

Nicotine's Effects on the Brain & Body & How to Quit Smoking or Vaping | Huberman Lab Podcast #90

In this episode, I explain how nicotine impacts the brain and body, including its potent ability to enhance attention, focus, and alertness, increase blood pressure and metabolism and reduce appetite. I discuss nicotine's ability to increase the action of neurochemicals, including dopamine, norepinephrine, and acetylcholine and activate sympathetic (alertness-promoting) neural circuits. I also discuss common nicotine delivery methods, such as cigarettes, vaping, dip, and snuff, and how they each create their own unique experience and how they, but not nicotine itself, cause cancer and other adverse health effects. I also explain science-based tools to permanently quit smoking cigarettes or vaping, including peer-reviewed clinical hypnosis tools, antidepressants, and alternative nicotine replacement (patches, lozenges, gums etc.). As nicotine is one of the most widely used substances with billions of users — most of whom report wanting to quit — this episode ought to be of interest to former/current nicotine users, those who want to quit smoking or vaping and/or those interested in learning the biology behind how nicotine impacts the brain and body.

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Timestamps

00:00:00 Nicotine

00:02:47 Momentous Supplements

00:03:41 Tool: Brief Daily Meditation & Focus

00:05:59 The Arrow Model of Focus, Alpha GPC & Garlic Supplements

00:10:43 Thesis, InsideTracker, ROKA

00:14:35 Nicotine Effects vs. Methods of Delivery, Acetylcholine

00:19:55 Where is Nicotine Found? Nicotinic Acetylcholine Receptors

00:25:12 Nicotine & Effects on the Brain: Appetite, Dopamine & GABA

00:30:58 AG1 (Athletic Greens)

00:32:11 Nicotine, Acetylcholine & Attentional "Spotlighting"

00:37:29 Nicotine, Norepinephrine & Alertness/Energy

00:41:10 Nicotine & Effects on Appetite & Metabolism

00:46:47 Nicotine & Effects on Body: Sympathetic Tone

00:51:29 Nicotine & Cognitive Work vs. Physical Performance

00:55:08 Nicotine Delivery Methods & Side Effects, Young People & Dependency

00:58:35 Smoking, Vaping, Dipping & Snuffing: Carcinogens & Endothelial Cells

01:02:34 Smoking, Vaping, Dipping & Snuffing: Negative Impacts on Lifespan & Health

01:09:23 How to Quit Smoking, Nicotine Cravings & Withdrawal

01:13:56 Vaping & Nicotine, Rates of Effect Onset, Dopamine, Addiction & Depression

01:25:06 Tool: Quitting Smoking & Clinical Hypnosis, Reveri

01:30:16 Bupropion (Wellbutrin) & Quitting Smoking

01:36:24 Tool: A Nicotine Replacement Schedule to Quit Smoking, Nicotine Patch/Gum

01:41:52 Tool: Biological Homeostasis & Nicotine Withdrawal, The "First Week" Strategy

01:51:39 Zero-Cost Support, YouTube Feedback, Spotify & Apple Reviews, Sponsors, Momentous Supplements, Neural Network Newsletter, Instagram, Twitter, Facebook

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- Welcome to the Huberman Lab Podcast, where we discuss science and science based tools for everyday life. I'm Andrew Huberman, and I'm a professor of neurobiology and ophthalmology at Stanford School of Medicine. Today we are discussing nicotine. Nicotine is one of the most commonly consumed substances on the entire planet. There are literally billions of people that ingest nicotine on a daily basis. Most of those people consume nicotine via smoking, and in particular smoking tobacco. Tobacco contains nicotine and it contains a bunch of other things as well, which we will talk about. And the burning of tobacco liberates nicotine and makes it accessible to the various cells and tissues of the body. But of course, there are other sources of nicotine as well. Some people consume nicotine through dip, that is placing tobacco on the inside of the lip or in the cheek. Some people consume nicotine via snuff, which is literally the shoving of tobacco leaves up the nostrils and allowing the tobacco to access the nervous system and other areas of the body by permeating into the mucosal membranes, that is the lining, the soft lining of the nasal passages. And of course there are nicotine patches, nicotine gum, there's nicotine in pill form, there are toothpicks dipped in nicotine, et cetera. Today we are going to separate our discussion of nicotine from a discussion of

smoking and vaping and the other forms of delivery for nicotine. We will be talking about smoking and vaping and other routes of nicotine administration, both for sake of highlighting their detriments to health and, believe it or not, in certain cases, keep in mind very specific certain cases, the possible health benefits of delivering nicotine through specific modalities. Turns out those modalities do not include smoking cigarettes or vaping. And we are going to pay particular attention to vaping today because vaping use is on the rise, in particular in young people, and vaping use, and the fact that most tobacco that's consumed through vaping includes quite amount of nicotine has created a scenario where nicotine because of its ability to change certain chemicals in the brain can actually lead to addiction for a number of other substances related to vaping and vaping associated behaviors. If all of that seems like a lot to get your arms and your mind around right here at the outset, don't worry, I'll walk you through this, regardless of whether or not you have a background in biology or not. I promise that you'll come through at the end of this episode with a deep understanding of how nicotine works in the brain and body, some of its benefits, some of its potential drawbacks, and you'll have clear optics as to why smoking and vaping

00:02:47 Momentous Supplements

and other forms of nicotine delivery have the effects that they do on your biology and psychology. I'm pleased to announce that the Huberman Lab Podcast is now partnered with Momentous supplements. We partnered with Momentous for several important reasons. First of all, they ship internationally because we know that many of you are located outside of the United States. Second of all, and perhaps most important, the quality of their supplements is second to none, both in terms of purity and precision of the amounts of the ingredients. Third, we've really emphasized supplements that are single ingredient supplements, and that are supplied in dosages that allow you to build a supplementation protocol that's optimized for cost, that's optimized for effectiveness, and that you can add things and remove things from your protocol in a way that's really systematic and scientific. If you'd like to see the supplements that we've partnered with Momentous on, you can go to livemomentous.com/huberman. There you'll see those supplements. And just keep in mind that we are constantly expanding the library of supplements available through Momentous

00:03:41 Tool: Brief Daily Meditation & Focus

on a regular basis. Again, that's [livemomentous.com/huberman](https://www.livemomentous.com/huberman). Before we go any further, I just want to highlight a key takeaway from a previous episode, which is our episode on focus. And in fact was a toolkit for focus. So during the toolkit for focus episode, we talked about a large number of behavioral, pharmacologic, and another interventions that you can use to increase your level of concentration and focus for whatever purpose, cognitive endeavors, learning languages, focusing in school, on work, et cetera, or physical pursuits. Now one of the key takeaways is that there are really two key protocols that I believe everyone should understand and know about and why they work because they are so effective, and also because they dovetail nicely with some of the information that we're going to talk about today, which will explain why nicotine is so effective in increasing focus. And these two protocols are as follows. Data based on studies done in Wendy Suzuki's lab at New York University. And of course, Wendy was a guest on this podcast. So you can check out that episode if you like, but studies done in her laboratory point to the fact that a daily, very brief, in fact, only 13 minute meditation can vastly increase focus and focus ability, not just immediately after the meditation practice, but at all other times as well. So again, this is a meditation practice done daily for just 13 minutes. It's a very simple meditation practice where one sits or lies down, closes your eyes and directs your attention to a place just between your two eyes and right above it. So on your forehead. But just inside of that, and please understand that your brain does not have sensory receptors. So unlike focusing on your fingertips and the sensations there, if you focus on your brain, you can't actually sense anything in your brain except your thoughts. So the idea then is that you continually bring your focus back to that location just about an inch behind your forehead over and over again. And it's the refocusing of your attention to that location after it drifts that succeeds in increasing your focus ability, again, not just during the meditation and afterward, but at other times as well. So this 13 minute a day meditation is exceedingly simple and exceedingly effective. It should be performed every day, but if you miss a day, just go back to doing it. Don't despair too much. And you will see these positive effects, say the data. Also increase effects on mood and other

00:05:59 The Arrow Model of Focus, Alpha GPC & Garlic Supplements

positive aspects of mental health and performance. So that's the first tool in protocol. The second tool in protocol relates to the general what I called arrow model of focus. This was a model that I created in order to simplify the vast amounts of data on focus and concentration and how they are created by the various chemical systems within your brain. We're going to hear a lot about these chemical systems again today in the context of nicotine and they are as follows. You can think about focus on any goal or any endeavor as an arrow. So just imagine an arrow which has an arrow head and a shaft, and we'll add a third component to it in a moment. The head of the arrow, meaning the direction of your focus, is largely set by acetylcholine, which is a chemical in the brain. The shaft of the arrow is set by a chemical called adrenaline, also called epinephrine. Those are the same thing. In the brain typically it's referred to as epinephrine, and in the body, it's more commonly referred to as adrenaline, but those are the same neurochemical. Epinephrine slash adrenaline represents the shaft of the arrow and it's providing the energy for which to focus. And then we can put behind that arrow a little propeller or a motor, if you like, and the propeller or motor in the context of this neurochemistry model is dopamine, which provides ongoing motivation. It pushes that arrow forward continually as you strive to focus on a particular thing. This particular arrow model, that is your ability to increase your focus, can be enhanced therefore by increasing acetylcholine, epinephrine, and dopamine simultaneously. And there are a lot of different ways to do that. But one of the more effective ways to do that via supplement protocols is so-called Alpha GPC. Alpha GPC taken in 300 milligram form 10 to 30 minutes before a about of cognitive work or a about of physical work will increase your focus by way of increasing acetylcholine, and to some extent, increasing epinephrine as well. The dopamine increase will have to be achieved either through cognitive processing, that is telling yourself you're doing a good job and moving forward because thoughts really do impact your levels of dopamine, or some other sort of pro dopamine or dopamine increasing protocol also discussed in the toolkit for focus and our episode on dopamine for motivation and drive. So the key thing here to understand is that the 13 minute a day meditation is a very effective way to increase focus capacity. And then in the short term, if you want to provide a boost now and again to focus, 300 milligrams of Alpha GPC can be very effective. There are various sources for that that we'll link to one of them in the show note captions. By no means am I saying that you need to take alpha GPC. A number of people will certainly opt not to. And a number of people might be saying, well, I've heard that Alpha GPC can increase focus by way of increasing

acetylcholine and norepinephrine or epinephrine, but it can also increase TMAO, which is a kind of a negative marker of cardiac health and cardiovascular health. For that reason, I and many others will take 600 milligrams of a garlic capsule, which can offset that TMAO increase. It remains uncertain as to how much Alpha GPC one needs to take before increasing TMAO levels to a point where it's of concern that you would even need to take the garlic capsule. But I just mention it in any case, because it's a pretty simple fix. Garlic has other health benefits too, of course, and for most people, 300 milligrams of Alpha GPC taken every once in a while. I certainly don't encourage people to take Alpha GPC every time they want to focus. I always emphasize behavioral tools first, then focusing on nutritional tools and on occasion using supplement based tools to encourage increased levels of focus. And then of course there are a various number of different prescription compounds that if you're working with a board certified physician, they could prescribe you if you need additional tools for focus, things like Ritalin, Adderall, Modafinil, Armodafinil, Vyvanse, et cetera, for many people are going to be important and maybe even necessary for people with ADHD, et cetera, but that's a category into itself. And as I always say, I'm not a physician, so I don't prescribe anything. I'm a professor, so I profess many things. And today I just wanted to pass along or redirect your attention to that episode on focus and highlight those two tools, the 13 minute a day meditation, and 300 milligram Alpha GPC for increasing focus capacity and for acutely, that is temporarily giving an additional boost for a about of focus. And of course, if you choose not to use those protocols, that's perfectly fine too, there's certainly no obligation. They are simply available to you should you choose to try them. And if nothing else you now have in mind the neurochemistry of acetylcholine, epinephrine slash adrenaline, and dopamine, and that will really set the stage for understanding just how effective and why nicotine is so effective at increasing focus, motivation,

