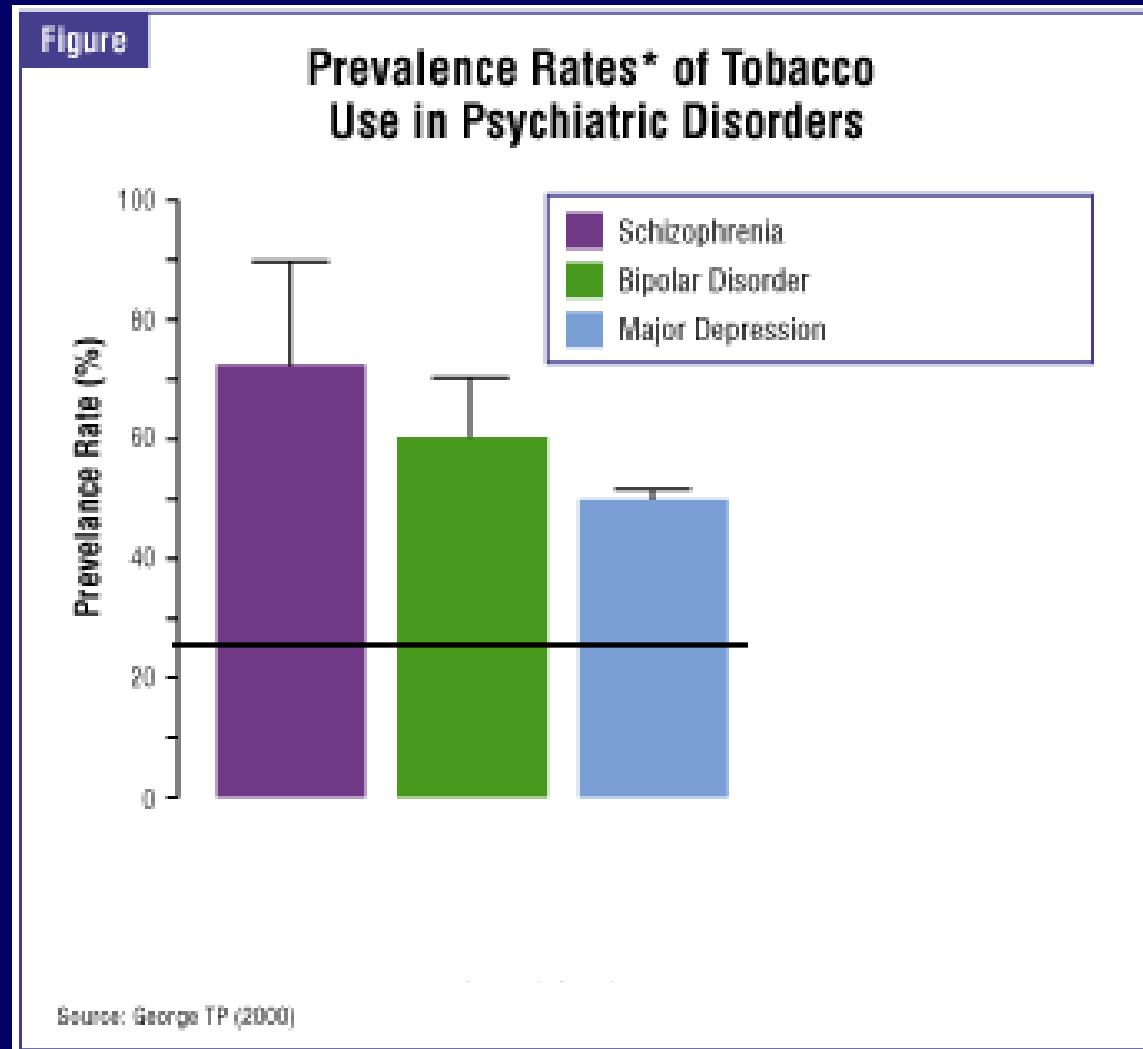




Innovative Approaches to Understanding the Links between Nicotine and Depression

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Comorbidity Between Smoking and Depression



Possible relationships between Smoking and Depression

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1. Smoking \longrightarrow Antidepressant

- "Self-Medication" Hypothesis (nicotine patches improve mood in non-smoking depressed patients (Salin-Pascual et al.)

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2. Smoking → Depression

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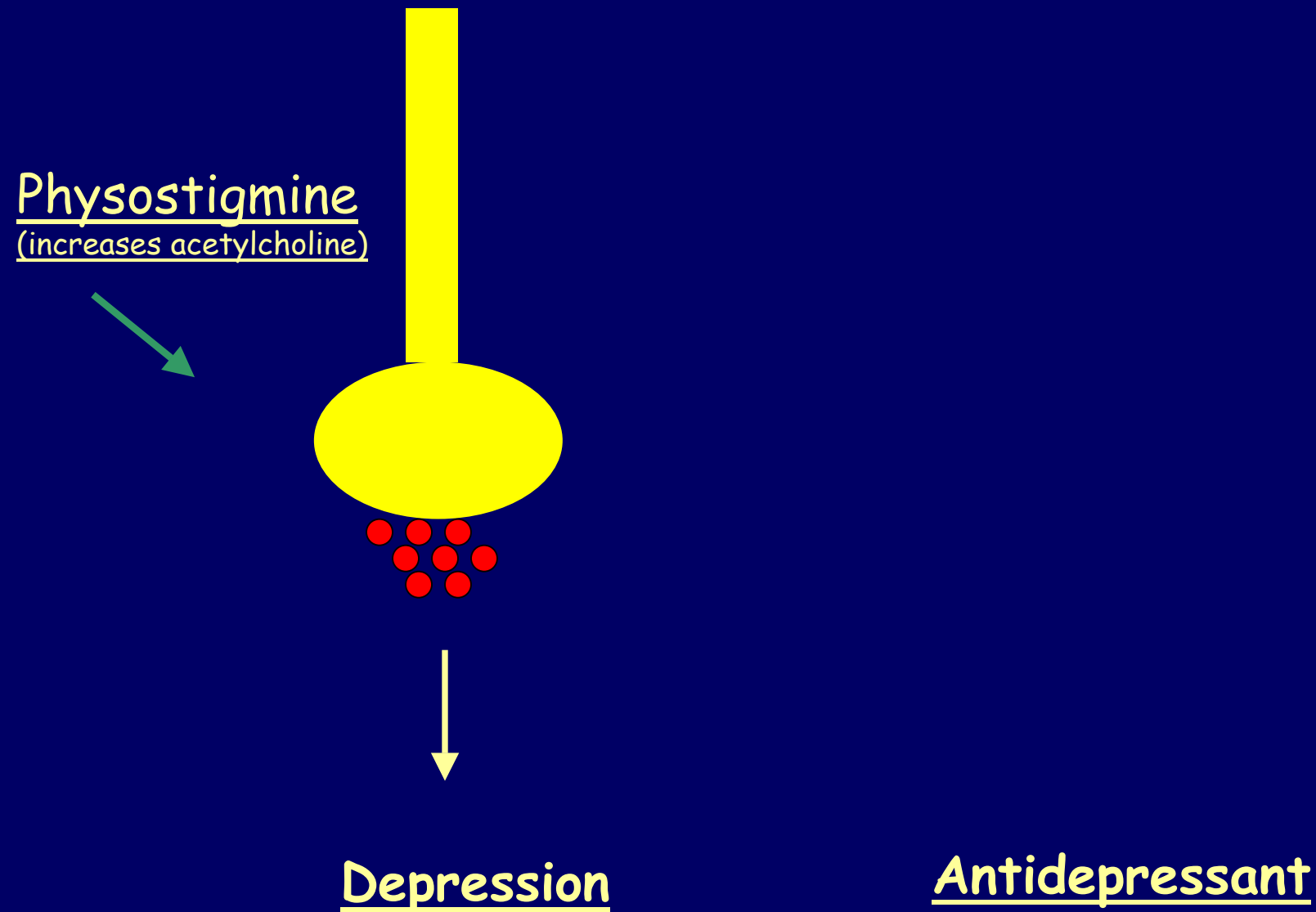
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3. Shared Genetic Predisposition

