Smoke Gets in Your Brain

by Henry A. Lester

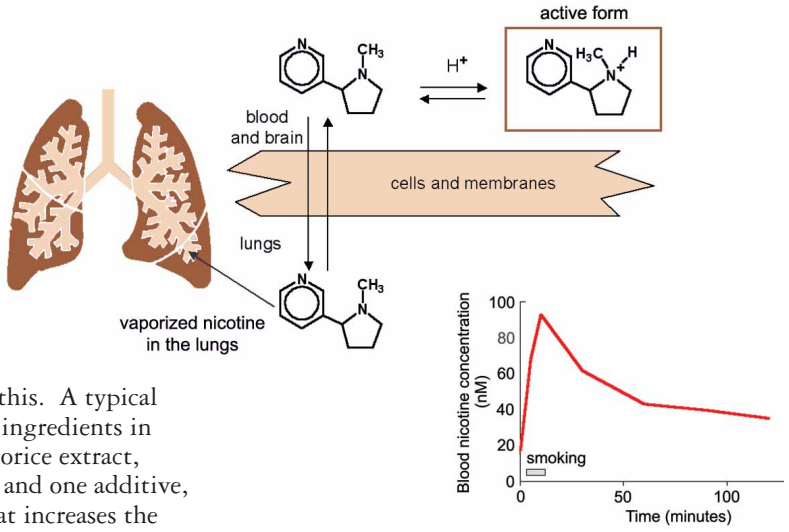
If smokers are self-medicating with nicotine, what does this tell us about the brain? To understand just what nicotine is doing to our nerve cells at the molecular level, and why it is so addictive, my laboratory has designed mice genetically altered to be hypersensitive to it. I'd like to tell you about our first results with these mice, and what we're learning from them. It turns out that these mice also have implications for other human conditions, such as Parkinson's, Alzheimer's, alcoholism, epilepsy, and pain.

Let's start with a person who has taken a puff on a cigarette and now has vaporized nicotine in his or her lungs. How does the nicotine get to the brain? On this journey, nicotine must cross a number of cells and membranes, such as those separating the lungs from the blood and the blood from the brain. Nicotine accomplishes its journey rather well, because in the uncharged form membranes are very permeable to it. But the form that is active on cells does have a charge, because it has picked up a proton (H^+). This is a common theme with drugs of both therapy and abuse such as morphine, heroin, and cocaine: they enter the bloodstream and get to the brain fairly rapidly, then take on a slightly different form—typically by gaining a proton—in order to act on each drug's specific receptor in the brain. If the nicotine molecule gained a proton too early, it wouldn't be able to pass through the lungs and into the blood.

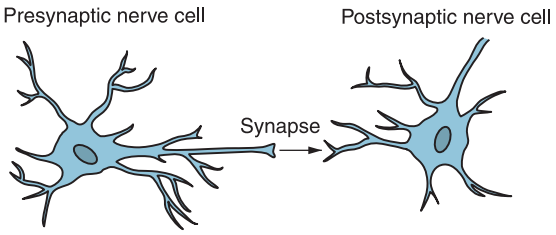
Cigarette manufacturers know this. A typical Marlboro, for example, has many ingredients in addition to tobacco (including licorice extract, glycerol, carob beans, and cocoa), and one additive, simple ammonium hydroxide, that increases the pH of the fluid layer lining the lungs. This prevents the average nicotine molecule from becoming protonated, keeping it in the uncharged state appropriate for crossing the lungs. South American Indians know this trick too, and chew their coca leaves with a dash of powdered lime to keep the cocaine solution nonacidic.

Nicotine concentrations in the blood (and presumably in the brain as well) increase within minutes after just a few puffs, and they also decrease rapidly after smoking stops. In ways we don't yet fully understand, this rapid pulse of nicotine is probably important for some of the subsequent events, including addiction. A nicotine patch is not addictive, because it releases a steady, much lower concentration that partially blunts the response to these pulses. Although the pulse of nicotine is brief, on a time scale of minutes, it appears as quite a high concentration over a long period of time to the actual cells and synapses involved.

Nicotine gets into almost all areas of the brain, but the brain cells I'd like to emphasize first are

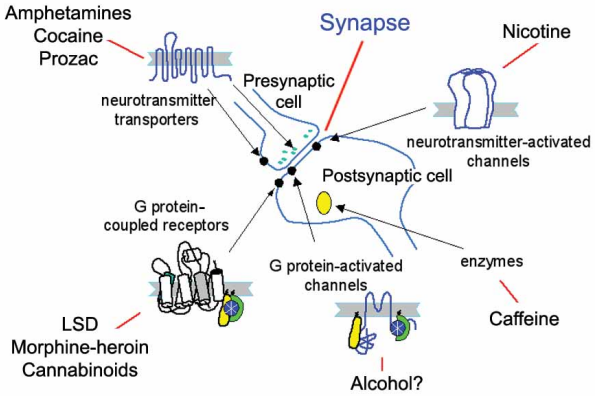


Levels of nicotine in the blood rise quickly after just a few puffs on a cigarette, right, because the uncharged molecule can pass across membranes with ease. Once it reaches the brain it activates by taking on a charge.