00:10:43 Thesis, InsideTracker, ROKA

and even as you'll soon hear, working memory and cognitive capacity. Before we begin, I'd like to emphasize that this podcast is separate from my teaching and research roles at Stanford. It is however part of my desire and effort to bring zero cost to consumer information about science and science related tools to the general public, and keeping with that theme, I'd like to thank the sponsors of today's podcast. Our first sponsor is

Thesis. Thesis makes custom nootropics, and to be quite direct, I do not like the word nootropics because it translates to smart drugs, and to be direct again, there is no such thing as a smart drug. That is there's no such thing as a drug that can make you smarter because there is no circuit in the brain for being smart. There are circuits in the brain for focus. There are circuits in the brain for task switching. There are circuits in the brain related to creativity and so on and so forth. So the idea that there would be a single smart drug or nootropic is simply foolish. And fortunately Thesis understands this and therefore has created custom notropics that are designed to get you into the states of mind and body that are optimal for your goals. I've been taking Thesis nootropics for quite a while now, and I've been extremely pleased with the results. I take a clarity formula that's specifically designed for me prior to long bouts of cognitive work. And I take an energy formula prior to particularly challenging physical workouts. To get your own personalized nootropic starter kit, you can go online to takethesis.com/huberman. Take a three minute quiz and Thesis will send you four different formulas to try in your first month. Again, that's takethesis.com/huberman and use the code Huberman at checkout to get 10% off your first box. Today's episode is also brought to us by InsideTracker. InsideTracker is a personalized nutrition platform that analyzes data from your blood and DNA to help you better reach your health goals. I've long been a believer in getting regular blood work done for the simple reason that many of the factors that impact your immediate and long-term health can only be analyzed with a quality blood test. One of the major issues with blood tests or DNA tests, however, is that typically you'll get your data back and you won't know what to do with those data. InsideTracker has solved this problem by creating a personalized platform where when you get numbers back about your hormones, metabolic factors, et cetera, it will direct you to specific protocols in the realms of nutrition, exercise, supplementation. And that includes things to do, things to consider, and things not to do in order to bring those numbers into the ranges that are optimal for your immediate and long-term goals. If you'd like to try InsideTracker, you can visit insidetracker.com/huberman to get 20% off any of InsideTracker's plans. Again, that's insidetracker.com/huberman to get 20% off. Today's episode is also brought to us by ROKA. ROKA makes eyeglasses and sunglasses that are the absolute highest quality. The company was founded by two all American swimmers from Stanford, and everything about ROKA eyeglasses and sunglasses were designed with performance in mind. I've spent a lifetime working on the biology of the visual system. And I can tell you that your visual system has to contend with a number of

important challenges in order for you to be able to see clearly. Now ROKA understands this and everything about their eyeglasses were designed in order for you to see with optimal clarity regardless of activities. ROKA eyeglasses and sunglasses are superb for wearing while you run or cycle. In fact, they were originally designed for that purpose. They're extremely lightweight. In fact, most of the time, I can't even remember that they're on my face, and they won't fall off if you get sweaty. In addition, ROKA eyeglasses and sunglasses have a terrific aesthetic. So while a lot of so-called performance eyeglasses out there will make you look like a cyborg if you want to, and they do have those varieties, they also have varieties of aesthetic choices that you would be very comfortable wearing to work or to school or just out and about. And that's one of the reasons I like them. I don't really have to think about having too many pairs of sunglasses or eyeglasses. I can just have one or two of each pair and I'm good to go no matter where I go. If you'd like to try ROKA eyeglasses and sunglasses, you can go to ROKA, that's roka.com, and enter the code Huberman to save 20% off on your first order.

00:14:35 Nicotine Effects vs. Methods of Delivery, Acetylcholine

Again, that's roka.com and enter the code Huberman at checkout. Let's talk about nicotine and how nicotine impacts our brains, our bodies, our mental performance, our mental health, our physical performance, and our physical health. Now once again, I want to remind everybody that we really need to separate out a discussion about nicotine from the discussion about the delivery device for nicotine. In other words, when we're talking about nicotine, we are not necessarily talking about smoking. Although we might be. There are things associated with smoking and with vaping and other means of getting nicotine into our system that have their own effects, both negative, and in some cases positive. Indeed later, we will talk about how you can actually use nicotine to get over smoking addiction. This won't come as a surprise to many people, but what perhaps will come as a surprise is the fact that many people actually use nicotine-like substances or nicotine itself in order to relieve nicotine addiction. So we'll talk about that and what that looks like and offer various protocols for you later in the episode. I also want to mention here at the outset that I have a long standing interest in nicotine. In fact, early in my scientific career, I did research on nicotine and its role in brain development. And I've had a long standing interest in neuroplasticity, the brain's ability to change in

response to experience. And so experiments that have been done by close colleagues and friends of mine have really emphasized the fact that acetylcholine, and in particular, when acetylcholine activates so-called nicotinic receptors, something you'll learn more about in a little bit, that can actually serve as a gateway or a trigger for directed rewiring of the brain. So this is fascinating. We think of nicotine as something that we take, but actually we have receptors that is locations in the brain to which nicotine binds and can exert its effects. And those receptors did not come about because of the existence of tobacco or the existence of vaping pens, or because of the existence of anything in the outside world. The fact that there are nicotinic receptors in our brain and body tells you that acetylcholine and nicotine themselves have very important roles in normal brain and body function, so much so that I often like to point to an anecdote of a very well known Nobel prize winning neuroscientist. I won't reveal who they are. They're not a faculty member at Stanford, but many neuroscientists know of this person and many people in the outside world know of this person. And they are also well known for their love of nicotine. I once sat in this person's office, and he, I will reveal it as a he, consumed no fewer than three pieces of nicotine gum during that relatively short conversation of about 45 minutes. And that was surprising to me. And I asked him why he was taking so much nicotine through nicotine gum. And he replied that for years, he had been a chronic smoker, which on the one hand had greatly impaired his cardiovascular health and his fitness, no surprise there. And we'll talk a little bit more about what the underlying reasons are, but most everyone, if not everyone knows that smoking cigarettes or smoking in general really impairs lung health. There's just simply no question about it. There are some more or less unhealthy ways to smoke, but the quite honest message is that smoking of any kind is going to disrupt lung endothelial function, lung function, blood vessels, and so forth. It's going to make it harder to breathe with vigor, take deep breaths, deliver oxygen to tissues, et cetera. That said, he also pointed out that the data on nicotine specifically are pointing to the fact that nicotine can be, can be protective against certain forms of cognitive impairment. And that is why he continued to chew nicotine containing gum. And he swore by the focus enhancing and motivation enhancing effects of nicotine containing gum. Now that is not a call to arms for you to run out and start chewing or consuming nicotine containing products. We will talk about those products later in the episode, some of their potential advantages, some of their potential disadvantages. Now I share this anecdote because it nicely separates nicotine from the delivery device through which nicotine arrives. Now I haven't talked to this

individual in a few years to see whether not the nicotine is working to stave off any kind of Alzheimer's or neurodegenerative or cognitive impairment that would come with age. This gentleman is getting up in the years and seems quite sharp nonetheless, but then again was always exceedingly sharp. The point is nicotine is a substance that can both promote cognitive function, and under some conditions, if taken to inappropriate, or I should say to extreme dosages, can also impair cognitive function. So today we really need to have a nuanced conversation about nicotine, one that includes some of the benefits, some of the drawbacks, in particular for children, certainly for people that are pregnant, for people that have addictive tendencies, and for people that have depression and any other kind of mood disorders. What I will tell you soon is that nicotine can be very powerful as a mood modulator and many people who have tried to quit nicotine mainly through the form of smoking will find that their mood can drop substantially. So nicotine does a lot of things in the brain and body.

00:19:55 Where is Nicotine Found? Nicotinic Acetylcholine Receptors

And so I'd like to begin by talking about what exactly nicotine is and how it impacts your brain and body. So what is nicotine and where is it found? Now obviously nicotine is found in the tobacco plant, but nicotine is also found in nightshades. That is tomatoes, eggplant, and sweet peppers. Although the concentrations of nicotine in tomatoes, eggplants, and sweet peppers is vastly lower than it is in the tobacco plant. You actually can also find nicotine in potatoes. Now why is nicotine present in potatoes and tomatoes and in the tobacco plant at all? Well, nicotine is a plant alkaloid. We'll get into alkaloids a little bit later, but it is thought that these alkaloids evolved in plants as a way to prevent insects from eating them. And without going into a lot of insect biology, the reason or the rationale behind this explanation is that nicotine is not only a substance in tobacco that people use or in the various medications that people use, but it's also used as a pesticide because it can dramatically disrupt the nervous system of insects. It can render them infertile, which is not to say that it renders humans infertile. We want to say, again, it is not the case that nicotine renders humans infertile, but it can make certain insects infertile. It can actually disrupt their motor function and their brain function, and the reasons that it has such different effects on insects, in other words, it can kill them or prevent them from reproducing, and therefore explains why plants probably evolved to have this plant alkaloid, nicotine. In humans, because of the differences in receptors for

nicotine, where they're located, and the types of receptors, the effects of nicotine on humans is quite a bit different. And again, it does not cause infertility in humans. Although I will talk a little bit later about some double blind peer-reviewed studies conducted in humans that indicate that for instance, nicotine can reduce penile girth, that is the girth of the penis, and can lead to certain forms of sexual dysfunction. And those changes are largely downstream of changes in blood flow and endothelial cell function. Endothelial cells are the cells that make up blood vessels and other vascular type tissues within the brain and body. So nicotine is found in these plants. And what we can know for sure is that at some point in human evolution, somebody or some group of people, either, and here, I'm completely guessing, it's a just so story, but someone or some group must have inhaled the smoke from the tobacco plant or put the dried leaves of the tobacco plant against some mucosal tissue, and you know the different mucosal linings of their body by which substances can pass through, that's right. Any of the mucosal soft lining tissues of the body will allow certain substances, not all certain substances to pass in. That's why people can put tobacco in their mouth and a certain amount of nicotine makes it into the bloodstream, put tobacco up their nose, certain amount of nicotine gets into the bloodstream. I haven't heard of people putting tobacco in other orifices of their body containing mucosal tissue. And I'm certainly not suggesting people do that, but you get the idea and how nicotine gets from these plants, these dried leaves into the bloodstream. Burning tobacco leads to a heat induced change in the availability of nicotine. And this is why smoking tobacco or vaping tobacco, simply by heating it up, allows the nicotine to be liberated and go into the bloodstream simply by inhaling it into the lungs. We will get back to smoking of various kinds later. But right now let's just keep our attention on how nicotine is pulled from these plants and into the human body. Now whether by inhalation or whether or not by placing in contact with the mucosal tissue of the mouth or other mucosal containing orifice of the body, the nicotine then gets into the bloodstream. And once it's in the bloodstream, it only exerts its effects because it binds to certain so-called nicotinic receptors. So the nicotinic receptors are of the acetylcholinergic variety. I know this is a lot to think about and a lot to hear if you haven't heard about this, but it's actually quite simple. Anyone can understand this. Acetylcholine is a molecule, a chemical that is that's released in the brain and body. And when it binds to receptors, that is little parking spots on cells, it changes the way those cells behave. Those cells can increase their activity and release other chemicals. They can become electrically active, they can do any number of different things. When we

ingest nicotine, it gets into the bloodstream and eventually some of that will get into the brain and some of it gets into the body. And in both of the brain and body, there are the so-called nicotinic acetylcholine receptors. Now the so-called family, and indeed they are a family, this is how we refer to groups of receptors of related design and genetic background just like humans. You have a family of these acetylcholine receptors that are of the nicotinic variety. So maybe on one street in your neighborhood, you know the Joneses and another street, you know the Chows and another street, well in your body, you have the nicotinic acetylcholine receptors, and then you have the so-called muscarinic acetylcholine receptors. Today it's really simple. Nicotine only binds to the nicotinic acetylcholine receptors and there are a bunch of different ones on a bunch of different tissues.