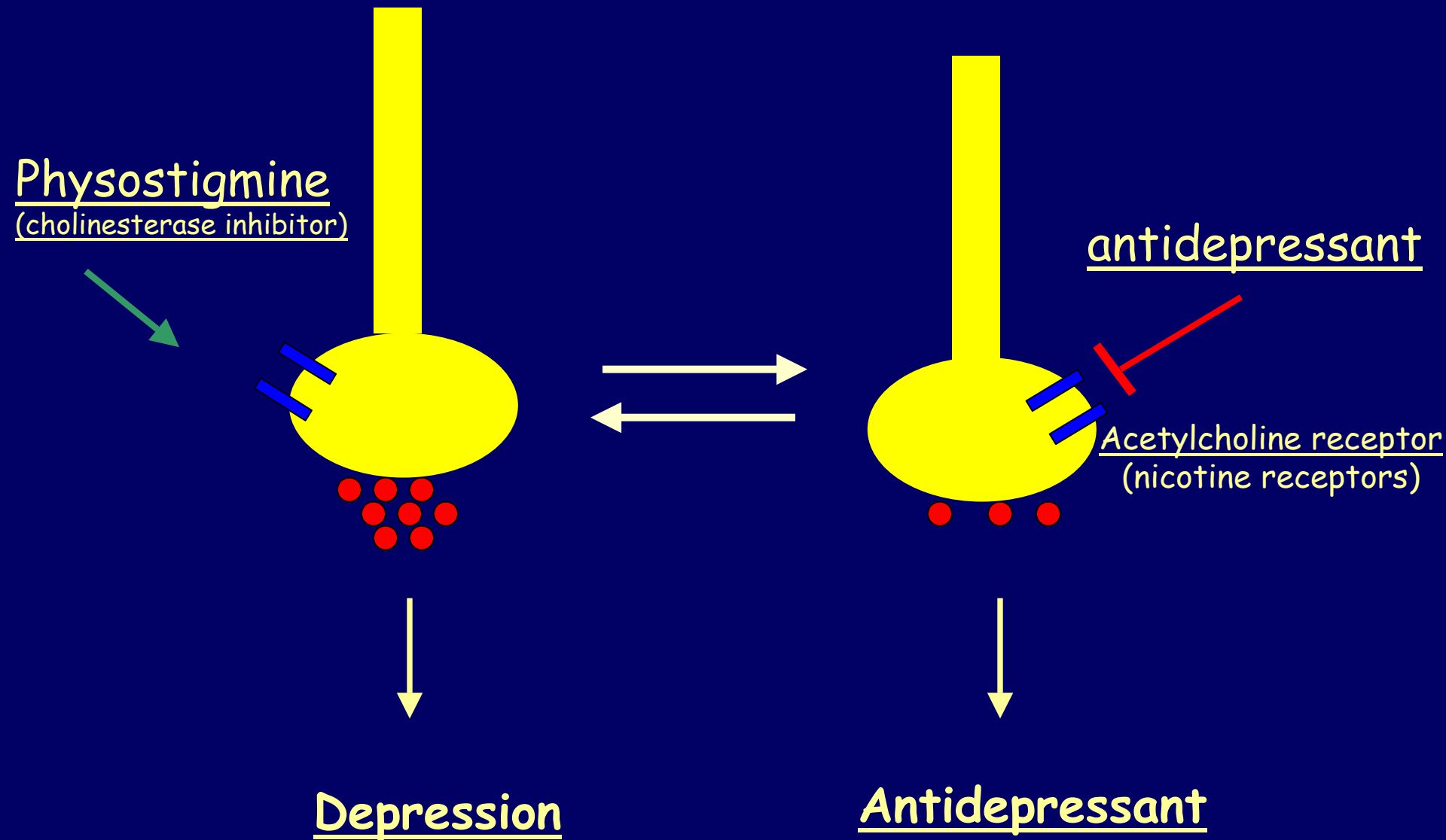
- Higher correlation between smoking and depression in identical than fraternal twins (Kendler et al., 1993).

