Dr. Charles Zuker: The Biology of Taste Perception & Sugar Craving | Huberman Lab Podcast #81

My guest this episode is Dr. Charles Zuker, PhD, Professor of Biochemistry, Molecular Biophysics and Neuroscience at Columbia University and an Investigator with the Howard Hughes Medical Institute. Dr. Zuker is the world's leading expert in the biology of taste, thirst and craving. His laboratory explores the mechanisms of taste perception, focusing on how our conscious and unconscious processing of specific foods and nutrients guide our actions and behaviors. We discuss the neural circuits of taste, the "gut-brain axis," the basis of food cravings and the key difference between wanting (craving) and liking (perceiving) sugar. We also explore how taste perception relates to specific food satiety, thirst, to our emotions, and expectation. We also consider how sugar containing and highly-processed foods can hijack the natural balance of the taste and digestive systems. Dr. Zuker provides a true masterclass in the biology of taste and perception that ought to be of interest to anyone curious about how the brain works, our motivated behaviors and the neural, chemical perceptual aspects of the mind.

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[light rock music] - 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 my guest is Dr. Charles Zuker. Dr. Zuker is a professor of biochemistry and molecular biophysics and of neuroscience at Columbia University School of Medicine. Dr. Zuker is one of the world's leading experts in perception. That is how the nervous system converts physical stimuli in the world into events within the nervous system that we come to understand as our sense of smell, our sense of taste, our sense of vision, our sense of touch, and our sense of hearing. Dr. Zuker's lab is responsible for a tremendous amount of pioneering and groundbreaking work in the area of perception, for a long time his laboratory worked on vision, defining the very receptors that allow for the conversion of light into signals that the rest of the eye and the brain can understand. In recent years, his laboratory is focused mainly on the perception of taste. And indeed his laboratory is responsible for discovering many of the taste receptors leading to our perception of things like sweetness, sourness, bitterness, saltiness, and umami. That is savoriness in food. Dr. Zuker's laboratory is also responsible for doing groundbreaking work on the sense of thirst. That is how the nervous system determines whether or not we should ingest more fluid or reject fluids that are offered to us. A key feature of the work from Dr. Zuker's laboratory is that it bridges the brain and body. As you'll soon learn from today's discussion. His laboratory has discovered a unique set of sugar sensing neurons that exist not just within the brain, but a separate set of neurons. That sense sweetness and sugar within the body. And that much of the communication between the brain and body leading to our seeking of sugar is below our conscious detection. Dr. Zuker has received a large number of prestigious awards and appointments as a consequence of his discoveries in neuroscience. He is a member of the National Academy of Sciences, the National Academy of Medicine, and the American Association for the Advancement of Science. He is also an investigator with the Howard Hughes Medical Institute. For those of you that are not familiar with the so-called HHMI, the Howard Hughes Medical Institute, Howard Hughes Medical Institute investigators are selected on an extremely competitive basis. And indeed they have to come back every five years and prove themselves worthy of being reappointed as Howard Hughes investigators, Dr. Zuker has been a Howard Hughes investigator since 1989. What all that means for you as a viewer and or listener of today's podcast, is that you are about to learn about the nervous system and its ability to create perceptions in particular, the perception of taste and sugar sensing from the world's expert on perception and taste. I'm certain that by the end of today's podcast, you're not just going to come away with a deeper understanding of our perceptions and our perception of taste in particular. But indeed you will come away with an understanding of how we create internal representations

00:03:05 Momentous Supplements

of the entire world around us and in doing so, how we come to understand our life experience. I'm pleased to announce that the Huberman Lab Podcast is now partnered with Momentous Supplements. We often talk about supplements on the Huberman Lab Podcast and while supplements aren't necessary for everybody, many people derive tremendous benefit from them. For things like enhancing the quality and speed with which you get into sleep or for enhancing focus or for hormone support. The reason we partnered with Momentous Supplements is several fold. First of all, their supplements are of the absolute highest quality. Second of all, they ship internationally, which is important because many of our podcast listeners reside outside the US. Third, many of the supplements that Momentous makes and most all of the supplements that we partnered with them directly on are single ingredient formulations. This is important for a number of reasons. First of all, if you're going to create a supplement protocol that's customized for your needs, you want to be able to figure out which supplement ingredients are most essential and only use those and supplements that combine lots of ingredients simply won't allow you to do that. So in trying to put together a supplement protocol for yourself, that's the most biologically effective and cost effective single ingredient formulations are going to be the most useful. If you'd like to see the supplements that we partner with Momentous on, you can go to livemomentous.com/huberman, and there you'll see many of the supplements that we've talked repeatedly about on the Huberman Lab Podcast episodes. I should mention that the catalog of supplements that are available at livemomentous.com/Huberman is constantly being expanded. So you can check back there, livemomentous.com/huberman to see what's currently available.

00:04:35 Thesis, ROKA, Helix Sleep

And from time to time, you'll notice new supplements being added to the inventory. 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 in 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 for frequent listeners of this podcast, you may remember that I'm not a big fan of the word nootropics because the word nootropics means smart drugs or smart compound. And the reason I don't like that phrase is that the brain has many different circuits that it uses in order to perform things like focus or task switching or creativity. So the idea that there's a single thing that we would call a smart drug is simply not in concert with the biology. Well, Thesis understands this, and as a consequence has developed custom nootropic formulations that are tailored to your unique needs. So for instance, Thesis will allow you to try different blends over the course of a month and determine which blends of specific ingredients work best for you to focus or for you to gain motivation and energy for workouts or for cognitive work of some sort. I've been using Thesis custom nootropics for well over six months now. And they completely transform the way that I do cognitive work and indeed the way that I do physical fitness, if you want to try your own personalized nootropic starter kit, you can go online to takethesis.com/huberman. There you'll just do a brief three minute quiz and Thesis will send you four different formulas to try in your first month. 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 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 and with the biology of the visual system in mind, I spent my lifetime working on the visual system, and I can tell you that your visual system has to contend with a number of very important challenges in order to be able to see the world around you clearly, things like adjusting for background illumination so that when you go from a sunny area to a shady area, you can see what's in front of you still with crystal clarity. ROKA takes all of that into account when designing their eyeglasses and sunglasses, their eyeglasses and sunglasses also have some unique qualities for instance, because they were initially designed for performance with things like running and cycling. If you get sweaty, they won't fall off your face. Also they're extremely lightweight. In fact, most of the time, I don't even remember that I'm wearing them. I wear ROKA eyeglasses at night. So I wear readers and I wear sunglasses often during the day, if it's very bright or if I'm driving, 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 your first order. Today's episode is also brought to us by Helix Sleep. Helix Sleep makes mattresses and pillows that are uniquely tailored to your sleep needs. I've talked repeatedly about the fact that sleep is the foundation of mental health, physical health, and performance. So getting adequate deep sleep is absolutely essential. Now, one of the key things to getting a great night's sleep is to make sure that the surface that you're sleeping on is the right one for you. Helix understands this, and they've created a sleep quiz. That is you go to their website and you fill out a brief quiz that asks questions like you sleep on your side, your back, your stomach. Do you tend to run hotter cold during the night? Maybe you don't know the answers. In which case you simply say you don't know, by taking that quiz, they will match you to a mattress that is ideal for your sleep needs. I took that quiz and I matched to the so-called Dusk, D-U-S-K mattress. And I've been sleeping on that mattress for some time now, and it's the best sleep that I've ever had. So if you're interested in upgrading your mattress to one, that's uniquely tailored to your sleep needs, you can go to helixsleep.com/huberman, take their two minute sleep quiz, and they'll match you to a customized mattress. And you'll get up to $200 off any mattress order and two free pillows. They have a 10 year warranty and you get to try out that mattress for a hundred nights, risk free. They'll even pick it up for you if you don't love it, but I do believe that you will love it because you'll be sleeping far better than you have before. Again, if you're interested, you can go to helixsleep.com/huberman to get up to $200 off

00:08:35 Sensory Detection vs. Sensory Perception

and two free pillows. And now for my discussion with Dr. Charles Zuker, Charles, thank you so much for joining me today. - My pleasure. - I want to ask you about many things related to taste and gustatory perception, but maybe to start off and because you've worked on a number of different topics in neuroscience, not just taste, how do you think about perception, or rather, I should say, how should the world and people think about perception, how it's different from sensation and what leads to our experience of life in terms of vision, hearing, taste, et cetera? - So the brain is an extra ordinary organ that weights maybe 2% of your body mass. Yet it consumes anywhere between 25 to 30% of all of your energy and oxygen. And it gets transformed into a mind and this mind changes the human condition. It make, it changes, it transforms fear into courage, conformity into creativity, sadness into happiness. How the hell does that happen? Now, the challenge that the brain faces is that the world is made of real things. You know, this here is a glass, and this is a cord and this is a microphone, but the brain is only made of neurons that only understand electrical signals. So how do you transform that reality into nothing that electrical signals that now need to represent the world? And that process is what we can operationally define as perception, in the senses, let's say olfactory, other taste, vision we can very straightforwardly separate detection from perception, detection is what happens when you take a sugar molecule, you put it in your tongue and then a set of specific cells now sense that sugar molecule that's detection, you haven't perceived anything yet. That is just your cells in your tongue, interacting with this chemical. But now that cell gets activated and sends a signal to the brain and now detection gets transformed into perception. And he's trying to understand how that happens. That's been the maniacal drive, of my entire career in neuroscience. How does the brain ultimately transform detection into perception so that it can guide actions and behaviors?