00:25:12 Nicotine & Effects on the Brain: Appetite, Dopamine & GABA

And the differences in those receptors dictate what sorts of effects the nicotine will have on those tissues. So let's talk about what those effects are, and let's do that by dividing the effects of nicotine into effects on the brain, so everything from the neck up, and on the body, the so-called central nervous system and the periphery. Although I want to point out that your spinal cord is part of the central nervous system. So in fairness to the reality, your brain and spinal cord are all central nervous system. Everything else is considered the periphery. Now there are a lot of different nicotinic acetylcholine receptors, but for those of you that want to know, you aficionados, or if you're ultra curious about this, the main effects of nicotine in the brain are mediated by nicotine binding to the so-called alpha four beta two receptor. Alpha four beta two receptor. Even if you don't care about receptor subtypes, that's going to come up later when we discuss why nicotine suppresses appetite. In fact, one of the major reasons why people don't want to quit smoking, or they quit smoking or another form of ingesting nicotine, and then they relapse, they go back to smoking or ingesting nicotine in some other way is because indeed nicotine will increase metabolism and reduce hunger in large part by binding to this alpha four beta two receptor in a particular area of the brain. We're going to return to that in a little bit, but if you've ever heard that nicotine kills the appetite, indeed it does. It's not the behavior of smoking itself. It's not because you always have a cigarette in your mouth that you're not eating more food. Although I suppose that might be a minor effect. There are direct effects of nicotine on both appetite, that is, it reduces

appetite and direct effects on metabolism, that is, it increases metabolism through its effects on some other areas of the brain and body we'll talk about in a moment. Now within the brain, nicotine binds to this alpha four beta two receptor in various locations in the brain. And there are three and maybe a fourth that we'll talk about neurochemical effects of nicotine after you ingest it. First things first, when you ingest nicotine by smoking nicotine containing tobacco, or if you place tobacco in contact with the mucosal lining of the nasal passages of the mouth, takes about two to 15 minutes for that nicotine to enter the bloodstream. Smoking hits the bloodstream faster, vaping even faster, I should mention for a variety of reasons and placing tobacco directly in contact with the mucosal lining is going to be the slowest. Now as I mentioned before, nicotine gets into the bloodstream and then because nicotine can pass through the so-called blood brain barrier, the BBB, which is basically a fence around the brain, because it can pass through the blood brain barrier, it's going to have very rapid effects on the brain in these four major categories of neurochemicals and neural circuits. The first of those categories, this is a very important one, this is one that was brought up in the episode on dopamine, motivation, and drive. And I think not just all scientists, but all human beings should know that within their brain, they have what is called the mesolimbic reward pathway. The mesolimbic reward pathway if you just want to call it, the dopamine reward pathway is, as the name suggests, a set of connections between a brain area called the ventral tegmental area. You don't have to remember the names of these things, of course, but if you want to, that's fine too. The ventral tegmental area or VTA connects to another area called the nucleus accumbens. Now here's what's very important. Nicotine triggers the release of dopamine from the nucleus accumbens. This is what gives nicotine its rewarding properties. It increases motivation. It tends to give a not so subtle, but very transient increase in feelings of wellbeing and alertness and motivation. And that's because of the increase in dopamine caused by nicotine directly within the nucleus accumbens. Nicotine also triggers the release of certain neurochemicals from the ventral tegmental area itself. And those impinge on nucleus accumbens and increase dopamine levels further. This is what makes the rewarding properties or sometimes referred to as the reinforcing properties of nicotine so powerful. This is why so many billions of people ingest nicotine in one form or another. It's also why nicotine is so hard to quit because there's a potent increase in dopamine from multiple neural circuit pathways within this mesolimbic reward circuitry. Now within the mesolimbic reward circuitry, there's an interesting feature. There are accelerators that essentially push out more dopamine, get

more dopamine released, and there are breaks of the so-called GABAergic variety. GABA's an inhibitory neurotransmitter. You don't need to know too much about it to just understand that nicotine both increases dopamine, but also decreases the activity of GABA. And so this is like pushing on the accelerator for dopamine, but also removing the brake. So there's a two pronged effect of nicotine on reinforcement reward dopamine related pathways, the feel good motivation pathways. And that is an increase in dopamine and a decrease in GABA. And again, that's all mediated through this mesolimbic reward pathway, involving the ventral tegmental area and the nucleus accumbens. So if you can conceptualize even just 5% of what I just told you, or even if you can just remember nicotine increases dopamine and that's why it feels so good, it makes you want more of it, you will have everything you need to know in mind in order to understand both why nicotine is so highly used, and indeed abused, why it's so hard to quit, and that will point to avenues as to how to quit or reduce intake. And it also points to how nicotine can actually be used in an antidepressant way should you choose. And we will talk about what the various criteria are for choosing that, but just to understand nicotine increases motivation,

00:30:58 AG1 (Athletic Greens)

it decreases negative feelings of mood, it increases positive feelings of mood and motivation. Before we continue with today's discussion, I'd like to just briefly acknowledge our sponsor Athletic Greens, now called AG1. Athletic Greens, AKA AG1, is an all in one vitamin mineral probiotic drink that also has adaptogens and digestive enzymes. I've been taking Athletic Greens since way back in 2012. So I'm delighted that they're sponsoring the podcast. The reason I started taking Athletic Greens and the reason I still drink Athletic Greens twice a day is that it supplies total foundational coverage of my vitamin and mineral needs. And it supplies important nutrients that I need to support my gut microbiome, the gut microbiome, as many of you know, supports the immune system. It also supports the so-called gut brain axis, which is vital for mood, for energy levels, for regulating focus, and many other features of our mental health and physical health that impact our daily performance and high performance in any endeavors we might be involved in. If you'd like to try Athletic Greens, you can go to athleticgreens.com/huberman and claim a special offer. They're giving away five free travel packs plus a year's supply of vitamin D3K2 with every order. And of course,

vitamin D3K2 are vital for all sorts of things like hormone health and metabolic health and K2

00:32:11 Nicotine, Acetylcholine & Attentional "Spotlighting"

for cardiovascular health and calcium regulation. Again, you can go to athleticgreens.com/huberman to claim that special offer. The second major effect that nicotine has in the brain is that it increases acetylcholine. Acetylcholine is a neuromodulator that exists in you and me, it is released from multiple sites in the brain. And the two major sites are the nucleus basalis, so these are a collection of neurons in the front and base of your brain, and from some brain stem areas. And there are a bunch of different ones back there in your brain stem, which is indeed in the back that release acetylcholine that include the locus coeruleus as kind of a minor site, the pedunculopontine nucleus. There are a bunch of these different areas, that parabrachial nucleus. There are a bunch of these things back there. We don't have to go into all the names, but just understand that they're little pockets of neurons, nerve cells located in the front and the back and some extent in the middle of your brain, but really in the front and the back of your brain, that can serve two major role, here they are. Acetylcholine released from nucleus basalis leads to a sort of spotlighting or highlighting of particular neural circuits in the brain. What do I mean by this? Well let's say you're working on a puzzle. Let's say it's a cognitive puzzle. Maybe you're doing a word puzzle, or nowadays I've heard of this Wordle thing. I'm on Twitter and people are always posting their Wordle thing and I have no idea what it is, but I'm guessing it's some sort of puzzle. I'm guessing it's like a crossword puzzle, and here, if I'm wrong, I don't know, educate me. Tell me what Wordle is. Somebody put it in the comments and tell me if I should play it or not. Here's the deal. When acetylcholine is released from nucleus basalis, the neurons are there in the base of the brain, but they extend axons, which are like little wires elsewhere in the brain. And when acetylcholine is released, it tends to be released at particular locations in the brain that are associated with whatever activity we happen to be doing. So if I'm doing Wordle, here I'm talking about it as if I've ever done it, doing a crossword puzzle or Wordle, well the neurons that were involved in trying to figure out the solution to that Wordle or crossword puzzle are active, and then acetylcholine is released from the little wires, the little endings of these cells in nucleus basalis. And all of a sudden those neural circuits get a boost. They become more active,

and believe it or not, our ability to perform that crossword puzzle or at least focus on that Wordle or crossword puzzle gets enhanced. It literally increases our attention for that and not anything else is enhanced. So it's literally like a neurochemical attentional spotlight. Nicotine increases acetylcholine and thereby focus and concentration and mental performance, not by changing the neural circuits that are activated per se, but rather by making more acetylcholine available at those release sites. So it's as if the spotlight got more intense, the highlighter is more intense than it would be otherwise. And I should also mention because of the so-called pharmacokinetics, the time course in which nicotine has its effects, which are pretty short lived, we'll talk about those in a moment, this enhancement in cognitive performance and attention, it's going to be very transient, probably on the order of about 30, maybe 45 minutes, the half life of nicotine, depending on how it's ingested and whether or not you have food in the gut and what else is in the bloodstream, et cetera, it's going to be anywhere from one to two hours, but typically the effects of nicotine will come on in about two to 15 minutes as I mentioned before, and then will last anywhere from about 30 to 45 minutes. This is why in the old days, and still to some extent in certain areas of the world, but less so in the United States and certainly in Europe as well, we don't see quite as many people smoking cigarettes, for reasons we can discuss later. But you would see these chain smokers who are trying to maintain constant levels of nicotine in their brain and bloodstream. Now perhaps they didn't know that nicotine has this one to two hour half life, but they could sense no doubt the cognitive and the physical effects of nicotine, including this cognitive enhancement effect and highlighting of neural circuits effect. And they would notice they would smoke a cigarette and then for the next five to 45 minutes have heightened focus and then they would start to drop off. So they smoke another cigarette. So in other words, they're trying to maintain a constant level of nicotine for whatever activities they needed to perform. Obviously chain smoking because of the terrible effects of smoking, I'll talk about those terrible effects, but I'm sure you've heard of them before, cancer, depletion of just about every organ and body tissue to the point that it can actually be measured how many years of your life you're peeling off in terms of lifespan and health span by smoking. Well the terrible effects of smoking are indisputable, but the positive effects of nicotine on this circuitry, part of the reason why people would chain smoke in the first place rather than get one big peak of concentration and focus and then just let it disappear after 45 minutes. So what we have is a scenario where dopamine is going up in the mesolimbic pathway. That's why smoking or ingesting nicotine in any other way

feels good and makes us feel motivated. And then the increase in acetylcholine, especially from nucleus basalis in the front of the brain, is the reason why it can increase our ability to focus on particular types of endeavors, particular mental work that we're doing, or maybe even particular physical work. Although I should mention anytime I'm pairing the words nicotine and physical work, it's obvious that because of the ways that smoking impairs lung function, those two things really run counter to one another. In other words, if you are thinking about ingesting nicotine through smoking or vaping in order to improve physical performance, that's a terrible idea.