Cholinergic Hypothesis of Depression (Janowsky et al., 1972)



Cholinergic Hypothesis of Depression

(Shytle et al., 2003)



Classical antidepressants inhibit nicotine receptors

TCAs:

- amitriptyline
- clomipramine
- desipramine
- imipramine
- nortriptyline

MAOI:

- phenelzine

NE Reuptake Inhibitors:

- nisooxetine
- reboxetine

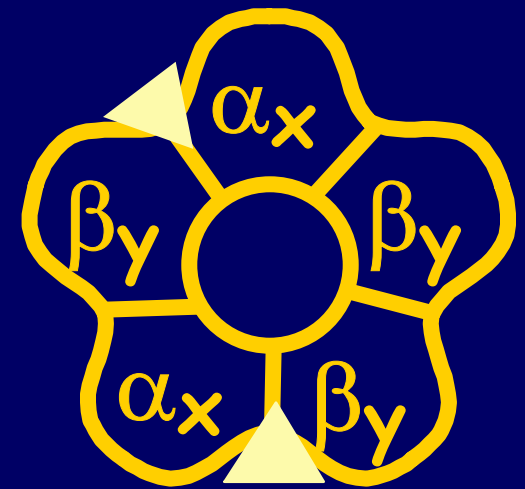
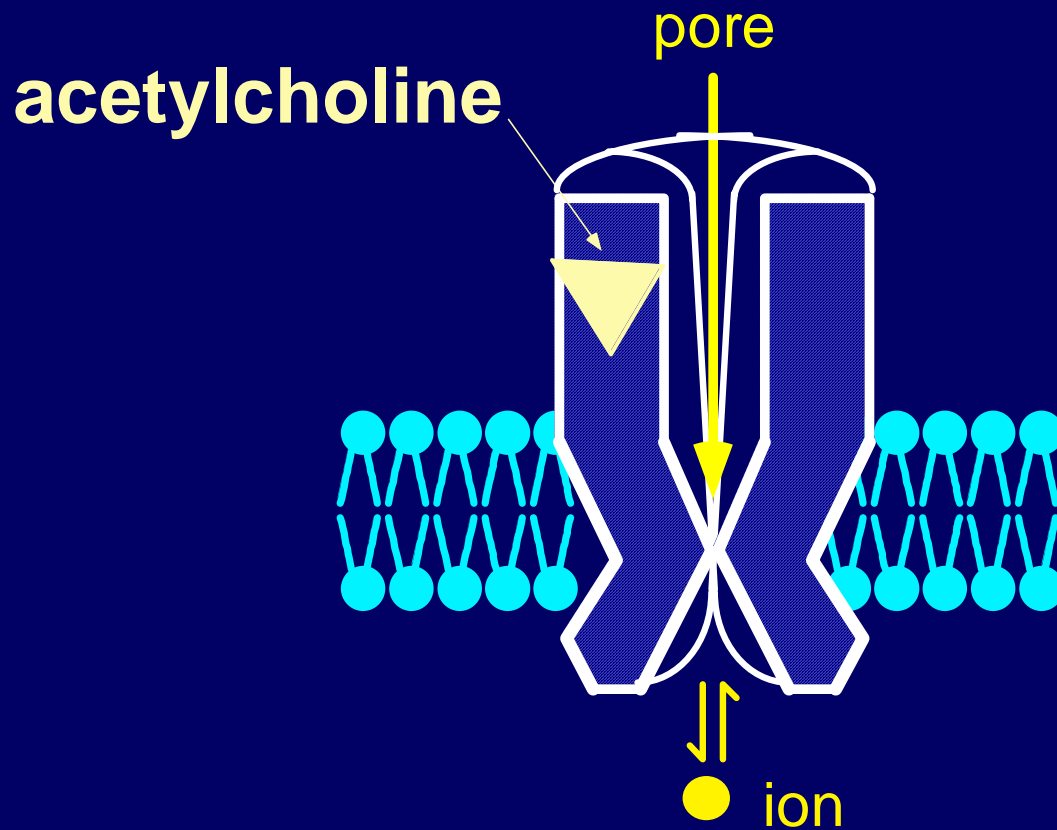
SSRIs:

- citalopram
- fluoxetine
- paroxetine
- sertraline

Atypical/Mixed Action:

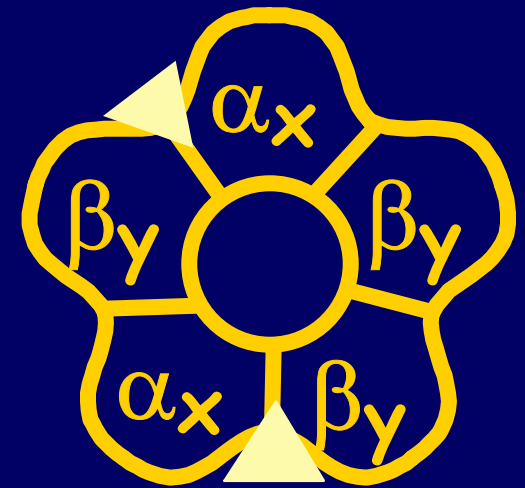
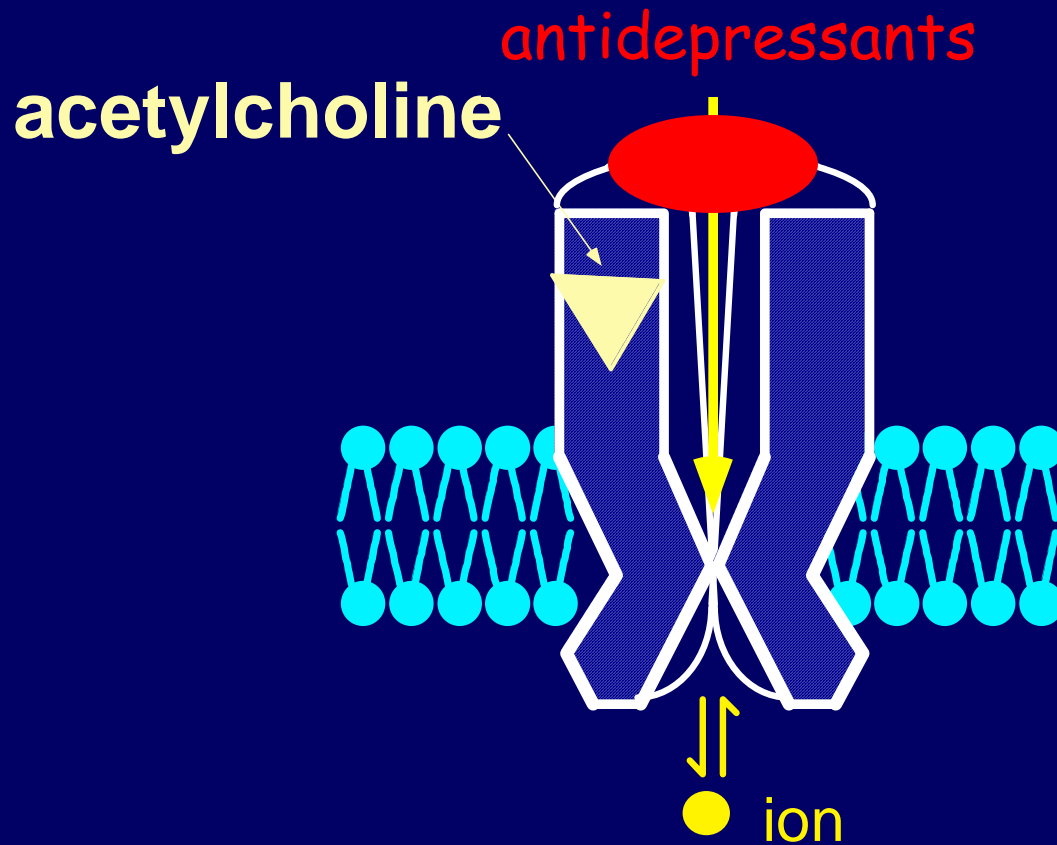
- bupropion
- nefazodone
- nomifensine
- venlafaxine