00:11:48 Individual Variations within Perception, Color

Does that make sense? - Absolutely. And is a very clear and beautiful description, a sort of high level question related to that. And then I think we can get into some of the intermediate steps. I think many people would like to know whether or not my perception of the color of your shirt is the same as your perception of the color of your shirt. - Excellent question. Am I okay to interrupt you as I'm guessing what you're going? - Interruption is welcome on this podcast. The audience will always penalize me for interrupting you, and will never penalize you for interrupting me. - Good, I like the one way penalize. Now, given what I told you before that the brain is trying to represent the world based in nothing but the transformation of these signals into electrical languages that now neurons had to encode and decode. It follows that your brain is different than my brain. And therefore it follows that the way that you are perceiving the world must be different than mine, even when receiving the same sensory cues. And I'll tell you about an experiment is a simple experiment yet brilliant. That demonstrates why we perceive the world, how we perceive the world different. So in the world of vision, as you know, well now we have three classes of photo receptor neurons that sense three basic colors, red, blue, and green. Blue, green, and red if we go from short to long wavelength and these three are sufficient to accommodate the full visible spectra, I'm going to take three light projectors, and I'm going to project with one into a wide screen, a red light, and the other one green light, I'm going to overlap the two beams. And on the screen, there's be yellow. This is the superposition when you have two beams of red and green, and then I'm going to take a third projector and I'm going to put a filter that projects right next to that mixed beam, a spectral pure yellow. And I'm going to ask you to come to the red and green projectors and play with intensity knobs so that you can match that yellow that you're projecting to the spectrally pure next to it. Is this making sense? - Perfect sense. - And I'm going to write down the numbers in those two volume intensity knobs and then I'm going to ask the next person to do the same. And then I'm going to ask every person around this area of Battery Park in New York to do the same, and guess what, we're going to end up with thousands of different number combinations. - Amazing. - So for all of us, is yellow enough that we can use a common language, but for every one of us, that yellow is going to be ever so slightly differently. And so I think that simple psychological experiment beautifully illustrates how we truly perceive the world differently. - I love that example. And yet, in that example, we know the basic elements from which color is created. If we migrate into a slightly different sense, let me pick a hard one, like- - Sound. - Sound, olfaction. - Very hard then to do an experiment that will allow us to get that degree of granularity and beautiful causality, where we can show that A produces and leads to B. If I give you the smell of a rose, you can describe it to me. If I smell the same rose, I can describe it also, but I have no way whether the two of us are experiencing the same, but it's close enough that we can both pretty much say that it has the following enough features

00:16:20 Perceptions & Behaviors

or other determinants, but no question that your experience is different than mine. - The fact that it's good enough for us to both survive that your perception of yellow and my perception of yellow at least up until now is good enough for us both to survive. - You got it. - Raises a thought about a statement made by a colleague of ours, Marcus Meister at Caltech. It's never been on this podcast, but in a review that I read by Marcus, at one point, he said that the basic function of perception is to divide our behavioral responses into the outcomes downstream of three basic emotional responses. Yum. I like it. Yuck. I hate it. Or meh, whatever. What do you think about, I'm not looking to establish a debate between you and Marcus, without Marcus here. - I understand that. - But what I like about that is that it seems like we know the brain is a very economical organ in some sense, despite its high metabolic demands and this variation in perception from one individual to the next, at once, seems like a problem because we're all literally seeing different things. And yet we function, we function well enough for most of us to avoid death and cliffs and eating poisons and so forth and to enjoy some aspects of life one hopes. So is there a general statement that we can about the brain, not just as a organ to generate perception, not just as an organ to keep us alive, but also an organ that is trying to batch our behaviors into general categories of outcome? - I think so, but, and again, I think the world of Marcus too, and I think he's right that broadly speaking, you could categorize a lot of behaviors falling into those two categories and that's 100%

likely to be the case for animals in the wild where the choices are not necessarily binary, but they're very unique and distinct. Do I want to eat this? Do I want to kill that? Do I want to go there? Or do I want to go here? We humans deviated from that world long ago. And learned to experience life where we do things that we should not be doing. - Some of us more than others. - Exactly. You know, in my own world of taste, the likelihood that an animal in the wild will enjoy eating something bitter it's inconceivable, yet we love tonic water. We enjoy, we like living on the edge. We love enjoying experiences that makes us human. And that goes beyond that simple set of categories, which is yummy, yukky, ah, who cares. And so I think it's not a bad palette, but I think it's overly reductionist for certainly what we humans do. - I agree. And since we're here in New York, I can say that the many options, the extensive variety of food,

00:20:19 The 5 Taste Modalities

flora and fauna in New York explains a lot of the more nuanced behaviors that we observe. Let's talk about taste because although you've done extensive work in the field of vision, and it's a topic that I love you could spend all day on taste is fascinating. First of all, I'd like to know why you migrated from studying vision to studying taste. And perhaps in that description, you could highlight to us why we should think about and how we should think about this sense of taste. - My goal has been to understand, as I highlighted before how the brain does its magic, you know what part you might wonder, ideally, I like to help contribute to understand all of it. You know how do you encode and decode emotions? How do you encode and decode memories and actions? How do you make decisions? How do you transform detection into perception? And the list goes on and on. But one of the key things in science, as you know, is ensuring that you always ask the right question so that you have a possibility of answering it. Because if the question cannot be tractable or reduced to an experimental path that helps you resolve it, then we end up doing some really fun science, but not necessarily answering the important problem that we want to study. Make sense? - From a first person perspective, yes. The hardest question, the most important question is what are you going to try and answer. - You got it. And so for example I will have to understand the neural basis of empathy. - [Andrew] There's a big market for that. - 100%, but I wouldn't even know. I mean, at the molecular level, that's what we do. How do the circuits in your brain create that sense? I have no clue how to do it. I can come up with ways to think about it, but I like to understand what in your brain makes someone a great philanthropist. What is the neural basis of love? I wouldn't even know where to begin. So if I want to begin to study these questions about brain function, that can cover so many aspects of the brain, I need to choose a problem that affords me that window. But in a way that I can ask questions that get me answers and among the senses that have the capacity of transforming detection into perception of being stored as memories or creating emotions, of giving you different actions and perceptions as a function of the internal state. You know, when you're hungry, things taste very differently that when you're sated, how, why? When you taste something, you now remember this amazing meal you had with your first date, how does that happen? So if I want to begin to explore all of these things that the brain does, I felt I have to choose a sensory system that affords some degree of simplicity in the way that the input output relationships are put together. And in a way that still can be used to ask every one of these problems that the brain has to ultimately compute, encode and decode. And what's remarkable about the taste system at the time that I began working on this is that nothing was known about the molecular basis of taste. You know, we knew that we could taste what has been usually defined as the five basic taste qualities, sweet, sour, bitter, salty, and umami, umami is a Japanese word that means yummy, delicious. And that's nearly every animal species, the taste of amino acids. And in humans, it's mostly associated with the taste of MSG, monosodium glutamate, one amino acid in particular. - What are just by way of example, some foods that are rich in the umami evoking stimulation? - Seaweed, tomatoes, cheese, eh, and it's a great, great flavor enhancer. It enriches our sensory experience. And so the beautiful thing of the system is that the lines of input are limited to five. You know, sweet, sour, bitter, salt and umami, and each of them has a predetermined meaning, you are born liking sugar and disliking bitter. You have no choice. These are hard wire systems, but of course you can learn to dislike sugar and to like bitters, but in the while, let's take humans out of the question, these are a hundred percent predetermined. You are born with that specific valance value for each taste of sweet, umami and low salt are attractive taste qualities. They evoke appetitive responses, I want to consume them.

00:26:18 Aversive Taste, Bitter Taste

And bitter and sour are innately, predetermined to be aversive. - Could I interrupt you just briefly and ask a question about that exact point for something to be appetitive to and some other taste to be aversive and for those to be hardwired, can we assume that the sensation of very bitter or of activation of bitter receptors in the mouth activates a neural circuit that causes closing of the mouth, retraction of the tongue and retraction of the body and that the taste of something sweet might actually induce more licking? - 100%, you got it, the activation of the receptors in the tongue that recognize sweet versus the ones that recognize bitter activate an entire behavioral program. And that program that we can refer as appetitiveness or aversion it's composed of many different subroutines, in the case of bitter is very easy to actually look at, see them happening in animals. Because the first thing you do is you stop licking. Then you put unhappy face, then you squint your eyes and then you start gagging. And that entire thing happens by the activation of a bitter molecule in a bitter sensing cell in your tongue. - It's incredible. - It's again, the magic of the brain, how it it's able to encode and decode these extraordinary

00:28:00 Survival-Based & Evolutionary Reasons for Taste Modalities, Taste vs. Flavor

actions and behaviors in response of nothing but a simple, very unique sensory stimuli. Now, let me say that this pallet of five basic tastes accommodates all the dietary needs of the organism. Sweet to ensure that we get the right amount of energy, umami, to ensure that we get proteins and that essential nutrient, salt, the three appetitive ones to ensure that we maintain our electrolyte balance, bitter to prevent the ingestion of toxic nauseous chemicals, nearly all bitter tasting things out in the wild are bad for you, and sour, most likely to prevent ingestion of spoil acid, fermented foods. And that's it. That is the pallet that we deal with. Now, of course, there's a difference between basic taste and flavor, flavor is the whole experience. Flavor is the combination of multiple tastes coming together together with smell, with texture, with temperature, with the look of it that gives you what you and I would call the full sensory experience. But, but we scientists need to reduce the problem into its basic elements. So we can begin to break it apart before we put it back together. So when we think about the sense of taste, and we try to figure out how these lines of information go from your tongue to your brain and how they signal and how they could integrate it and how they trigger all these different behaviors. We look at them as individual qualities, so we give the animals sweet, or we give them a bitter. We give them sour, we avoid mixes because the first stage of discovery is to have that clarity as to what you're trying to extract so that you can hopefully meaningfully make a difference by being able to figure out how easy that A goes to B to C and to D, does this make sense? - Yeah, almost like the primary colors to create the full array of the color spectrum.