00:37:29 Nicotine, Norepinephrine & Alertness/Energy

The logic isn't there and the health detriments are certainly there. The third neurochemical pathway that's strongly activated when nicotine is brought into the central nervous system into the brain is epinephrine, or in particular norepinephrine, which is related to epinephrine. Now, earlier I said epinephrine is the same as adrenaline. That's still true. Norepinephrine is closely related to epinephrine, and for today's discussion, we're going to use them interchangeably. Although I realize as I say that that the medical students and some biology students are probably going to have a minor seizure when I lump norepinephrine and epinephrine. I don't do that to be too much of a lumpster, in science, we talk about lumpers and splitters. Lumpers are people that like to oversimplify a little bit, splitters are people that really like to detail. You'll see a lot of splitters on social media from time to time, they'll say, wait, you didn't mention the alpha two beta six receptor yet. Okay look, I get it. And I am all for having splitters in the room, but for sake of today's discussion and for ease of digestibility of some of this, just want to point out that norepinephrine, epinephrine, and adrenaline, I'm going to treat as a common pool of similar, in fact, very similar molecules that all have the same net effect, at least in the context of this discussion and that's to increase levels of alertness, energy, and arousal. And the way that nicotine accomplishes those increases in alertness and arousal and energy within the brain is by triggering the release of norepinephrine from a little cluster of neurons in the back of the brain called locus coeruleus, tiny cluster of neurons that offers up, or I should say has, because they're always there from birth has these little wires, these axons that extend many, many places in the brain, not every place, but virtually every place and can sprinkler the brain with norepinephrine, essentially serve as a wake up signal, elevating levels of energy. And when that combines with the

acetylcholine from nucleus basalis, which causes attentional spotlighting, increases in concentration and focus, and with the feel good properties of dopamine and the motivating properties of dopamine released from the mesolimbic reward pathway. Now you can start to get a picture of why nicotine is such a powerful molecule. It's making people feel motivated and good. It's making people feel focused and it makes people feel alert when they would otherwise feel a little bit sleepy. So this is a really powerful compound, in fact, going back to our earlier discussion about focus and some tools for focus, and I encourage you if you're interested to please check out the episode on focus, there are a number of different tools and protocols there to increase focus. But here we are talking about one molecule, nicotine, found in plants like tomatoes and potatoes and the tobacco plant. And it can be synthesized in a laboratory and ingested through a patch or a gum or even a pill or a toothpick dipped in nicotine. One molecule that can trigger activation of all the circuits for focus and motivation in one fell swoop. That is remarkable. That is absolutely remarkable. And here we haven't even touched on some of the psychological components of focus, right? Whether or not we're interested in something, whether or not we're excited about it or not. This is a very, very powerful system. So powerful in fact, that I think we can really place nicotine right up there at the top, right next to caffeine as the molecule that has fundamentally changed human evolution, human consciousness, and human experience. Even if you're somebody who's never ingested nicotine, this absolutely has to be true because you have these nicotinic receptors, which is to say that acetylcholine that's naturally released without any external trigger within your brain and body, or I should say without any trigger from nicotine in particular is binding these nicotinic acetylcholine receptors

00:41:10 Nicotine & Effects on Appetite & Metabolism

and is creating these effects in your brain and body, just absolutely staggering. Now earlier I mentioned the appetite suppressing and indeed metabolism increasing effects of nicotine. And while that's a fairly niche component of what nicotine does, I mean, it's an important one, but it's not the major reason why most people consume nicotine. I'd like to take a moment and talk about that now, because we are in the brain and we're talking about the effects of nicotine in the brain. And so it seems to me the appropriate time to talk about this. Now we can have this conversation about nicotine and appetite and metabolism in a very simple and straightforward way. If you'd like to learn more about

the biology of metabolism and appetite and how those things are mediated by neural components, so not just stuff like your liver, et cetera, we have episodes on that, but really the neural components of hunger and appetite. I encourage you to check out our episode on hunger and appetite. But in that episode, we had a discussion. And it's one that I'll just briefly summarize now that you have a collection of neurons that sits right above the roof of your mouth or so called the hypothalamus. Hypo means below and thalamus is right above it, hypothalamus. So the small collection of neurons in the hypothalamus to a number of different things related to sex behavior, aggression, mediating the temperature of your body, et cetera, but also appetite and suppressing appetite. And within the hypothalamus, there's a compact collection of these little neurons, which we referred to as the POMC, P-O-M-C neurons. And the name comes from the fact that they express certain peptides. And we won't get into that now, but the POMC neurons have a very profound impact on whether or not you feel hungry or whether or not you do not feel hungry, whether or not your appetite is suppressed. It turns out that when nicotine gets into the bloodstream and then into the brain, some of that nicotine binds to nicotinic alpha four beta two containing nicotinic receptors. Again, these sub units of receptors, but basically the nicotine binds some of those parking spots, parks there. And as a consequence, these POMC neurons increase their electrical activity and appetite is suppressed. And that's because the POMC neurons have outputs to various areas of the brain and body controlling everything from how full we feel to whether or not our blood sugar goes up or down, which can impact our hunger, and believe it or not, whether or not we have a tendency to want to move the jaw of our mouth in order to chew food. Yes, believe it or not, the neural circuitry associated with appetite and suppression of appetite actually dictates whether or not you prefer to, or I should say are more biased or less biased to moving your mouth, that is chewing. Which makes perfect sense when you hear it. One way to suppress appetite is to sew the jaw shut neurally, or at least make it less likely to open your mouth and put food in it. Actually that reminded me of a story. I'll just interrupt myself to tell a brief story that there's a famous Nobel Laureate who won the Nobel Prize for something totally distant from appetite. But once turned to a friend of mine at a meeting and said, I discovered the biological mechanism for losing weight. And my friend said, well of course, ingest fewer calories than you burn. Calories in, calories out, fundamental rule of thermodynamics. And basically the fundamental rule of weight loss, weight gain, or weight maintenance. And he said, no, it's actually the gene that controls whether or not

you open your mouth. Now he was making a very nerdy joke. So if you didn't register that as a joke, that's about as funny as neuroscience or biology jokes get. There are a couple funnier ones, but that one's kind of considered on the funnier side. So this is why we're not considered comedians. But the point of the matter is that whether or not you crave or desire or impulsively want to put things in your mouth and chew it, will actually dictate how many calories that you eat. And so I find it remarkable and indeed important to know that these POMC neurons are actually inhibiting the opening and the movement of the mouth for chewing. So when we smoke or when we ingest nicotine in any other way, you activate these POMC neurons, you suppress appetite, but in part you do that by actually limiting the impulse to chew. Incredible, at least to me. Now in addition to limiting appetite by changing one's desire to ingest food and chew it and actual craving of food by regulation of blood sugar, et cetera, there do seem to be some quite direct effects of nicotine on metabolism, and the effects on metabolism aren't enormous. These are increases in metabolism that are about 2% up to about 5%, but I want to emphasize that those are transient increases in metabolism. Nonetheless, people that quit smoking often find that their appetite goes up, they sometimes gain weight. They sometimes do not depending on whether or not they offset that increase in appetite with increased physical exercise or with decrease food intake in other ways. But there does seem to be this direct effect of ingesting nicotine on metabolism, which I find is interesting because if you look in the literature, one of the reasons why people are reluctant to quit ingesting nicotine, if for instance, they want to quit using the delivery device to nicotine that's causing such problems for their health like smoking or vaping or whether or not they find themselves quote unquote addicted to, or have the habit of ingesting nicotine. In part, that's likely due to be the dopamine effects, because dopamine is highly reinforcing and rewarding. It feels good, so people want to do more of it. But it's also that for many people and here the data really point to the fact that a lot of the younger female smokers or younger female vapers, or when I say that, of course I mean younger females that vape, are doing that because they like the appetite suppressing effects,

00:46:47 Nicotine & Effects on Body: Sympathetic Tone

which of course opens up an entire conversation about the sociology of body imagery, et cetera, a topic for a future podcast. So nicotine has certain effects on the brain by virtue of the fact that nicotine binds these nicotinic acetylcholine receptors. And those

receptors are found on some, but not all neural circuits within the brain. And we talked about some of them already, mesolimbic, the POMC neurons, et cetera. Now when we ingest nicotine, it goes from the bloodstream to all the tissues and organs of the body. How does it do that? I mean, amazing. It can pass to everything, the brain, the body, it does that because nicotine is fat soluble. And now when anytime people hear the word fat, they tend to think about body fat, subcutaneous fat, or maybe they think about dietary fat. What I mean by fat soluble in the context of nicotine being fat soluble is that the cells of your body have an outer layer, so-called outer membrane. And it's made up of lipid, of fat, very particular types of lipids in fact. Nicotine has this remarkable ability to move through that fatty tissue. Not all molecules have that ability, but nicotine does. So it can move relatively freely through the brain and body and relatively freely from outside of cells, extracellular space to intracellular space. So it can get into cells, it can do that within the brain. We talked about those effects and it can do that within the body. Now anytime we're talking about the body, we can be talking about any number of things, but today I'm going to refer to the periphery and the body in more or less the same way, but keep in mind in the back of your head, pun intended, you have your brain, your eyes, and the spinal cord. And those three things make up your central nervous system. The peripheral nervous system and the periphery, which is the rest of your body, the contain your organs and so forth outside of the nervous system, things like your liver and your stomach, et cetera, that's what we're going to talk about now because nicotine has profound effects on the organs of the body that are separate from, but that occur in parallel at the same time as the effects of nicotine on the brain. So let's talk about what some of those effects are. When nicotine makes it into the bloodstream, again, within two to 15 minutes of ingesting it, depending on the delivery device, your heart rate will increase, blood pressure will increase, and the contractibility of the heart tissue will actually increase. So what that essentially speaks to is an increase in so-called sympathetic tone. And when I say that, I don't mean an increase in sympathy for others of the emotional sort. What I mean is an increase in the sympathetic activity of the sympathetic arm of the autonomic nervous system, which is real mouthful and mindful of ideas. But all you need to know is that it's a generalized system that increases levels of alertness and physical readiness. So it makes you ready for action, makes you ready for thought. It's balanced by a whole other system called the parasympathetic nervous system, which is basically the so-called rest and digest system, which is a system of neurons and organs, et cetera, that put your body and your brain into a state of not being

able to think clearly, to digest, and to fall asleep. So nicotine increases heart rate, blood pressure, and contractibility of the heart. So it's going to cause more blood flow in theory, although it also tends to constrict blood vessels in many locations in the body. This explains the decrease in penile girth effect of nicotine, in particular nicotine ingested by smoking or vaping. That's right, smoking and vaping reduces penis size and also will have damaging effects on the blood lining endothelial tissue. So over time it actually is impairing blood's ability to get to the penis chronically as well as to other organs of the body. But when people ingest nicotine acutely, and let's say they do that by Nicorette patch or by toothpick dipped in nicotine, it will have some of these same effects, but when not smoking tobacco, when bringing nicotine into the bloodstream through other mechanisms, many, if not all of the disruption of the endothelial cell function can be bypassed, but the effects on penile girth, the effects on reducing blood flow to various tissues is still present during the effects of nicotine, which as I mentioned last about one to two hours. The half life is about one to two hours, depending on a number of factors, not interesting for today's discussion. So when nicotine gets into the bloodstream, it's making us more alert, it's preparing our body for readiness. The heart is pumping harder. Epinephrine, that is adrenaline, is released from the adrenal glands, which right atop our kidneys. So everything is pointed toward creating more readiness to move, more readiness to think. And again, this is happening in parallel with all the effects of

00:51:29 Nicotine & Cognitive Work vs. Physical Performance

neurochemistry that are happening with the brain that we talked about a few minutes ago. Now what's interesting about nicotine is that while it causes this global increase in readiness and alertness and attention and mood, et cetera, it also has the effect of somewhat relaxing skeletal muscle. Now that might seem counterintuitive to those of you out there that already know what I'm about to tell the rest of you who didn't know it previously, that your muscles are able to contract because of the effects of acetylcholine released from neurons in your spinal cord that spit out acetylcholine onto the muscle and bind to what? Nicotinic acetylcholine receptors. Put into plain English, nicotinic receptors are also the ways in which your muscles can get activated. So therefore, why would it be that increasing nicotine would cause relaxation of the muscles? And that has to do with some of the neural circuits that are upstream of the muscles and has to do with a little bit of how the autonomic nervous system is a range in terms of which receptors go where, a

topic and kind of rabbit hole of a conversation far too deep for right now, at least in the context of this already somewhat detailed discussion of the effects of nicotine. But if we were to zoom out and just think about the effects of nicotine, we now have a very clear picture. Reward pathways are turned on. Attention is turned on. Alertness is turned on. You feel better than you felt a few minutes ago. Your blood pressure is up. Your heart rate is up. Your preparedness for thinking is elevated as well. And yet your body is somewhat relaxed. That's a very interesting state of mind and body. Interesting because it's somewhat ideal for cognitive work. Like if you were going to sit down and work on a book or you're going to sit down and try and figure out a hard math problem, or you're going to write a letter that's been really challenging for you to write, or maybe that you're really excited to write, but that you've been slow to get out the door for whatever reason. I'm talking about my own habits of procrastination. Well that state of being very alert, but your body being relaxed is almost, if not the optimal state for getting mental work done, because if you're feeling agitated in your body and you want to physically move your body, it's very hard to do cognitive work. At least the sorts of cognitive work that involve typing or writing or these sorts of things. It's also the exact opposite of the optimal state for physical performance, which is one of yes, also alertness, yes, also motivation and elevated mood. That's all wonderful stuff to have in mind, literally when you are exercising or competing in sport or something of that sort. But under those conditions, you really also want to have a fast reaction time, a low latency for muscle activation so that you can make coordinated muscle movements in the ways that you need to, which is of course what's required of physical endeavors. That tells us a few things, first of all, it tells us that nicotine is going to be generally a bad idea for a pre-workout tool or for enhancing physical performance, however, it's apt to be, and in fact is an excellent tool for enhancing cognitive ability. And of course, that triggers my mind to return to the anecdote about my Nobel prize winning colleague who ingests nicotine by way of nicotine containing gum in order to increase levels of cognitive focus. Certainly not for going out and playing sport. In fact, despite the fact that he is very, very tall, he often points to himself in an appropriately funny way that despite being on the basketball team of his high school, he is probably the worst player that ever existed. And they only positioned him there because of his height.

