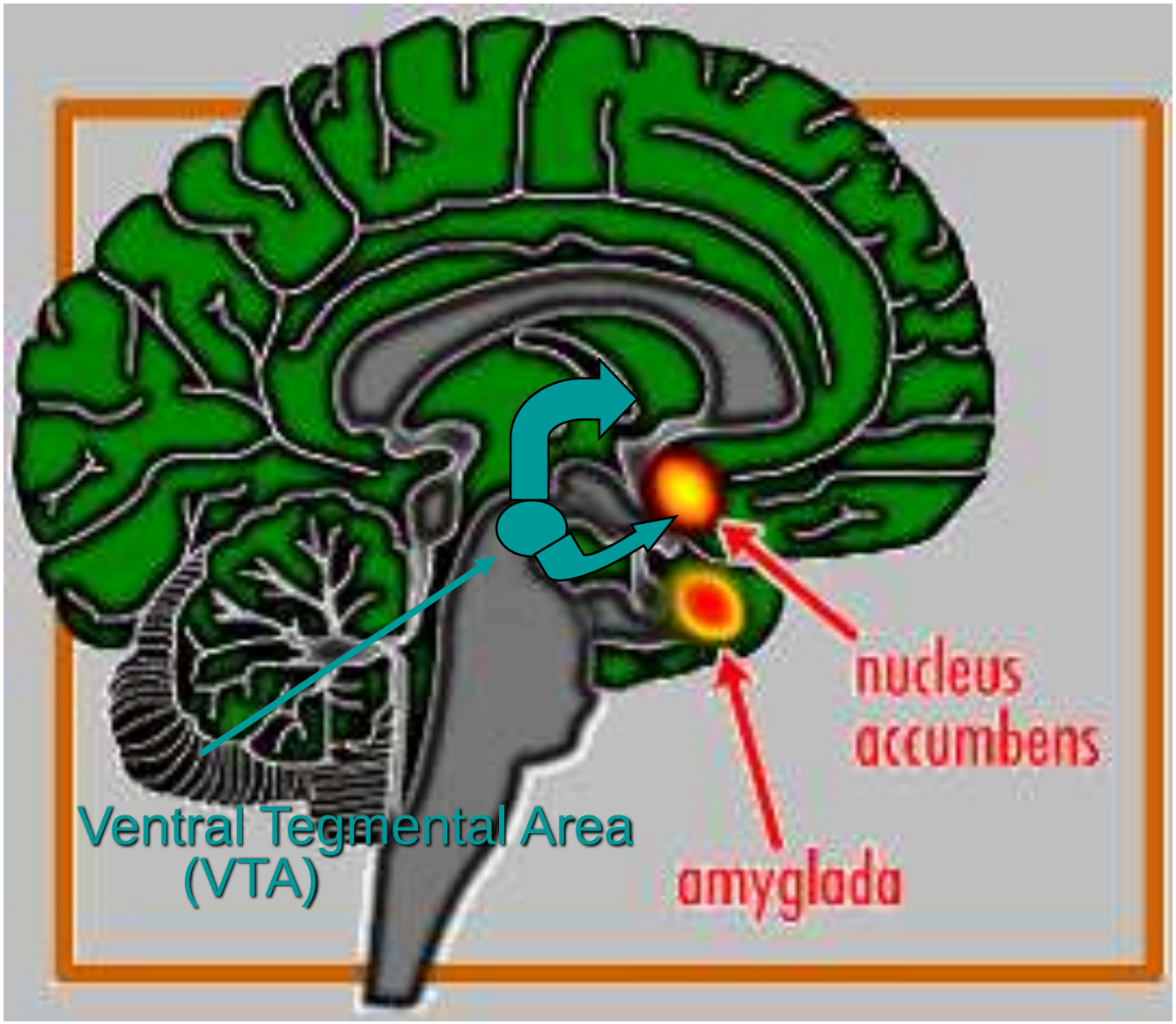
Nicotine binds to specific receptors in most parts of our brain



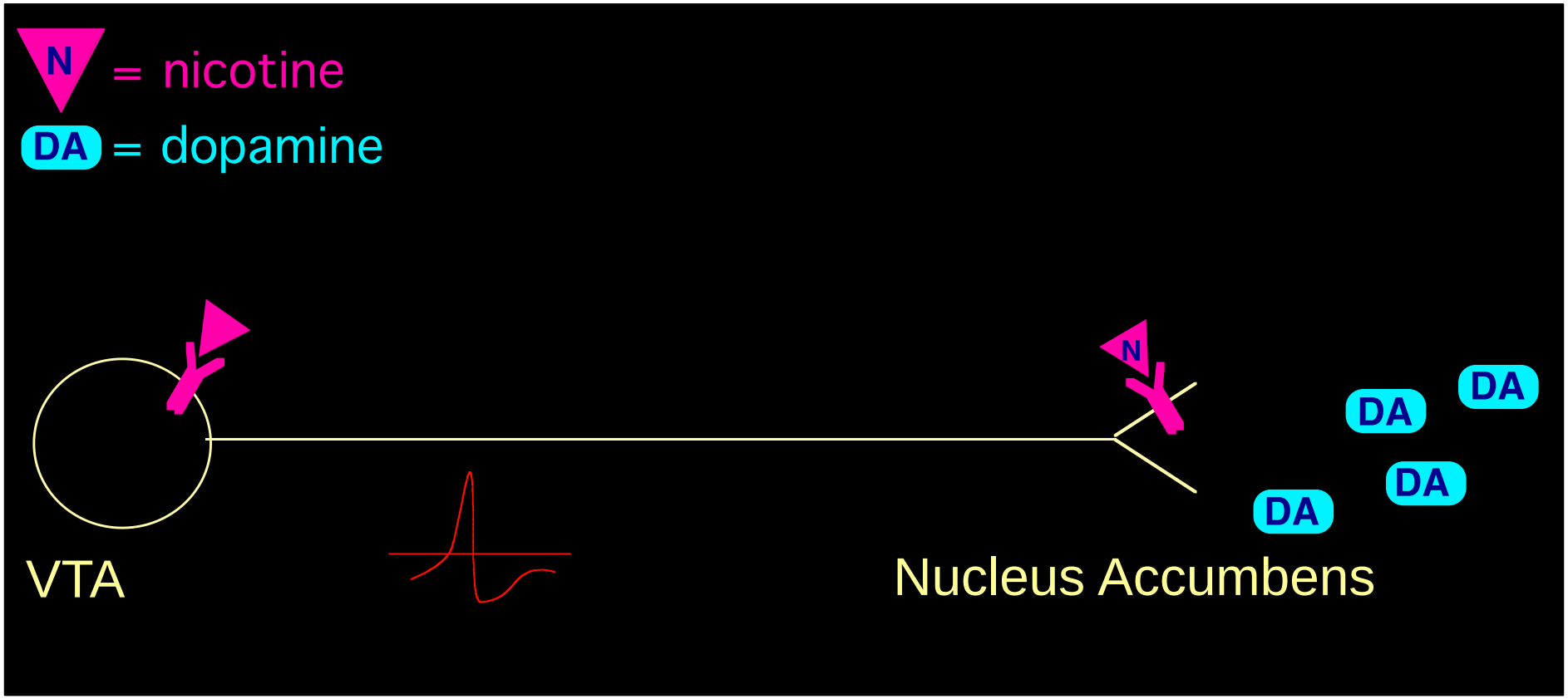
What do nicotine receptors do in the brain?



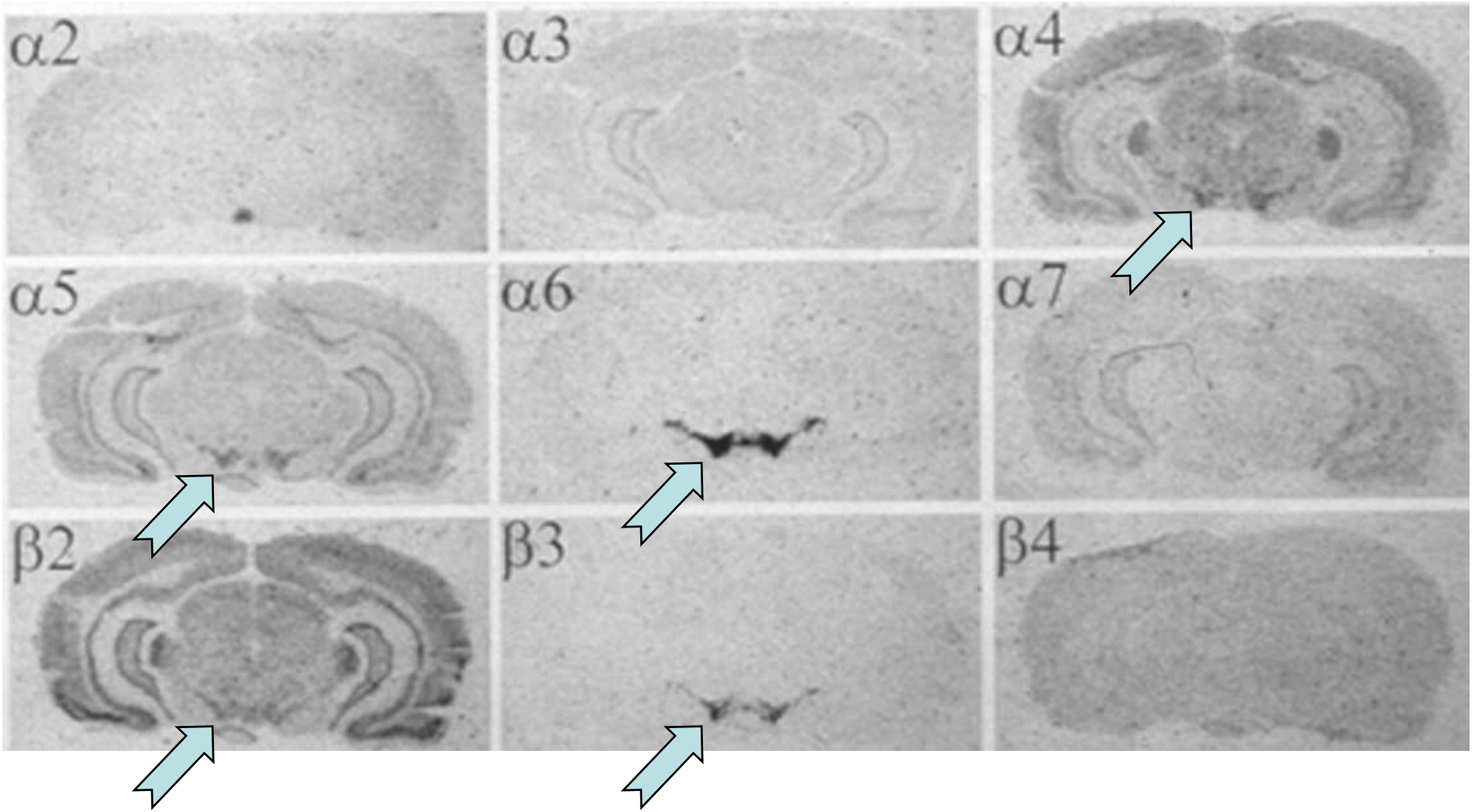
The VTA uses the neurotransmitter dopamine to signal reward in our brains



Nicotine increases dopamine (DA) release



Many nicotine receptors are in the VTA

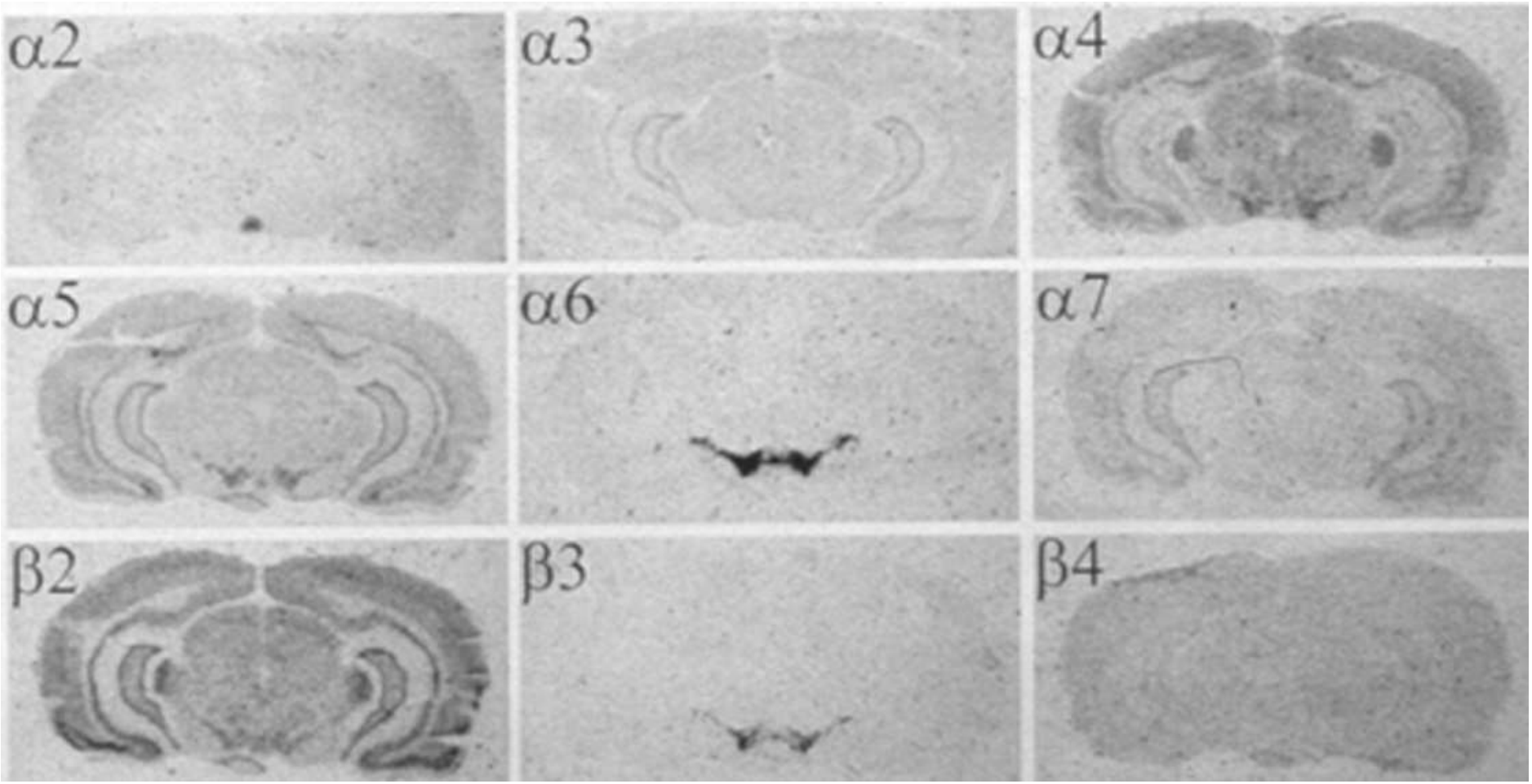


How can we find out which nicotine receptors are important for the reward signal that initiates smoking?