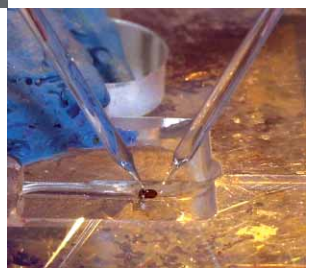


Signals between nerve cells are carried across the synapse by neurotransmitter molecules.

Some recreational drugs work by taking the place of neurotransmitters as they cross this gap; others work on nearby molecules.



Left: A patch-clamping rig set up to record the flow of ions through receptor channels in the large immature egg cell (oocyte) of the frog *Xenopus*.



Right: The egg is bathed in one type of chemical while glass pipettes doubling as electrodes inject it with another type. As receptor channels open and close in response to these chemicals, the electrodes measure the currents set up by the flow of ions.

those in the so-called pleasure/reward system deep within the midbrain. Some of these, the dopaminergic cells, respond to acetylcholine or nicotine by releasing dopamine.

In the brain, impulses move between two nerve cells across a gap called the synapse. It's a miniature chemical jump. The signal is electrical while it propagates within the presynaptic cell toward the synapse, but it's transformed into chemistry, in the form of a molecule called a neurotransmitter, in order to pass across the synapse. Once the neurotransmitter has got to the other side and reached special receptors on the outer membranes of the postsynaptic cell, the impulse continues on its way as an electrical signal.

Acetylcholine is the normal transmitter used in many synapses in the brain, and is received by acetylcholine receptors on the postsynaptic nerve cell. This starts the firing of an electrical signal, and triggers the release of dopamine. Having completed its task, acetylcholine is rapidly broken down by an enzyme called acetylcholinesterase.

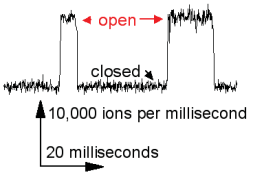
A typical acetylcholine synapse is a wondrous biophysical machine, specialized to act on a time scale of a thousandth of a second over a distance scale of just a couple of microns—about two millionths of a meter.

The nicotine molecule mimics acetylcholine in certain key ways that we are now beginning to appreciate, and binds to the same receptors. But because it can't be broken down by acetylcholinesterase, it persists at the synapse for minutes rather than milliseconds, and excites the postsynaptic neurons to fire rapidly for long periods, releasing large amounts of dopamine. This induces a feeling of pleasure (which is what smoking's all about), although we don't really know *how* the pleasure arises.

The synapse is also the site of action of many other recreational drugs that mimic neurotransmitters. LSD, morphine, heroin, and cannabinoids act on molecules called G protein-coupled receptors; amphetamines and cocaine (as well as some therapeutically useful drugs such as Prozac) act on neurotransmitter transporters; and caffeine and alcohol act partially in this neighborhood as well. Nicotine acts on a neurotransmitter-activated receptor bearing the full name of nicotinic acetylcholine receptor (because acetylcholine is the usual transmitter, and nicotine can mimic it), so let's take a closer look at one of these.

The receptor straddles the cell membrane. The part that senses nicotine or acetylcholine molecules is on the outside of the cell, and other key parts are inside the cell. It is partially an electrical machine: current flows through it, but not as electrons or protons. In a cell, current flows as ions, primarily sodium and potassium, moving through a channel down the middle of the receptor, and past a constriction that acts as a gate to control the flow.

Right: The acetylcholine binding site at atomic resolution has five aromatic amino acids. Red represents oxygen; blue, nitrogen; gray, carbon. Below: A recording from a nicotinic acetylcholine receptor channel.

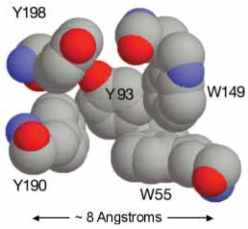


For many years, neuroscientists have pursued two goals: first to record individual currents through an ion channel, and second to visualize the structure of an ion channel at the atomic scale. The first goal was made possible by an idea that occurred simultaneously to Richard Feynman at Caltech and Erwin Neher in Germany in the 1970s. I didn't believe Feynman, so I didn't follow this up, and Neher did the experiments himself. He perfected the single-channel recording technique between 1976 and 1980, receiving the Nobel Prize with his partner Bert Sakmann in 1991. The clever circuit Neher developed, called a patch clamp, allows us to measure the currents that flow through an individual channel in response to acetylcholine or nicotine (the traces are so similar, it's hard to tell the difference).

The patch clamp enables us to measure a channel opening even if it lasts only about a tenth of a millisecond, and even if it does so only once every 20 minutes or so. That's about 1 part in 10 million; very rarely in biology does one have the chance to work with such precision. In the recording shown on the left, the nicotinic acetylcholine channel gate is initially closed and no current flows. It opens when exposed to acetylcholine or nicotine, and a current of about 10,000 ions per millisecond flows through, corresponding to about one picoampere. It typically stays opens for between one and two milliseconds.

The receptor has five subunits arranged around the channel on the axis of symmetry, two made of one kind of protein (yellow in the diagram below left) and three of other, very similar proteins (blue). The part that receives the acetylcholine or nicotine molecule is outside the cell. We've recently learned the X-ray crystallographic structure of a molecule that's so very much like this external part of the receptor that we can use it as a guide for our experiments. For instance, the region labeled π is where the actual binding takes place. We don't yet have such good resolution for the region of the receptor inside the cell, but we think that the bottom of the channel has a little barrier on the axis, so that the ions must pass out the sides through five rudimentary "windows."