00:30:14 Additional Taste Modalities: Fat & Metallic Perception

- Exactly. - Before I ask you about the first and second and third stages of taste and flavor perception, is there any idea that there may be more than five? - There is, for example, what about fat? - I love the taste. - Oh, I love fat too. And I love the texture of fat, especially if it's slightly burnt, like in South America, when I visited Buenos Aries, I found that at the end of a meal, they would take a steak, the trimming off the edge of the steak, burn it slightly, and then serve it back to me. And I thought that's disgusting. And then I tasted it and it's delightful. - It is. - There's nothing quite like it. - This goes back to this notion before that we like to live on the edge. And we like to do things that we should not be doing, Andrew, but on the other hand, look at those muscles. - I don't suggest anyone eat pure fat. The listeners of this podcast will immediately, I'm sure there'll be a YouTube video soon that I like eating pure fat. I'm not on a ketogenic diet, et cetera, but fat is tasty as evidenced by the obesity problem that exists in this country. - We'll talk about that. You know, in a little bit about the gut brain axis, I think it'll be important to cover it because it's the other side of the taste system. And so missing taste, one is fat, although like you clearly highlighted a lot of fat taste in quotation marks is really the feeling of fat rolling on your tongue. And so there is a compelling argument that a lot of what we call fat taste, it's really mechanosensory, it's somatosensory cells, cells that are not responding to taste, but they're responding to mechanical stimulation of fat molecules rolling on the tongue that gives you that perception of fat. - I love the idea that there is a perception of fat, regardless of whether or not there's a dedicated receptor for fat, mostly because it's evoking sensations and imagery of the taste of slightly burnt fat. - For example. And another one you could argue is metallic taste. You know, I know exactly what it tastes like. You know, if you ask me to explain it, I will have a hard time, what are the palettes of that color that can allow me to define it? It wouldn't be easy, but I know precisely what it tastes like, take take a penny, put it in your mouth and you know what it tastes like. - Or blood. - Or blood. That's another very good example. And is there really a receptor for metallic taste or it's nothing but this magical combination of the activation of the existing lines, think of it as lines of information, just separate lines, like the keys of a piano. Sweet, sour, bitter, salt, umami, you play the key and you activate a one chord. And that one chord in the case of a piano leads to a note, you know a tune and in the case of taste leads to an action and a behavior, but you play many of them together. And something emerges that it's different than any one of the pieces. And it's possible that metallic, for example, represents the combination of the activity just in the right ratio makes of these other lines. - Makes sense.

00:34:02 Tongue “Taste Map,” Taste Buds & Taste Receptors

And it actually provides a perfect, your example of the piano provides a perfect segue for what I'd like to touch on next, which is if you would describe the sequence of neural events leading to a perceptual event of taste. And I'm certain that somewhere in there you'll embed an answer to the question of whether or not we indeed have different taste receptors distributed in different locations on our tongue. Or elsewhere in the mouth. - Yes. So let's start by the banking that old tale and myth. - Who came up with that? - There are many views, but the most prevalent is that there was an original drawing describing the sensitivity of the tongue to different tastes. So imagine I can take a Q-Tip, this is a thought experiment, and I'm going to dip that Q-Tip in salt and in quinine as something bitter and glucose as something sweet. And I'm going to take that Q-tip, ask you to stick your tongue out and start moving around your tongue and ask you, what do you feel? And then I'm going to change the concentration of the amount of salt or the amount of bitter and ask, can I get some sort of a map of sensitivity to the different tastes? And the argument that has emerged is that there is a good likelihood that the data was simply mistranslated as it was being drawn. And of course, that led to an entire industry. This is the way you maximize your wine experience, because now we're going to form the vessel that you're going to drink from so that it acts maximally on the receptors which happen. Now, there is no tongue map. All right, we have taste buds distributed in various parts of the tongue. So there is a map on the distribution of taste bud, but each taste bud has around a hundred taste receptor cells. And those taste receptor cells can be of five types, sweet, sour, bitter, salty, or umami. And for the most part, all taste buds have the representation of all five taste qualities. Now there's no question that there is a slight bias for some taste, like bitter, is particularly rich at the very back of your tongue. And there is a teleological basis for that, actually a biological basis for that. That's the last line of defense before you swallow something bad. And so let's make sure that the very back of your tongue has plenty of these bad news receptors so that if they get activated, you can trigger a gagging reflex and get rid of this that otherwise may kill you. - Makes good sense. - But the notion that all sweet is in the front and salt is on the side. It's not real. Go ahead. - Oh, I was just going to ask, first of all, thank you for dispelling that myth. And we will propagate that information as far and wide as we can. 'Cause I think that's the number one myth related to taste. The other one is, are there taste receptors anywhere else in the mouth, for instance, on the lips? - The palette, the palette, not the lips. So it's in the pharynx at the very back of the oral cavity, the tongue and the palette and the palette is very rich in sweet receptors. - I'll have to pay attention to this the next time I eat something sweet. - When you pull it up, yeah. Now the important thing is that after the receptors for these five, the detectors, the molecules that send sweet, sour, bitter, salt, umami, these are receptors, proteins found on the surface of taste receptor cells that interact with these chemicals. And once they interact, then they trigger the cascade of events, biochemical events, inside cell that now sends an electrical signal that says there is sweet here, or there is salt here. Now having these receptors and my laboratory identify the receptors for all five basic taste classes, sweet, bitter, salt, umami, and most recently sour. Now completing the palette. You can now use these receptors to really map where are they found in the tongue in a very rigorous way. This is no longer about using a Q-Tip and trying to figure out what you're feeling, but rather what you have in your tongue. This is not a guess. This is now a physical map that says the sweet receptors are found here. The bitter are found here. And when you do that, you find that in fact,

00:39:34 Burning Your Tongue & Perception

every taste bud throughout your oral cavity has receptors for all of the basic taste classes. - Amazing. And as it turns out, and I'm sure you'll tell us important in terms of thinking about how the brain computes, encodes and decodes this thing we call taste. I'm going to inject a quick question that I'm sure is on many people's minds before we get back into the biological circuit, which is many people, including myself, are familiar with the experience of drinking a sip of tea or coffee that is too hot, and burning my tongue is the way I would describe it. - Horrible. - Horrible. And then disrupting my sense of taste for some period of time afterward. When I experienced that phenomenon, that unfortunate phenomenon have I destroyed taste receptors that regenerate, or have I somehow used temperature to distort the function of the circuit so that I no longer taste the way I did before? - Excellent question. And the answer is both. It turns out that your taste receptors only live for around two weeks, and this, by the way, makes sense because here you have an organ, the tongue, that is continuously exposed to everything you could range from the nicest, to the most horrible possible things. - Use your imagination. - And so you need to make sure that these cells are always coming back in a way that can reexperience the world in the right way and there are other organs that have the same underlying logic. Your gut, your intestines are the same way. Amazing. Again, they're receiving everything that you ingest. God forbid what's there, from the spiciest to the most horrible tastings or the most delicious. And again, those intestinal cells whose role is to ultimately take all these nutrients and bring them into the body. Also renew in a very, very fast cycle, olfactory neurons in your nose is the example. So then A, yes, you're burning a lot of your cells and is over for those. The good news is that they're going to come back, but we know that when you burn yourself with tea, they come back within 20 minutes, 30 minutes, an hour, and these cells are not renewing in that timeframe. They're not listening to your needs. They have their own internal clock. And so you are really affecting, you're damaging them in a way that they can recover. And then they come back and you also damage your somatosensory cells. These are the results that feel things, not taste things. And then you wait half an hour or so, and then my goodness, thank God, it's back to normal. - And most of the time, I don't even notice the transition realizing,