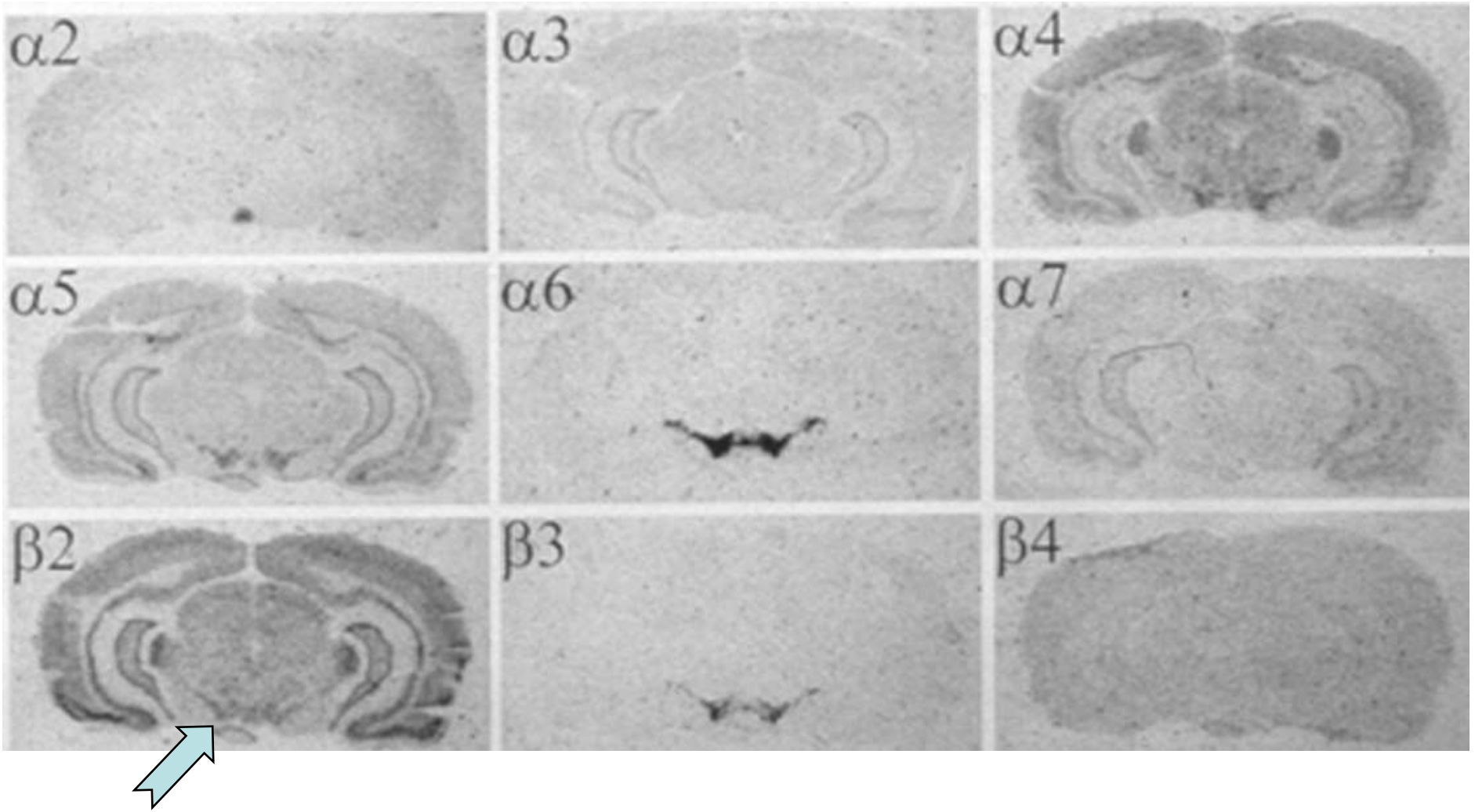
We can manipulate the genes for different nicotine receptors in mice