And I guess his head was designed to prevent balls from entering the basket. In any event, nicotine does seem to be very good at enhancing cognitive function, at least in the short term, which is not to say that it isn't without its side effects, which we will talk about. And again, those are side effects that are independent of smoking or vaping or other forms of ingesting nicotine. For instance, dipping or chewing tobacco is known to cause a 50 fold, yes, 50 fold increase in mouth cancers, things like leukoplakia and just generally is terrible for your health. I'm sorry to break it to you, but if you're dipping or you're using snuff or things of that sort, certainly I'm not going to tell people what to do. That's not my role in life, but you are dramatically increasing the probability of an oral cancer or of a mucosal lining cancer of some sort. So it's not just that smoking and vaping are bad for your health. These other forms of delivery for nicotine can be bad for your health as well. Now whether or not ingesting nicotine by way of nicotine containing gum or patch or toothpick or other method is dangerous, for other reasons is a discussion that's important, right now, it appears that provided the dosages are kept reasonable. We'll talk about what reasonable means a little later, and the frequency is kept relatively low. So not relying on these things constantly. There may in fact be some benefit to ingesting nicotine from time to time, provided that you are not still developing your brain. Now in reality, neuroplasticity goes on throughout the lifetime. Your life is actually one long developmental arc. It's not like development occurs and then stops, but certainly for people before puberty, during puberty, and probably for the next 15 to 20 years after puberty, avoiding nicotine is probably a good idea. Now of course, development is your entire life. It's not like development starts and then ends, but certainly for people that are 25 years old or younger, ingesting nicotine as a way to enhance cognitive function is probably not the best idea. And certainly, please, for those of you that are 15 years old or younger, ingesting nicotine in any form, unless it's prescribed by your doctor for a very specific clinical reason, to me seems just like a terrible idea based on all the data that I've read. And the reason for that is it's going to create a scenario of nicotine dependence in order to achieve heightened levels of mood and alertness, et cetera, and that's bad. And what we're effectively talking about is an addiction for nicotine directly, not necessarily the delivery device method like smoking or vaping, although it could pull that in as an addictive or habit forming behavior as well, but you want to let your neural circuits develop to the point where again, unless there's a clinical need for a prescribed drug from a licensed physician or psychiatrist, et cetera, that you're not relying on chemical enhancement of these circuits. For people who are 25

years or older, and again, that's not a strict cutoff, but roughly 25 years or older, but for those of you that are thinking about using nicotine to enhance cognitive function as adults and your brain development is slowing down, right. Never ceases, but is slowing down or has slowed down to the point where we would say developmental plasticity is largely over and you're now operating in the context of adult neuroplasticity. Well, in that case, there may be instances in which increasing acetylcholine, dopamine, et cetera, by way of nicotine ingestion might be a good idea, but certainly not by smoking, vaping,

00:58:35 Smoking, Vaping, Dipping & Snuffing: Carcinogens & Endothelial Cells

or by direct contact of tobacco to the mucosal lining tissue of the mouth or nose, so called dipping or snuffing. For the last 20 minutes or so, we've been talking about the biology of nicotine specifically, how it impacts the brain, how it impacts the body, why it feels so good, why it can enhance focus. And we've largely set aside smoking, vaping, dipping tobacco, and snuffing, and the negative effects that those all have on mental and physical health. Working down from the top of the head to the bottom of the feet, we can say that smoking, vaping, dipping, and snuffing negatively impact every organ and tissue system and cell of the body by virtue of the fact that they all damage the endothelial cells. Again, the endothelial cells are the cells that make up the vasculature, which delivers blood and other nutrients to all the cells and organs and tissues of the body. And those endothelial cells are strongly and negatively impacted by all of the practices that I just described. Now the way that that happens varies a little bit from each one to the next, for instance, it has been estimated that cigarettes contain anywhere from 4,000 to 7,000 toxins. Now the word toxins is a real buzzword these days, you hear about detoxes and toxins, but more specifically, we know that it contains carcinogens. These are cancer promoting compounds. For instance, we know that the tar in cigarettes, even low tar cigarettes, as well as the ammonia within cigarettes, as well as the formaldehyde contained within cigarettes, as well as the carbon dioxide that's generated from smoking those cigarettes are all carcinogens. Carbon dioxide also has the negative effect of depleting the amount of oxygen that's delivered to any and all of our tissues by way of the impact of carbon dioxide binding hemoglobin and preventing hemoglobin from delivering oxygen to the tissues of the body. So while there may be 4,000 or 4,500 or 7,000 toxins, depending on which cigarette, which papers they happen to be rolled in, whether or not they're filtered or non-filtered, the type of tobacco, et cetera, et cetera,

there are a tremendous number of toxins. And there are some very potent carcinogens within that long list of toxins. Again, ammonia, tar, formaldehyde, and carbon dioxide being the most potent of those carcinogens. Now the fact that there are carcinogens in cigarettes sometimes lead cigarette smokers and particularly the cigarette smokers that have the hardest time quitting or that enjoy their cigarettes the most from saying, well, listen, everything is a carcinogen or everything kills you. Well certainly that's not a true statement. And while there are other carcinogens in the environment, so it environmental hazards like solvents. And even if you work in a laboratory, for instance, we use in the laboratory, DNA intercalating dyes, these are literally dyes that allow us to see the DNA structure of cells and see the proteins they make and see the RNAs they make. And it's very important to wear gloves when you work with those things, because as the name suggests, they intercalate, they actually get in between the strands of DNA and separate them. They are mutagens, they mutate DNA. They are often carcinogens as well. So we have them in our laboratory, but we take certain precautions to not have them negatively impact our health, safety protocols and so on. We hear that there are carcinogens in car exhaust and bus exhaust and in all sorts of things like pesticides and that's all true. So in the argument of probabilities, one would say, well, if there are all these other carcinogens in the environment, why would you compound their carcinogenic effect by smoking or vaping or dipping or snuffing? But that usually doesn't get people to quit smoking or doing those things because of the powerful reinforcing effects of nicotine itself. So again, nicotine is the reinforcing element by way of triggering that dopamine reinforcement pathway, the mesolimbic reward pathway. And of course there are all the other additional effects of increased focus, such as increased ability to pay attention to work or to others that lead to other rewards. And so then it becomes a situation of compounding rewards. So it's not really about the cigarette, it's about the nicotine, and it's not really about the nicotine, it's about the dopamine that the nicotine evokes. And then it's not really about the dopamine that the nicotine evokes directly per se,

01:02:34 Smoking, Vaping, Dipping & Snuffing: Negative Impacts on Lifespan & Health

but also about all the positive effects that that increased dopamine results in. So we can easily circle back to the negative effects of smoking, vaping, dipping, and snuffing, and say the endothelial cells are disrupted. The endothelial cells are involved in delivery of blood and other nutrients to every tissue of the body and smoking vaping, dipping, and

snuffing contain carcinogens, which are cancer promoting. And because the epidemiological studies are out there, we can actually arrive at some very clear numbers as to how much life one will lose from ingesting nicotine by way of those four delivery devices, or I should say any one of those four delivery devices. Although I should also mention that many people who are vaping are also smoking cigarettes is becoming increasingly common. A lot of people are using vaping in one context and cigarettes in another, dipping in one context, vaping in another. But even for those that only smoke or only vape or only dip or only snuff, the negative effects are dramatic and calculable. So it is thought that for every pack of cigarettes consumed per day, so you could average that out if you're a two a day cigarette smoker or a pack a day cigarette smoker, two pack a day. For every pack of cigarettes smoked per day, we can reliably estimate a 14 year reduction in lifespan. So cigarettes are literally peeling years off your life. Now because of the way that the brain works and the way that human beings anticipate the future and can be grounded both in the present and the future or the present and the past, that's just how the mind works, right? That's why we can think about the future, but also realize where we are in time and space today. Because of that, many people will say, well, I enjoy cigarettes or I enjoy vaping. And so at least while I'm here, I'm enjoying it. And that's because the dopamine system is not very good at understanding opportunity costs. That is what we would be doing in those 14 years and what we would be enjoying and the enrichment that we would get if we were to live into those 14 years. So at some level the smoker or vaper is being rational when they say, yeah, but I enjoy this. And so the years lost, I can't really register that because it's hard to register what you don't have and what you've never had. On the other hand, we can also point to the statistic that there is this 50 fold increase in mouth cancers from dipping. And there are nasal cancers as well that are greatly increased by snuffing and from smoking, and now we know based on data from vaping that the endothelial cell damage and the direct effects of damage to the lungs from tars, and even if people are vaping, which tends to have lower tars than do cigarettes, even for people that are vaping, greatly increased probability of stroke, of peripheral vascular disease. So this is peripheral pain because remember, blood is delivering, not just blood, but other nutrients and it's clearing things out from tissues. So there's an accumulation of literally toxins and debris that cells generate all the time, which is healthy, but then the normally is cleared away by the endothelial cells and by other cell types of the immune system, that's all increased in people that engage in these nicotine delivery device behaviors. Rates of heart attack, rates of stroke, rates

of cognitive decline are all increased. Now you might say cognitive decline, I thought that nicotine increases the likelihood that we can maintain healthy neural function and cognitive capacity. It might even increase cognitive capacity in a potent way in the short term, and indeed it does. However, cigarette smoking and vaping are now known to dramatically decrease cognitive function because one of the key things about the brain is that it is the most metabolically demanding organ, which means it consumes a lot of glucose. Or even if you're ketogenic, you need ketones, you need nutrients getting to the neurons in other cell types of the brain and nervous system in order for it to function properly. And when you disrupt a vasculature through this endothelial cell dysfunction, you get things like interstitial, which just means in the spaces between dysfunction. So it's not just beating up the endothelial cells themselves, but the spaces between the cells is being disrupted. There's a lot of debris that accumulates there. And as a consequence, the brain just simply will not function as well. So you start getting short term memory lapses, you start getting working memory lapses, working memory is the sort of memory if someone tells you their seven digit phone number, typically nowadays people just share their info, but seven digit phone number or a sequence of numbers or an address and your inability to remember that. So you're walking back to the kitchen sink and you can't remember what you were trying to remember just a short moment ago, that's working memory. Working memory suffers, long term memory, projective or intergrade memories into the future. How can you remember things in the future that haven't occurred yet? Well this is more of a memory for future plans or ideas and planning for things that are to come. So what we can very reliably say is that currently more than 1 billion, billion, more than 1 billion people consume tobacco in order to get their nicotine because that's really the reinforcing element within tobacco, more than 1 billion people consume tobacco in the form of cigarettes every day. A growing number of people, more than half a billion people now are starting to vape. The estimates range from 200 million to 500 million. And there's a lot of debate about this because a lot of people are hybrid smokers and vapers, meaning they do one or both depending on time of day and location, as I mentioned before, but now you start to see how you can get to the number that billions of people are consuming tobacco. Because of course you also have your people that are dipping and your people that are snuffing. And as I mentioned before, you have people that are engaging in multiple of these behaviors. So billions of people on planet Earth, anywhere from one eighth to a quarter of human beings, incredible right? Anywhere from one eighth to a quarter of human beings are consuming

tobacco in one form or another in order to get their nicotine one way or another. And as a consequence, are peeling years off their life, dramatically increasing the probability of cancer, stroke, heart attack, peripheral neuropathies, brain dysfunction, meaning cognitive dysfunction, memory impairment, sexual dysfunction. There are a number of studies that have looked at increases in cortisol. And while minor, those increases do exist. Decreases in growth hormone, and while minor, those decreases exist, but even setting aside the negative impact on endocrine, on hormone factors, it's very, very clear that smoking, vaping, dipping, and snuffing are among the worst things that we can do for our health.