00:42:54 The “Meaning” of Taste Stimuli, Sweet vs. Bitter, Valence

as you tell me, and I'll later, I'll ask you about the relationship between odor and taste. But as a next step, along this circuit, let's assume I ingest some, let's keep it simple. A sweet taste. - Let's make it even simpler. But at the same time, perhaps more informative, let's compare and contrast sweet and bitter as we follow their lines from the tongue to the brain. So the first thing is that the two evoke diametrically opposed behaviors. If we have to come up with two sensory experience that represent polar opposites, it will be sweet and video. There are not two colors that represent polar opposites because you could say black and white, they are polar opposites, one detects only one thing. The other one detects everything, but they don't evoke different behaviors. - Even political parties have some overlap. - Sweet and bitter are the two opposite ends of the sensory spectrum, now, a taste can be defined by two features. Again, I'm a reductionist, so I'm reducing it in a way that I think it's easier to follow the signal. And the two features are its quality and its valance and valance with a little V that's what we say in Spanish, with a V, means the value of that experience, right? Or in this case of that stimuli and you take sweet, sweet has a quality, an identity, and that's what you and I will refer to as the taste of sweet. We know exactly what it tastes like, But sweet also has a positive valance, which makes it incredibly attractive and appetitive, but it's attractive and appetitive, as I'll tell you in a second independent of its identity and quality. In fact, we have been able to engineer animals where we completely remove the valance from the stimuli. So these animals can taste sweet, can recognize it as sweet, but it's no longer attractive. It's just one more chemical stimuli. And that's because the identity and the valence are encoded in two separate parts of the brain. In the case of bitter, again, it has on the one hand its identity, its quality, and you know exactly what bitter tastes like. - I can taste it now, even as you describe it. - But it also has a valence and that's a negative valance because it evokes aversive behaviors. Are we on? - Absolutely. And it comes to mind. I remember telling some kids recently that we're going to go get ice cream and it was interesting. They looked up and they started smacking their like, they'll actually. - The anticipatory response. Absolutely. When we talk about the gut brain maybe we'll get there. So then the signals, if we follow now, these two lines, they're really like two separate keys at the two ends of this keyboard. And you press one key and you activate this cord. So you activate the sweet cells throughout your oral cavity. And they all converge into a group of sweet neurons in the next station, which is still outside the brain, it's one of the taste ganglia. These are the neurons that innervate your tongue and the oral cavity. - Where do they sit approximately? - Around there. - Right here around there. The lymph nodes, more or less? - You got it. And there are two main ganglia that innervate the vast majority of all taste buds in the oral cavity. And then from there that sweet signal goes onto the brain stem. The brain stem is the entry of the body into the brain. And there are different areas of the brain stem. And there are different groups of neurons in the brain stem. And there's this unique area in a unique, a topographically defined location in the rostral side of the brain that receives all of the taste input. - A very dense area of the brain. - A very rich area of the brain. Exactly. And from there, the sweet signal goes to this other area higher up on the brain stem. And then it goes through a number of stations where that sweet signal goes from sweet neuron to sweet neuron, to sweet neuron, to eventually get to your cortex. And once it gets to your taste cortex, that's where meaning is imposed into that signal. It's then, and only then this is what the data suggests that now you can identify this as a sweet stimuli. - [Andrew] And how quickly does that all happen? - You know, the time scale of the nervous system it's fast. - So within less than a second. - [Charles] Yeah, absolutely. - I rarely mistake bitter for sweet. Maybe with respect to people and my own poor judgment, but not with respect to taste. - And in fact, we can demonstrate this because we can stick electrodes at each of these stations, conceptually, and we can stimulate the tongue, and then we can record the signals pretty much time log the stimulus delivery. You deliver the stimuli and within a fraction of a second, you see now the response in this following stations, now it gets to the cortex, and now in there you impose meaning to that taste. There is an area of your brain that represents the taste of sweet in taste cortex and a different area that represents the taste of bitter. In a sense, there is a topographic map of these taste qualities inside your brain. Now we're going to do a thought experiment. Now, if this group of neurons in your cortex really represents the sense of sweet and this added different group of neurons in your brain represents the taste, the perception of bitter, then we should be able to do two things. First, I should be able to go into your brain, somehow silence those neurons, find a way to prevent them from being activated. And I can give you all the sweet you want, and you'll never know that you're tasting sweet. And conversely, I should be able to go into your brain, come up with a way to activate those neurons while I'm giving you absolutely nothing. And you're going to think that you are getting that full percept and that's precisely what we have done. And that's precisely what you get. This of course is in the brain of mice. - But presumably in humans it would work similarly. - Absolutely the same, zero doubt. I have no questions. So this attests to two important things, the first to the predetermined nature of the sense of taste, because it means I can go to these parts of your brain in the absence of any stimuli. And have you throw the full behavioral experience. In fact, when we activate in your cortex, these bitter neurons, the animal can start gagging, but it's drinking only water, but the animal thinks that's getting a bitter stimuli. [audience applauds] This is amazing. - And so, and the second, just to finish the line so that it doesn't sound like it teaches two things and then I only give you one lesson. It is that it substantiates this capacity of the brain to segregate, to separate in this nodes of action, the representation of these

00:51:55 Positive vs. Negative Neuronal Activation & Behavior two diametrically opposed percepts. Which is sweet, for example, versus bitter. - The reason I say amazing, and that is also amazing is the following, you told us earlier, and you're absolutely correct, of course, that the end of the day, whether or not it's one group of neurons over here, and another group of neurons over there, which is the way it turns out to be, electrical activity is the generic, common language of both sets of neurons. So that raises the question for me, of whether or not those separate sets of neurons are connected to areas of the brain that create this sense of valence or whether or not they're simply created connected, excuse me, to sets of neurons that evoke distinct behaviors of moving towards and inhaling more and licking or aversive are we essentially interpreting our behavior and our micro responses or are micro responses and our behaviors the consequence of the percept? - Excellent, excellent question. So first answer is they go into an area of the brain where valence is imposed, and that area is known as the amygdala and the sweet neurons go to a different area than the bitter neurons. Now I want to do a thought experiment because I think your audience might appreciate this. Let's say I activate this group of neurons and the animal increases licking and I'm activating the sweet neurons. And so that's expected because now it's tasting this water as if it was sugar. Now this Moses transforming water into wine in this case we're going to, and today's Passover, so this is an appropriate example, we're transforming it into sweet. But how do I know that activating them is evoking a positive feeling inside, a goodness, a satisfaction, or I love it versus I'm just increasing licking, which is the other option, because all we're seeing is that the animal is leaking more. And we're trying to infer that that means that he's feeling something really good versus you know what, that piano line is going back straight into the tongue. And all it's doing is forcing it to move faster. Well, we can actually separate this by doing experiments that allows to fundamentally distinguish them and imagine the following experiment, I'm going to take the animal and I'm going to put them inside a box that has two sides. And the two sides have features that make him different. One has yellow little toys. The other one has green toys. One has little black stripes. The other one has blue stripes. So the animal can tell the two halves, I take the mouse, put them inside this arena, this play arena. And it will explore and potter around both sides with equal frequency. And now what I'm going to do is I'm going to activate these neurons, these sweet neurons, every time the animal is on the side with the yellow stripes. And if that is creating a positive internal state, what would the animal now want to do? It will want to stay on the side with the yellow stripes. There's no licking here. The animal is not extending its tongue every time I'm activating this neurons. This is known as a place preference test. And it's generally used, it's just one form of many different tests to demonstrate that the activation of a group of neurons in the brain is imposing, for example, a positive versus a negative valance. Whereas if I do the same thing by activating the bitter neurons, the animal will actively want now to stay away from the side where these neurons are being activated.

00:56:16 Acquired Tastes, Conditioned Taste Aversion

- And that's precisely what you see. - [Charles] And that's precisely what we see. - Many people, including myself, are familiar with the experience of going to a restaurant, eating a variety of foods. And then fortunately doesn't happen that often, but then feeling very sick. I learned coming up in neuroscience that this is one strong example of one trial learning, that from that point on, it's not the restaurant or the waitress or waiter, or the date, but it's my notion of it had to have been the shrimp that leads me to then want to avoid shrimp in every context, maybe even shrimp powder. - You got it. - For a very long time. I can imagine all the evolutionarily adaptive reasons why this such a phenomenon would exist. Do we have any concept of where in this pathway it exists? - We do, we know actually a significant amount at a general level. In fact, more than shrimp, oysters are even a more dramatic example, one bad oyster is all you need to be driven that way for the next six months. - I think because the texture alone is something that one learns to overcome. I actually really enjoy oysters. I despise mussels, despise shrimp, not the animal, but the taste and yet oysters, for some reason, I've yet to have a bad experience. - It's like, uni, by the way texture is hard to get over, but once you get over, it's delicious. - That's what they tell me. We were both in San Diego at one point, and I'll give a plug to Sushi Ota, is kind of the famous place, and they have amazing uni and I've tried it twice. And I'm oh for two. It somehow the texture outweighs any kind of the deliciousness that people report. - It's a very acquired taste. It's like beer, I grew up in Chile, that's where the accent comes from in case anyone wonder. And by the time I came here to graduate school, I was 19, too old to overcome my heavy Chilian accent. So here I am, 40 years, 50 years late, not quite 40 plus- - We appreciate it. - And I still sound like I just came off the boat. So in Chile, you don't drink beer when you're young, you drink wine. Chili's a huge wine producer. So when I came to the US, all of my classmates were drinking beer because they had finished college where they were all you're drinking and graduate school, you're working 18 hours a day every day, the way they relax, let's go and have some beers. - And beer is cheaper. - And beer is cheap, and we were being clearly underpaid may I add. I couldn't do it. It's an acquired taste. It was too late by then. And here I am 60 plus. And if you take all the beer I've drank in my entire life, I would say they add to less than an eight ounce glass of water. - Impressive. Well, your health is probably better for it. - I'm not sure. - Your physical health anyway. - So it goes back to acquired taste. This is the connection to uni and to oysters. Now, going back to the one trial learning this is the great thing about our brains, certain things we need to repeat a hundred times to learn them, hello operator. Can I have the phone number for sushi Ota, please? And then she'll give it to you over the phone, at least in the old days. And then you need to repeat it to yourself over and over and over, over the next minute. So you can dial sushi Ota, and five minutes later, it's gone. That's what we call working memory. Then there is the short term memory. We park our car. And if we're lucky, by the end of the day, we remember where it is. And then there is the long term memory. We remember the birthdays of every one of our children for the rest of our lives. Well, there are events that a single event is so traumatic that it activates the circuits in a way that it's a one trial learning. And the taste system is literally at the top of that food chain. And there is a phenomenon known as conditioned taste aversion. You can pair an attractive stimuli with a really bad one, and you can make an animal begin to vehemently dislike for example, sugar. And that's because you've conditioned the animals to now be averse to these otherwise nice taste because it's been associated with malaise. And when you do that, now you could begin to ask why has change in the signal as it travels from the tongue to the brain in a normal animal versus an animal where you have now transformed sweet from being attractive to being immersive. And this is the way now you begin to explore