We can manipulate the genes for different nicotine receptors in mice

The β2* nicotine receptor is the most widespread

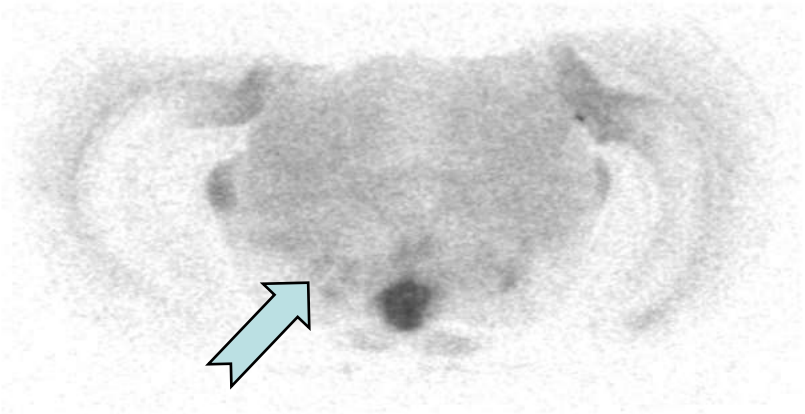


The β2* nicotine receptor is found in the VTA

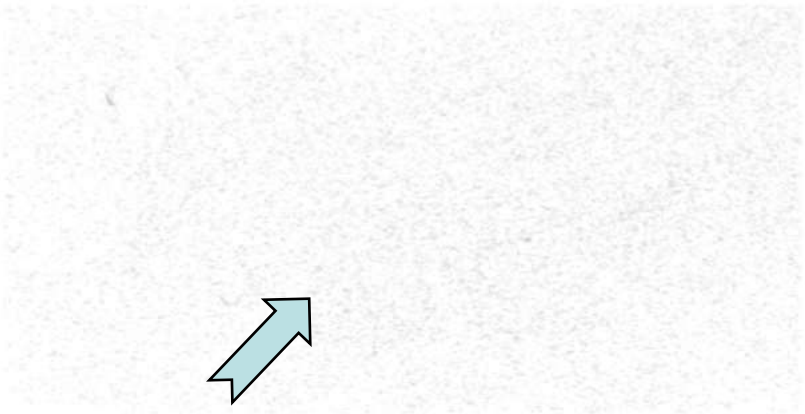


Nicotine binding goes away without the β2* nicotine receptor

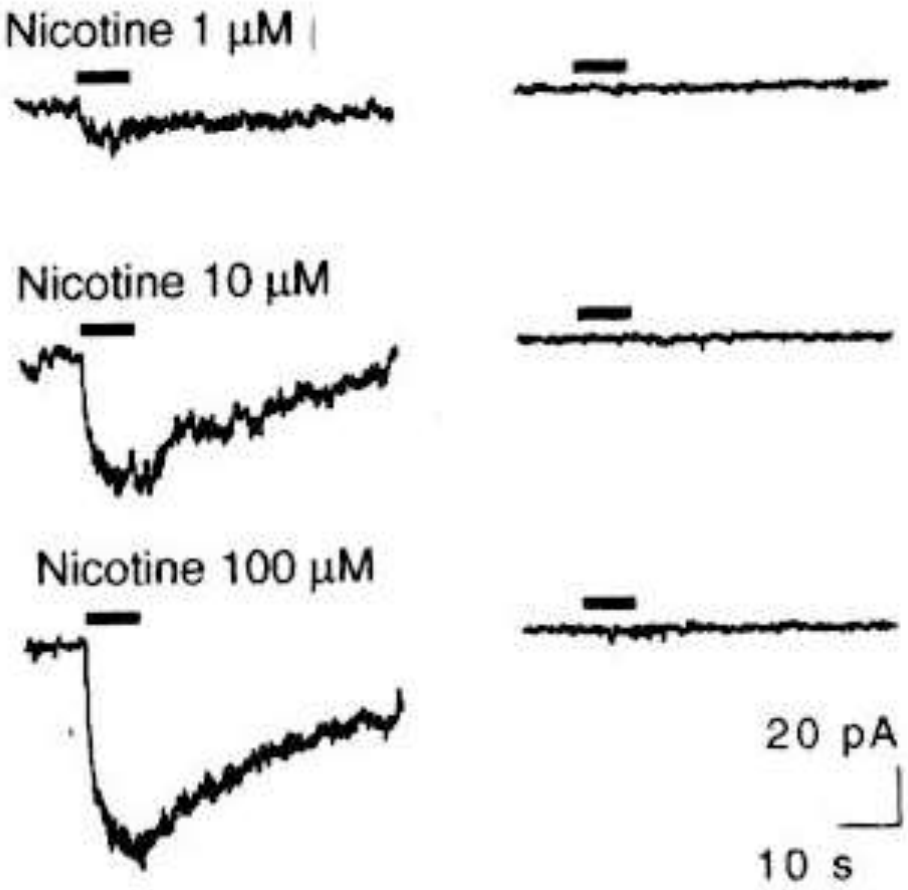
normal mouse brain



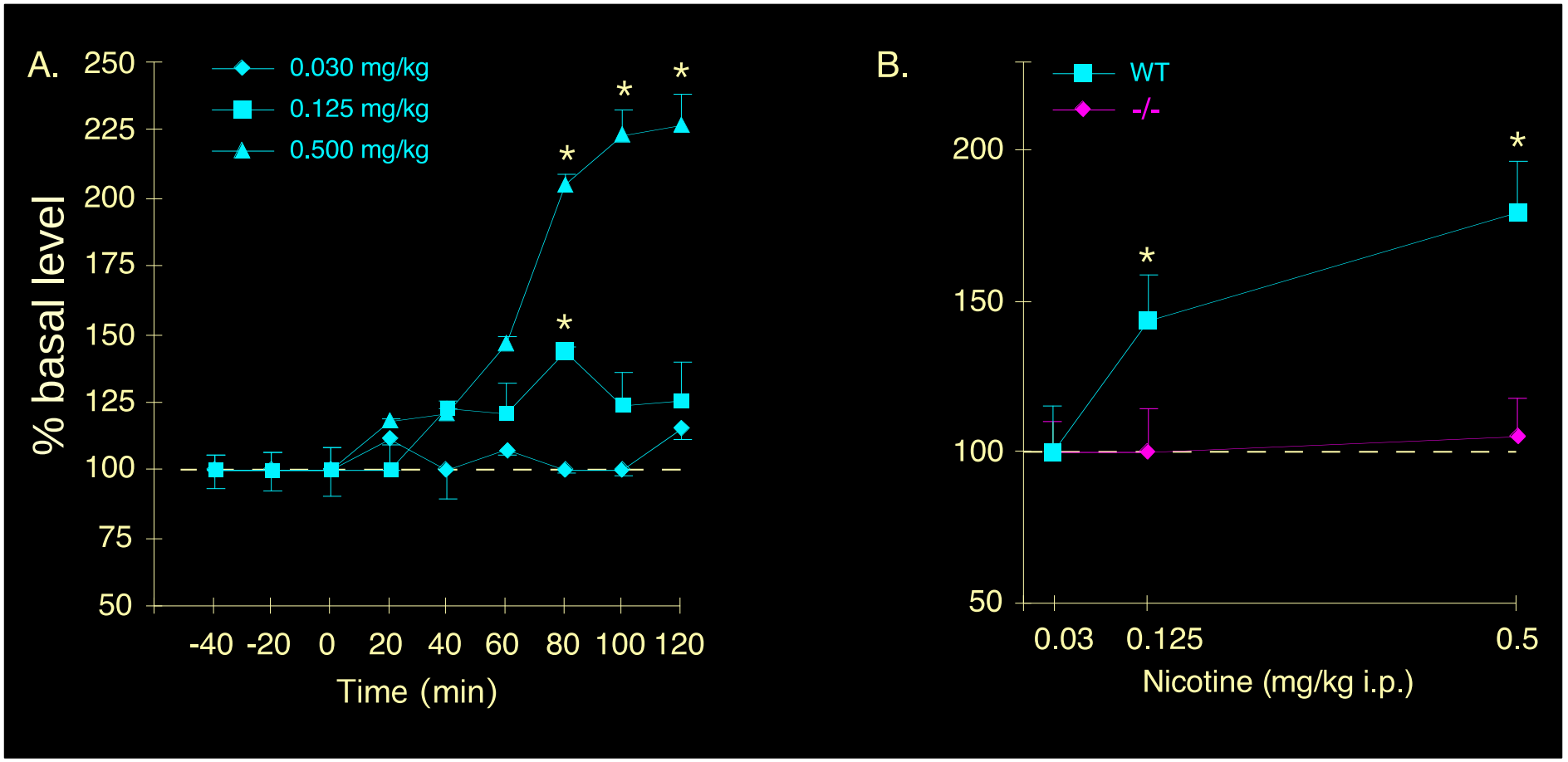
mouse brain without β2

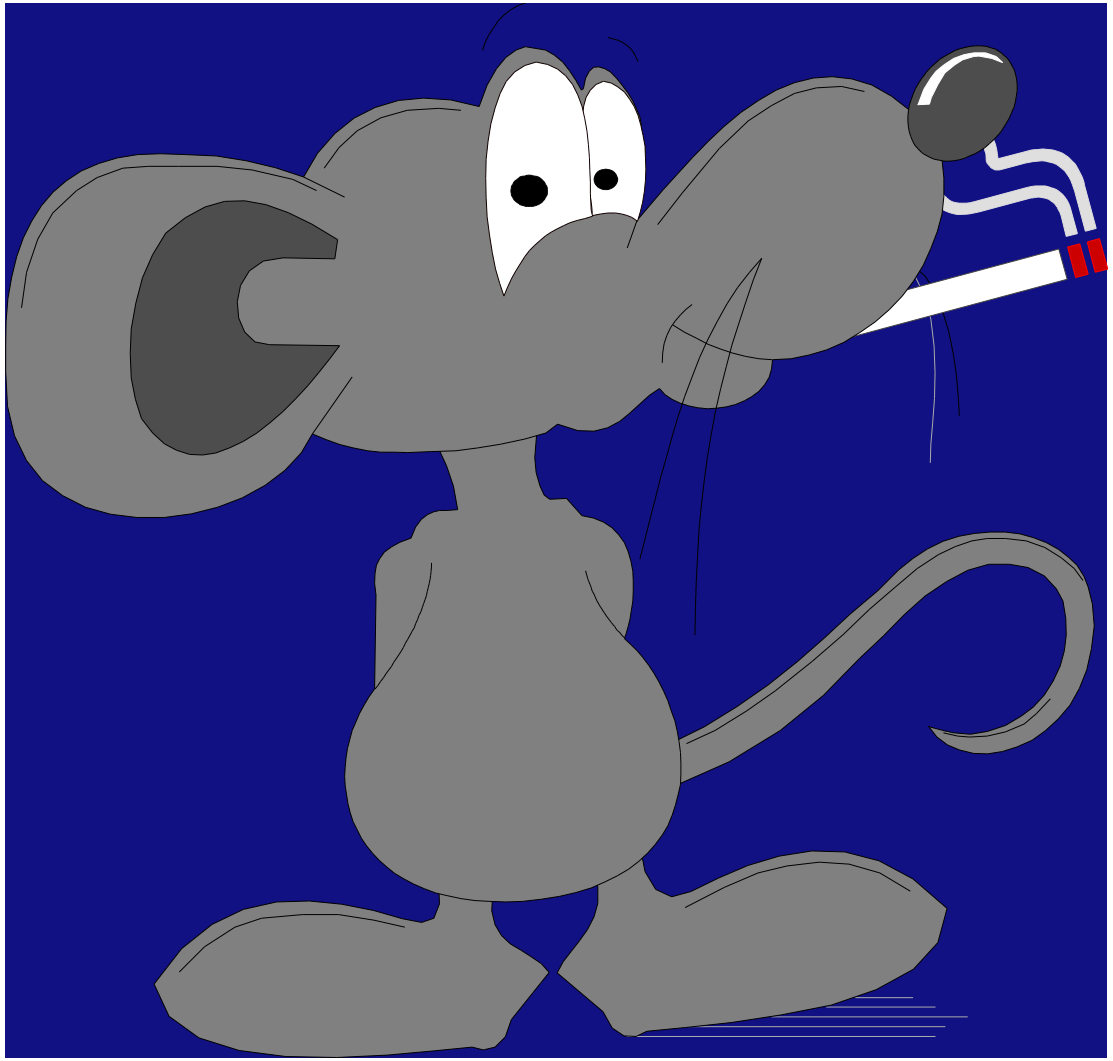


Nicotine-induces electrical currents in DA cells

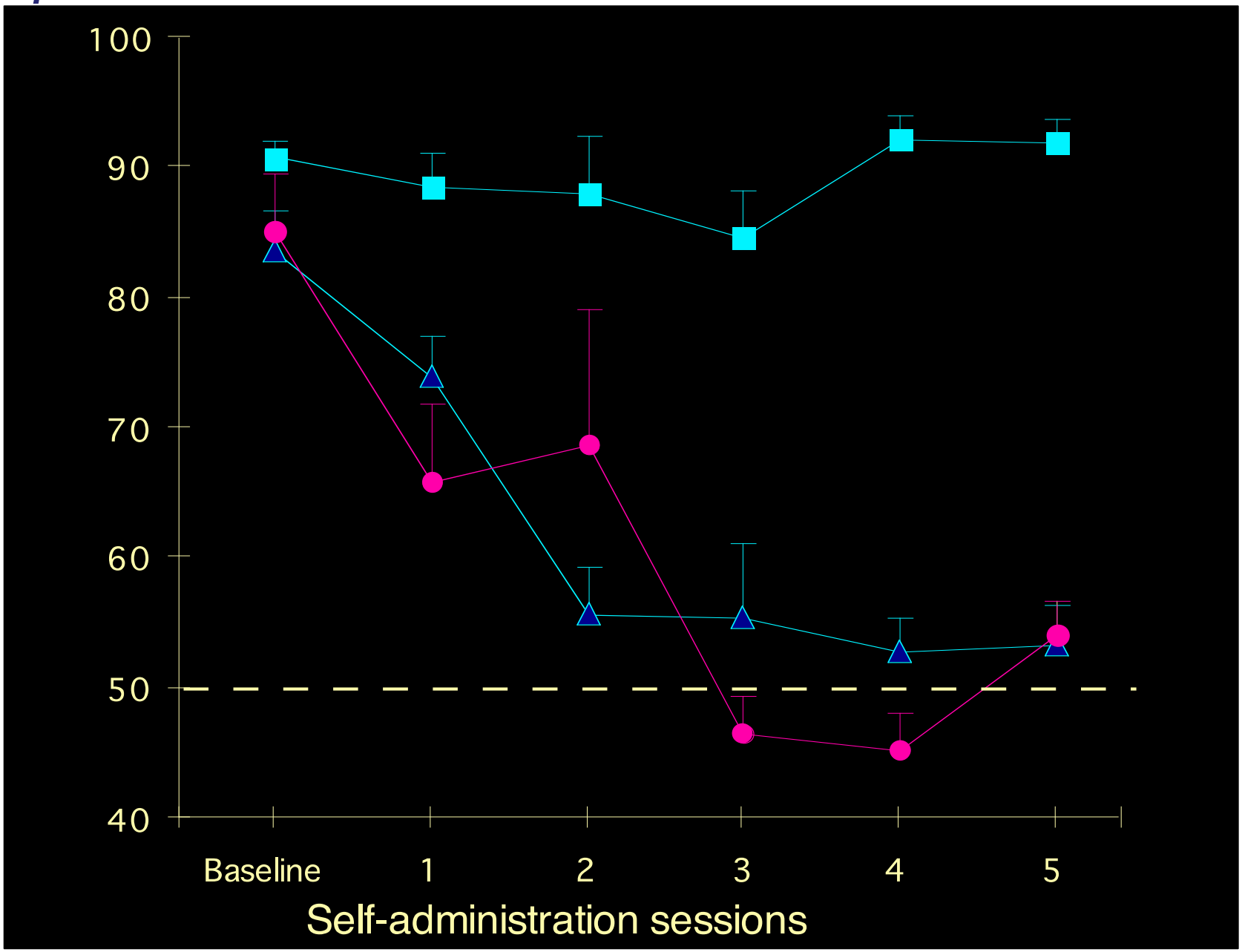


Nicotine can't increase dopamine (DA) in mice without the β2 nicotine receptor

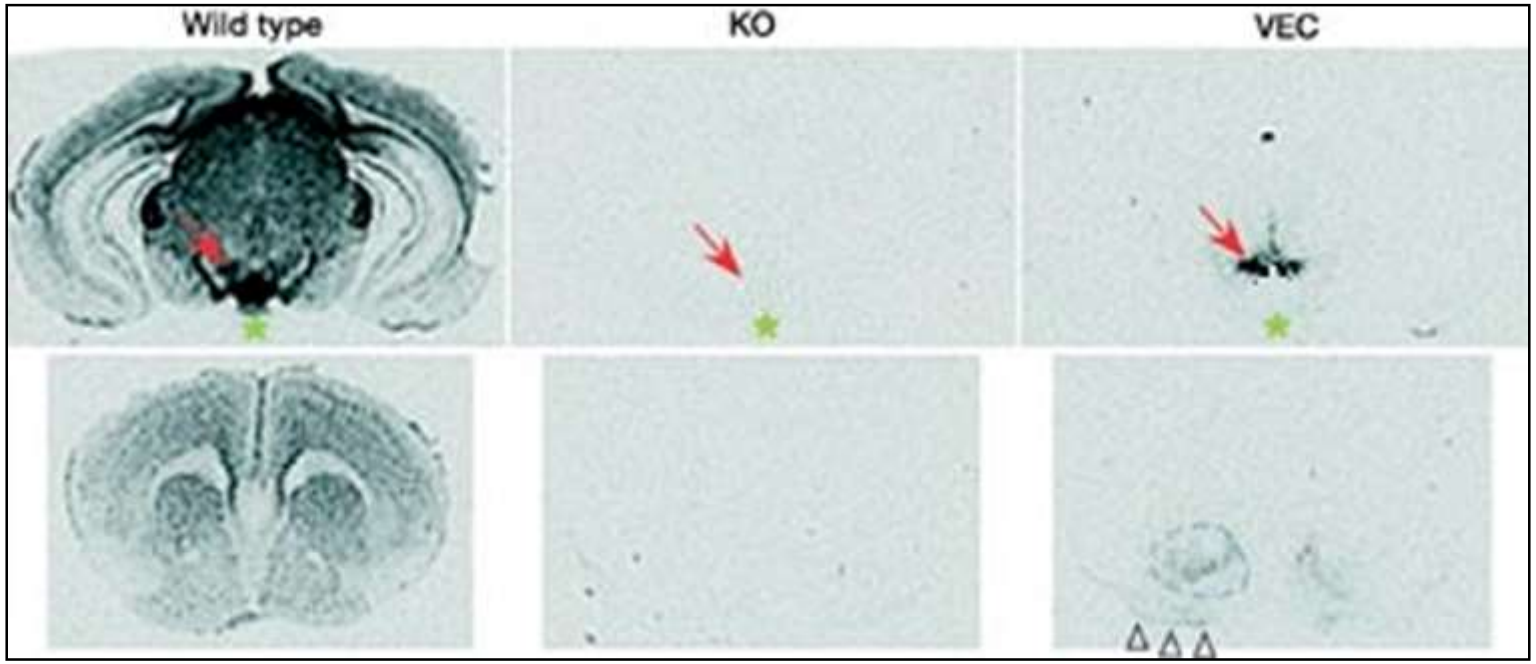




β2 knockout mice will not work for nicotine



Nicotine receptors in VTA are needed for reward



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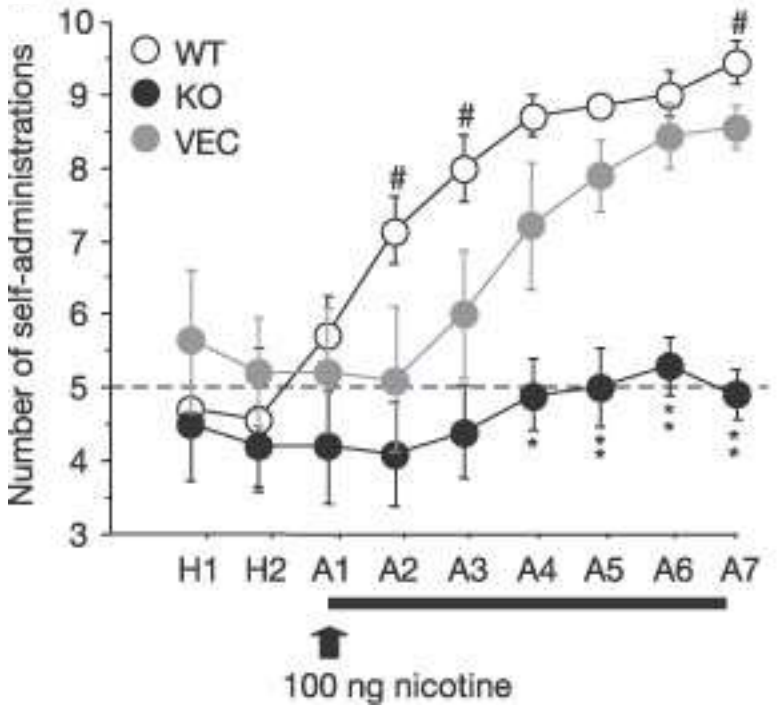
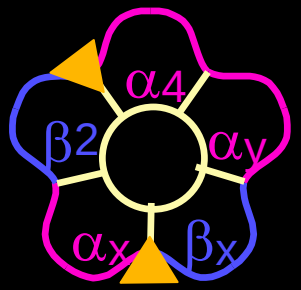


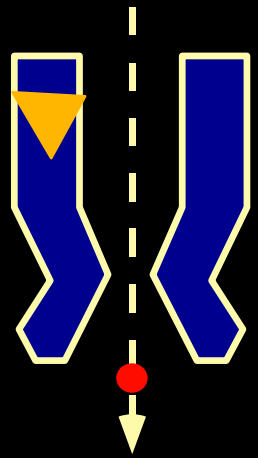
Summary: nicotine addiction

= nicotine

= dopamine

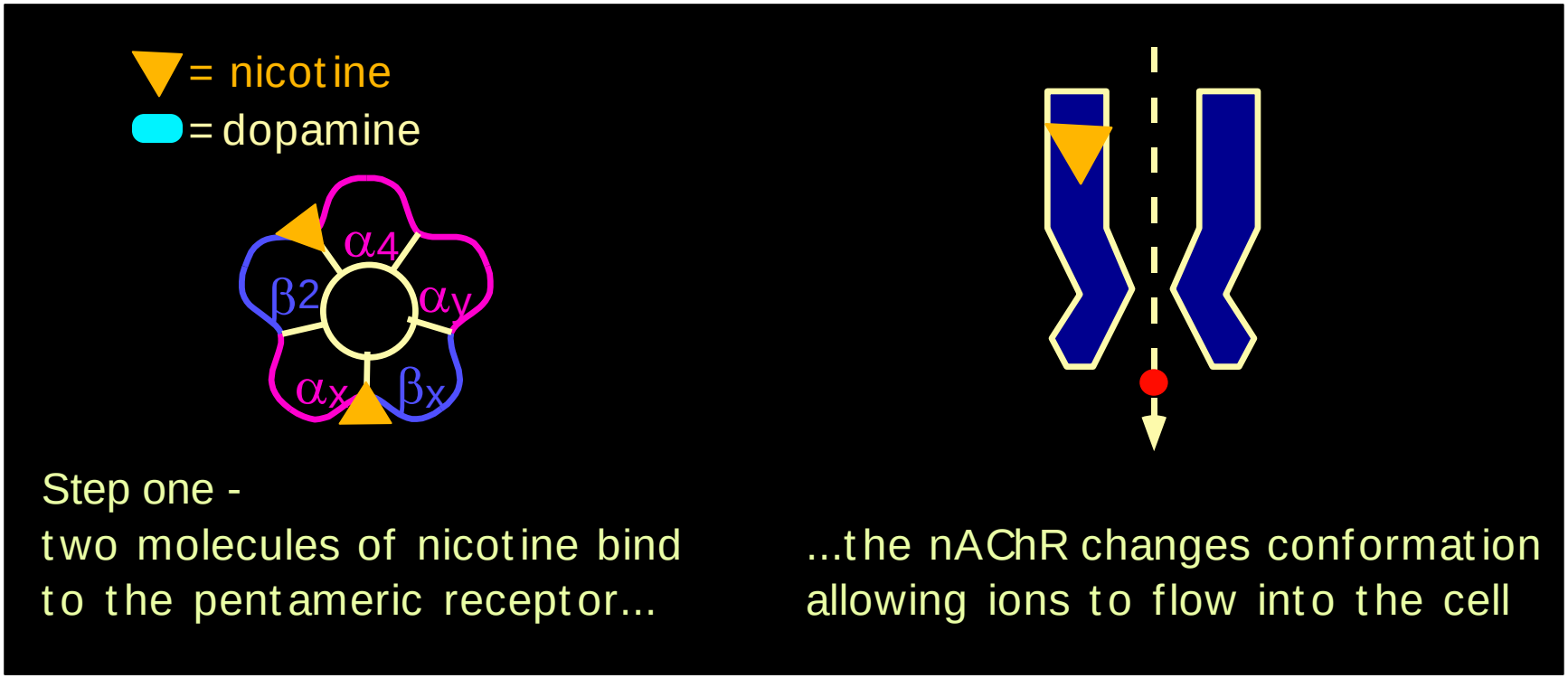


Step one -
two molecules of nicotine bind to the pentameric receptor...



...the nAChR changes conformation allowing ions to flow into the cell

Summary: nicotine addiction



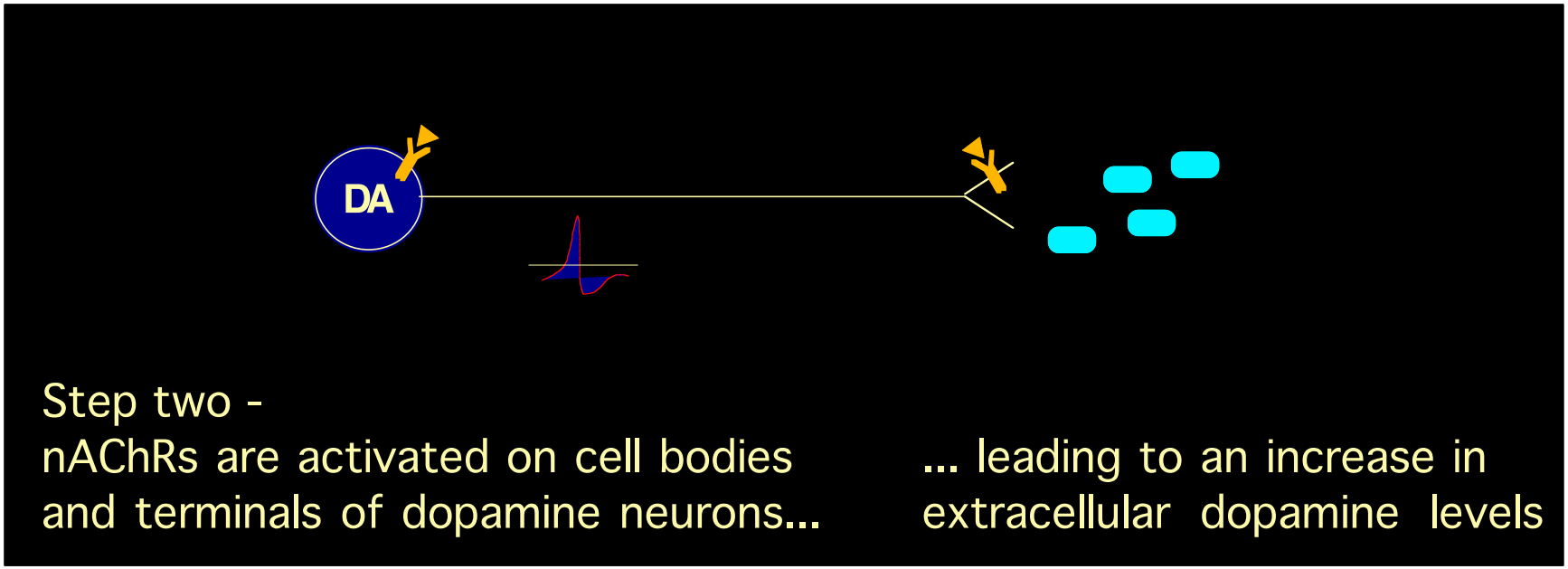
Together the field has identified the α4/β2* nAChR, along with α6, as essential for the initial rewarding effects of nicotine.

Summary: nicotine addiction

Step two -
nAChRs are activated on cell bodies and terminals of dopamine neurons...

... leading to an increase in extracellular dopamine levels

Summary: nicotine addiction



Together the field has identified the ventral tegmental area (VTA) as essential for the rewarding effects of nicotine.

Summary: nicotine addiction

Summary: nicotine addiction

This is a success story for the ability of basic science to lead to effective treatment for behavioral disorders, since animal studies on the $\alpha 4/\beta 2^*$ nAChR lead to development of varenicline as an effective smoking cessation aide in humans.

Why do people smoke despite negative effects on health?

People who are depressed are more likely to smoke.

40-60 % of patients with depression smoke.

Why do people smoke despite negative effects on health?