01:09:23 How to Quit Smoking, Nicotine Cravings & Withdrawal

They are among the leading causes of preventable death and debilitating life conditions, which may lead you to the question as to why in the world would people do this? Well it turns out most of them don't want to. In the best surveys that one can find of if you could quit smoking, if you could quit vaping, would you, what you find is that at least for cigarette smokers, 70% want to quit. They would love to quit. And yet they find that to be exceedingly difficult. And the reason they find it to be exceedingly difficult is because of all the brain neurochemistry that we talked about before. The reason I spent close to 20 minutes talking about dopamine and the mesolimbic pathway, acetylcholine and nucleus basalis, and epinephrine, and the relaxation of muscles in the periphery and the increase in readiness in the body and brain is that all of those combine to make nicotine one of the most powerful and potent cognitive enhancers and to some extent physical enhancer, although, as I mentioned before, the total number of physical exercise or physical sport promoting effects of nicotine is very, very small, if not zero. There are certain conditions under which one might imagine using nicotine specifically for cognitive enhancement where performance of complex motor skills would sort of outweigh the negative effects on the neuromuscular system, our ability to generate coordinated movements. There was actually an excellent study looking at the effects of nicotine, not by smoking delivery, but by different delivery mechanism in which they looked at performance of hitters in baseball. The experiment was kind of an interesting one, even though these were fairly skilled baseball players, what they had them do was hit a ball off a tee, as I recall growing up and I admittedly I didn't play much baseball, but you start off on tee-ball and then you would go, I think it was to pitching machine. Then they would

use actual pitchers who throw the ball. But in this case it was a couple of different baseball related tasks. They'd have people hit the ball off a tee, but they had to direct that hit toward a ball atop another tee. So it's fairly precise targeting that's required in order to knock that ball off the other tee. So this is an activity that involves not just motor output, but coordinated motor output, and not just coordinated motor output, but directed, coordinated output that requires some, as we would say, top down processing. This isn't the kind of thing that can be done reflexively. This is the kind of thing where the forebrain, the prefrontal cortex in particular has to be heavily involved in order to suppress certain actions and then create other actions. So the basic takeaway of the study is that nicotine delivered by way of nicotine gum, not by smoking, dipping, or snuffing was able to increase cognitive performance and motor output. So a rare circumstance where a specific set of demands that involved both cognitive engagement and physical engagement showed a slight but significant improvement. But again, in most cases, nicotine is just simply not going to improve physical output if it's delivered through a smoked cigarette, through vaping, through dipping, or through snuffing. So if all these behaviors are terrible for essentially every aspect of our health, frankly, I mean, when you look at the literature, it's terrible for pregnant women, it's terrible for kids, it's terrible for older people, it's terrible for younger people. You really cannot find a scenario in which smoking, vaping, dipping, or snuffing are good for us. And yet people like the effects on the brain and they feel quite addicted to them, even if they say they're not, most of those people would be unwilling to give up their practice of nicotine delivery for more than a few hours. In fact, if you look at the effects of withdrawal and we are going to talk about what withdrawal of nicotine looks like, what you find is that as soon as four hours after the last ingestion of nicotine by way of cigarette or vaping or dipping or snuffing, what people start to experience is some agitation, craving for nicotine, of course. And while craving is kind of a vague concept, it's actually a very specific biological mechanism. It's the drop in dopamine that's starting to occur so much so that there's a drop in dopamine below baseline. That is the increase in dopamine that would normally be experienced from smoking, vaping, dipping, or snuffing is now not happening. And in fact, the levels of dopamine are dropping below where they would've been even without performing that behavior. So that's what craving is. And withdrawal is an increased sense of that craving as well

01:13:56 Vaping & Nicotine, Rates of Effect Onset, Dopamine, Addiction & Depression

as a lot of negative stuff like stomach aches or nausea or irritability, and often collections of all of those. So because these nicotine delivery approaches are so terrible for our health, and also because as many as 70% of people who smoke would like to quit, but either feel they can't because they've tried and failed repeatedly often, or because it's just too scary, meaning the reinforcing properties are too strong and therefore they can't imagine living without them or the withdrawal effects are too strong and they can't imagine living with those. Well then is there hope for quitting smoking, vaping, snuffing, or dipping? And the short answer, fortunately is yes, there are excellent ways to do that. And some of them are single event treatments. And we're going to talk about those shortly, but before we do that, I want to highlight one very brief point, which is that nicotine is not the cause of cancer. Nicotine is not the carcinogen, it's the other things in tobacco or associated with the nicotine delivery device that are causing cancer. And I should mention the other negative impacts on our health in particular by way of disrupted endothelial blood vessel function. Now that leads us to this issue of vaping, because as many of you know, and probably are thinking as I've been delivering this information, people don't vape tobacco. The way that vaping pens are designed is that it includes some liquid, it involves heat, and it does not involve the burning off of tobacco. In fact, there's a constant updating of the engineering of these vape pens so that they can be very low heat. In some cases they use even non heating approaches to vaporize the nicotine and allow it to enter the bloodstream very quickly. I must say in a lot of ways, vaping resembles crack cocaine. The reason why vaping and crack cocaine are so similar is the speed of entry of nicotine into the bloodstream. This isn't an episode about cocaine, but I just want to very briefly touch on some of the delivery routes for cocaine because they parallel a lot of the delivery routes for nicotine. And we can learn a lot about drug pharmacokinetics and dopamine if we look at the parallels between cocaine and nicotine. I'll preface this by saying cocaine is a terrible drug. It is actually a schedule two drug in the United States, which means that it has a very, very limited yet still present medical application, mainly as an anesthetic in certain laboratory and hospital conditions. But aside from that, it's very clear that cocaine is one of the most debilitating drugs that humans can use because of the way that it impacts the dopamine system. And it basically creates a loop whereby the only thing that can really trigger dopamine release is cocaine. And as I've said before, the way that I define addiction is it's a progressive narrowing of the things that bring people pleasure. Cocaine certainly falls

into the category of addictive drugs, strongly addictive drugs. And in fact, it has the additionally pernicious feature that after using cocaine for some period of time, the amount of dopamine that's released becomes progressively lower and lower and lower so that people can never get back to a state in which dopamine release is ever as great as it was the first time they did cocaine or prior to doing cocaine. Now with a long period of no cocaine use whatsoever and protecting the dopamine system in a number of different ways, people can often, not always but often recover their dopamine system, if not completely then near completely. So by all means, if you have a problem with cocaine, quit, find a way to quit, get treatment, get over that one way or another. We have an episode with an expert guest, Dr. Anna Lembke, who's a physician and the chief of the Stanford School of Medicine dual diagnosis addiction clinic, a world expert in dopamine and addictive substances and addictions of all kinds. You can find that episode at hubermanlab.com. It's filled with information about how to get over different types of addictions, including cocaine addiction. Also check out her absolutely phenomenal and indeed important book "Dopamine Nation", which touches on some of this as well. And in the show note captions for the episode where Dr. Lembke was my guest, you can also find some additional resources related to that. So cocaine is terrible. That needs to be acknowledged. It should be avoided and you should find a way to quit it if you are currently using. With that said, the delivery mechanism for cocaine strongly parallels the delivery mechanisms for nicotine. That is people will snort cocaine, which is a lot like snuffing or dipping. That is when people snort cocaine, they're bringing cocaine into proximity or into contact, really with the mucosal lining of the nasal passages, which then allows the psychoactive substances to permeate into the bloodstream. Very seldom do people eat it, although that does happen from time to time, people will inject it, as so-called mainlining, which is a very rapid entry into the bloodstream because it's direct application to the bloodstream by way of injection. And then there's crack cocaine, which is essentially like a vaporizing of the cocaine from a so-called cocaine rock, that somewhat resembles vaping of nicotine. So while the vape pen involves a liquid that's sold, a cartridge that contains nicotine and often other flavors as well, flavorings I should say, both crack cocaine and vaping cause very rapid increases in the relative substances that are psychoactive, in the case of cocaine, that would be cocaine and the increase in dopamine in the brain and body I should mention. And in the case of vaping, there's a very rapid increase in blood concentrations of nicotine, much faster than occur with cigarette smoking or other modes of nicotine delivery. So that speed of onset turns

out to be a critical parameter because the speed of onset of nicotine is going to also determine the speed of release of dopamine in the nucleus accumbens and ventral tegmental area, that mesolimbic reward pathway. And with the mesolimbic reward pathway, it's not just about the peak, meaning the maximal amount of dopamine that's released, but it's the time course, how steep the curve is, how quickly that dopamine increases that's going to determine how reinforcing, how habit forming and indeed how addictive a particular substance is. One of the major important differences between vaping and cigarette smoking is that the onset of dopamine release from vaping is faster. And even a subtle increase in the rate at which dopamine increases in the mesolimbic reward pathway can make a given amount of nicotine much more habit forming and addictive. Now this probably explains the fact that many, many more people, in particular, young people age 25 and younger are vaping at phenomenal rates. People are starting to vape in just about everywhere. You see this in restaurants, you see it on the street, indeed you even see it in the classroom. This has actually become sort of sport of sorts. Certainly not something I encourage. In fact, when I learned about this from a new college student is telling me that many college students are actually bringing vape pens into the classroom. I think this is also happening in high schools and even junior high schools. This is a really concerning practice. And here I'm not trying to come across as the anti vaping crusader, but I must say given the negative effects on one's health in the long term, but also given these exceedingly powerful reward properties of nicotine entering the bloodstream quickly, and dopamine being released very quickly from the mesolimbic reward pathway, what we're seeing out there makes total sense. Young people's brains are essentially getting wired to the expectation that dopamine is going to be increased dramatically and quickly under their control, except it's under their control only in a very narrow set of circumstances. Recall the definition of addiction, a progressive narrowing of the things that bring you pleasure. We can change that statement to also say a progressive narrowing and specific kinetics, that is specific time course of the things that bring you pleasure. Now that's a bit of a nerdier statement than a progressive narrowing of the things that bring you pleasure. But what we are going to see in the next few years, I believe is an entire generation of young people for which a very large percentage of them are going to be seeking out a pattern or feeling because to the person taking it, they're not looking at their dopamine levels rising in their blood. They're experiencing this as an increase in focus, an increase in alertness, an increase in mood and wellbeing that is very rapid, very dramatic, and that simply cannot be