When the structure of the external part at atomic resolution was published, many people were surprised that the binding site was a box lined by aromatic (benzene-containing) amino acids and open at one end. In this arrangement, the amino acids lacked negative charges to attract the positively charged acetylcholine molecule. But this aromatic box was not a surprise to us at Caltech, because my colleague and collaborator Dennis Dougherty, the Hoag Professor of Chemistry, had been hypothesizing for the last 10 years that acetylcholine binds to aromatic rather than negatively charged groups.



Dougherty & Lester, *Nature* 411: 252 (2001)
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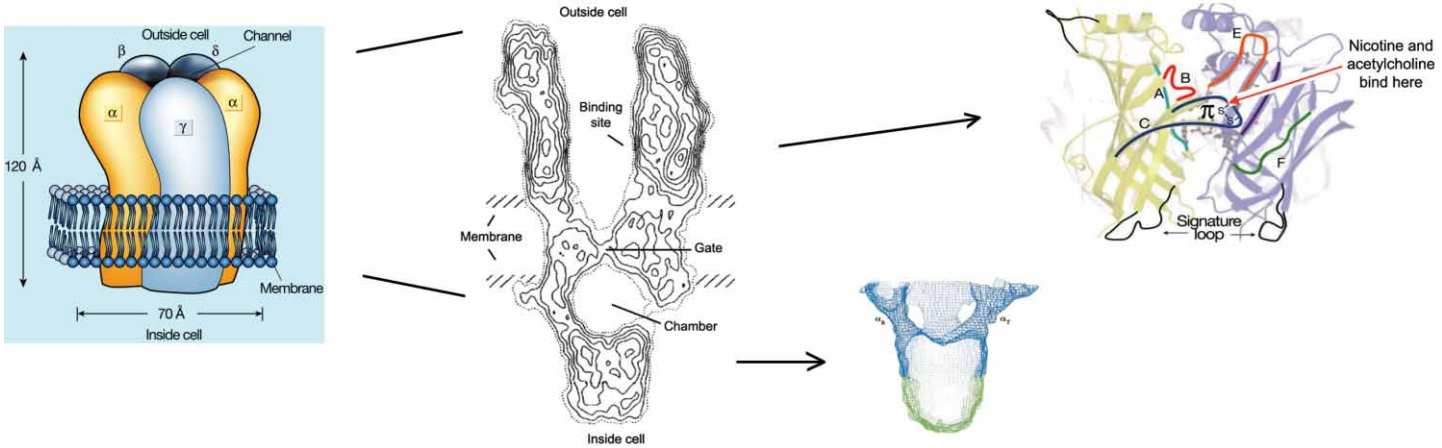
Even the resolution of about three angstroms in the X-ray image shown here isn't good enough to tell us where in the box acetylcholine or nicotine actually binds. But the Dougherty and Lester groups have also done a series of experiments to specify this binding, using a combination of quantum mechanics and biological measurements



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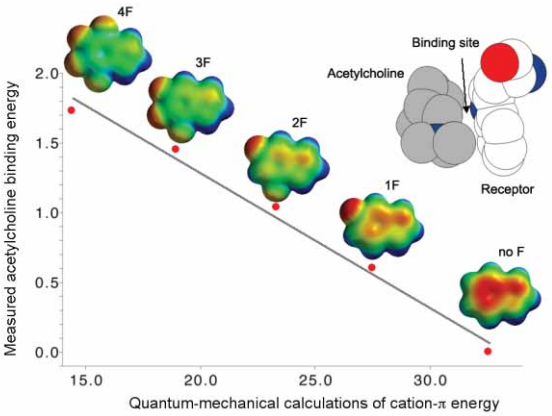
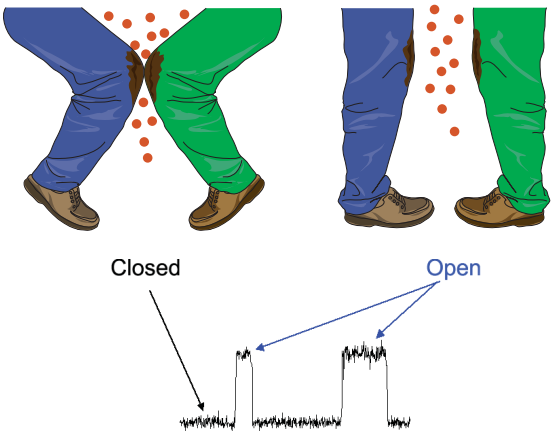
Building up a picture of a nicotinic acetylcholine receptor, from left to right: Five subunits arranged around a central channel make up the region that sticks out of the cell; an X-ray composite view through the central axis of the whole receptor; another composite view of the region inside the cell, showing the chamber and some of the windows; the protein structure of the α (yellow-green) and β, γ, or δ (lavender) subunits at the level of individual proteins, showing the position of the acetylcholine or nicotine binding site (π).