Major depressive disorder (MDD)

- MDD is a chronic, debilitating, relapsing illness with great cost to the individual, families and society
- Estimates suggest that 8-12% of people will experience MDD in their lifetime
- Existing antidepressant therapies (tricyclic drugs, selective serotonin reuptake inhibitors, MAO inhibitors, non-classical antidepressants, ECT, cognitive-behavioral therapy) work for about 50-70% of patients

There is a real need for new treatments for MDD

Nicotine patch can work as an antidepressant

- Nicotine patch can have antidepressant effects in depressed nonsmokers and depressed smokers

…but intravenous nicotine can increase symptoms of depression

- Nicotine patch can have antidepressant effects in depressed nonsmokers and depressed smokers
- Intravenous (i.v.) nicotine produces symptoms of depression in non-smoking, non-depressed patients

Why would intravenous nicotine increase depressive symptoms and nicotine patch decrease depressive symptoms?

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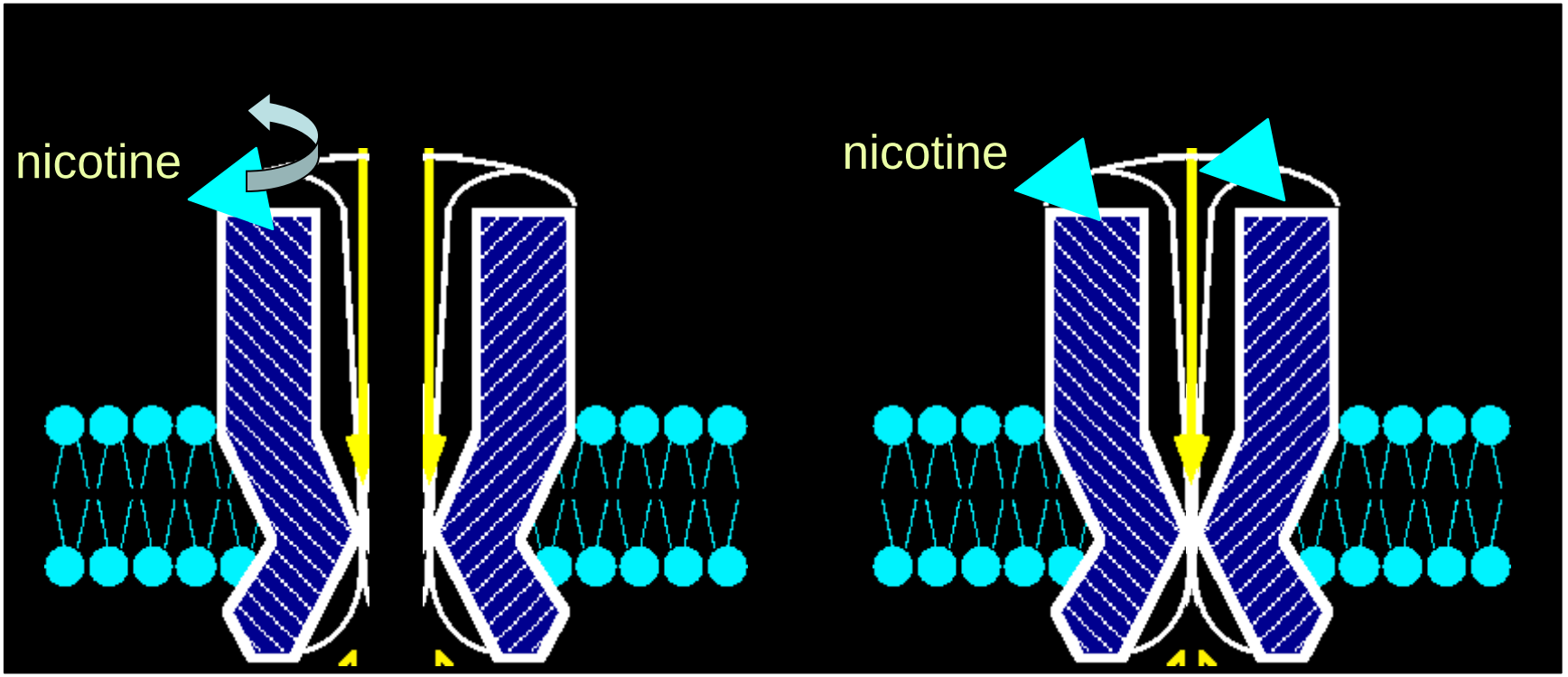
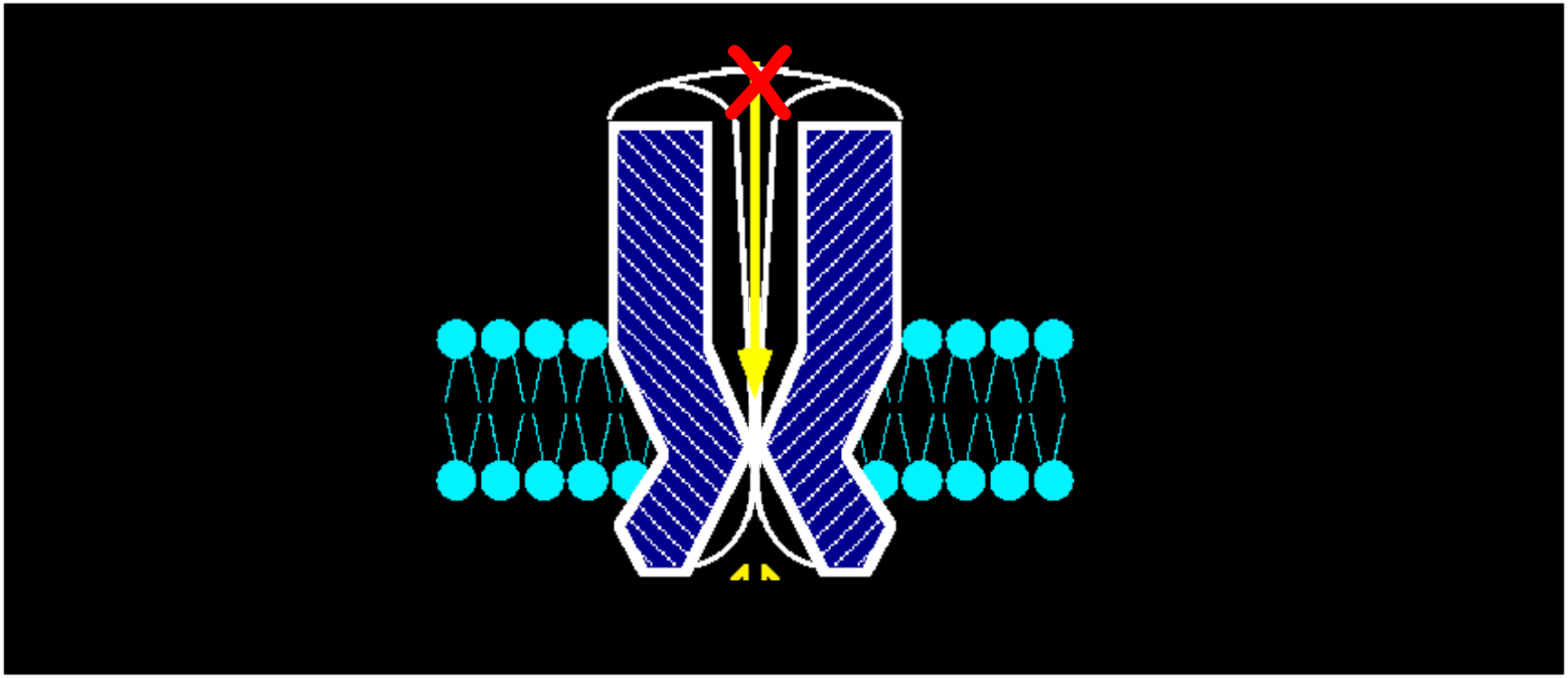


i.v. nicotine is:
Fast
Activates (turns on) receptors

Patch nicotine is:
Slow
Desensitizes (turns off) receptors

Our Hypothesis:

Maybe blocking nicotine receptors to prevent ACh action is antidepressant.



Our Hypothesis:
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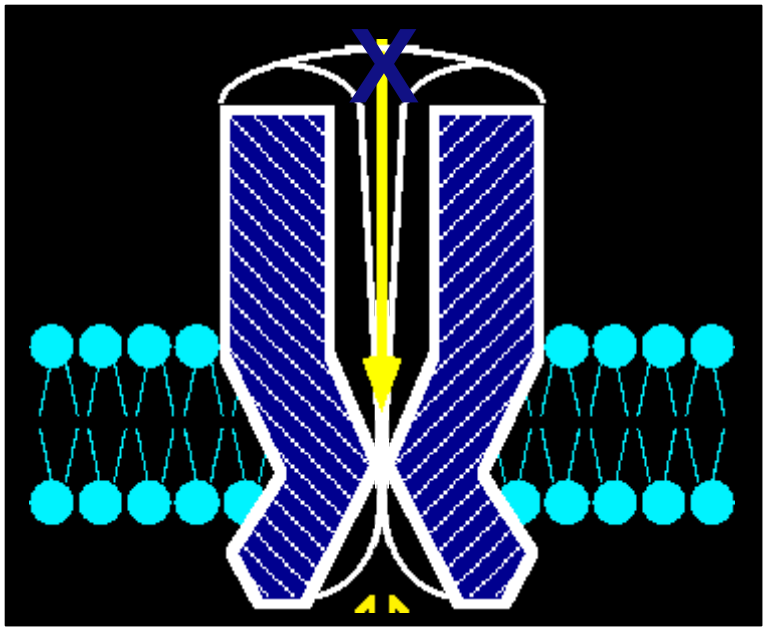

Smokers are going through cycles of activating and blocking their nicotine receptors throughout the day.

Janowsky: Increasing ACh in humans induces symptoms of depression

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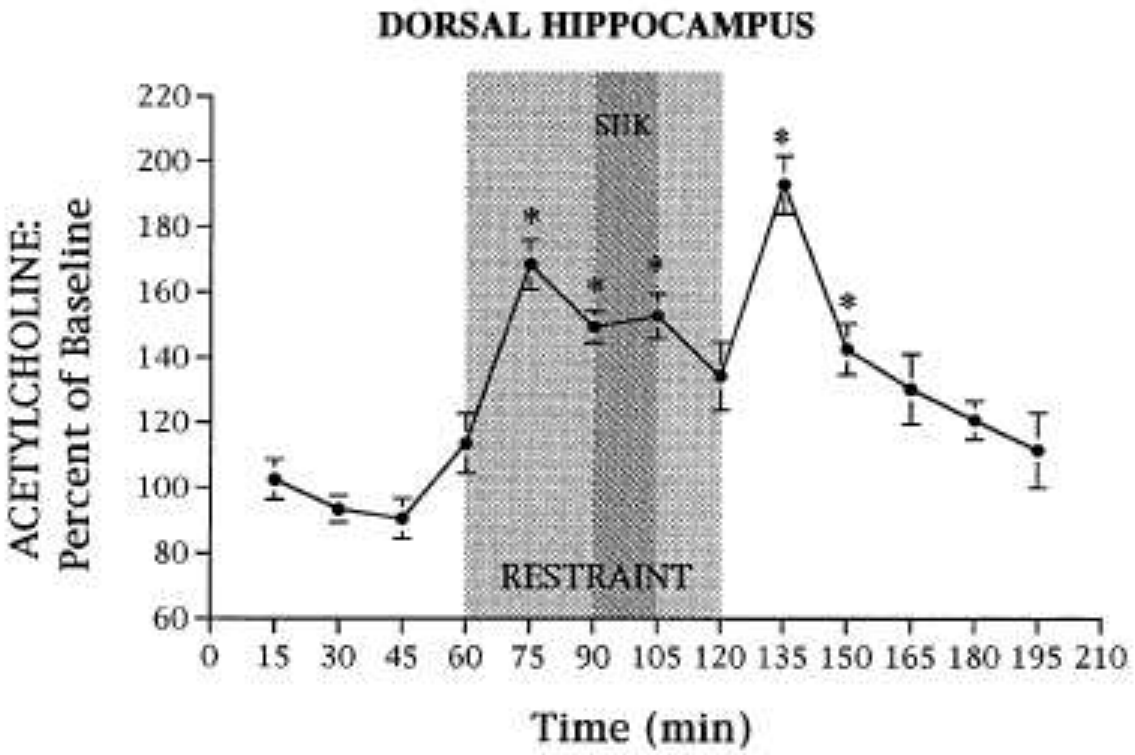
Physostigmine induction of depressive symptomatology in normal human subjects

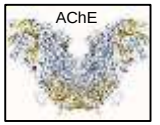
Samuel C. Risch, Robert M. Cohen, David S. Janowsky, Ned H. Kalin, N. Sitaram, J. Christian Gillin, Dennis L. Murphy

Stress induces ACh release in the brain



Mark, Rada & Shors, Neuroscience, 1996

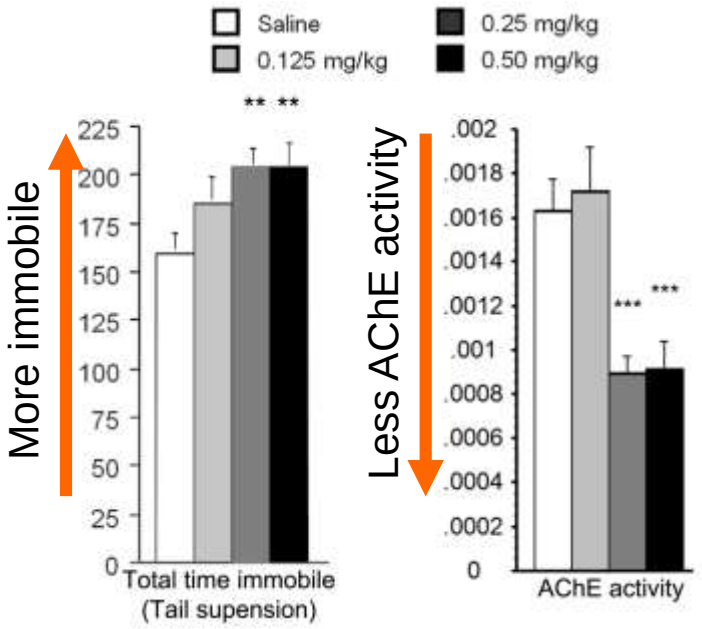
Can we replicate Janowsky's findings in mice?