recreated by any other substance. And that's a very concerning scenario, concerning because that mesolimbic reward pathway is the only pathway, the only pathway by which you can achieve the rewarding properties of any kind of endeavor, not just vaping of course. It is the way in which people achieve satisfaction from reaching a relationship goal or an athletic goal or an educational goal, any kind of goal or sense of satisfaction. And so it comes as no surprise that vaping is strongly associated with increased levels of depression, especially when vaping use drops off. Why would that be? If people are getting so much more dopamine so much more quickly from vaping, shouldn't they be feeling better? That brings us back to the critical, and I should say, defining feature of the dopamine reward pathway for motivation and wellbeing, which is that initially a given substance will cause, let's say an eight out of 10, again, arbitrary units, but eight out of 10 increase in dopamine. But with repeated use, what ends up happening is that even at similar or higher levels of ingestion, so not just one inhalation a minute, but maybe two inhalations a minute or an inhalation every 30 seconds. Now it's level four out of 10 activation of dopamine and then three and then two. And eventually it drops below baseline. Now the whole system can be recovered by abstinence from nicotine consumption, but the dopamine system is applied to everything, all sense of wellbeing, all sense of motivation. So during the period in which one is abstaining from nicotine and vaping in particular, people do not feel good. They feel miserable. That's why it's called withdrawal. It's associated with a bunch of psychological and physiological symptoms that all lead back to trying to get to the same levels of dopamine release in the same patterns that were experienced when one initially started vaping. So I'm not trying to paint a dark picture here, but frankly, the picture is very dark. I'm very concerned about a practice of ingesting something that powerfully modulates the dopamine system with the sorts of kinetics that one sees from ingestion of crack cocaine in young people that has all these other negative health effects that in the short term is very powerfully rewarding, increased focus, wellbeing, et cetera, but that over a very brief period of time leads to a state in which the entire dopamine reward system is impaired and

01:25:06 Tool: Quitting Smoking & Clinical Hypnosis, Reveri

can become permanently impaired unless one intervenes in a very deliberate way. So people are directly controlling the rate of dopamine and the frequency of dopamine release by the duration and frequency of inhalations off the vape pen. And that's an

incredible thing because what it does is it sets up the mesolimbic reward pathway for an expectation that dopamine will be delivered on that schedule. So that's one of the things that makes vaping in particular so hard to quit. Vaping is actually harder to quit than cigarette smoking for most people. Now does that mean that cigarette smoking is fairly easy to quit for most people? No. 70% of people who smoke cigarettes report that they would like to quit if they thought they could. The success rate of quitting smoking when people try to go just cold turkey, just quit with no assistance whatsoever. They might tell their family and friends, hey, I'm quitting, that's it, is exceedingly low, it's 5%. So 5% of the people that say, that's it, I'm not smoking again. Despite cancer diagnosis, I'm not smoking again. Despite the fear of the negative health effects, I'm not going to ever smoke again. Despite the financial cost, the health cost. I could list off a huge number of things that it does that are negative, but you already know these or you've heard them, it makes your skin worse, as I mentioned it lowers libido, it disrupts hormones, it disrupts vascular function, brain function. It does all these terrible things. And yet most people who try and quit simply can't. And of the 5% that succeed in quitting, a full 65% of them relapse within a year. So that's a very depressing picture, but it's not to say that people cannot quit. And in fact, they can. There are a couple of methods that have been shown to help people quit. Some are behavioral and some are pharmacologic. I just want to touch on the behavioral ones first because it turns out that there's a quite powerful method for quitting nicotine ingestion by way of cigarette smoking, which also carries over to vaping. This is beautiful work that's been done by my colleague, in fact, close collaborator, although I was not involved in the research that I'm about to describe at Stanford. And his name is Dr. David Spiegel. He is our associate chair of psychiatry. He's been a guest on the Huberman Lab Podcast, and he is a world expert, if not the world expert in the clinical applications of hypnosis. Now when I say hypnosis, a lot of people think stage hypnosis, which is the hypnotist trying to get people to do certain things and say certain things, not necessarily against their will because they actually have to agree. But the hypnotist is dictating what the person thinks, says, and does. Clinical hypnosis is vastly different from that. Clinical hypnosis is where the person, the patient actually directs their own brain changes toward a specific emotional or behavioral goal. Work from Dr. David Spiegel's laboratory done in 1993, but that now has been repeated many, many times that has carried over into some more modern studies and I will provide links to those studies in the show note captions so that you can access them. Those studies have shown that using a specific form of hypnosis, people can

achieve complete and total cessation of cigarette smoking. And there's no reason to believe this doesn't also carry over to vaping through one single hypnosis session. And the success rates are incredibly high when one considers that normally it would be only a 5% success rate. The success rate with this particular hypnosis developed at Stanford School of Medicine by Dr. David Spiegel is 23% of people who do this hypnosis one time succeed in quitting smoking. Now in the old days, which actually wasn't that long ago, before the advent of smartphones and before the internet took off to the extent that it has now, this was done by having someone come into the clinic and Dr. Spiegel himself or one of his colleagues would take somebody through the hypnosis. Nowadays, you can access this hypnosis. There's a wonderful app that was developed by Dr. David Spiegel and others. It's called Reveri, R-E-V-E-R-I. I've talked about this app a few times on the podcast before, because there are hypnosis scripts within the app for enhancing sleep, for improving ability of fall asleep if you wake up in the middle of the night, for focus, and a number of other behavioral and emotional changes. There's also a function in the Reveri app for smoking cessation, which exactly parallels the sort of in laboratory and in clinic approaches that Dr. Spiegel would use were you to show up at his clinic or his laboratory. And since that's not possible for the large number of people out there, if you or somebody else is trying to quit smoking or vaping or dipping or snuffing for that matter, I strongly encourage you to check out the Reveri app. You can find it easily by going to reveri.com. It's available in various formats. Some of it is available free, some of it is behind a paywall, but given the tremendously negative impact of smoking, vaping, dipping, and snuffing, the hypnosis for smoking cessation that Reveri has seems at least to me as a very powerful and worthwhile resource. So please check that out

01:30:16 Bupropion (Wellbutrin) & Quitting Smoking

if you're somebody who's trying to quit ingesting nicotine by any of the four methods that I just described. Now of course, there are other methods that people have used to successfully quit smoking or vaping or other forms of nicotine delivery. And there's actually an excellent review on this topic. So before diving into a few of the specifics about some of the pharmacology of using nicotine itself to quit smoking or nicotine itself to quit vaping, or the use of various things, even SSRIs, antidepressants to quit smoking or vaping. I just want to point you to a review article that if you'd like to get a complete survey of all the options that are available, there's an excellent review on this. It was

published just a couple of years ago in 2020. And the title of the article is "Pharmacologic Approach to Smoking Cessation: An Updated Review for Daily Clinical Practice". And even though this is mainly focused on smoking cessation, it carries over quite nicely to vaping. And it details a number of statistics, the fact that every year, 700,000 or more people die because of smoking related diseases. So there again you have the negative health effects that younger people are smoking, that women are smoking more nowadays. And that even though you see less smoking, typically in the US and Canada, and even in Northern Europe, some places, there are still many many people are smoking who would like to quit, but that 75% of people, at least according to this review earlier, I said 70%, but estimates are as high as 75% of people who try to quit smoking relapse within the first week. The first week, they just go right back to it. That's how powerfully reinforcing the nicotine is. Remember, it's the nicotine in the cigarette that's powerfully reinforcing, but it's also the oral habit, the motor habit. There is this thing about density of sensory receptors in the lips. People like bringing things to their lips, food, cigarettes, other lips in some cases, et cetera, there is a reinforcement pathway related to that for sort of obvious adaptive reasons. And as a consequence, there is a reinforcement, both from the behavior and from the dopamine released from the nicotine itself. And as I mentioned earlier, from the positive reinforcement that comes from increased focus. So the money that you make through work or your attentional ability or the fact that you're alert and people feel you present, all of that funnels back into positive reinforcement, behavioral reinforcement, and then what we would call addiction. So this review covers all of that and then steps beautifully through nicotine replacement therapy and various compounds, several of which I'm going to talk about now, which have been shown to increase that number that we talked about earlier of only 5% of people who try to quit with no other support pharmacologic or hypnosis or otherwise just say that's it, I'm not going to smoke again, or I'm not going to vape again, only 5% of people succeed in doing that. And even among those, many end up relapsing later, there are a couple pharmacologic approaches. One of the main ones that's received a lot of attention in recent years is Bupropion, sometimes referred to by its commercial name Wellbutrin. Now Bupropion is a compound that increases the release of dopamine and to a lesser extent epinephrine and some other neurochemicals as well. It's used for the treatment of depression and for smoking cessation. Now I want to point out again, I'm not a psychiatrist, so I'm not telling you to take Bupropion, AKA Wellbutrin, but I'm going to give you a little bit of the contour of what's typically done in terms of

Bupropion administration to help people get relief from some of the withdrawal symptoms of trying to quit smoking or vaping or other forms of nicotine ingestion. Typically Bupropion is taken in 300 milligram per day doses divided into two dosages of 150 milligrams each, or sometimes there's a slow release formula. The dosages will vary from person to person. I want to really emphasize that there is an increased seizure risk with Bupropion. It only occurs in a small fraction of the population, but nonetheless is a real concern for those members of the population. So for those of you with seizure risk, whether you know it or not, that's going to be a valid concern in terms of potential side effects. The other thing about Bupropion is that it has to be used with caution in patients that have liver disease or renal disease that can impact the amount that anyone can take meaning sometimes people have to take a much lower dose if they have renal disease or liver disease. And sometimes they can't take it at all. Sometimes if people are taking benzodiazepines for whatever reason or other sedatives, there are contraindications there, so Bupropion isn't a kind of one size fits all or magic bullet for quitting smoking, nonetheless, for people that can take it safely, and again, this is a prescription drug, a board certified psychiatrist or other physician is going to have to prescribe it for you if it's appropriate for you. And it moves that number of 5% success rate to about what one sees with the clinical hypnosis to about 20% of people will successfully overcome their nicotine, or I should say their smoking or vaping addiction. Now it's important to ask why this would work, right? It's not as if Bupropion is increasing nicotine per se. What it's doing is it's tapping on that mesolimbic reward pathway, increasing dopamine, or at least allowing dopamine levels to stay substantially elevated enough that people don't experience some of the drop in dopamine that leads to the withdrawal symptoms, the lessening of mood, et cetera. And it's no coincidence that Bupropion is also an antidepressant. It's a common antidepressant for people that experience negative side effects with the so-called SSRIs, the selective serotonin reuptake inhibitors that prevent them from taking those things like lessen libido or appetite, or in some cases increased appetite or any number of other side effects that some people, not all, but some people experience with SSRIs. They'll be prescribed Wellbutrin, Bupropion is the generic name. So Wellbutrin being the commercial name again, Bupropion is what they'll be prescribed instead with the caveats of seizure risk, renal disease, liver disease, et cetera. The outcomes with Wellbutrin for smoking cessation are pretty good if you think about an increase from 5% to 20%, that's pretty dramatic. And yet I also want to refer back to the incredible success of the clinical hypnosis approach. Again, you can find that at

reveri.com, the clinical hypnosis approach has a success rate of 23%.