01:01:44 Olfaction (Smell) vs. Taste, Changing Tastes over One’s Lifetime

how the brain changes, the nature, the quality, the meaning of a stimuli as a function of its state. - I have a number of questions related to that, all of which relate to this idea of context, because you mentioned before that flavor is distinct from taste because flavor involves smell, texture, temperature, and some other features, uni, sea urchin being a good example of, I can sense the texture. It actually it's, nah, I won't describe what it reminds me of, for various reasons. The ability to place context into, to insert context into a perception, or rather to insert a perception into context is so powerful. And there's an element of kind of mystery about it. But if we start to think about some of the more nuance that we like to live at the edge, as you say, how many different tastes on the taste dial to go back to your analogy earlier, the color dial, do you think that there could be for something as fixed as bitter, so for instance, I don't think I like bitter taste, but I like some fermented foods that seem to have a little bit of sour and have a little bit of that briny flavor. How much plasticity do you think there is there and in particular across the lifespan, because I think one of the most salient examples of this is that kids don't seem to like certain vegetables, but they all are hardwired to like sweet tastes. And yet you could also imagine that one of the reasons why they may eventually grow to incorporate vegetables is because of some knowledge that vegetables might be- - Good for you. - Better for them. So is there a change in the receptors, the distribution, the number, the sensitivity, et cetera, that can explain the transition from wanting to avoid vegetables, to being willing to eat vegetables simply in childhood to early development. Yes, so I going to take the question slightly differently, but I think it would illustrate the point. And I want to just use the difference between the olfactory system and the taste system to make the point, taste system five basic pallets, sweet, sour, bitter, salt, umami, each of them has a predetermined identity. We know exactly what and valence. These are attractive. These are aversive. In the olfactory system, it's claimed that we can smell millions of different odors, yet for the most part, none of them have an innate predetermined meaning, in olfactory system, meaning is imposed by learning and experience. - Even the smell of smoke? - So I'm going to give you, I'm going to make it differently. They are a handful of the millions of odors that were claimed that, that you could immediately tell me these are adversive and these are attractive. - Vomit. - So vomit, it's not correct because I can assure you that they're cultures and societies where things which are far less appealing than vomit do not evoke a adverse reaction. - Really? - Really, sulfur would be maybe a universal. I'm not talking pheromones. pheromones are in a different category that trigger innate responses, but nearly every other is afforded meaning by learning and experience. And that's why you like broccoli. And I despise broccoli because I remember my mother forcing me to eat broccoli. [audience applauds] I'm so sorry. - Same sensory experience. This accommodates two important things. In the case of taste, you have neurons at every station that are for sweet, for sour, for bitter, for salty, and umami, it's only five classes. So it's not going to take a lot of your brain. If we can, in fact, smell a million others, and everyone else of others had to have predetermined, meaning there's not going to be enough brain just to accommodate that one sense. And so evolution in its infinite wisdom, evolved a system where you put together a pathway and a cortex, olfactory cortex, where you have the capacity to associate every other in a specific context that now gives it the meaning. Now let's go back to the original question then. So other than clearly plastic, mega plastic, because it's fundamental basis and neural organization, but taste, we just told you that predetermined, hardwired, but predetermined, hardwired doesn't mean that it's not modulated by learning or experience. It only means that you are born liking sweet and disliking bitter. And we have many examples of plasticity, beer being one example. So why do we learn to love beer and coffee. It's because it has an associated gain to the system and that gain to the system, that positive valance that emerges out of that negative signal is sufficient to create that positive association. And in the case of beer, of course, it's alcohol. The feeling good that we get after is more than sufficient to say, I want to have more of this. And in the case of coffee, of course, is caffeine activating a whole group of neurotransmitter systems that give you that high associated with coffee. So yes, this taste system is changeable. It's malleable, and it's subject subjected to learning and experience. But I like the olfactory system is restricted in what you could do with it because its goal is to allow you to get nutrients and survive. The goal of the olfactory system is very different. It's being used, not in our case, but in every animal species to identify friend versus foe, to identify mate, to identify ecological niches they want to be in. So it plays a very broad role that then requires that it be set up organized and function in a very different type of context. Taste is about, can we get the nutrients we need to survive? And can we ensure that we are attracted to the ones we need? And we adverse to the ones that are going to kill us, I'm being overly simplistic and reductionist. But I think it illustrates the huge difference between these two chemo sensory systems. - I don't think you're being overly simplicity. I think it illustrates the key intractable nature of this system and the way you've approached it. And I think it's important for people to hear that, because everybody, as we are as mystified with empathy and love, et cetera. So in a fairness to that,

01:09:14 Integration of Odor & Taste, Influence on Behavior & Emotion

I'm going to ask a sort of a high level question or abstract question. This was based on a conversation I had with a former girlfriend where we were talking about chemistry between individuals. Very complicated topic on the one hand. But on the other hand, quite simple in that certain people, for whatever reason, evoke a tremendous sense of arousal, for lack of a better word, between two people, one would hope, at least for some period of time. - I didn't know this was that kind of a podcast. - No, well, the reason I, but this has to do with taste because she said something, I think in part to maybe irritate me a bit, but we were commenting not about our own experience of each other, but of someone that she was now very excited about we're on good terms. And she said, "What do you think it is, this thing of chemistry?" So maybe she was trying to- - Warn you of what's coming. - Warn me what's coming. And she said, "I have a feeling something about it is in smell and something about it is actually in taste, literally the taste of somebody's breath." That's the way she described it. And I thought that it was a very interesting example for a number of reasons, but in particular, because it gets to the merging of odor and taste. But also to the idea that of course the context of a new relationship, I'm assuming that, and in fact, they're both attractive people, et cetera. There's a whole context there, but I've had the experience of the odor of somebody's breath being aversive. Not because I could identify it as aversive. - Because you just didn't like it. - But because I just didn't like it. - But that's because you associated with added odors that trigger that negative aversive reaction, by the way. - Absolutely. There are certain perfumes to me that are aversive. - [Charles] You got it. - And there are other sense, I can recall a sense of skin, of foods, et cetera, that are immensely appetitive. So I've experienced both sides of this equation myself. And she was describing this and to me more than tasting wine, which is the typical example where people inhale it and then they drink it, to me, this seems like something that more people might be able to relate to, that certain things and people smell delicious. Even mothers describing the smell of their baby's head. - A mother, or us. - [Andrew] Of course, men too, yeah. - I mean our own babies when in their necks, that's the magical place. - Their neck. - The back of their neck. - There you go. - Oh my goodness. I have a grandchild now. So I know exactly what, Rio, that's his name, smells like. - Okay. So more beautiful examples. It's always more fun to think about the beautiful positively appetitive examples. The smell of the back of your grandson's neck. I mean, you could get more specific than that, but not a lot more specific exactly. So what is going on in terms of the combination of odor and taste given that these two systems are so different? - Yes, and they come together, ultimately there is a place in the brain where they come together to integrate the two into what we would call that sensory experience. And I'll tell you an experiment that you could do that demonstrates this. I think it's good for the, for your audience here to get a sense of how we approach these problems so that we can get in a meaningful scientific answers. So we know where the olfactory cortex is in the brain. We know where the taste cortex is in the brain. They're in two different places. We can go to each of these two, cortexes, put color traces, we put green in one, we put red in the other and we see where the colors go to. That's a reflection of where those neurons are projecting into their next targets. Once they get the signal, where do they send the signal to? And then we reason that if odor and taste come together somewhere in the brain, we should find an area that now it's getting red and green color. And we found such an area. And next we anticipated, we hypothesized that maybe this is the area in the brain of the mouse, corresponding area in the brain of humans, that integrates odor and taste. It's known as, the term normally used is multisensory integration. And if this is true, we could do the following experiment. We can train a mouse to lick sweet. And if they guess correctly, that that is supposed to be sweet. They should go now to the right port, to the right side, to get a water reward. If they go to the lift, when it was sweet, then they're incorrect and they get no reward and they actually get a time out. Now the mice are thirsty, so they're very motivated to perform. And if you repeat this task a hundred times, a hundred trials, incredibly enough, this animal learned to recognize the sweet and execute the right action. And by their action, we now are being told what that animal is tasting. We can make it more interesting and we can give him sweet and bitter and say, if it's sweet go to the right and if it's bitter go to the left. And after you train him this mice with 90% accuracy, it'll tell you, when you randomize now the stimuli, what was sweet and what was bitter? We can now do the same experiment, but now mix taste with odor and say, if you got odor alone, go to the right or push this lever in mice. If you get taste alone, go to this other part or push this other lever. And if you get the two together, do this something else. And if you train the mice, the mice are able now to report back to you when it's sensing taste alone, odor alone, or the mix. Makes sense? - Makes sense. - Now we can go to the brain of this mice and go to this area that we now uncover, discover as being the side of multisensory integration between taste and odor, and silence it, prevent it from being activated experimentally. And if that area really represented the integration of these two, the animals should still be able to recognize the taste alone. They still should be able to recognize the other alone, but should be incapable now to recognize the mix, and exactly as predicted. That's exactly what you get. All right? - The brain is basically a series of engineered circuits, complex. - You got it. And our task is to figure out how can we extract this amazing architecture of these circuits in a way that we can begin to uncover the mysteries of the brain. - And why certain people's breath tastes so good and other people's not so good. - Exactly. So I never answered that,