Structure of nicotine receptors



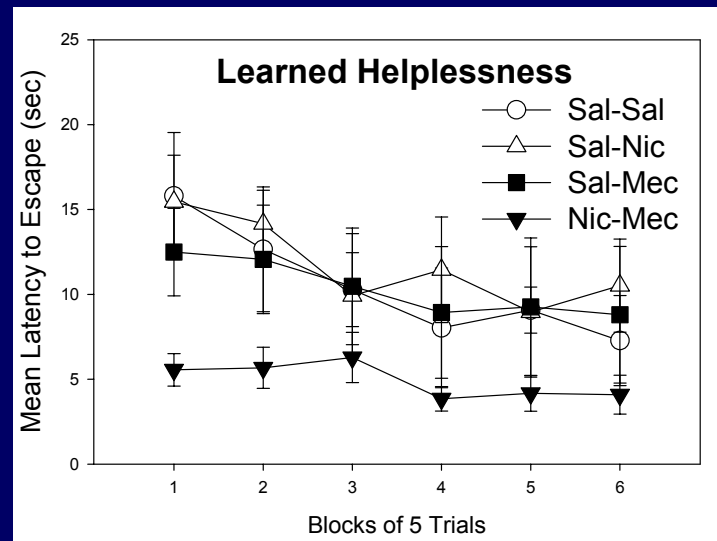
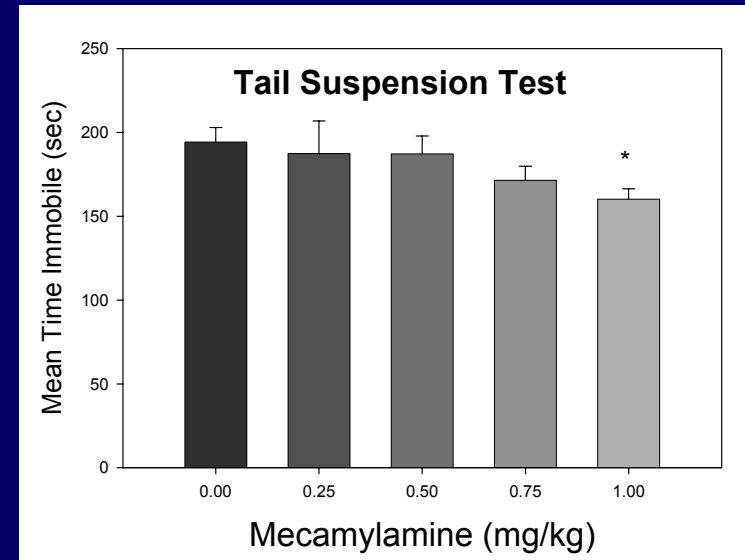
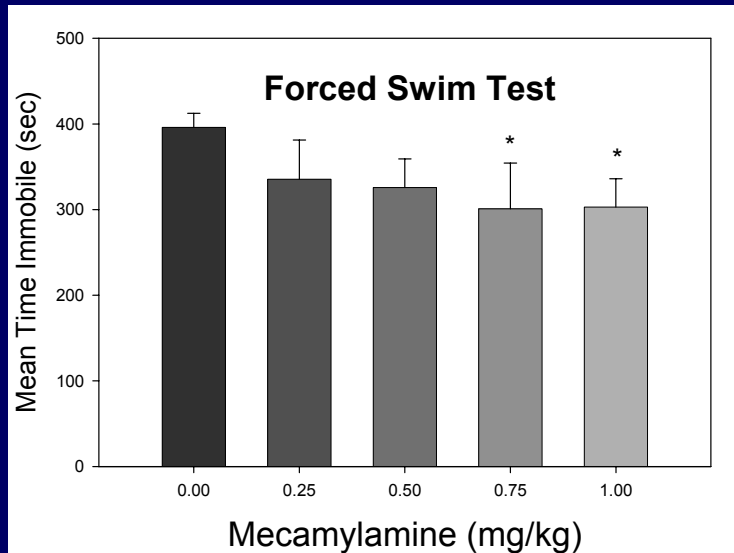
neuronal type
nicotine receptors