Acetylcholine binding energy was measured in frog eggs with unnatural receptors incorporating one to four fluorine (F) atoms, and plotted against the theoretical binding energy of these modified amino acids.

on immature frog eggs. In the eggs, we produced a series of acetylcholine receptors in which the side chain of a particular existing amino acid, number 149, was replaced by unnatural side chains that are like benzene except that either one, two, three, or four fluorine atoms have taken the place of some of the hydrogen atoms. The face of a benzene ring has a negative charge, so that it can attract the positive acetylcholine molecule, and fluorine makes this face less negative. Dougherty's group calculated the energy of the interaction between a positive charge and the modified benzene rings. When we plotted this calculated binding energy against an experimental measurement proportional to the binding energy obtained in our modified frog eggs, we noted a straight line. This is always exciting for a scientist, because it tells us we've guessed correctly what's happening. In this particular case, we're satisfied that we know to a precision of roughly half an angstrom where the acetylcholine molecule binds. It is near the face of the benzene ring that is part of the side chain at amino acid 149. We think that we will need this level of resolution to design better drugs for nicotinic acetylcholine receptors, and the so-called cation-π experiment that I've just related describes the best data presently available.

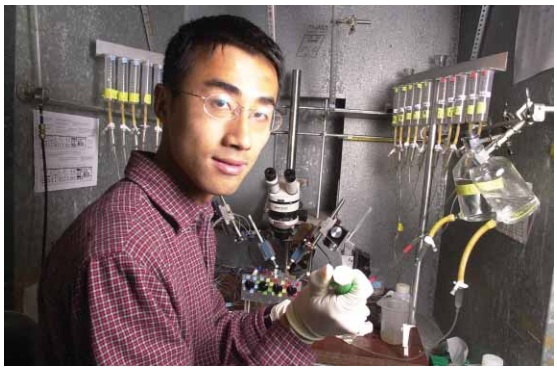


The gate of the receptor is made up of five rods, one from each subunit. When the channel is closed, left, the rods are bent like oily knees into the center of the channel. When acetylcholine binds they straighten out, right, allowing ions to flow through the watery gap that opens up.

About 50 angstroms below the acetylcholine binding site is a gate that opens and closes to stop the flow of ions on the axis of the channel, which you will remember is composed of those five nearly symmetrical subunits. Nigel Unwin of the Laboratory of Molecular Biology in Cambridge believes these subunits are shaped like five bent rods on the axis of the channel—rather like five Caltech professors standing in a circle with their knees sticking into the middle. When the channel is closed, the "knees" are quite oily and therefore won't let sodium and potassium ions through. But when acetylcholine binds, these five knees act with a coordination that might prove uncommon for professors: all five rods rotate, removing the oily knees and revealing a watery stripe in the channel. The sodium and potassium ions now face an environment resembling water rather than oil, and they obligingly flow through. The flow of sodium into and potassium out of the cell is an electrical current that provides the little ramps of voltage change that, in turn, eventually trigger nerve impulses in the postsynaptic cell. When the acetylcholine or nicotine leaves the binding site, the knees snap back into place, closing the channel again.

How do these angstrom-level movements, ion flows, and other biophysical events govern the biological process of nicotine addiction? Let's think first about what addiction actually is. Addiction means that someone will self-administer a drug

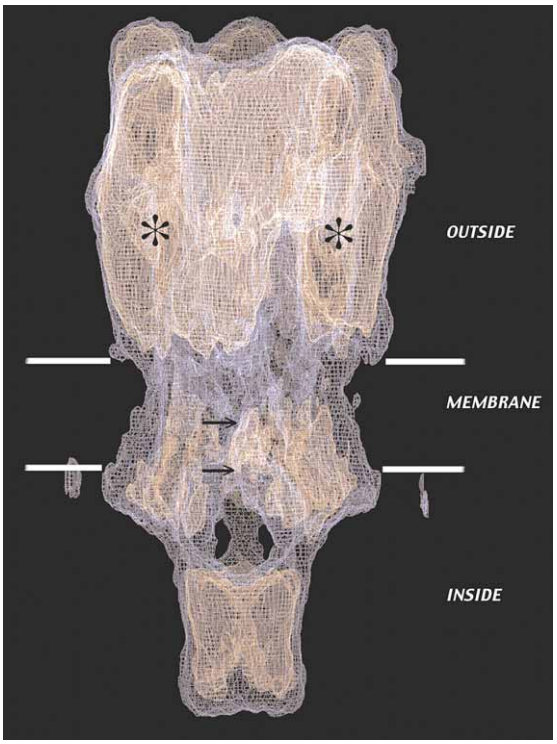
Graduate student Tingwei Mu recording the electrophysiology of a frog egg with unnatural amino acids incorporated into the receptors.



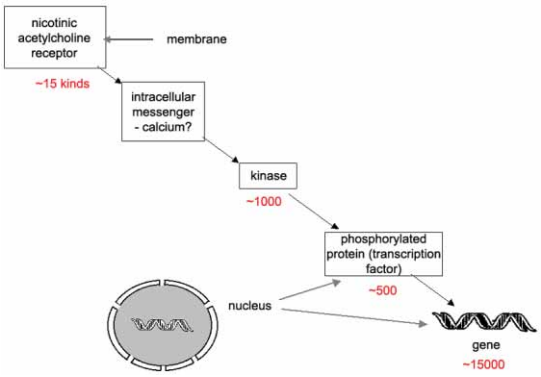
even though it might not be good for them, or at the expense of positive beneficial actions. A similar definition applies to animals. The gold standard for studying nicotine addiction in animals is an experiment called self-administration. A rat or mouse will press a lever to administer nicotine to itself, even though there might be food, or some other pleasurable activity, available. What physiological changes occur during these addiction processes, and how can we study them in molecular terms?