01:17:26 Sensitization to Taste, Internal State Modulation, Salt

but I told you how we can figure out where in the brain it's happening. - As we've been having this discussion, I thought a few times about similarities to the visual system or differences to the visual system, the visual system, there are a couple of phenomenon that I wonder if they also exist in the taste system, and the visual system we know for instance, that if you look at something long enough and activate the given receptors long enough, that object will actually disappear. We offset this with little micro eye movements, et cetera, but the principle is a fundamental one. This habituation or desensitization, everyone seems to call it something different, but you get the idea of course, in the taste system, I'm certainly familiar with eating something very, very sweet for the first time in a long time. And it feel tastes very sweet, but a few more licks, a few more bites, and now it tastes not as sweet, with olfaction, I'm familiar with the odor in a room I don't like, or I like, and then it disappearing. So similar phenomena, where does that occur? And can you imagine a sort of a system by which people could leverage that? Because I do think that most people are interested in eating, not more sugar, but less sugar. - I think we have better ways to approach that. And we can transition from taste into these other circuits that makes sugar so extraordinarily impossible not to consume. - Impossible, exactly. - So where does the desensitizing happen. That's the term that we use, and it's, I think happening at multiple stations, it's happening at the receptor level. I.e. the salt in your tongue that are sensing the sugar, as you activate this receptor and it's triggering activity after activity after activity, eventually you exhaust the receptor again, I'm using terms which are extraordinarily loose. - But for sake of this discussion. - For the sake of this discussion the receptor gets to a point where he undergoes a set of changes, chemical changes, where it now signals far less efficiently, or it even gets removed from the surface of the cell. And now what will happen is that the same amount of sugar will trigger far less of a response. And that is a huge side of this modulation. And then the next, I believe is the integrated again, loss of signaling that happens by continuous activation of the circuit at each of these different neural stations.

You know, there is from the tongue to the ganglia, from the ganglia to the first station in the brain stem, a second station in the brain stem, to the thalamus, then to the cortex. So there are multiple steps that this signal is traveling. Now, you might say why, if this is a label line, why do you need to have so many stations? And that's because the taste system is so important to ensure that you get what you need to survive, that it has to be subjected to modulation by the internal state. And each of these nodes provides a new site to give it plasticity and modulation, not necessarily to change the way that something tastes, but to ensure that you consume more or less or differently of what you need. I'm going to give you one example of how the internal state changes the way the taste system works. Salt is very appetitive at low concentrations. And that's because we need it. It's our electro lite balance requires salt. Every one of our neurons uses salt as the most important of the ions with potassium to ensure that you can transfer these electrical signals within and between neurons, but at high concentrations, let's say ocean water, it's incredibly aversive. And we all know this because we are going to the ocean. And then when you get it in your mouth, it's not that great. However, if I salt deprive you, and we can do this in experimental models quite readily, now this incredibly high concentration of salt, one molar sodium chloride becomes amazingly appetitive and attractive. What's going on in here. Your tongue is telling you, this is horrible, but your brain is telling you, I don't care. You need it. And this is what we call the modulation of the taste system by the internal state. - And presumably if one is hungry enough, even uni will taste good. Just hit you hit it right on the money. No, no, this is exactly correct. Or if you're thirsty and hungry, you suppress hunger so that you don't waste water molecules in digesting food. Why? Because if you're thirsty and you have no water, you will die within a week or so, but you can on a hunger strike as long as you have water for months, because you're going to eat up all your energy reserves. Water is a different story. So you could see, or that there are multiple layers at which the taste system that guides our drive and our motivation to consume the nutrients we need has to be modulated in response to the internal state. And of course, internal state itself has to be modulated by the external world. And so that I think is a reason why, what could otherwise, would've been an incredibly simple system from the tongue to the cortex in one just wire. It's not, because you have to ensure that each step you give the system

01:24:05 Taste & Saliva: The Absence of Taste that level of flexibility or what we call in neuroscience, plasticity. - I think we're headed into the gut. But I have a question that has just been on my mind for a bit now, because I was drinking this water and it has essentially no taste. Is there any kind of signal for the absence of taste despite having something in the mouth and here is why I ask, what I'm thinking about is saliva. And while it's true that if I eat a lot of very highly palatable foods that does change how I experience more bland foods, I must confess when I eat a lot of these highly processed foods I don't particularly like them. I tend to crave healthier foods, but that's probably for contextual reasons about nutrients, et cetera. But I could imagine an experiment where- - You see a taste of no taste. - Right, is there a taste of no taste, because in the visual system there is. You close the eyes and you start getting increases in activity in the visual system, as opposed to decreases, which often surprises people. But there are reasons for that because everything is about signal to noise, signal to background. - It's a good question. I can tell you that most of our work is trying to focus on how the taste system works, not how it doesn't work well, but you know. - Yeah, I know you're being playful. And I knew when inviting you here today, I was setting myself up for, actually on a different- - We're trying to learn things. - Yeah, I know. - However- - All right, listen, I was weaned in this system of a, and I'll say it here for the second. Actually I recorded a podcast recently with a very prominent podcast with Lex Friedman Podcast. And I made reference to the so-called New York neuroscience mafia. I won't say whether or not we are sitting in the presence of the New York neuroscience mafia member, but in any event, I know the sorts of ribbing that they provide for those listening, this is the kind of hazing that happens. Benevolent hazing in academia. I'm the target. - Of course, it's- - It's a sign of love. - Exactly. - He's going to tell me that. - And it's always about the science in the end, right. But it's an interesting question. Look, I am, I don't know the answer and I don't even know how I would explore it in a way that it will rigorously teach me, eh, but. - Let me tell you why I'm asking. And then I'll offer an experiment that I'd love to see someone here in the lab do. I'm thinking about saliva. - No, no, no, but that we know, that we can figure it out. - Obviously. But the question is whether or not the saliva in a fed state is distinct from the saliva in an unfed state, such that it modulates the sensitivity, the response. - It's not the sensitivity, the experiment has been done. - [Andrew] It has been done. And so the answer is no. - It's not. And the way you could do the experiment is because we use artificial saliva. - There's such a thing? I know there's artificial tears, but. - No, no, we, I don't mean that you go to Walgreens that you get, I mean, we, in my laboratory, we know the composition of saliva and so you can make such a thing, and you can take taste cells in culture or in a tongue where you wash it out, and then you can apply artificial saliva. And what happens is that the system is being engineered to desensitize, to become agnostic for saliva to become invisible. And there is no difference on the state of the animal. - Great, well, this is the reason to do experiments. - [Charles] Yeah, absolutely. - So it doesn't defeat any grand hypothesis. It's just a pure curiosity. - You know that curiosity kills the cat? - I do, but saves the career of a scientists every single time. - That's what drives us, absolutely. - Every single time. - It's the story of our lives. - Exactly.