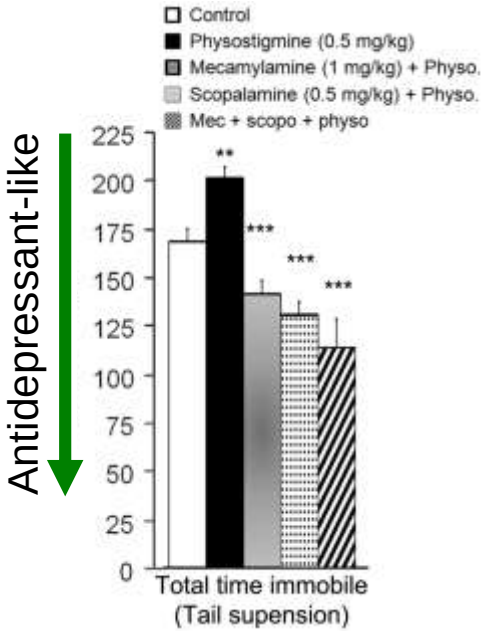
Mineur, et al, PNAS, 2013

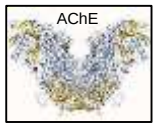
Increasing ACh induces stress-related behaviors in mice

Physostigmine



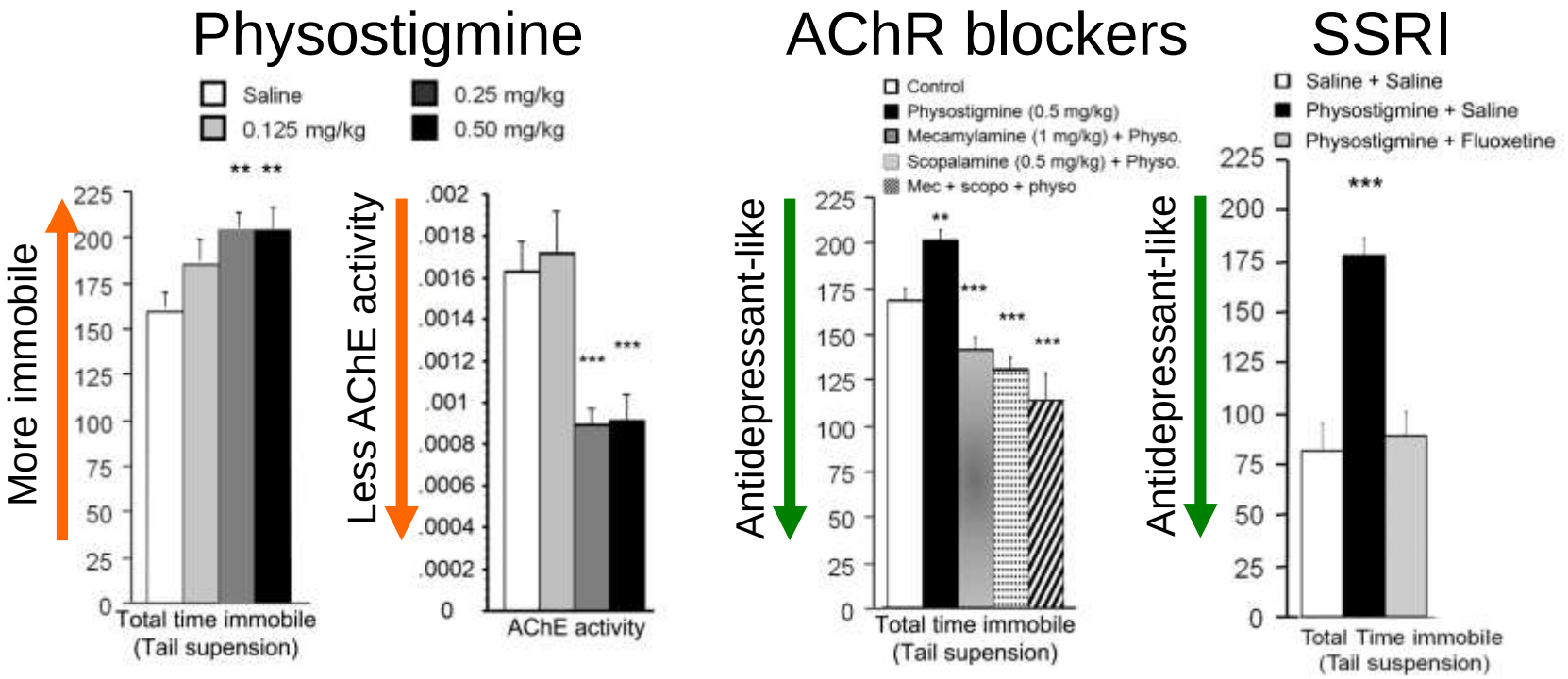
AChR blockers

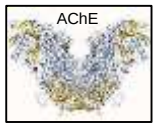




Mineur, et al, PNAS, 2013

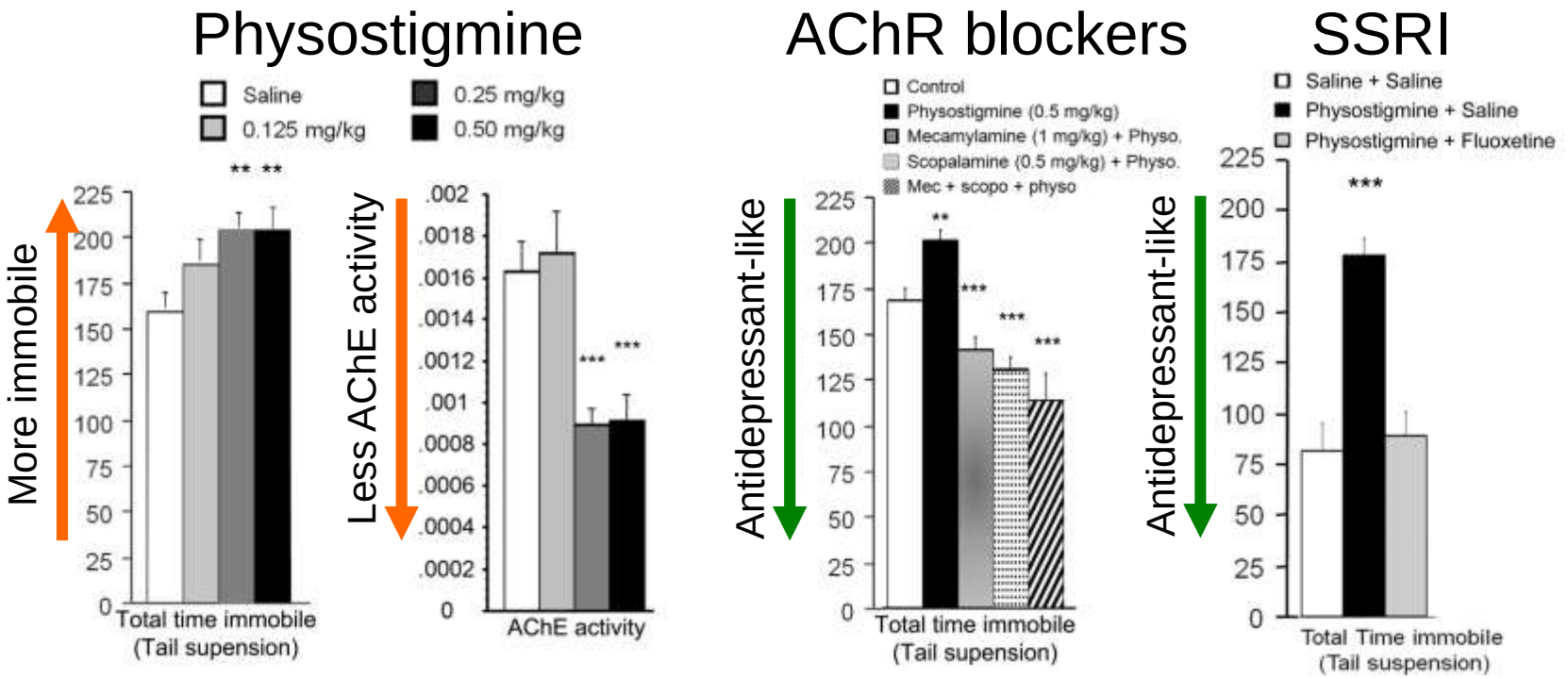
Increasing ACh induces stress-related behaviors in mice that can be reversed by an antidepressant (Prozac)

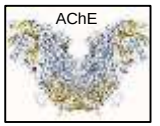




Mineur, et al, PNAS, 2013

Does ACh signaling in the brain underlie stress-induced behaviors?

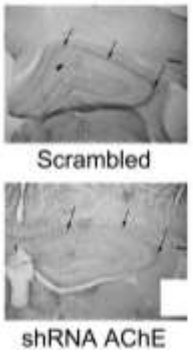


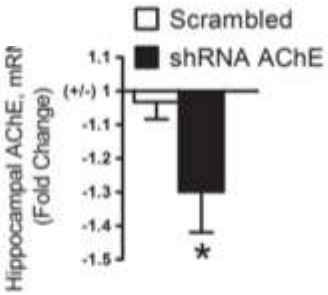


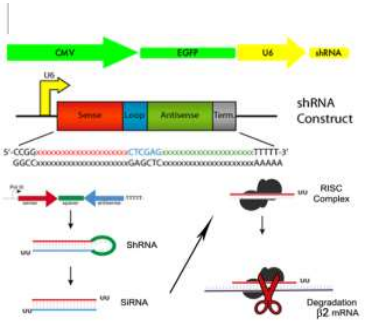
Mineur, et al, PNAS, 2013

Increasing ACh in mouse hippocampus induces behaviors sensitive to anxiolytics

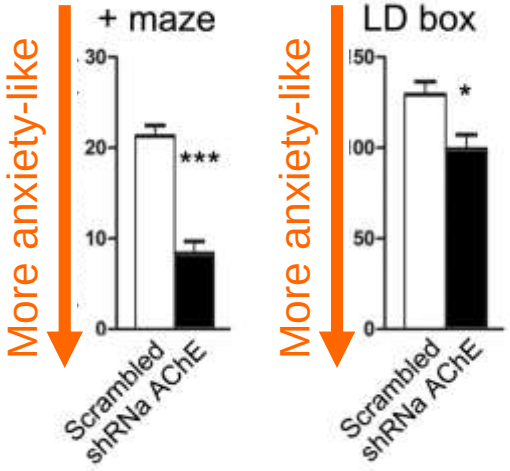
Knockdown

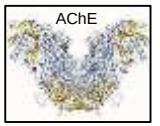






Anxiety-like

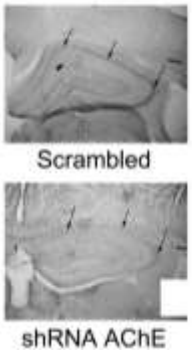


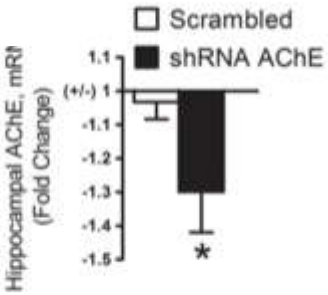


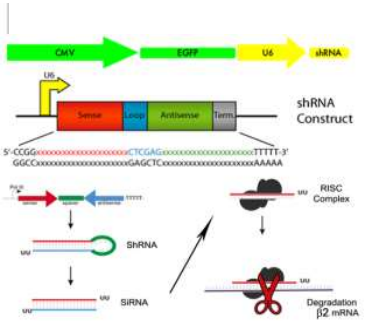
Mineur, et al, PNAS, 2013

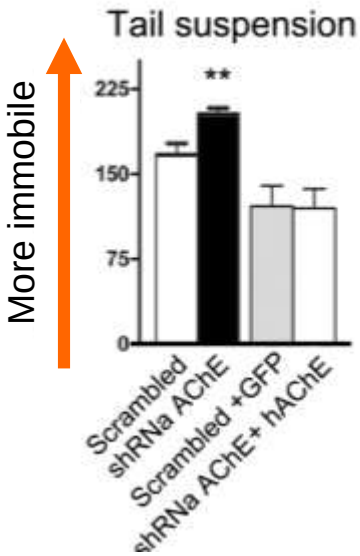
Increasing ACh in mouse hippocampus induces behaviors sensitive to antidepressants

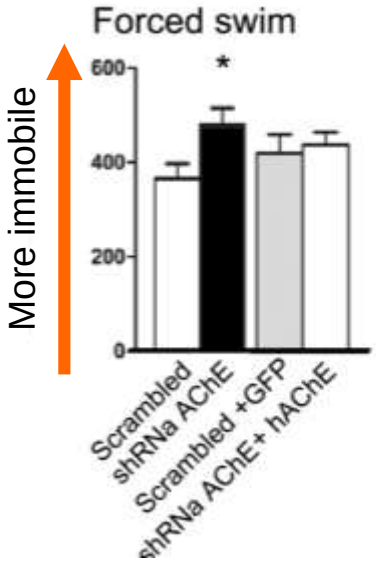
Knockdown

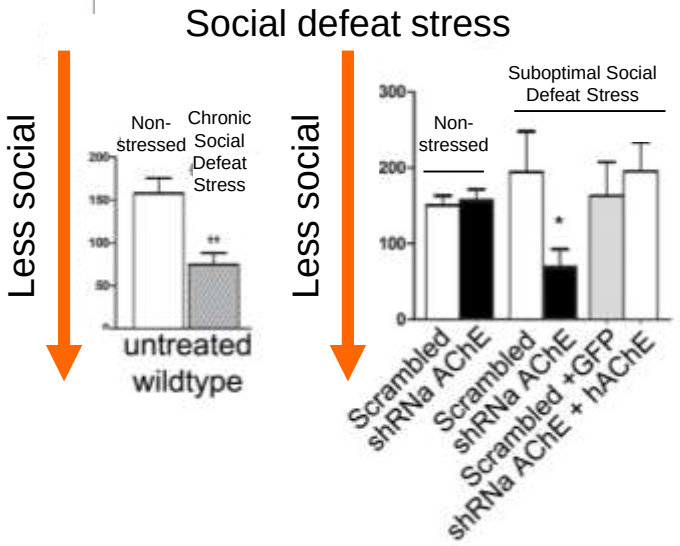


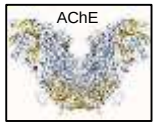










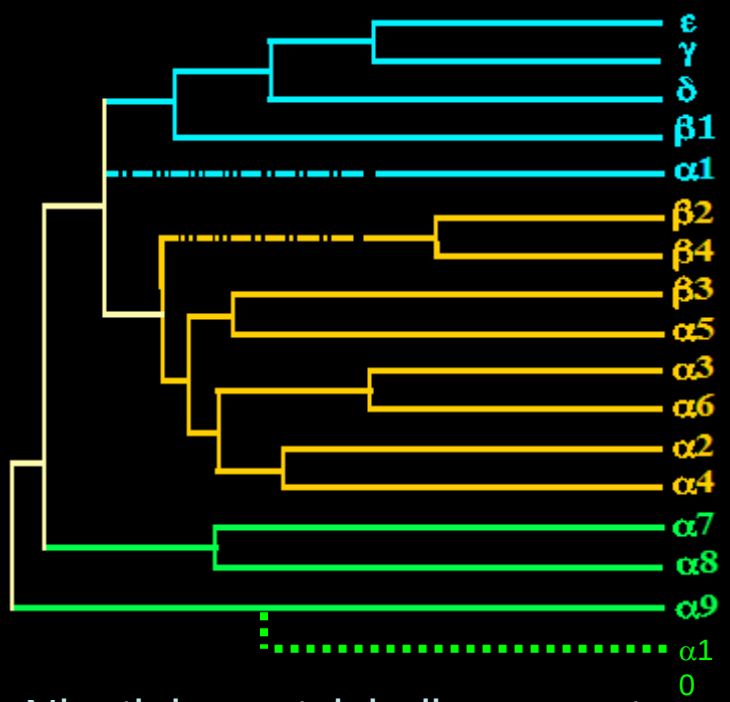


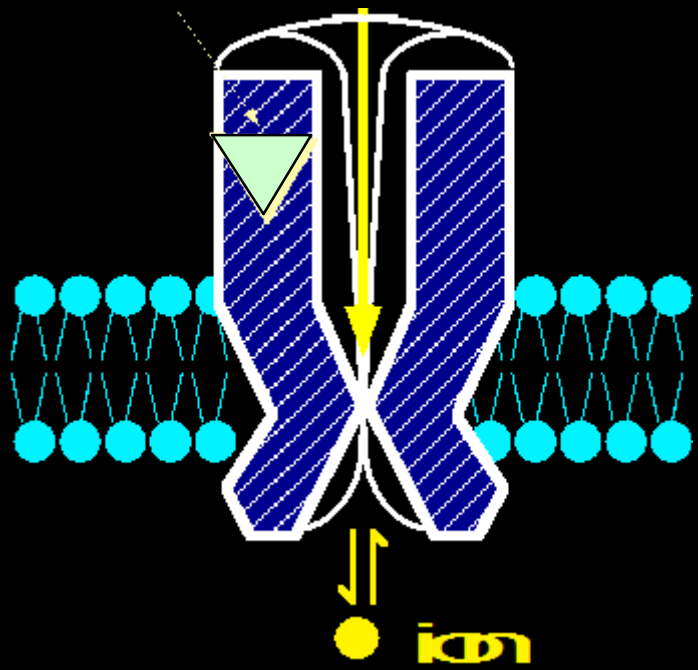
Mineur, et al, PNAS, 2013

Increasing ACh signaling in mice and humans induces stress-related behaviors

Do changes in acetylcholine levels in brain occur in depressed human subjects?