Biologists now believe that, like many other changes in an organism's behavior, addiction is caused by a process that links events at the surface of a cell to events at the level of the genes. This is called a "signal transduction pathway." Such pathways often lead to changes in the repertoire of genes expressed by the cell (each cell normally expresses a subset of the 30,000 or so genes in the human genome). "Changes in gene expression" is nearly synonymous with "new proteins are made," and these new proteins lead to changes in the cell's function. In the case of nicotine, the community has worked out some of the pathway. We know that a nicotinic acetylcholine receptor is activated, and that this leads to a small molecule that acts as an intracellular messenger. We don't know which one it is yet, but most researchers bet that the major intracellular messenger in this pathway is calcium, because when the channel opens up, some calcium flows into the cell along with sodium. Calcium then activates another kind of protein called a kinase, which (sometimes indirectly) adds phosphate to, and activates, a protein called a transcription factor. This binds to the DNA and changes the type and amount of genes expressed. It's a complicated pathway that still needs to be broken down into individual steps before we can understand it fully, but it's my personal bet that nicotine addiction will be the first addiction to be solved, because we already know so much about it. Knowing which molecules are involved will help us to design better pharmaceuticals that could interfere with or change the addiction.

Which nicotinic receptor starts the pathway? There are, in fact, about 15 different kinds of nicotinic acetylcholine receptors. How do we find the one involved in most of the responses to nicotine? Biologists approach this problem by using "knockout" mice. They identify a molecule that might be a good candidate, then isolate the DNA corresponding to the gene that codes for this molecule. In test tubes and cultured cells, the candidate gene is interrupted (knocked out) with another, easily detectable, marker protein, which is often a jellyfish protein that fluoresces green under

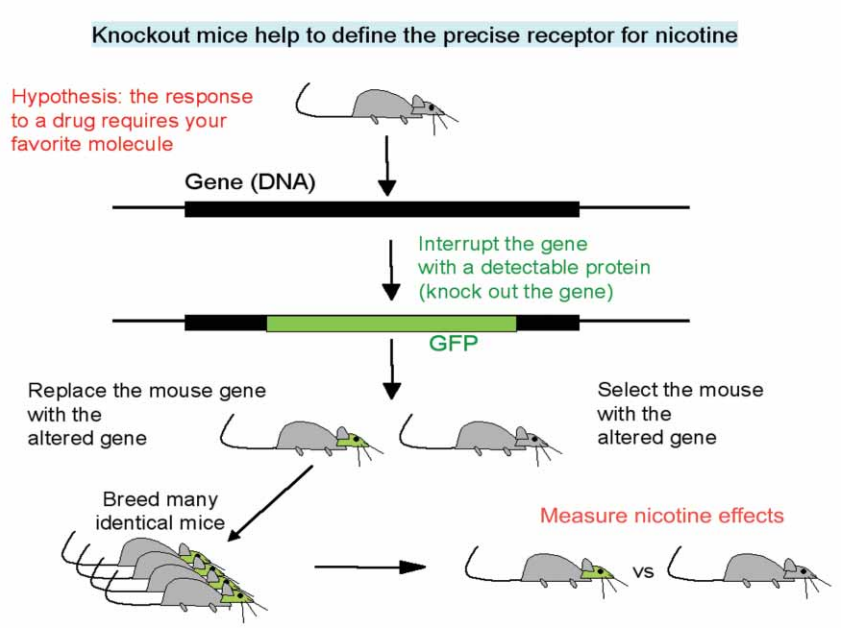


N. Unwin: The Croonian Lecture 2000. *Phil. Trans. R. Soc. Lond. B* (2000) 355 p.1813. ©The Royal Society.



Left: The probable signal transduction pathway for nicotine. Above: A neuroscientist's view of the entire nicotinic acetylcholine receptor. Asterisks indicate the sites where acetylcholine (or nicotine) binds. Within the membrane, the upper arrow points to the best guess of where the "knee" is, and the lower arrow points to the narrow part of the channel when it is open. Below this are the five windows through which ions flow into the cell.

UV light called green fluorescent protein. A strain of mice is then constructed carrying the altered gene and many identical mice are bred. This takes one to two years, so it requires a real commitment to do these experiments. Then—in the present case—they compare the effects of nicotine on the knockout and normal (wild-type) mice. This was done in several laboratories throughout the world in the 1990s, and the firm conclusion was that, of



the 15 or so nicotinic acetylcholine receptors, the most important receptor for nicotine addiction was the one with the classy name of $\alpha4\beta2$. (There are about 10 types of nicotinic α subunits, and about seven types of receptor β, γ, or δ subunits, and the full brain receptor may have two $\alpha4$ subunits and three $\beta2$ subunits, adding up to the five-subunit structure we discussed earlier.)