Structure of nicotine receptors

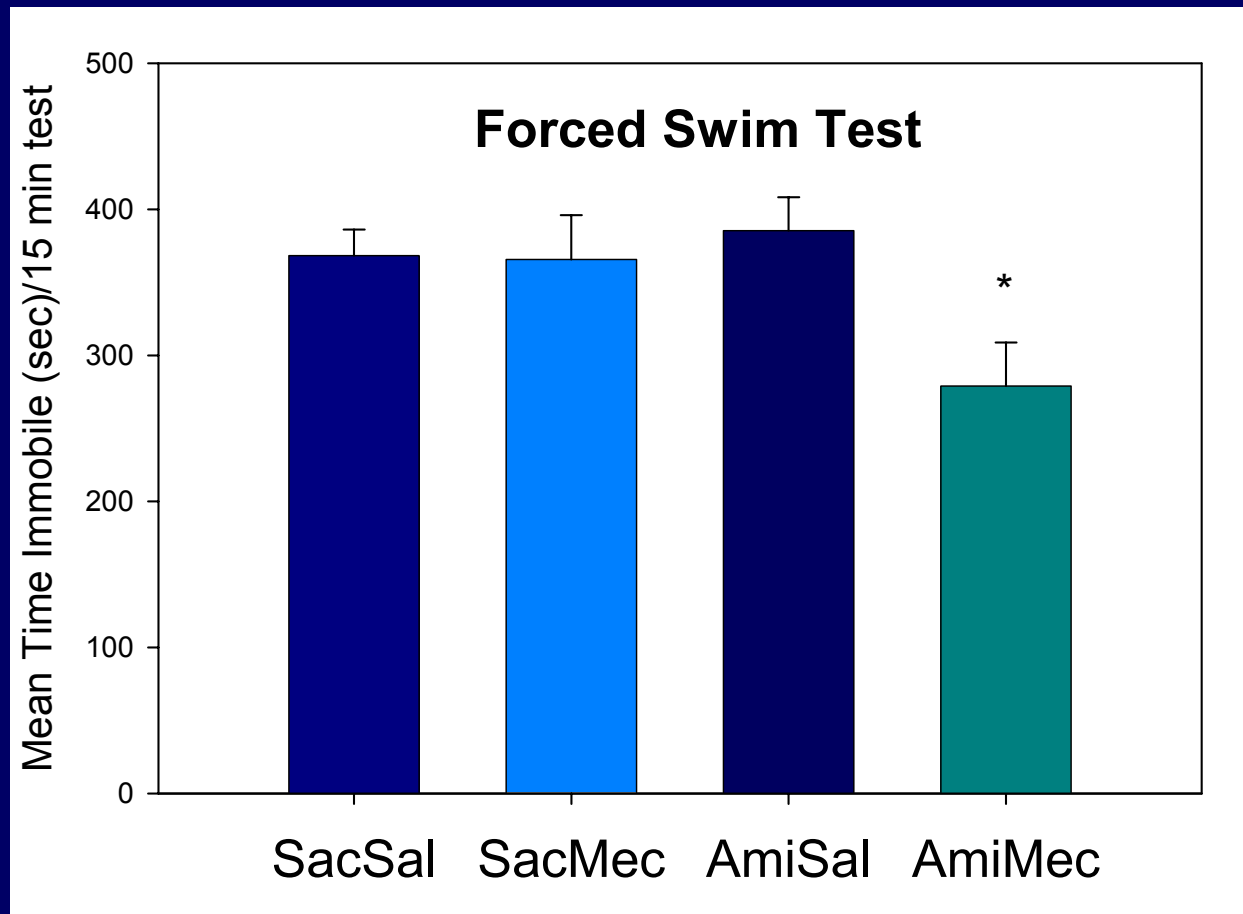


neuronal type
nicotine receptors

The nicotine receptor blocker mecamylamine acts like an antidepressant in three mouse depression models



Brief treatment with the tricyclic antidepressant amitriptyline plus nicotine receptor blockade is antidepressant

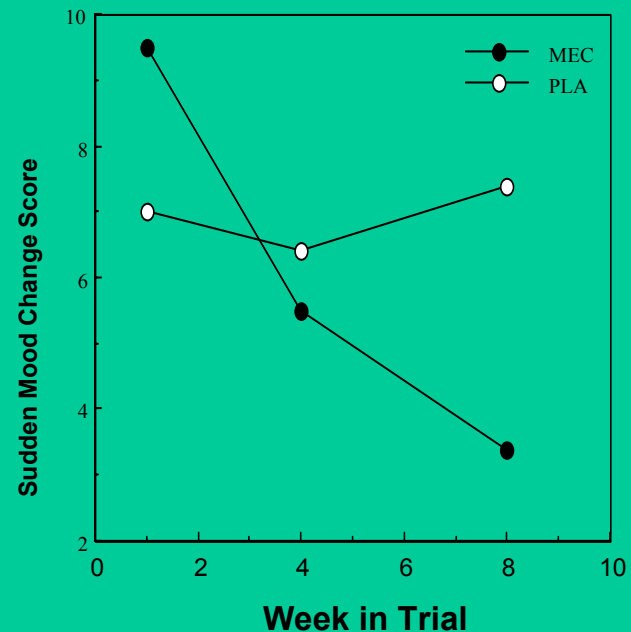


Nicotine receptor blockade has effects on mood in human subjects

- The nicotine receptor blocker mecamylamine has mood-stabilizing and antidepressant effects in patients with Tourette's Disorder.

Effects of Mecamylamine on 'Sudden Mood Changes'

(Shytle et al., 2002)



Summary I

The nicotine receptor blocker mecamylamine can act like a classical antidepressant in animal models of depression-like behavior.

Combining the nicotine receptor blocker mecamylamine with a classical antidepressant is antidepressant in animal models of depression-like behavior.

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Clinical implication: adding a nicotine receptor blocker to a classical antidepressant may improve treatment outcome in depressed patients (Tony George).