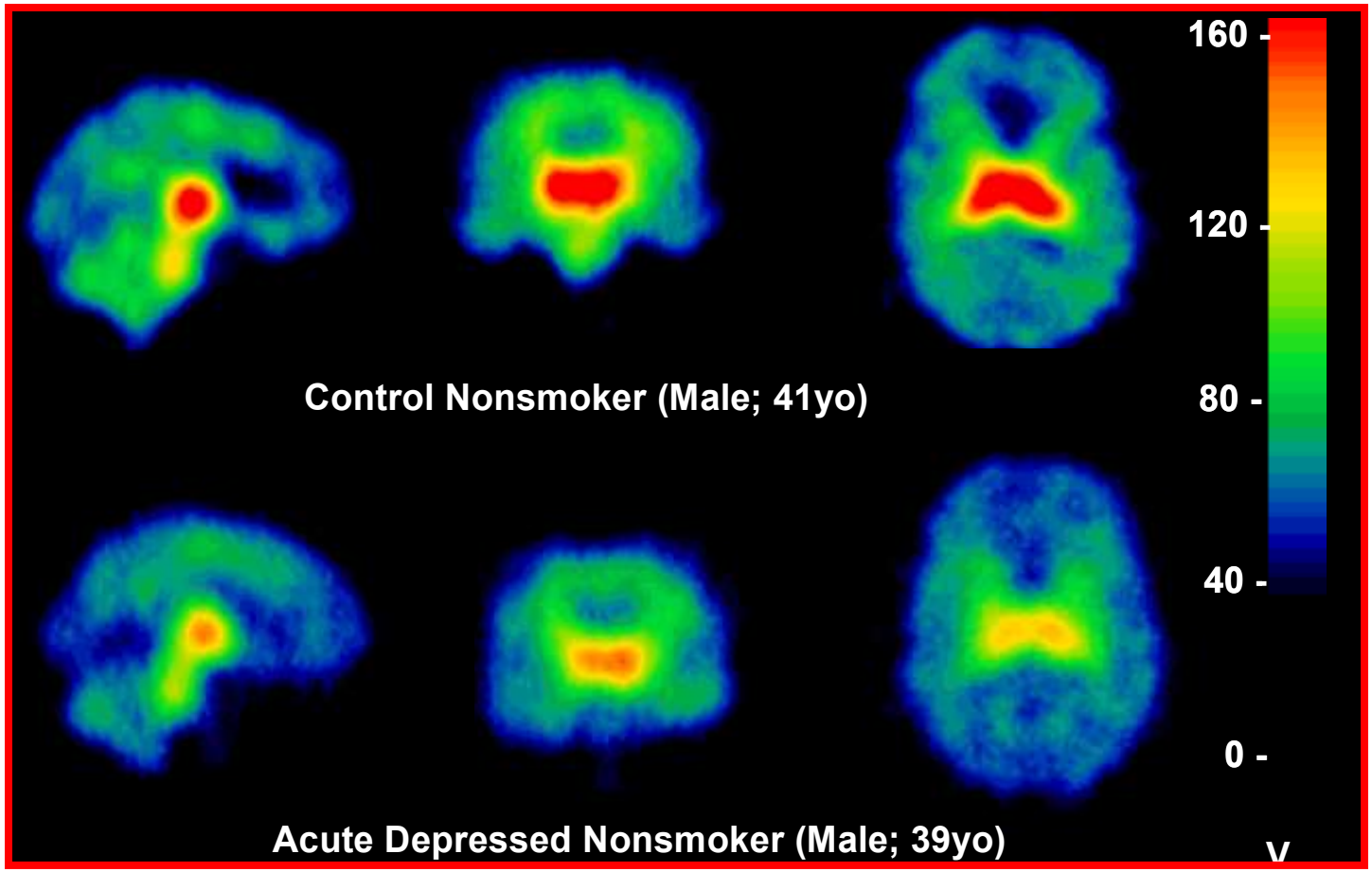
Nicotinic acetylcholine receptor tracer





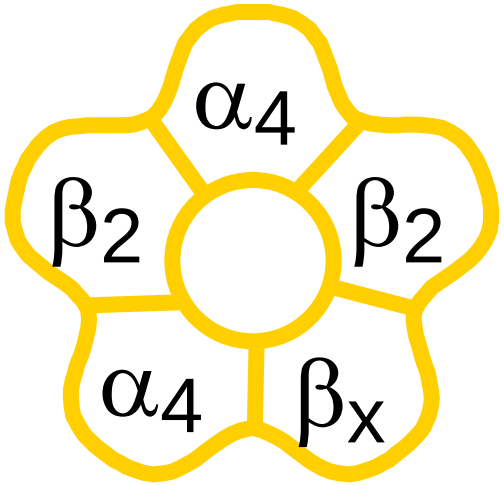
Nicotinic acetylcholine receptors (nAChRs) are the molecular targets for nicotine in the brain and periphery

Imaging of β2 nAChRs in human brain



Saricicek, et al, Am J Psychiatry, 2012

If depression is associated with increased ACh, what would we expect to see when imaging β2 nAChRs?



nicotinic receptors

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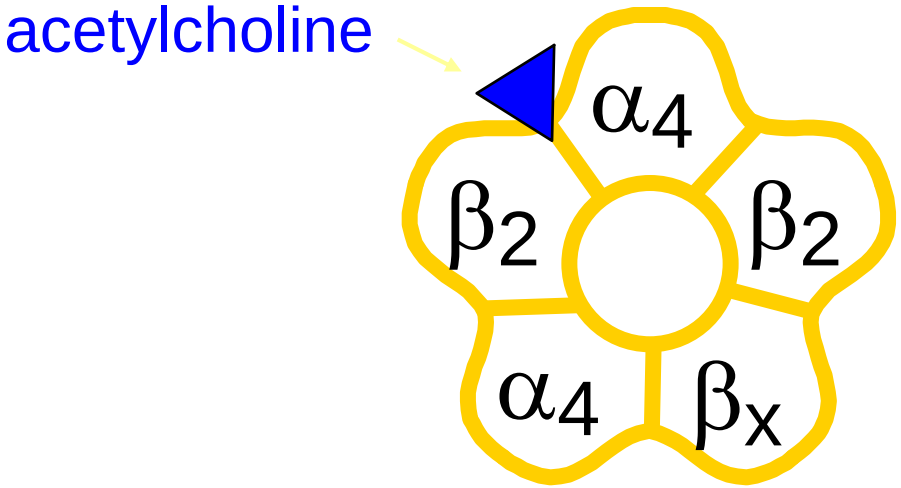

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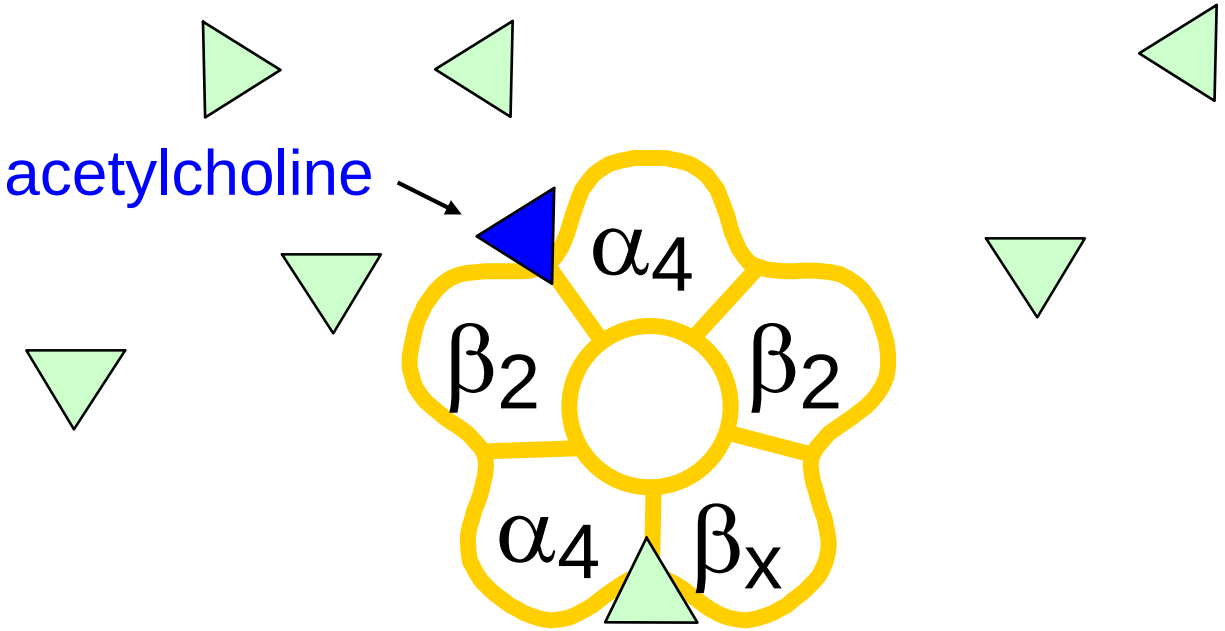
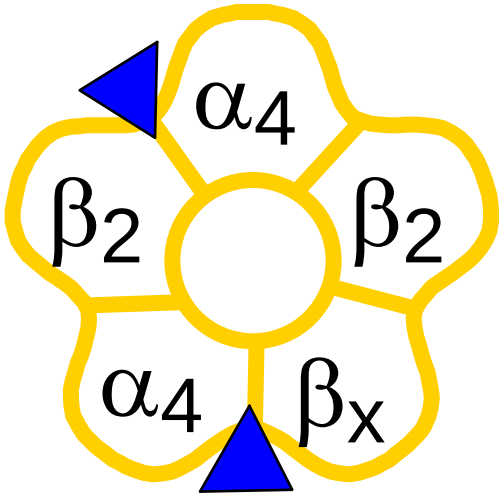


nicotinic receptors

If depression is associated with increased ACh, what would we expect to see when imaging β2 nAChRs?

↑ acetylcholine



nicotinic receptors

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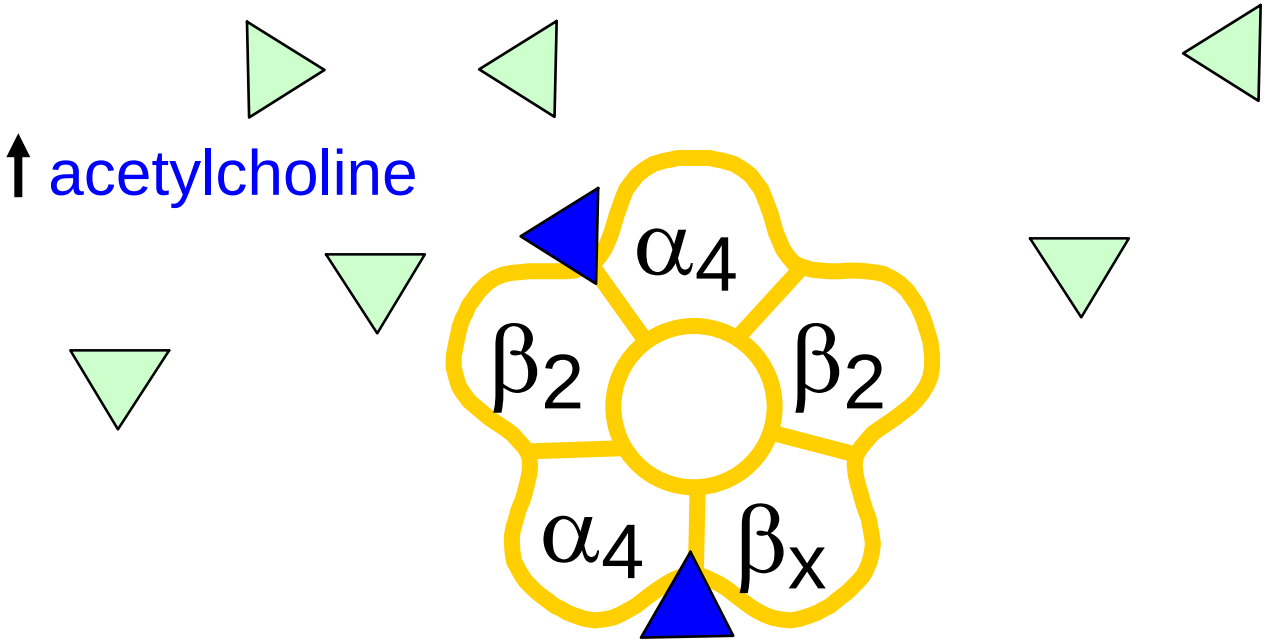
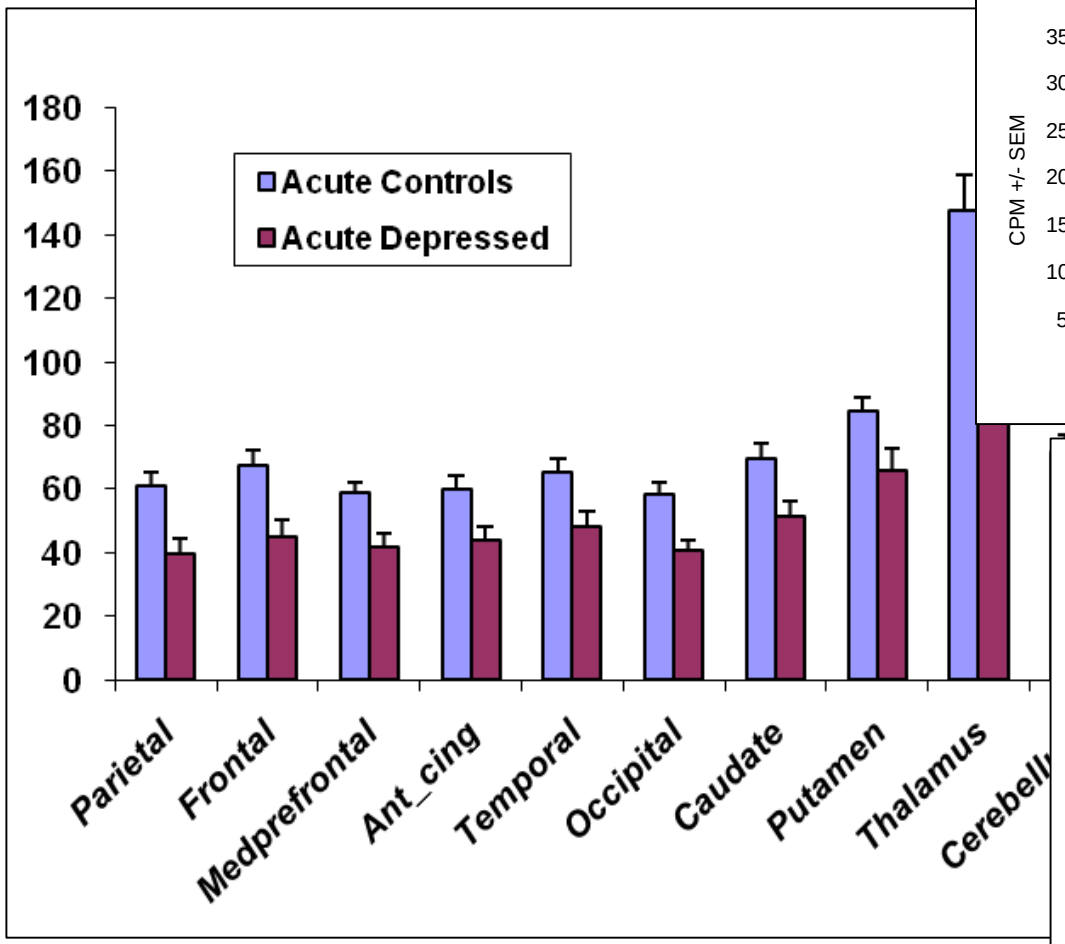
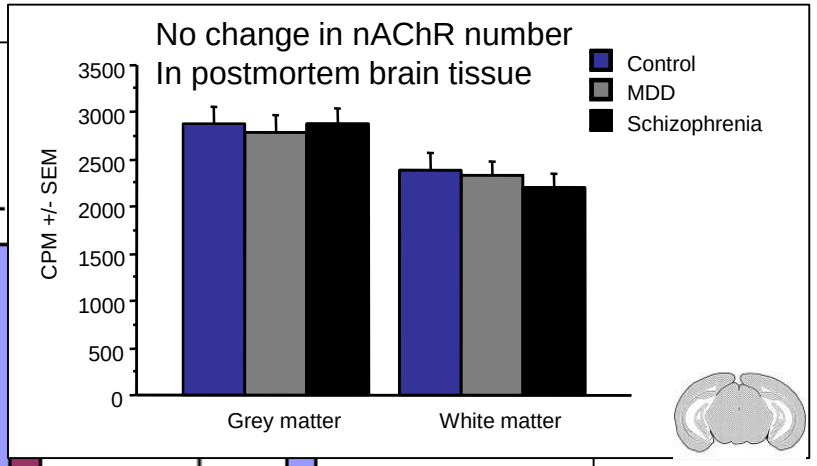
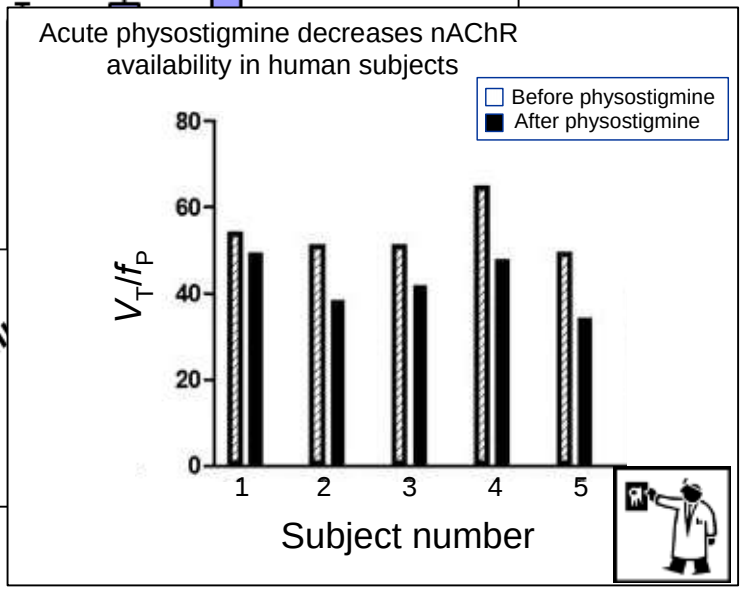


nicotinic receptors

Nicotinic receptors are bound to more ACh in actively depressed human subjects







Saricicek, et al, Am J Psychiatry, 2012, Esterlis et al, J Nuclear Med, 2013

Small trials suggested a nicotine receptor blocker can be antidepressant in patients