Can we go further in working out the pathway of nicotine addiction? We begin to have a problem when we try to do that, because there are about 1,000 kinases, 500 transcription factors, and 15,000 genes expressed in the brain. Sorting through these pathways by generating one genetically altered knockout mouse at a time would obviously be impractical. Therefore my research group, and other groups around the world, have adopted a different way of addressing the problem. We reasoned that instead of *eliminating* the response to nicotine, we would *accentuate* the response by making a hypersensitive nicotinic acetylcholine receptor that might emphasize the pleasure pathway, and allow us to find behaviors and molecules that are easily observable. By making changes to that oily knee, we set about designing an $\alpha4\beta2$ receptor that was hypersensitive to acetylcholine. We found that the less oily we made the knee, the longer it wanted to stay open rather than closed, so that we were able to design receptors that stayed open not for the normal 1 or 2 milliseconds, but for 20 or even 200 milliseconds. We produced a series of receptors with progressively less oily, more watery knees. Designing these and testing them in frog eggs is quite quick, only taking a month or so, but the next step, generating a mouse strain with the receptor, takes about two years. In contrast to the knockout procedure, these mice are called knock-ins.

What is the behavior of these hypersensitive knock-in mice? They are rather anxious, for a start. There are some classic tests for anxiety, and one is to put the mouse in a box with mirrors—mice like to be alone, and avoid such boxes. The hypersensitive mice avoid the mirrored box more than usual. They're also sedated by nicotine injections some hundredfold smaller than those that sedate normal mice. In a sense they act as though they're already addicted to their own acetylcholine, though it's not an analogy I'd pursue at the moment. When they're given slightly larger amounts of nicotine, an interesting behavior occurs. If you have a cat, you may have noticed that when you open a can of cat food, it sticks up its tail, and the tail quivers a little. This is a response associated with pleasure called a Straub tail, and it's a very nice response to score in a mouse because it doesn't hurt it. Our hypersensitive mice display an abnormally strong Straub tail response in response to low quantities of nicotine.

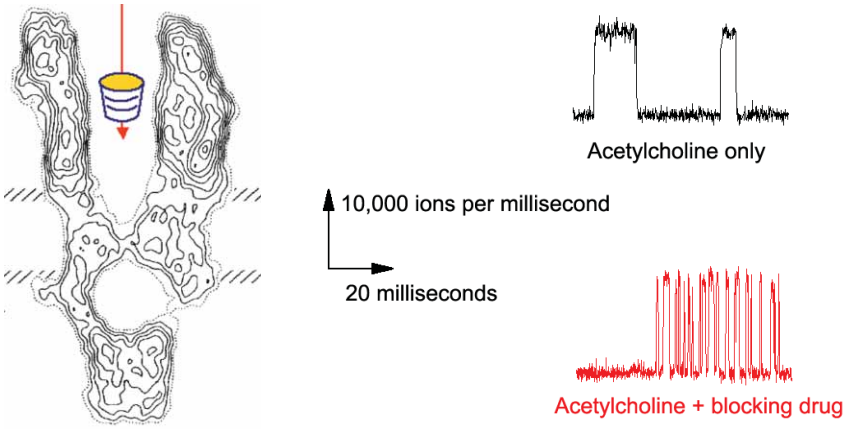
Do these hypersensitive mice self-administer extremely small amounts of nicotine? It's a bit embarrassing to admit this, but we don't know yet. Giving a seminar about your own research is a bit like buying a new computer—you'd always rather wait another six months. Although we don't know the answer to the question yet, these hypersensitive mice have already revealed a lot of other interesting characteristics.

A hypersensitive mouse sports a Straub tail after a small amount of nicotine.

A knock-in mouse that might have the same mutation in one of the receptor subunits that causes ADNFLE epilepsy in humans.

While we were working on generating these strains of hypersensitive mice, neurologists in Melbourne, Australia, were defining a newly recognized human disease called autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). The name basically says it all: autosomal means it's inherited through one of the chromosomes other than X and Y; dominant means that only one copy of the altered gene is enough to cause the disease; nocturnal means that these seizures occur at night; and frontal lobe means they start in the forebrain. Seizures arise during non-REM sleep, and begin with the sensation called an aura that many epileptic patients describe, which is why they're often confused with nightmares rather than diagnosed as seizures, especially in children. As you may already have guessed, some ADNFLE patients carry a mutation in the $\alpha 4$ subunit of the nicotinic acetylcholine receptor, and others have a mutation in the $\beta 2$ subunit. Furthermore, the mutations occur very near the oily knee that holds the channel open or closed for varying amounts of time.

Channel blockers work by binding in the receptor channel and desynchronizing the electrical signals in the cell.



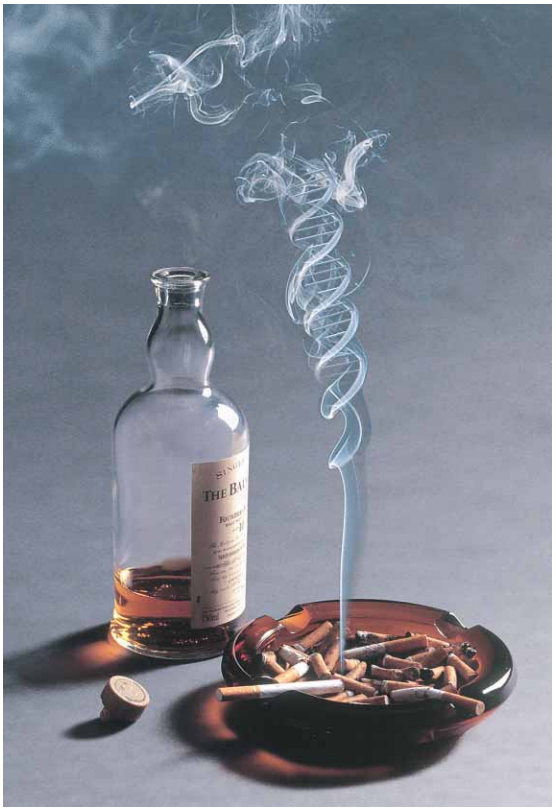
Are the receptors of ADNFLE sufferers like knockouts—nonfunctional nicotinic acetylcholine receptors—or are they like hypersensitive knock-ins and excessively functional? We had one big clue: although ADNFLE can be controlled only partially in children, it *can* be controlled in adults with channel blockers. These are drugs that enter the receptor and bind in place of acetylcholine, like a cork plugging a drain, and prevent current flow. This desynchronizes the electrical signal in the cell, so that it can't efficiently activate nerve impulses further on down the line. A channel blocker would block a hypersensitive receptor, which opens for too long, but wouldn't have any effect on a knockout receptor, which would never open, so this is an indication that ADNFLE patients have probably got hypersensitive nicotinic acetylcholine receptors.

