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:
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.
Structure of nicotine receptors

Acetylcholine

Muscle type nicotine receptor

Brain type 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

Example: $\beta_2^*$ receptor

WT

$\beta_2$ KO
The $\beta_2^*$ nicotine receptor is the most widespread
The $\beta_2^*$ nicotine receptor is found in the VTA.
Nicotine binding goes away without the $\beta_2^*$ nicotine receptor

normal mouse brain

mouse brain without $\beta_2$
Nicotine-induces electrical currents in DA cells

![Graph showing electrical currents induced by different concentrations of nicotine.](image)
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
Nicotine receptors in VTA are needed for reward
Summary: nicotine addiction

\[ ax^2 = n \]

\[ = \text{nicotine} \]
\[ = \text{dopamine} \]

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 $\alpha_4/\beta_2^*$ nAChR, along with $\alpha_6$, 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.
Together the field has identified the ventral tegmental area (VTA) as essential for the rewarding effects of nicotine.
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.
People who are depressed are more likely to smoke.

40-60% of patients with depression smoke.
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

Why do people smoke despite negative effects on health?
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?
Why would intravenous nicotine increase depressive symptoms and nicotine patch decrease depressive symptoms?

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.
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Maybe blocking nicotine receptors to prevent ACh action is antidepressant.

Smokers are going through cycles of activating and blocking their nicotine receptors throughout the day.
Janowsky: Increasing ACh in humans induces symptoms of depression
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

- More immobile
- Less AChE activity

AChR blockers

- Antidepressant-like

Mineur, et al, PNAS, 2013
Increasing ACh induces stress-related behaviors in mice that can be reversed by an antidepressant (Prozac)

Physostigmine

More immobile

Less AChE activity

AChR blockers

Antidepressant-like

SSRI

Antidepressant-like

Mineur, et al, PNAS, 2013
Does ACh signaling in the brain underlie stress-induced behaviors?

**Physostigmine**
- More immobile
- Less AChE activity

**AChR blockers**
- Antidepressant-like

**SSRI**
- Antidepressant-like

-Mineur, et al, PNAS, 2013-
Increasing ACh in mouse hippocampus induces behaviors sensitive to anxiolytics

Knockdown

Anxiety-like

More anxiety-like

Mineur, et al, PNAS, 2013
Increasing ACh in mouse hippocampus induces behaviors sensitive to antidepressants

Dockdown

More immobile

Tail suspension

Forced swim

More immobile

Social defeat stress

Less social

Scrambled

shRNA AChE

Scrambled + hAChE

Non-stressed

Chronic Social Defeat Stress

Suboptimal Social Defeat Stress

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
Imaging of $\beta_2$ nAChRs in human brain

If depression is associated with increased ACh, what would we expect to see when imaging $\beta_2$ nAChRs?
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$\uparrow$ acetylcholine

nicotinic receptors
If depression is associated with increased ACh, what would we expect to see when imaging \( \beta_2 \) nAChRs?
Nicotinic receptors are bound to more ACh in actively depressed human subjects

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

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

A Preliminary Study

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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.
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

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.
Medications targeted to highly specific nicotinic subtypes could be useful in helping 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.
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