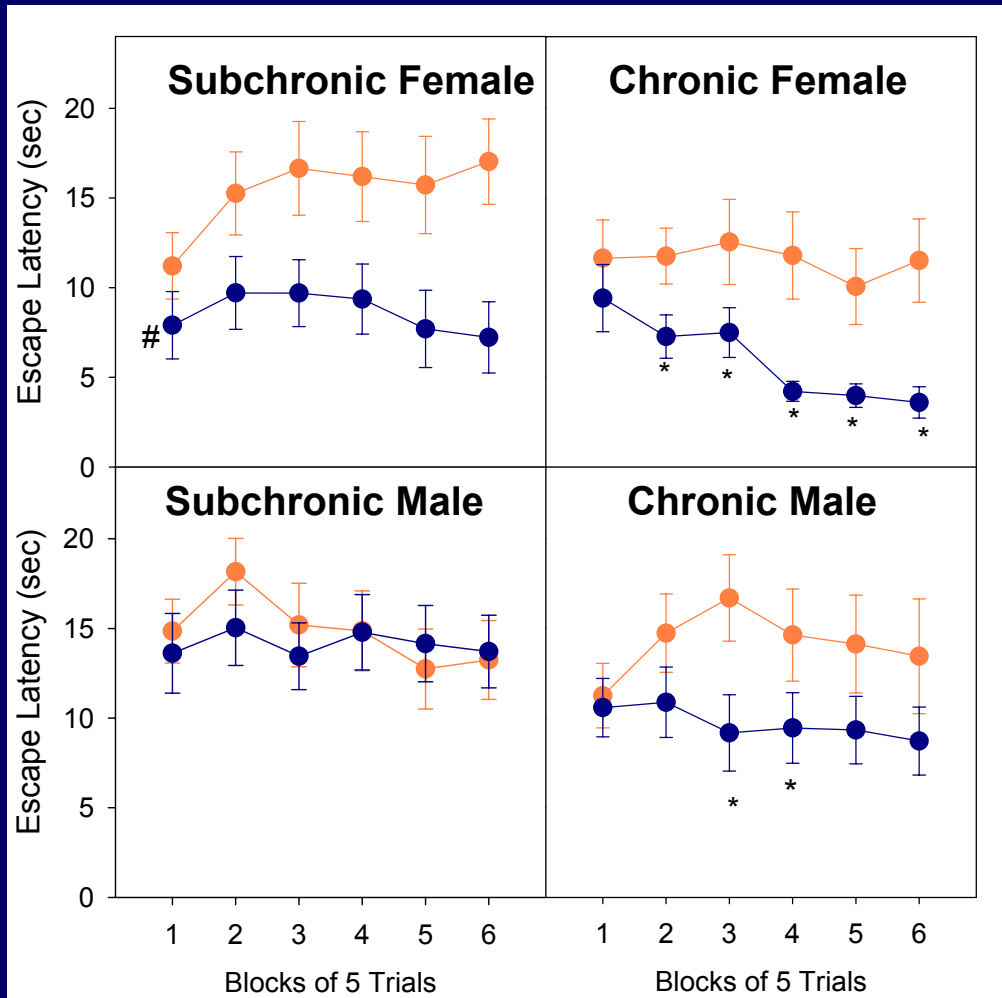
nAChR knockout mice lack high affinity nicotine receptors throughout the brain

Question:

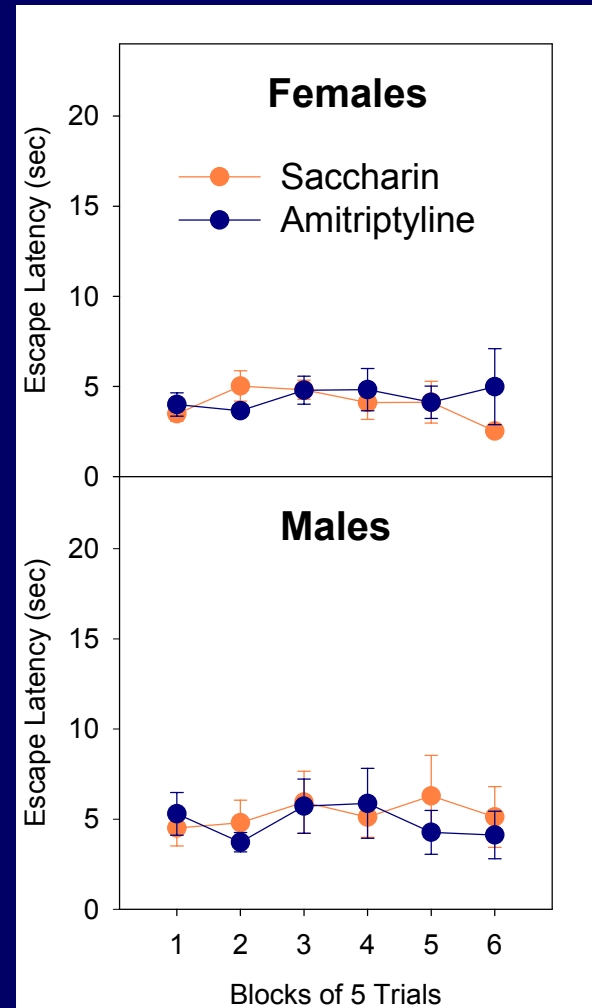
Are nicotine's effects on depression-like behaviors mediated through these nicotine receptors?