Mecamylamine

BRIEF REPORT

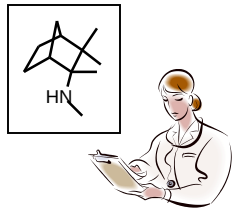
Nicotinic Antagonist Augmentation of Selective Serotonin Reuptake Inhibitor–Refractory Major Depressive Disorder

A Preliminary Study

Tony P. George, MD, FRCPC,†‡ Kristi A. Sacco, PsyD,* Jennifer C. Vessicchio, LCSW,* Andrea H. Weinberger, PhD,* and R. Douglas Shytle, PhD§‖*

(*J Clin Psychopharmacol* 2008;28:340–344)

Background: There is evidence for nicotinic hypercholinergic



But a large trial by AstraZeneca did not see an effect – so the full blocker may not be ideal

Mecamylamine

BRIEF REPORT

Nicotinic Antagonist Augmentation of Selective Serotonin Reuptake Inhibitor–Refractory Major Depressive Disorder

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Mecamylamine

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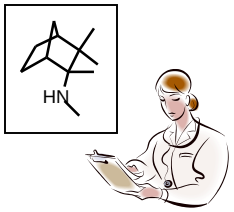
Targacept Presents Data from Highly Successful Phase 2b Trial of TC-5214 as Augmentation Treatment for Major Depressive Disorder

Six Point Advantage over Placebo (p<0.0001) on Primary Outcome Measure (HAM-D

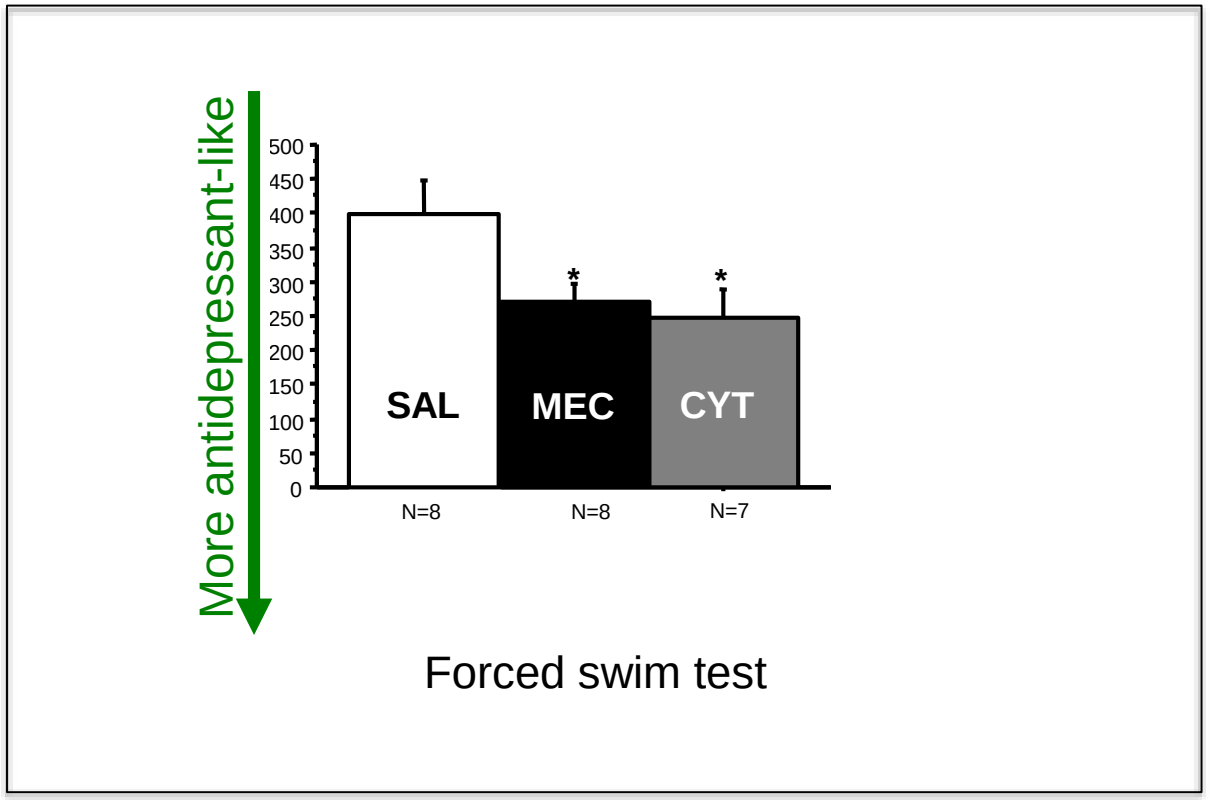
Highly Statistically Significant Results (p<0.0001) on All Primary and Secondary Outcome Measures

Winston-Salem, NC

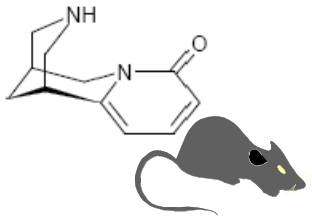


Can we use this mouse model of an anxiety- and depression-like state to identify the sites and receptors of cholinergic signaling important for these behaviors to identify more selective potential therapeutics?

Both the nicotine blocker MEC and partial blocker CYT are antidepressant-like in mice



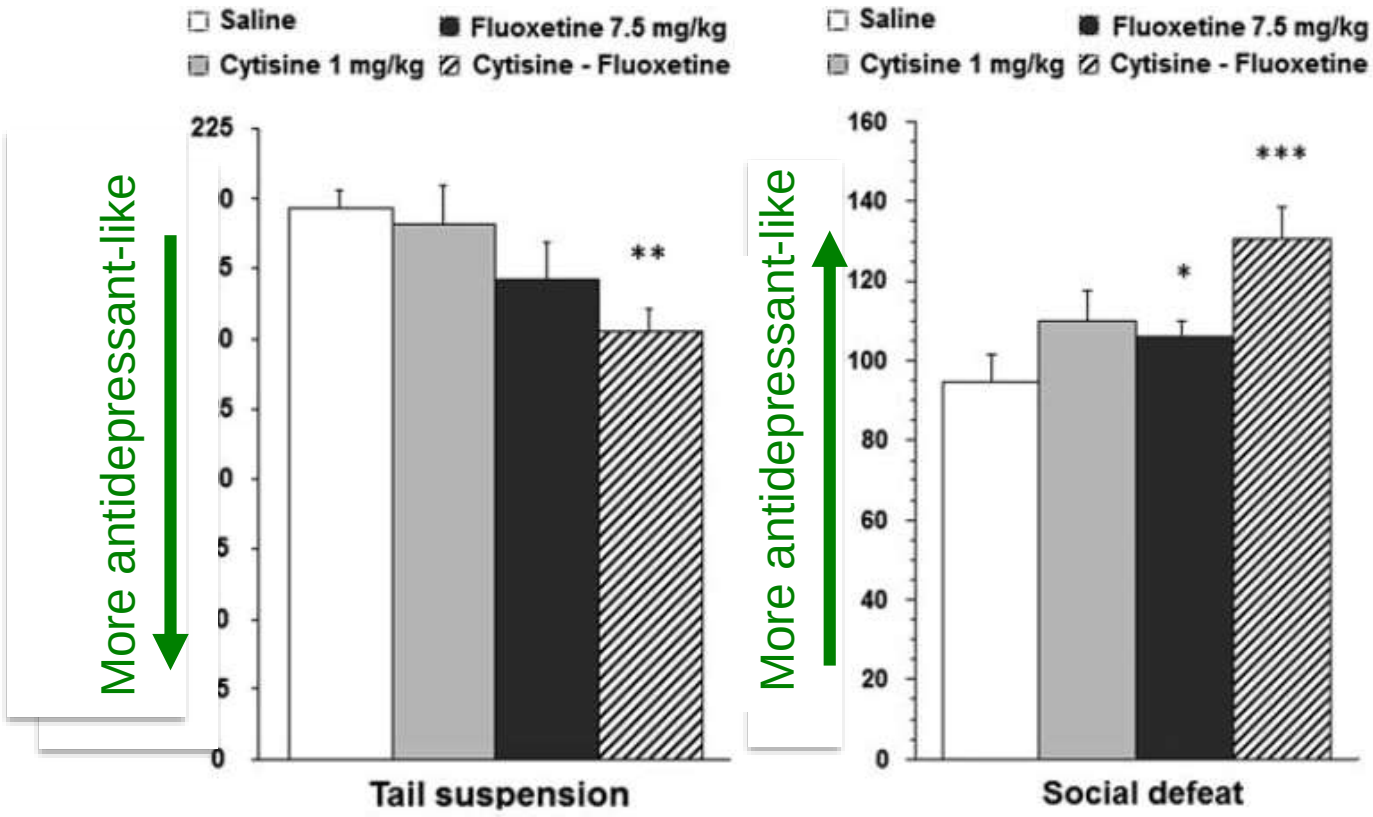
Mineur et al, Neuropharmacology, 2007

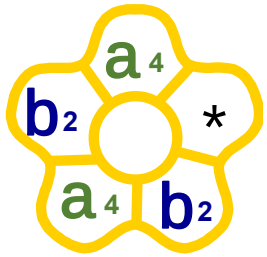


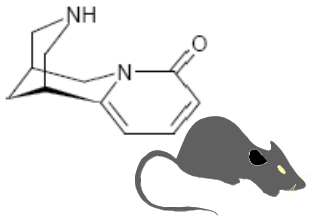
Decreasing acetylcholine signaling has antidepressant-like effects in mice

Does this effect share mechanisms with antidepressants used in humans?

CYT and Prozac work together to be antidepressant-like in mice

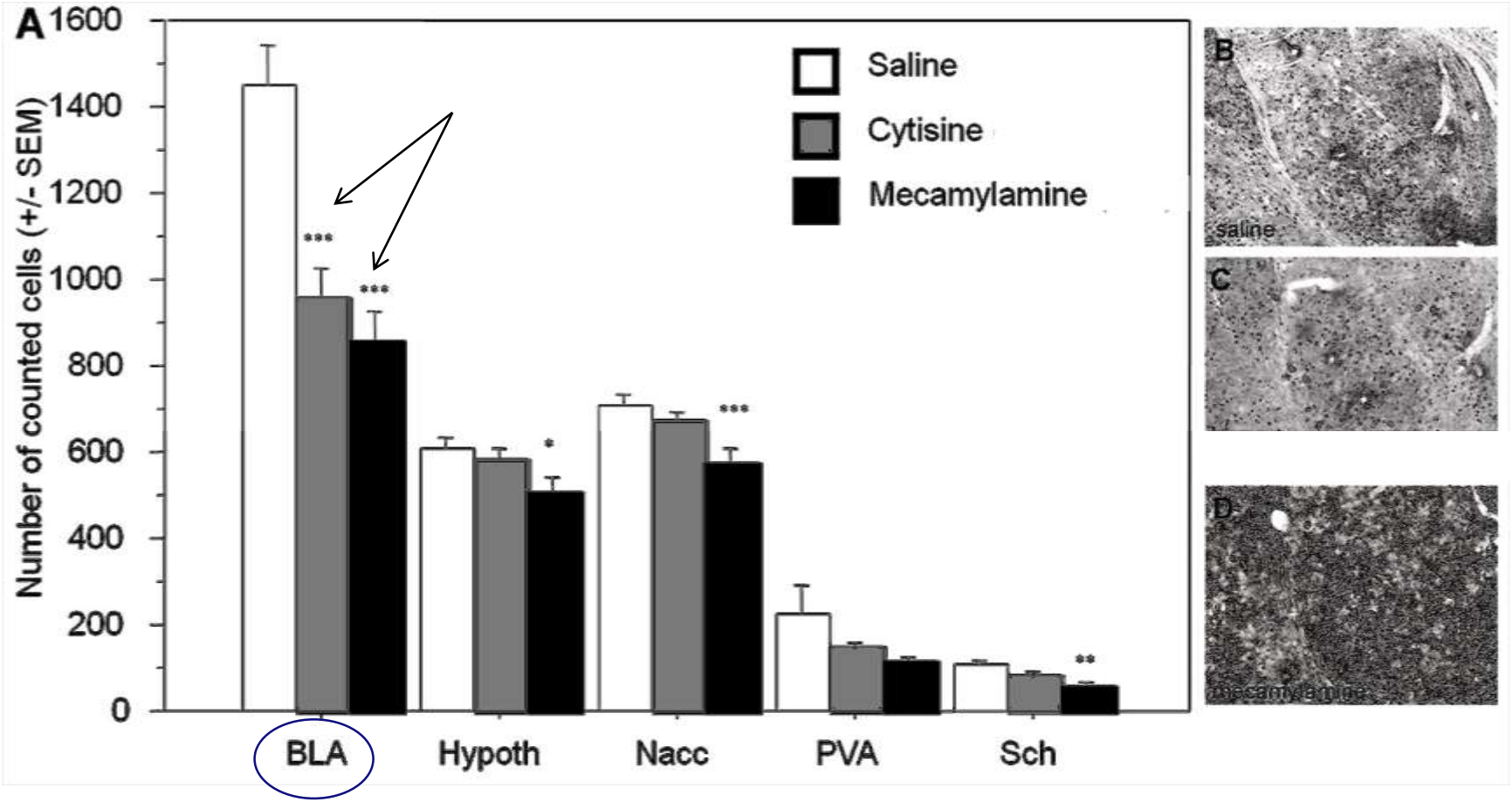


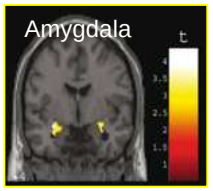


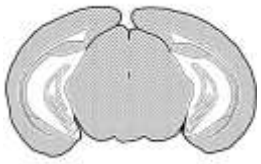


Mineur et al, 2015, NPP

MEC and CYT are antidepressant-like and decrease activity in mouse amygdala (BLA)

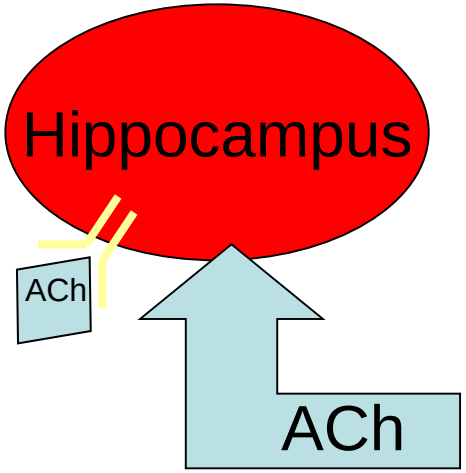




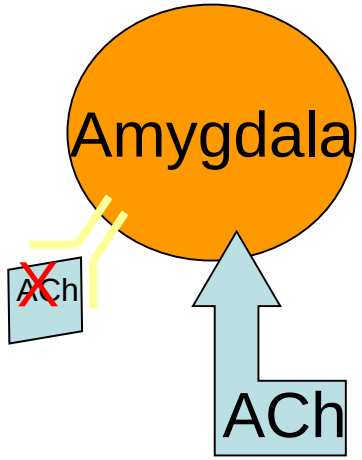


Mineur et al., Neuropharmacology, 2007

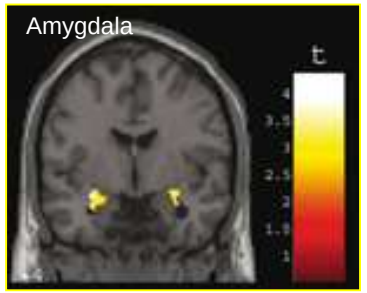
Can blocking nicotine receptors in amygdala alter stress-related behaviors?