01:36:24 Tool: A Nicotine Replacement Schedule to Quit Smoking, Nicotine Patch/Gum

So it's very closely aligned with, if not exceeding the success rate with Bupropion. Of course there are other pharmacologic approaches to quitting smoking or vaping. All of them generally circle back to increasing dopamine and/or norepinephrine in order to offset some of the withdrawal symptoms of smoking cessation or vaping cessation. A very common approach for people to try and quit smoking or vaping is to use nicotine itself to try and prevent people from seeking nicotine through a cigarette or a vape pen. What I mean by that is people using a nicotine patch or nicotine gum or other nicotine delivery device that is not cigarettes and not vaping in order to maintain levels of nicotine in their bloodstream, which of course means maintain levels of nicotine in their brain and body to the same extent that they would if they were smoking or vaping, maybe even gradually taking down the total amount of nicotine in their brain and body by reducing the number or size of nicotine gum pieces that they ingest each day, or keeping the patch on for a shorter amount of time or getting a lower dose patch that releases less nicotine total or over time. All of those approaches have been shown to be reasonably successful, I'll get to the numbers in a few minutes, but reasonably successful in allowing people to quit smoking or vaping. Again, most of the data is on cigarette smoking because vaping is a relatively new phenomenon. Although quite troublingly, it's a very rapidly increasing behavior, especially in the young population. So that's why I'm kind of lumping these two things together because I think very soon we are going to need an all out campaign for how to counter vaping addiction. So what do we know about smoking cessation using nicotine itself? Is the patch best? Is nicotine gum best? Turns out that a combination of approaches is best, so somewhat surprising, but it was very clear from the literature that I was able to find that using nicotine patches for some period of time and then switching to a gum and then perhaps switching to a nasal spray, that's going to be the most effective. Then the question is how long to continue each of those and whether or not to overlap them. It seems as if doing one for about a week and then switching to another for about a week and then switching to another is one reasonable and reasonable approach that many people have used successfully. Why would that be? It all has to do with the different rates of absorption of nicotine into the bloodstream, and then the downstream consequences of that on the dopamine, acetylcholine, epinephrine,

and other systems of the brain and body. And while there hasn't been an extremely detailed study of the exact kinetics of how the nasal sprays versus the transdermal patches versus the gums, et cetera, work, there's a logical structure to it that will immediately make sense to you. First of all, the transdermal patches provide a fairly steady state dopamine release across the day. And oftentimes people are wearing them at night as well. This is relevant because if people are ingesting nicotine by way of smoking and vaping, hopefully they're not waking up in the middle of the night just to smoke or vape. Believe or not, some people do that, but of course, while people are asleep, they are not smoking or vaping. They always tell you don't fall asleep with a cigarette in your mouth, you'll burn the whole house down, but exceedingly rare to have people are smoking in their sleep. So people wake up in the morning and because the half life of nicotine from smoking or vaping is very short, anywhere from one to two hours, they're essentially in a state of withdrawal at the point where they wake up in the morning. How can I say that? Remember, withdrawal sets in about four hours after the last ingestion of nicotine by cigarette or by inhalation from the vape pen. So people are waking up in nicotine withdrawal and then immediately going into the behavior of ingesting nicotine, or very soon after waking for most people. So nicotine patch is going to be very effective for a week or so, again, talk to your physician about the best approach for this, but then switching to a nasal spray or switching to nicotine gum for about a week, which is going to change the kinetics of that nicotine absorption into the bloodstream and change the release of dopamine and other neurochemicals within the brain. That's going to keep the system intentionally off balance so that it never comes to expect one single pattern or amplitude of dopamine release. And that is a very powerful way for a, let's just call it a quitting method to work. Because as I've always said, the most powerful schedule of dopamine is going to be this random intermittent reward. This is what's used in the casinos in order to take your money. And generally they do, on average, they take your money more than you take theirs, and they take more of it. Not just more often because they use this random intermittent schedule. The random intermittent schedule is one in which you don't really know when the peaks in dopamine are going to arrive. And so there isn't this expectation and craving. And then all of a sudden when dopamine is released, it's extremely high. That's how they get you to continue playing, even though basically you're losing money and your dopamine is dropping, they elevate it every once in a while. Nicotine replacement can be used in a similar way, but in a benevolent way, in order to help you get over smoking or vaping by

keeping the total amounts of dopamine variable around the clock and by changing the amount of dopamine that's released, it seems to help people behaviorally and psychologically

01:41:52 Tool: Biological Homeostasis & Nicotine Withdrawal, The "First Week" Strategy

because they don't come to expect having a particular amount of dopamine in their brain and blood at any given time. And this is an important point because it brings us to this notion of homeostasis. Homeostasis is this tendency for biological systems to try and reach equilibrium. What goes up, goes down, et cetera. And to some extent to the same degree. So I'll talk about this right now in the context of nicotine use withdrawal, and then the period in which people no longer crave nicotine. So you can imagine that if we were to measure your heart rate, your blood pressure, and your overall levels of alertness and wellbeing and mood, let's just give that some value. Let's say it runs from zero to 10, again, arbitrary units. Let's just take all those physiological measures and the subjected measure of your mood. And let's measure it four times an hour across the day, across the waking hours. What we would find is a line that would kind of squiggle a bit, maybe a nice text comes in that you really like, maybe you get not so good news and your kind of autonomic arousal is all over the place, but on average is kind of a squiggly line where it increases in the morning because that's typically when body temperature and autonomic arousal increase. And then towards the afternoon, it's going to come sloping down. And then right before sleep, there'll be an increase again, if you've ever felt that you kind of run around a lot before sleep and then it goes down, that's kind of the typical contour of autonomic arousal, mood, et cetera, across the day, removing of course life events and things like psychiatric illness and depression and et cetera. That's the typical arc of that. Now let's superimpose on whatever that contour is for you, nicotine. So you get a little bolus as we say, a little bit of nicotine from smoking a cigarette or from taking an inhalation on a vape pen, what ends up happening is there's an increase in blood pressure, increase in heart rate, increase in mood, increase in alertness, all the things we talked about earlier. Over time, the body starts to adjust so that the baseline upon which that nicotine induced increase in arousal would occur is actually reduced, right? Why would that be? Well, the body and the brain, your physiology seeks homeostasis. So if there's a big increase in all those things like blood pressure and mood, et cetera, typically your baseline will drop a little bit to compensate for that over time, after a couple

days or even weeks of ingesting nicotine. So let's say you wake up, you're typically take an inhalation off your vape, or you have a cigarette around nine or 10:00 AM and you do that daily. You get used to a certain level of mood and alertness and wellbeing for that time of day. And then if you smoke again in the afternoon, let's say you also get accustomed to a certain level of mood and alertness and wellbeing for that time of day. Again, it'll vary depending on life events, but your system sort of gets used to it and your baseline will drop to compensate for those peaks so that the peaks aren't quite as high as they were when you first started using nicotine. Now you decide to quit. So now what we're talking about is transitioning from the consumption to what we're going to call the withdrawal phase. So now what happens is you say, that's it, I'm going cold turkey. I know there's only a 5% success rate, but I'm going to just go cold turkey or somebody will say, no, I'm going to use the Reveri app. Or somebody says, no, I'm going to use Bupropion or another method or nicotine patch or something of that sort. Setting aside the nicotine patch or the nicotine delivery device and only focusing on approaches for getting through withdrawal that have no direct effects on nicotine. So not using the nicotine patch, but say the hypnosis or Bupropion, which can increase dopamine, but it doesn't increase nicotine directly. What happens? The day that you quit, that homeostatic mechanism in your brain and body that sets your level of mood and arousal, et cetera, does not know and hasn't adjusted to the fact that you're not bringing in nicotine. You're not having that cigarette. You're not having that inhalation on the vape pen. So what ends up happening is that baseline, which has been adjusted down to offset the increases in mood and alertness, et cetera, when you smoke or vape is lower than it normally would be. So that 9:00 AM cigarette time or vape inhalation time no longer feels above baseline, it actually feels below baseline because what you're seeing is the lower amplitude of arousal that was there to offset the increase you were getting from vaping or smoking. And then in the afternoon, if normally you have a kind of phase of your afternoon you really enjoy, you go outside, you have a vape or a cigarette, you normally are feeling relaxed or you go out at night and you like to vape and you say, nope, I'm not going to do that anymore, you're going to feel much, much worse than you would've had you never started smoking or vaping. Now that's not much help to anyone who's already started smoking or vaping. But I say this because it's very important to understand that the reason why relapse rates are so high within the first week, 75% of people relapse within one week and overall failure rates are 95% is because people don't expect to feel even worse than they did prior to ever smoking or vaping. So that

first week is absolutely critical. And the beauty of understanding this is that if you can get through that first week, either by sheer grit or by finding other methods to increase dopamine, healthy methods I would hope, and certainly cold showers, ice baths have been shown to do that by the way. And this was described in Dr. Anna Lembke's book, "Dopamine Nation", cold showers can increase dopamine, exercise, positive social interactions. It's very likely that people will need to use other healthy methods to offset that reduction in dopamine if ever they stand to get through that first week. And again, if you can get through that first week, chances are quite a bit higher that you'll be able to maintain the cessation of smoking or vaping. And of course, hypnosis, things like Bupropion, can also assist in that, Bupropion by way of increasing dopamine pharmacologically, hypnosis through changes in neural circuitry that aren't completely understood, but seem to involve a remapping of some of the so-called default networks and some of the networks that are involved in kind of understanding of your own internal state. This stuff gets a little bit complicated and we're going to return to this in a upcoming episode of the Huberman Lab Podcast, but there are indeed legitimate changes in neural circuitry caused by clinical hypnosis that can at least partially explain why it is so effective in helping treat or allow people to stop smoking and vaping. So for those of you out there that, either here or are saying yourselves, I just can't seem to quit smoking or vaping or dipping or snuffing, hopefully an understanding of how that homeostasis process works and the time course of nicotine, depending on the delivery device, hopefully understanding that will allow you to develop a protocol. Maybe it involves hypnosis. Maybe it involves just understanding that the typical times in which you ingested nicotine through any of the different approaches of bringing it into your system are going to be particularly hard. But I don't just mean particularly hard. I mean, particularly hard, and you're going to need to do something specific to offset that decrease in overall autonomic arousal and dopamine, et cetera. Hopefully an understanding of that will allow you to get through that first week. And if you can make it past that first week, you stand a very good chance of never going back. However, I did consult with Dr. David Spiegel in anticipation of this episode, regardless of the method that you used to quit smoking or vaping, snuffing, or dipping, there's good evidence that a routine maybe once a month or even once a week hypnosis type approach to replenish or even enhance the neural circuits that are allowing you to stay away from nicotine is going to be a very good idea. And given that it's a purely behavioral intervention, I can see no reason as to why people wouldn't want to do that, go in and

reinforce, you know, tighten the bolts on that circuitry that are allowing you to not feel the impulse to smoke, not feel the impulse to vape. And just a very brief mention, there is a vast literature on the fact that when people have quit smoking or vaping or other form of consuming nicotine, that when they consume alcohol, there's a much higher probability of relapse. There are interactions between alcohol and nicotine that we'll cover in future episodes. But for those of you that want to quit, I want to assure you, despite the fact that 95% of people fail, with the appropriate tools, and I like to think within an additional understanding of the underlying biology and psychology and what you can expect and when to really dig your heels and when to reinforce your system with more dopamine through any of the number of the different protocols and tools that we've offered here and that you can find elsewhere in other episodes of the Huberman Lab Podcast, I have a high degree of confidence that you can quit smoking or vaping, dipping or snuffing. So today, typical of frankly all episodes of the Huberman Lab Podcast, we've covered a lot about the biology of a particular system. We talked about the biology of nicotine in particular, we talked about vaping and smoking, dipping and snuffing and the negative health consequences associated with those. I want to reemphasize that nicotine is not what causes cancer. It is the delivery device that causes cancer and the other negative health effects. That is not to say that people should be ingesting nicotine through any different methods simply to get a cognitive boost. There are certain circumstances where that might be appropriate for the occasional work about, certainly not for physical exercise, given what we talked about earlier, but of course there are more and more approaches to increasing, not just nicotine, but acetylcholine generally in order to achieve cognitive enhancement or physical enhancement, or I should say physical performance enhancement. Some of those we talked about earlier, such as Alpha GPC. In any event, nicotine, it should now be clear, is an immensely powerful substance. One of the most commonly ingested substances on the face of the earth and has been for a very long time. And now that you understand the underlying biology and the

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