Learned Helplessness

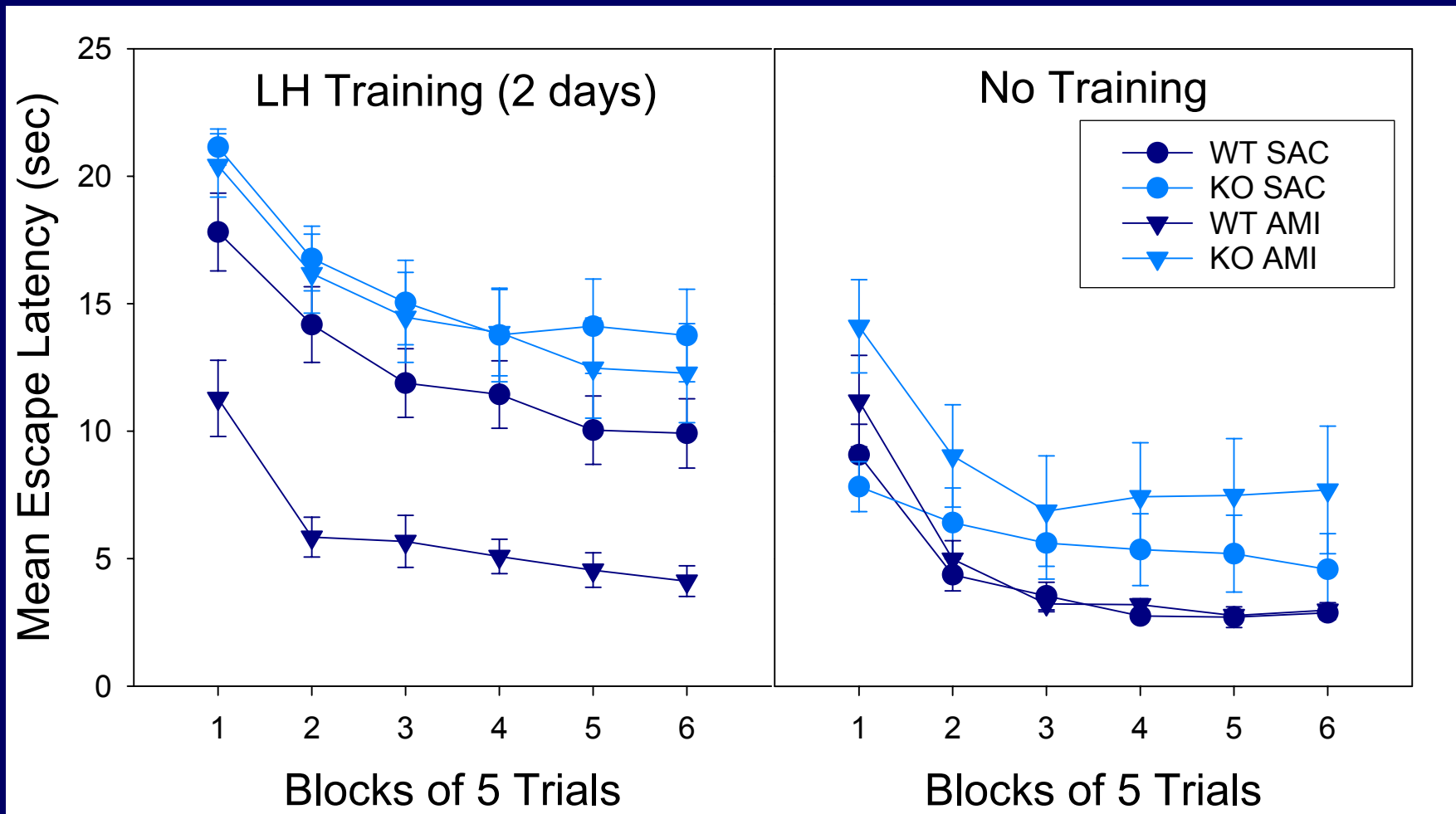
LH Training



No Training



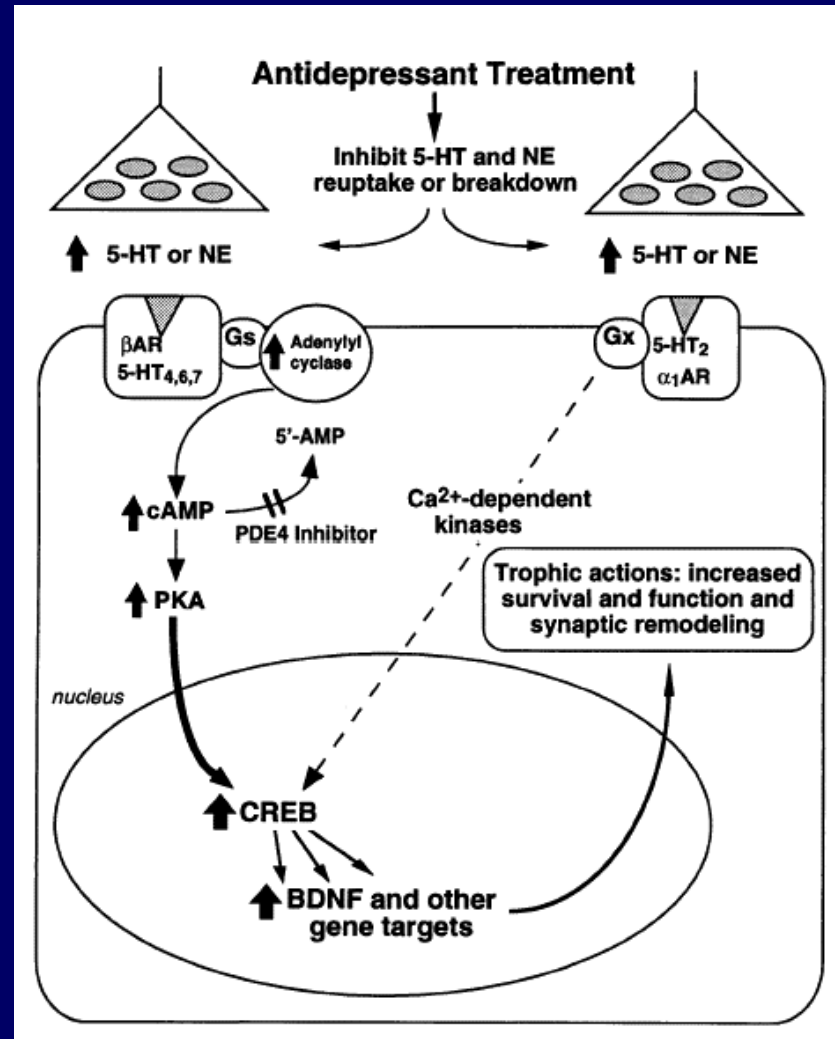
Amitriptyline is not antidepressant in nicotine receptor knockout mice