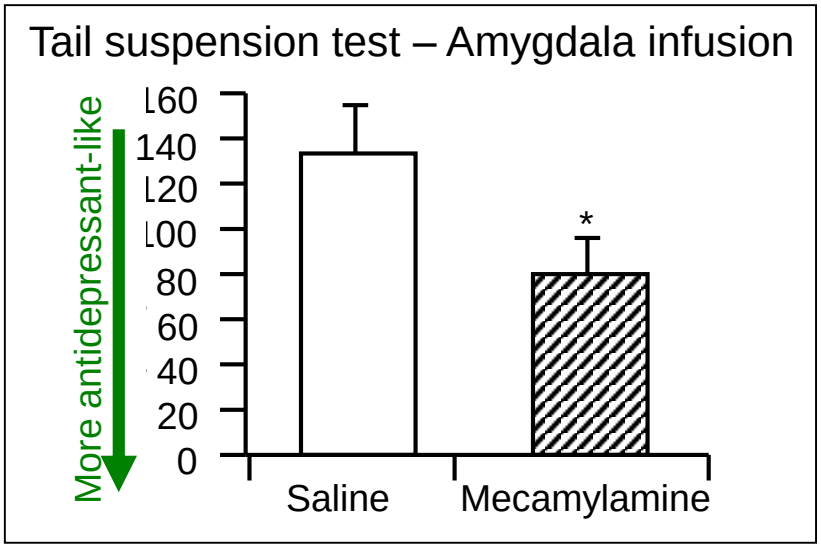
Increased depressive symptoms

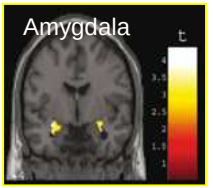


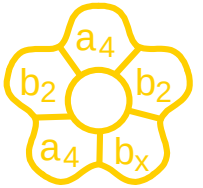
Decreased depressive symptoms



Blocking nicotine receptors in the amygdala is antidepressant-like

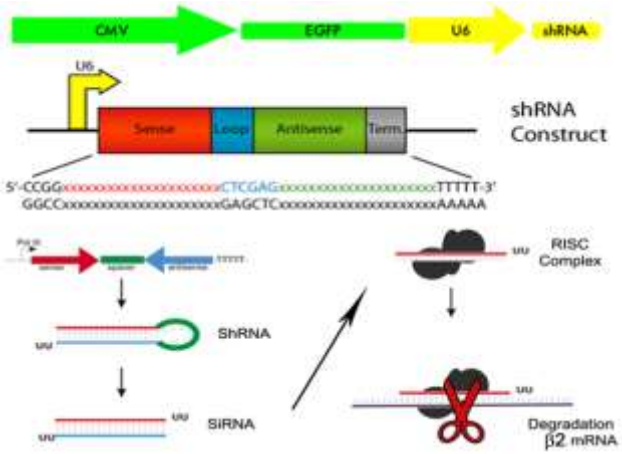


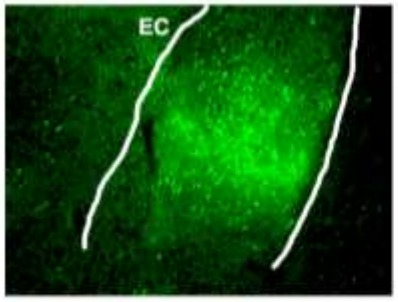




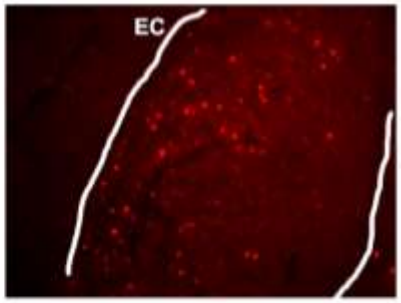
Mineur et al, NPP, 2015

Genetic deletion of nicotine receptors in amygdala decreases its activity

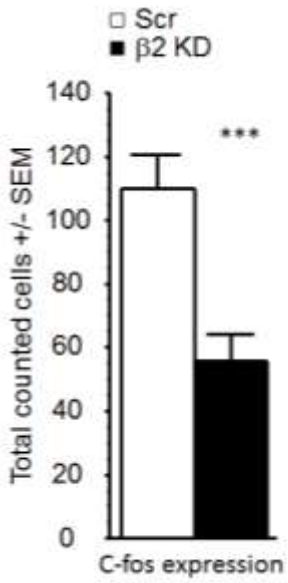


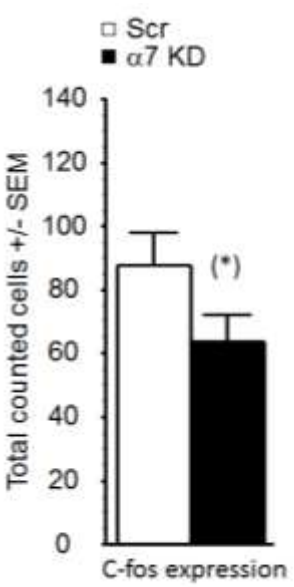


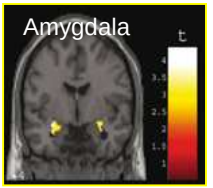
GFP after viral infusion in BLA (from Bregma -1.8)

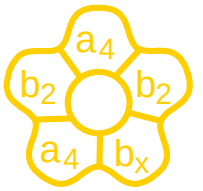


C-fos expression in BLA (from Bregma -1.8)



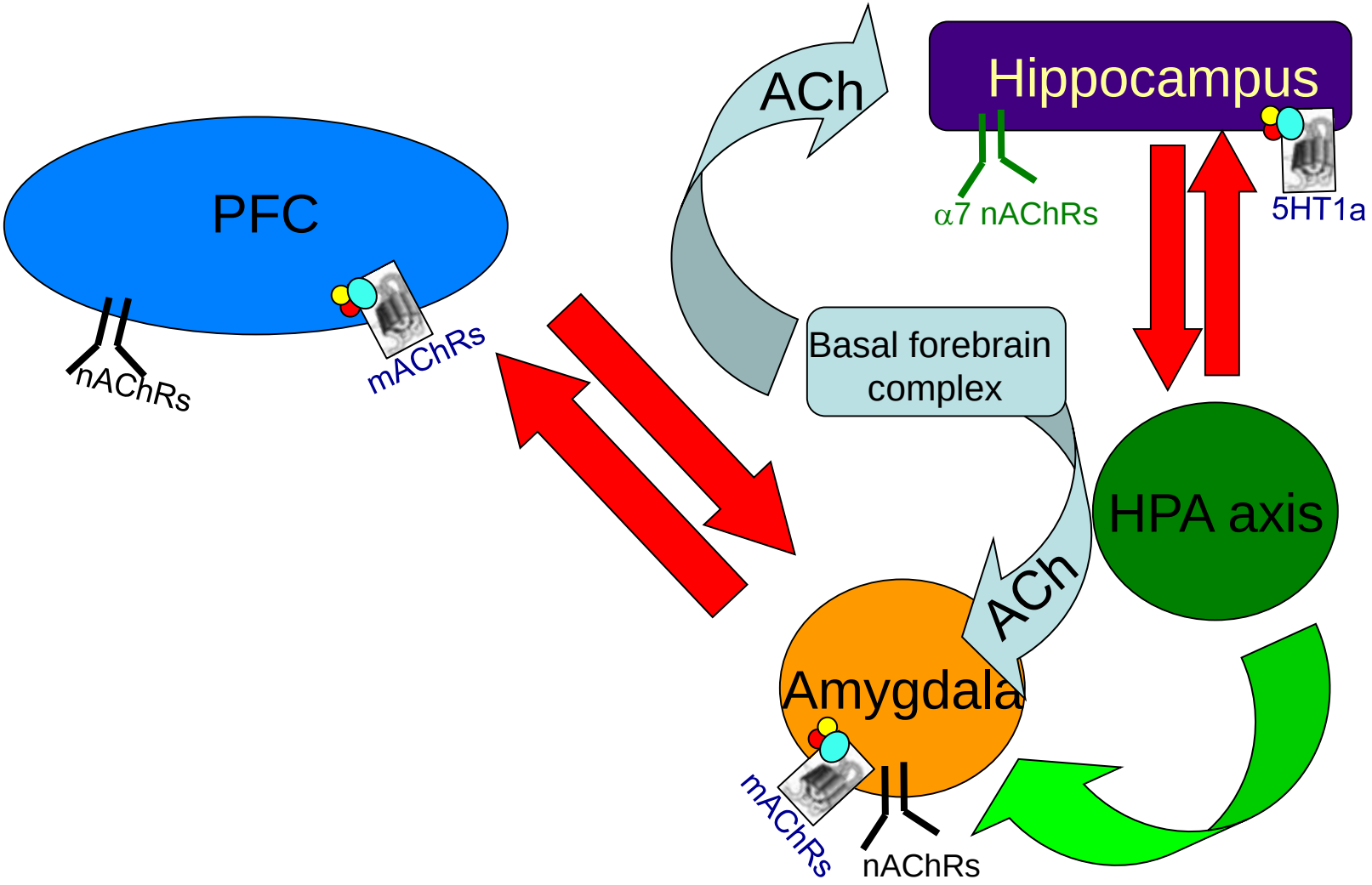




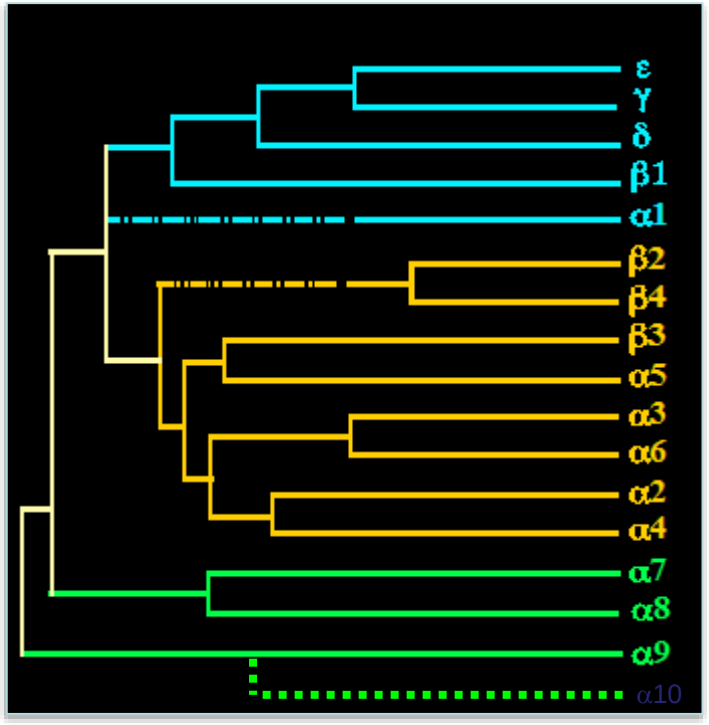


Mineur et al, NPP, 2015

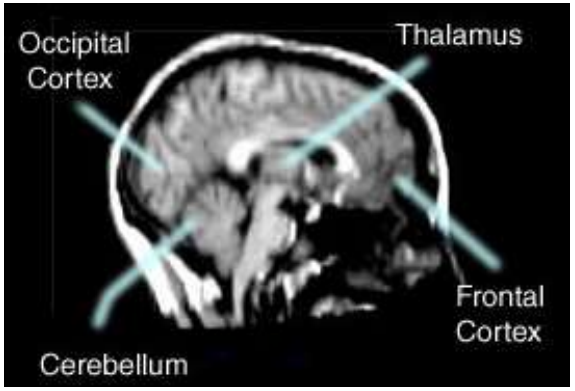
ACh effects on circuits involved in stress, anxiety, depression – in progress

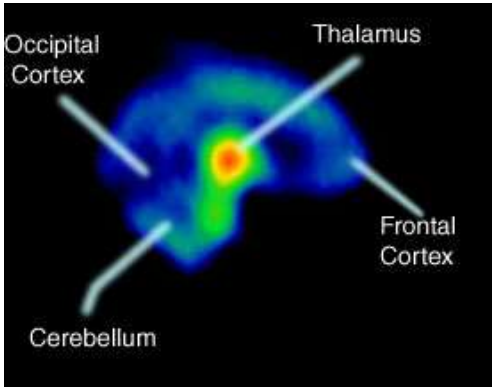


The problem :



Many nAChRs





Many brain areas expressing nAChRs

Many reasons people smoke

The good news:

A combination of molecular genetics and pharmacology in animal models and humans has made good progress in dissecting the nAChR subtypes and brain sites responsible for specific nicotine-dependent behaviors that drive smoking. Targeting these nAChRs is a success story for rational drug design and has resulted in the most effective current treatment for smoking.

The challenge:

Existing pharmacological agents used in humans do not target specific nAChR subtypes. In fact, agents that are somewhat selective, such as cytisine and mecamylamine, can have different selectivity for human receptor subtypes.

The hope:

Medications targeted to highly specific nicotinic subtypes could be useful in helping help motivate smokers who smoke for reasons other than nicotine reinforcement, such as self-medication of affective symptoms, to quit and may also help treat non-smokers with anxiety or depressive disorders.

Current lab members

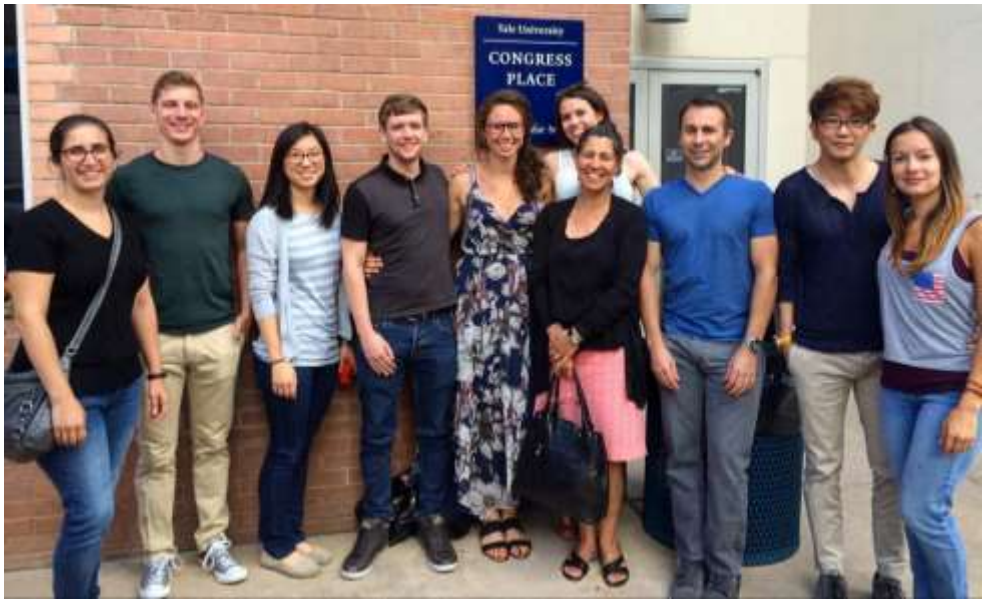
Cali Calarco
Rick Crouse
Nadia Jordan-Spasov
Angela Lee
Alan Lewis
Yann Mineur
Steven Pittenger
Samantha Sheppard
Wenliang Zhou

Collaborators

Zubin Bhagwagar
Ralph Dileone
Ron Duman
Irina Esterlis
Sherry McKee
Gerrit van Schalkwyk

Past lab members

Barbara Caldarone
Rebecca Rabenstein



Funding

NARSAD
NIDA
NIMH