So are our hypersensitive knock-in mice prone to nicotine-induced seizures? There's no doubt they are, as my postdoctoral colleague Carlos Fonck has shown. About 40 percent of human epilepsies are inherited, and many can't be controlled by drugs, so it would be a wonderful opportunity to have an animal model for one form of epilepsy that begins with an understood mutation in a gene, which leads to a change in the function of a membrane protein, which results in a change in the function of a nerve cell, and ultimately gives us an understanding of what's happening in the neuronal circuit. We've already generated knock-in mice that have the precise mutations that cause ADNFLE and we're looking forward to working with them.

Our knock-in mice could also be useful for research into Alzheimer's disease. Nerve cells degenerate in this disease, including some that make acetylcholine directly. The most successful Alzheimer's drugs now on the market are cholinesterase inhibitors. These block acetylcholinesterase, thereby helping to prolong the action of any acetylcholine still being secreted

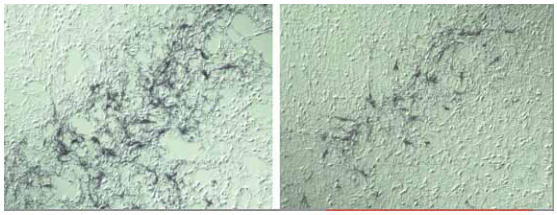
by the remaining nerve cells. Allan Collins of the University of Colorado suggested to us that if our hypersensitive mice were very sensitive to acetylcholine, they ought to respond to the increased amounts present when treated with these drugs. So we administered galantamine (Reminyl) and tacrine (Cognex), and the mice did indeed respond quite sensitively in the Straub tail assay. But I doubt that we'll make major progress on Alzheimer's disease using these particular mice, because the present research on this disease is concentrating on the way to prevent or decelerate cell death.

Now let's turn to alcohol. Some 80 percent of alcoholics are smokers. What's the common link? At this point, even the most enlightened people are tempted to shrug and invoke either moral or psychological phenomena. But psychology and moral reasoning both occur in the brain, and are now actively being investigated by neuroscientists. And there are multiple reports of genetic links between smoking and alcoholism. It's also probable that alcohol affects the same dopamine pleasure system as nicotine, opium, and amphetamines. We were interested to find that our hypersensitive mice are "cheap drunks"—they respond quite sensitively to alcohol, although they were generated by manipulations of *nicotinic* receptors. For instance, a much lower dose of alcohol is needed to calm a startled hypersensitive mouse than a startled normal mouse. We're interested in pursuing this link.



Eighty percent of alcoholics are smokers. What's the link? Photo illustration by Larry Harwood and Julianne Snider for the *Coloradan*, of the University of Colorado at Boulder.

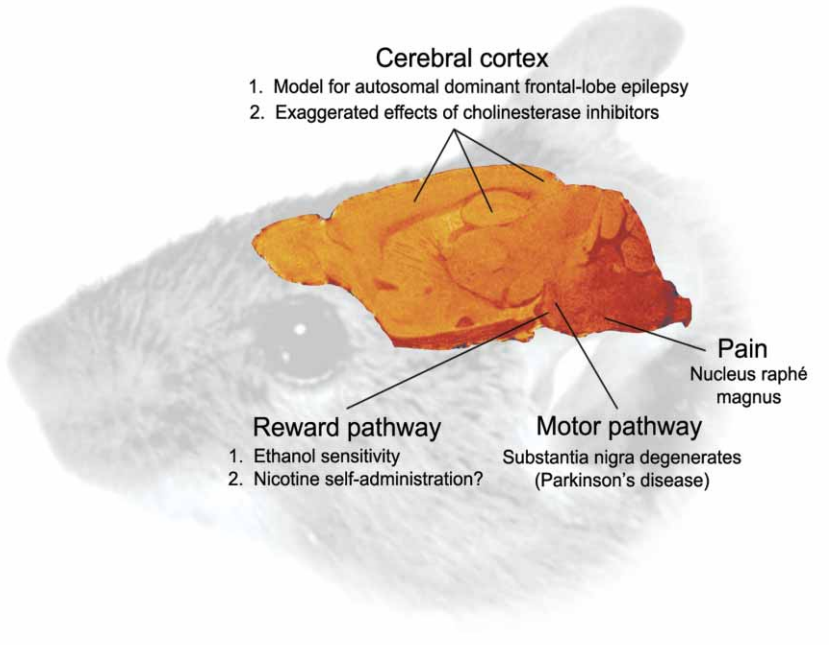
The most hypersensitive mice also have fewer nerve cells that make dopamine (stained black, right panel) than normal mice (left panel).