Intake and serum levels of amitriptyline

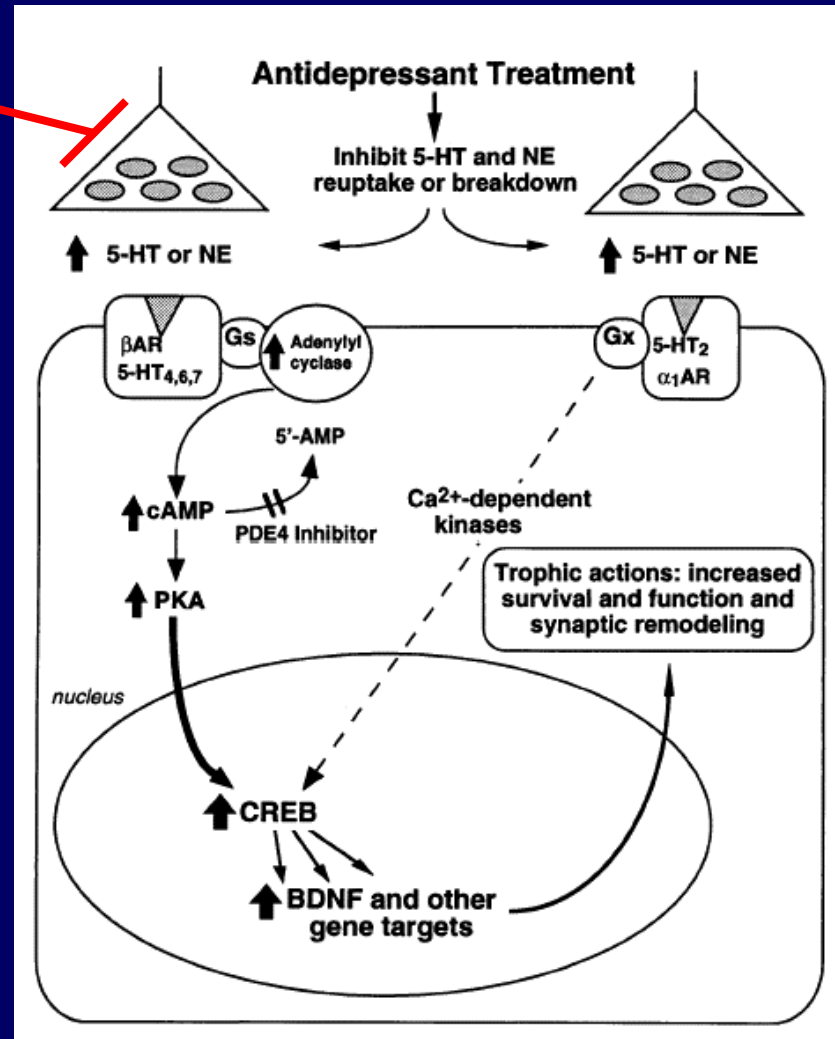
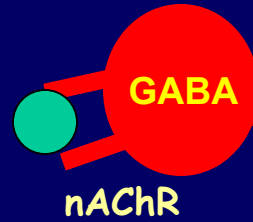
	Wild type	Knockout
Subchronic Intake (mg/kg/day)	16.7 (± 1.4)	15.2 (± 1.9)
Chronic Intake (mg/kg/day)	20.7 (± 0.94)	21.3 (± 0.81)
AMI/NOR Levels (ng/ml)	189.3 (± 44.1)	186.25 (± 32.6)

Adaptation in neurons in the hippocampus may underlie antidepressant effects



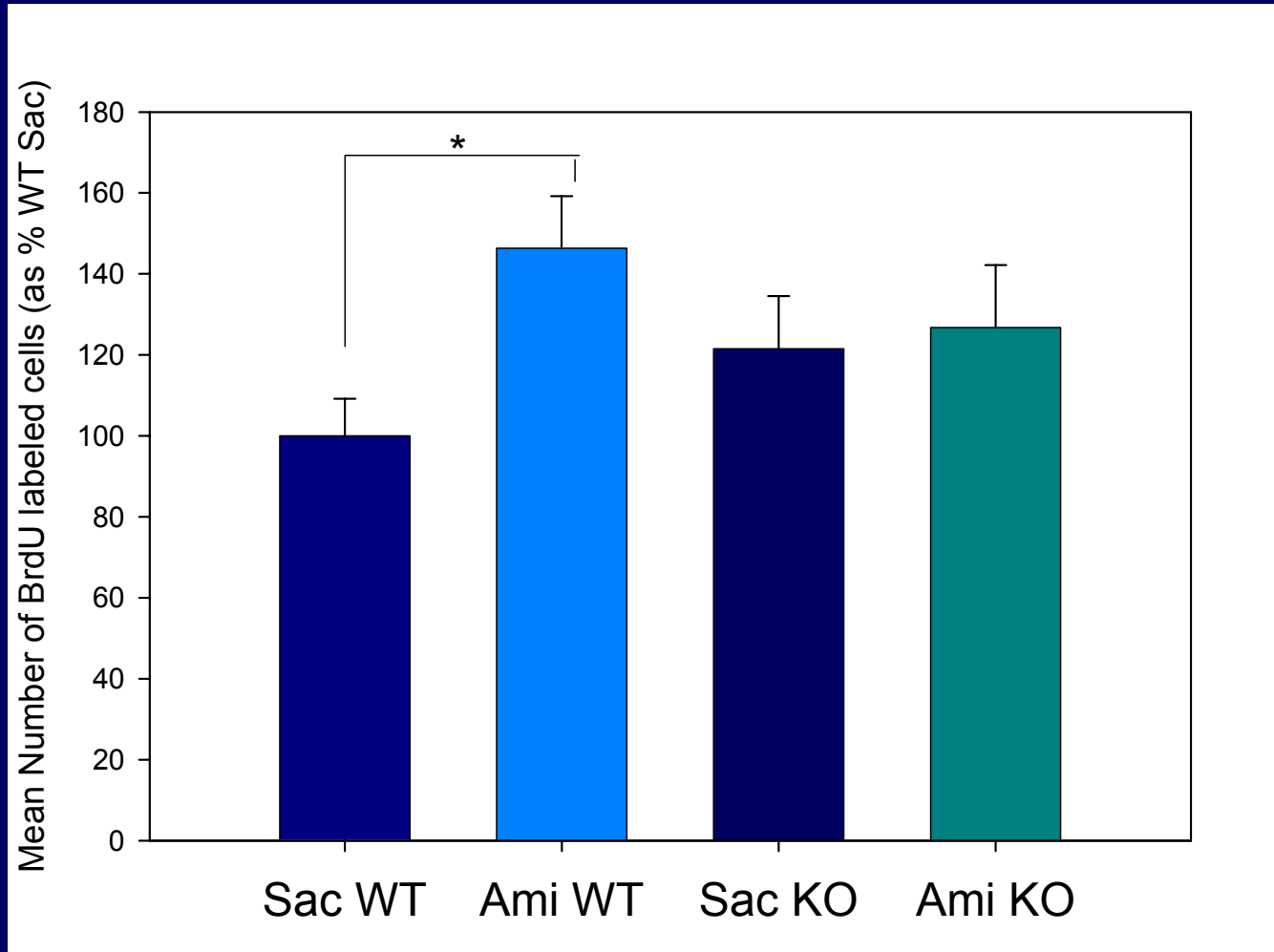
Blocking nicotine receptors may facilitate those adaptations

Antidepressants
Mecamylamine



Duman et al, Biol. Psychiatry 1999

Chronic amitriptyline increases birth of new neurons in adult mice



Summary II

High affinity nAChRs are involved in antidepressant response to amitriptyline, a tricyclic antidepressant.

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High affinity nAChRs are involved in antidepressant response to amitriptyline, a tricyclic antidepressant.

Clinical implication: smoking might alter the effects of a classical antidepressant in human beings.

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Conclusion: All three factors play a role in the interaction between smoking and depression.

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