01:28:10 Sugar & Reward Pleasure Centers; Gut-Brain Axis, Anticipatory Response

So if it's not saliva and apparently it is not, what about internal state and what aspects of this, the internal milieu are relevant because there's autonomic, there's a sleep and awake, there's stress. One of the questions that I got from hundreds of people when I solicited questions in advance of this episode was why do I crave sugar when I'm stressed, for instance, and that could be contextual, but what are the basic elements- - Because it makes us feel good by the way, we'll get to that. That's his answer. - Soothing. - It activates, what I'm going to generically refer to as reward pleasure centers in a way that it dramatically, changes our internal state. This is in why do we eat a gallon ice cream when we're very depressed? In fact, this is a good segue to go into this an entire different world of the body telling your brain what you need in important things like sugar and fat, but anyways, go ahead, you were going to ask something. - Well, no, I would like to discuss the most basic elements of internal state in particular, the ones that are below our conscious detection. And this is a, of course is a segue into this incredible landscape, which is the gut brain axis, which I think 15 years ago was almost a, maybe it was posters at a meeting. And then now I believe you and others, there are companies, there have companies, there are active research programs, and beautiful work. Maybe you could describe some of that work that you and others have been involved in. And a lot of the listeners of this podcast will have heard of the gut brain axis. And there are a lot of misconceptions about the gut brain axis. Many people think that this means that we think with our stomach because of the quote unquote, gut feeling aspect, but I'd love for you to talk about the aspects of gut brain signaling that drive or change our perceptions and behaviors that are completely beneath our awareness. - Yes. Excellent. So let me begin maybe by stating that, the brain needs to monitor the state of every one of our organs, it has to do it. This is the only way that the brain can ensure that every one of those organs are working together in a way that we have healthy physiology. Now, this monitoring of the brain has been known for a long time, but I think what hadn't been fully appreciated that this is a two-way highway where the brain is not only monitoring, but is now modulating back what the body needs to do. And that includes all the way from monitoring the frequency of heartbeats and the way that inspiration and aspirations in the breeding cycle operate to what happens when you ingest sugar and fat. Now, let me give you an example again, of how the brain can take what we would refer to contextual associations and transform it into incredible changes in physiology and metabolism. Remember Pavlov? So Pavlov in his classical experiments in conditioning, associative conditioning, he would take a bell, he would ring the bell every time he was going to feed the dog. And eventually the dog learned to associate the ringing of the bell with food coming. Now, the first incredible finding he made is the fact that the dog now in the presence of the bell alone will start to salivate. And we will call that neurologically speaking an anticipatory response. Okay, I could understand it. I get it. You know, neurons in the brain that form that association now represent food is coming. And they're sending a signal to motor neurons to go into your salivary glands to squeeze them. So you release saliva because you know food is coming, but what's even more remarkable is that those animals are also releasing insulin in response to a bell. Okay. This illustrates one part of this two-way highway, the highway going down, somehow the brain created these associations and there are neurons in your brain now that no food is coming and send a signal somehow all the way down to your pancreas that now it says release insulin because sugar is coming down. This goes back to the magic of the brain. It's a never ending source of both joy and intrigue. How the hell do they do this? I mean, the neurons. - I share your delight and fascination. There's not a day or a lecture or some talks are better than others or talk where I don't sit back and just think, it's absolutely amazing. - How. - It's amazing. - Now over the past, I don't know, dozen years it and with great force over the last five years now, the main highway that is communicating the state of the body with the brain, it has been uncovered as being what we now refer to as the gut brain axis. And the highway is a specific bundle of nerves which emerged from the Vagal ganglia, the nodus ganglia. And so it's the vagus nerve that is innervating the majority of the organs in your body. It's monitoring their function, sending a signal to the brain. And now the brain going back down and saying, this is going alright, do this, or this is not going too well, do that. - And I should point out as you well know, every organ, spleen, pancreas, lung. - They all must be monitored. In fact I now, I have no doubt that the diseases that we have normally associated with metabolism, physiology, and even immunity are likely to emerge as diseases, conditions, states of the brain. I don't think obesity is a disease of metabolism. I believe obesity is a disease of brain circuits. - [Andrew] I do as well. - And so this view that we have, been working on for the longest time, because, the molecules that we're dealing with are in the body, not in the head, led us to to view, of course this issues and problems has been one of metabolism, physiology, and so forth. They remain to be the carriers of the ultimate signal, but the brain ultimately appears to be the conductor of this orchestra of physiology and metabolism. All right, now let's go to the gut brain and sugar, maybe.

01:36:23 Vagus Nerve

- Please, please. No, I mean, the vagus nerve has in popular culture has been kind of converted into this single meaning of calming pathways, mostly because I actually have to tip my hat to the yogic community was among the first to talk about vagus on and on and on, there are calming pathways, so-called parasympathetic pathways within the vagus. But I think that the more we learn about the vagus, the more it seems like an entire set of neural connections, as opposed to one nerve. I just wanted to just mention that because I think a lot of people have heard about the vagus turns out experimentally in the laboratory, many neuroscientists will stimulate the vagus to create states of alertness and arousal when animals, or even people believe it or not are close to dying or going into coma stimulation of the vagus is one of the ways to wake up the brain counter to the idea that it's just this I way of calming oneself down. - And also of course, I mean, one has to be cautious they're in that. So the vagus nerve is made out of many thousands of fibers, individual fibers that make this gigantic bundle. And it's likely as we're speaking, that each of these fibers carries a slightly different meaning, not necessarily one by one, maybe five is 10, five is 20, do all right, but they carry meaning that's associated with their specific task. This group of fibers is telling the brain about the state of your heart. This group of fiber is telling the brain about the state of your gut. This is telling your brain about its nutritional state, this, your pancreas, this your lungs. And they are again, to make the same simple example, the keys of this piano. Yes, you're right. There is a lot of data, showing that activating the entire vagal bundle has very meaningful effects in a wide range of conditions. In fact, it's being used to treat untractable depression. - A little stimulator. - Epileptics seizures. But again, there are thousands of fibers carrying different functions. So to some degree this is like turning the lights on the stadium, because you need to illuminate where you lost your keys under your seat. Yet 10,000 bulbs of a thousand Watts each have just come on. Only one of this is pointing to where, and so I'm lucky enough that one of them happened to point to my side. So here you activate the bundle thousands of fibers. I'm lucky enough that some of those happen to do something, to make a meaningful difference in depression, or to make a meaningful difference in epileptics. But it should not be misconstrued as arguing that this broad activation has any type of selectivity or specificity, we're just lucky enough that among all the things that are being done, some of those happen to change the biology of these processes. Now, the reason this is relevant because the magic of this gut brain axis is the fact that you have these thousands of fibers really doing different functions and our goal. And along with many other great scientists, including Steve Lieder Lee, that started a lot of this molecular dissection on this vagal gut brain communication line at Harvard, is trying to uncover what each of those lines doing, what are each of those keys of this piano playing? - What's the latest there? Just as a brief update. I know Steven Lieder Lee, I think I was there when he got his Howard Hughes and I did not. So that was fun. Always great to get beat by excellent people. - First of all, I'm happy you didn't, because that way you can focus on this amazing podcast. - Well, thank you. That's very gracious of you. It's always feels better if not good to get beat out by excellent people. Steven is second to none. And he is defining, as you said, the molecular constituents of different elements of these many, many fibers, is there an update there, are they finding multiple parallel pathways? - They are, they are, some that control heartbeat. Some that control the respiratory cycle. Some that might be involved in a gastric movement. You know, this notion that you're full and you feel full in part because your gut gets distended your stomach, for example. And then there are little sensors that are reading that and telling the brain you're full. - So the textbooks will soon change on the basis of the Lieder Lee and other work. - In essence, I think we are learning enough about these lines, that could really help put together this holistic view of how the brain it's truly changing body physiology, metabolism, and immunity, the part that hasn't been yet developed, and that it needs a fair amount of work, but it's an exciting thrilling, journey of discovery is how the signal comes back to now change that biology. You know, the example I gave you before with Pavlov's dog. I figure out how the association created this link between the bell, 01:43:09 Insatiable Sugar Appetite, Liking vs. Wanting, Gut-Brain Axis

but then how does the brain tell the pancreas to release in the right amount of insulin? So, let me tell you about the gut brain axis and our insatiable appetite for sugar and fat. Insatiable for sugar, unquenchable for fat. And this is a story about the fundamental difference between liking and wanting. Liking sugar is the function of the taste system. And it's not really liking sugar, it's liking sweet, wanting sugar, our never ending appetite for sugar is the story of the gut brain axis, liking versus wanting. And this work is work of my own laboratory. You know, that began long ago when we discovered the sweet receptors and you can now engineer mice that lack these receptors. So in essence, these animals will be unable to taste sweet, a life without sweetness. How horrible. And if you give a normal mouse, a bottle containing sweet, and we're going to put either sugar or an artificial sweetener, they bottle sweet. They have slightly different tastes, but that's simply because artificial sweeteners have some off tastes. But as far as the sweet receptor is concerned, they both activate the same receptor, trigger the same signal. And if you give an animal, an option of a bottle containing sugar or a sweetener versus water, this animal will drink 10 to one from the bottle containing sweet. That's the taste system, animal goes samples, each one, licks a couple of licks and then says, that's the one I want because it's appetitive. And because I love it. - So it prefers sugar to artificial sweetener? - No, no, no, no, no, no. In this experiment, this experiment, I'm going to put only sweet in one bottle and it could be either sugar or artificial sweetener. It doesn't matter which one. We're going to do the next experiment where we separate those two, for now is sweet versus water. And sweet means sweet, not sugar. Sweet means anything that tastes sweet. And sugar is one example and Splenda is another example. - Aspartame, monk fruit, Stevia, doesn't matter. - I mean, there's some that only humans can taste. Mice cannot taste because their receptors between humans and mice are different, but we have put the human receptor into mice. We engineer mice and we completely humanize this mouse's taste world. But for the purpose of this conversation, we're only comparing sweet versus water, an option. My goodness, they will lick to know and from the sweet side 10 to one, at least versus the water, makes sense? All right, now we're going to take the mice and we're going to genetically engineer it to remove the sweet receptors. So this mice no longer have in their oral cavity, any sensors that can detect sweetness, be that sugar molecule be an artificial sweetener, be anything else that tastes sweet. And if you give this mice an option between sweet versus water, sugar versus water, artificial sweetener versus water, it will drink equally well from both because he cannot tell them apart because it doesn't have the receptors for sweet. So that sweet bottle tastes just like water. Makes sense? - Makes sense. - Very good. Now we're going to do the experiment with sugar from now on let's focus on sugar. So I'm going to give a mouse out sugar versus water. Normal mouse will drink from the sugar, sugar, sugar, sugar, very little from the water, knock out the sweet receptors, eliminate them. Mouse can no longer tell them apart. And they will drink from both. But if I keep the mouse in that case for the next 48 hours, something extraordinary happens when I come 48 hours later. And I see what the mouse is licking or drinking from, that mouse is drinking almost exclusively from the sugar bottle. How could this be? It cannot not taste it. It doesn't have sweet receptors during those 48 hours the mouse learn that there is something in that bottle that makes me feel good. And that is the bottle I want to consume. Now does the mouse identify that bottle? It does so by using other sensory features, the smell of the bottle, the texture of the solution inside, sugar, the high concentrations is kind of goopy, the side in which the bottle is in the cage. It doesn't matter what, but the mouse realize there is something there that makes me feel good. And that's what I want. And that is the fundamental basis of our unquenchable desire and our craving for sugar and is mediated by the gut brain axis. The first clue is that it takes a long time to develop, immediately suggesting a post-ingestive effect. So we reason if this is true and it's the gut brain axis that's driving sugar preference. Then there should be a group of neurons in the brain that are responding to post-ingestive sugar, and low and behold, we identify a group of neurons in the brain that does this and these neurons receive their input directly from the gut brain axis. - From other neurons. - You got it. And so what's happening is that sugar is recognized normally by the tongue, activates an appetitive response. Now you ingest it and now it activates a selective group of cells in your intestines that now send a signal to the brain via the vagal ganglia that says, I got what I need. The tongue doesn't know that you got what you need. It only knows that you tasted it. This knows that it got to the point that it's going to be used, which is the gut. And now it sends the signal to now reinforce the consumption of this thing, because this is the one that I needed. Sugar, source of energy. - And are these neurons in the gut? - So these are not neurons in the gut. So these are gut cells that recognize the sugar molecule. - [Andrew] I see. - Send the signal and that signal is received by the vagal neuron directly. - Got it. - And it sends a signal through the gut brain axis to the cell bodies of these neurons in the vagal ganglia, and from there to the brain stem to now trigger the preference for sugar. - Two questions. One, you mentioned that these cells that detect sugar within the gut are actually within the intestine. You didn't say stomach. Which surprised me. I always think gut as stomach, but of course- - They're intestines, because that's where all the absorption happens. - [Andrew] Got it. - So you want the signal, you see, you want the brain to know that you had successful ingestion and breakdown of whatever you consume into the building blocks of life, and glucose, amino acids, fat. And so you want to make sure that once they are in the form