Labarca et al., *PNAS* (2001) 98, p.2786 © The National Academy of Sciences.

In addition to the dopamine-producing cells of the pleasure/reward system, the only other major group of nerve cells that produce dopamine is located nearby in an area called the substantia nigra. The dopamine-producing cells of the substantia nigra help to set the activity level of a motor pathway that controls movement, and it's these nerve cells that degenerate in Parkinson's disease. The causes of this degeneration are still unknown, but there is no obvious genetic link, as only a very small fraction of cases are inherited. A persistent finding is that smoking appears to protect against it (yes, you *have* read correctly). Caroline Tanner of the Parkinson's Institute in Sunnyvale, California, has reported on a set of 43 identical pairs of twins distinguished by the fact that only one member of the pair had Parkinson's disease. In the 33 of these so-called discordant twin pairs containing at least one smoker, the twin without Parkinson's disease smoked an average of 10 pack-years (if a person smokes half a pack per day for four years, he has added two pack-years to his total; and so on) more than the twin that did not. We don't even know whether the protective effect of smoking involves nicotine itself or another component of smoke. However, on the theory that a nerve cell's adjustment to slight excess stimulation underlies the protective effect of smoking, a couple of drug companies are already working on drugs for Parkinson's disease based on derivatives of nicotine.

Our most hypersensitive mice—the ones that have the most watery amino acid at the knee and keep their channels open the longest—are born with few if any of the nerve cells that make dopamine. They seem to have degenerated even before the mice were born. These mice thus have a neonatal form of Parkinson's disease. We've traced this effect to the fact that the dopaminergic cells die from overstimulation. They're so sensitive to endogenous acetylcholine that their channels are constantly open, allowing sodium,



Mice hypersensitive to nicotine could help research into a variety of medical conditions affecting different parts of the brain.

calcium, and potassium ions to flow in and out. The cells completely exhaust their energy stores trying in vain to restore these ions, and as a result, they die. This phenomenon, called excitotoxicity, is thought to underlie several degenerative diseases. To study it further, we'd like to adjust the system. We don't want a mouse that never succumbs to Parkinson's disease; that's not a disease model. We don't want a mouse that dies at birth; that's not an appropriate model for Parkinson's disease. We want a "Goldilocks mouse," one that would acquire Parkinson's disease as an adult.

Finally, I'll note some work relevant to pain done by John Daly and his colleagues at the National Institutes of Health. Nearly 10 years ago, they studied the skin secretion from a poisonous South American tree frog, *Epipedobates tricolor*. This extract induces the Straub tail in mice, and Daly tracked the effect down to one particular molecule in the secretion, called epibatidine. Epibatidine has a structure similar to nicotine; it is the most potent known activator of some of the nicotinic acetylcholine receptors, including the $\alpha 4\beta 2$ receptor; and, most interestingly, it is a very effective painkiller (nicotine is also an analgesic). This story caught the attention of several drug companies, who are testing painkillers based on nicotine derivates. Sure enough, our hypersensitive mice are also exquisitely sensitive to the analgesic effects of nicotine.

I have been studying nicotinic receptors at Caltech since 1973, with colleagues born in 36 different countries. The research has been supported by the National Institutes of Health, the Sidney Stern Foundation, the Plum Foundation, and the Keck Foundation, as well as by California's 25-cents-per-pack tax on cigarettes. But a couple of years ago, the epibatidine story caught the eye of Paul Simon, whose song "Señorita with a Necklace of Tears" has the following verse:

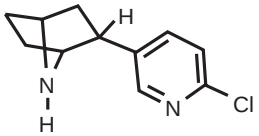
> Nothing but good news
> There is a frog in South America
> Whose venom is a cure
> For all the suffering that mankind
> Must endure
> More powerful than morphine
> And soothing as the rain
> A frog in South America
> Has the antidote for pain
> That's the way it's always been
> And that's the way I like it *

We need to brainstorm about endowing this research with the royalties from a song. □

Bren Professor of Biology Henry A. Lester came to biology from a background in the physical sciences. After a degree in chemistry and physics from Harvard followed by a PhD in electrophysiology from Rockefeller and two years of research at the Pasteur Institute in France he came to Caltech in 1973 to continue in this field, but over the last 20 years he has also embraced biochemistry, molecular biology, and, more recently, neurogenetics. On campus, he is one of the few professors known to all the undergraduates, because every year he introduces another 180 or so freshmen, many of whom have no previous knowledge of biology, to the required course "Drugs and the Brain." This article was adapted from a Watson Lecture given in October 2002.

PICTURE CREDITS: 16, 18, 20, 25 – Doug Cummings; 18, 20 – Dennis Dougherty; 18, 21-23 – Bob Paz; 25 – Russell Jacobs; 25 – J. De Leeuw, Belgian Herpetological Society

The South American tree frog *Epipedobates tricolor* secretes epibatidine, a powerful painkiller with a chemical structure similar to that of nicotine.



* "Señorita with a Necklace of Tears" was written, arranged, and produced by Paul Simon, and is on the album *You're the One*, © Paul Simon Music (BMI), 1999, 2000.