01:52:03 Tool: Sugar vs. Artificial Sweeteners, Curbing Appetite

that intestines can now absorb them, is where you get the signal back saying this what I want. Now let me just take it one step further. And this now sugar molecules activates this unique gut brain circuit that now drives the development of our preference for sugar. Now, a key element of this circuit is that the sensors in the gut that recognize the sugar do not recognize artificial sweeteners at all. - Because their nutrient value is uncoupled from the taste? - Generically speaking one can make that, but it's because it's a very different type of receptor. Turns out that it's not the tongue receptors being used in the gut. It's a completely different molecule that only recognizes the glucose molecule, not artificial sweeteners. This has a profound impact on the effect of ultimately artificial sweeteners in curbing our appetite, our craving, our insatiable desire for sugar, since they don't activate the gut brain axis, they'll never satisfy the craving for sugar like sugar does. And the reason I believe that artificial sweeteners have failed in the market to curb our appetite. Our need, our desire for sugar is because they beautifully work on the tongue. They liking to recognize sweet versus non-sweet, but they fail to activate the key sensors in the gut that now inform the brain

01:54:06 Cravings & Gut-Brain Axis

you got sugar, no need to crave anymore. - So the issue of wanting, can we relate that to a particular set of neurochemicals upstream, so the pathway is, so glucose is activating the cells in the gut that through the vagus that's communicated through the presumably the nodus ganglia and up into the brain stem. - Very good, and from there, where does it go? - Yeah, where does it go, and what is the substrate of wanting? Of course I think molecules like dopamine craving, there's a book even called the molecule of more, et cetera. Dopamine is a very diabolical molecule, as you know, because it evokes both a sense of pleasure-ish, but also a sense of desiring more, of craving. So if I understand you correctly, artificial sweeteners are, and I agree are failing as a means to satisfy sugar craving at the level of nutrient sensing. And yet if we trigger this true sugar evoked wanting pathway too much, and we've all experienced this, then we eat sugar and we find ourselves wanting more and more sugar. Now that could also be insulin dysregulation, but can we uncouple those? - I mean, look, if we have a mega problem with over consumption of sugar and fat, we're facing a unique time in our evolution where diseases of malnutrition are due to over-nutrition. I mean, how nuts is that? Historically, diseases of malnutrition have always been linked to undernutrition. And so we need to come up with strategies that can meaningfully change the activation of these circuits that control our wanting certainly in the populations at risk, and this gut brain circuit that ultimately it's the lines of communication that are informing the brain, the presence of intestinal sugar, in this example, it's a very important target in the way we think about, is there a way that we can meaningfully modulate these circuits? So I make your brain think that you got satisfied with sugar, even though I'm not giving you sugar. - So that immediately raises the question are the receptors for glucose in these gut cells susceptible to other things that are healthier for us. - That's very good. Excellent idea. And I think an important goal will be to come up with a strategy and identify those very means that allow us to modulate the circuits in a way that certainly for all of those, where this is a big issue, it can really have a,

01:57:30 Nutrition, Gut-Brain Axis & Changes in Behavior

you know, dramatic impact in improving human health. - I could be wrong about this. And I'm happy to be wrong. I'm often wrong. And told I'm wrong, that we have cells within our gut that don't just sense sugar, glucose to be specific, but also cells within our gut that sense amino acids and fatty acids. I could imagine a scenario where one could train themselves to feel immense amounts of satiety from the consumption of foods that are rich in essential fatty acids, amino acids, perhaps less caloric or less insulin dysregulating than sugar. I'll use myself as an example. I've always enjoyed sweets, but in the last few years, for some reason I've started to lose my appetite for them probably because I just don't eat them anymore. At first that took some restriction. Now I just don't even think about it. - And you're not reinforcing the circuits. And so you're in essence are removing yourself from, but you tend to be the exception. You know, we have a huge, a incredible large number of people that are being continuously exposed to highly processed foods. - And hidden, so called hidden sugars. - They don't even have to be hidden. You know, it's right there. - Hiding in plain sight. I agree so much is made of hidden sugars that we often overlook that there are also the overt sugars. - I mean, we can have a long discussion on the importance of coming up with strategies that could meaningfully change public health when it comes to nutrition. But I want to just go back to the notion of this brain centers that are ultimately the ones that are being activated by these essential nutrients. So sugar, fat, amino acids are building blocks of our diets. And this is across all animal species. So it's not unreasonable then to assume that dedicated brain circuits would've evolved to ensure their recognition, their ingestion and the reinforcement that that is what I need. And indeed animals evolve these two systems. One is the taste system that allows you to recognize them and trigger this predetermined, hardwired, immediate responses. Oh my goodness. This tastes so good. It's so sweet. I personally have a sweet tooth, and you know, oh my God, this is so delicious. It's fatty or umami, recognizing the amino acids. So that's the liking pathway, but in the wisdom of evolution, that's good, but doesn't quite do it. You want to make sure that these things get to the place where they're needed and they're not needed in your tongue. They're needed in your intestines where they're going to be absorbed as the nutrients that will support life. And the brain wants to know this, and it wants to know it in a way that it can now form the association between that I just tasted is what got where it needs to be. And it makes me feel good. And so now next time that I have to choose, what should I eat? That association now guides me to, that's the one I want. I want that fruit, not that fruit. I want those leaves, not those leaves, because these are the ones that activate the right circuits that ensure that

02:01:53 Fast vs. Slow Signaling & Reinforcement, Highly Processed Foods

the right nutrients got to the right place and told the brain, this is what I want and need. Are we on? - We're on. One thing that intrigues me and puzzles me, is that this effect took a couple of days, at least in mice. And the sensation, ah, sorry, the perception of taste is immediate. and yet this is a slow system. And so in a beautiful way, but in a kind of mysterious way, the brain is able to couple the taste of a sweet drink with the experience of nutrient extraction in the gut, under a context where the mouse and the human is presumably ingesting other things, smelling other mice, smelling other people. That's incredible. - But you have to think of it not as humans, remember we inherited the circuits of our ancestors and they through evolutionary from their ancestors. And we haven't had that many years to have fundamentally changed in many of these hardwired circuits. So forget as humans, let's look at animals in the wild. Which is easier now to comprehend the logic. You know, why should this take a long time of continued reinforcement given that I can taste it in a second? You want to make sure that this source of sugar, for example, in the wild is the best. Is the richest. It's the one where I get the most energy for the least amount of extraction, the least amount of work. I want to identify rich sources of sugar. And if the system simply responds immediately to the first sugar that gets to your gut, you're going to form the association with those sources of food, which are not the ones that you should be eating from. - Don't fall in love with the first person you encounter. - Oh my goodness, exactly. And so evolutionarily by having the taste system, giving you the immediate recognition, but then by forcing this gut brain axis to reinforce it only when sustained repeated exposure has informed the brain. This is the one you don't want to form the association before. And so when we remove it from the context of we just go to the supermarket, we're not hunting there in the wild where I need to form. And so what's is that highly processed foods are hijacking, co-opting these circuits in a way that it would've never happened in nature. And then we not only find these things appetitive and palatable, but in addition, we are continuously reinforcing, the wanting in a way that, oh my God, this is so great. What do I feel like eating? Let me have more of this. - You've just forever changed the way that I think about supermarkets and restaurants. There are understanding this fast signaling and this slower signaling and the utility of having both makes me realize that supermarkets and restaurants are about the most unnatural thing for our system ever, almost the equivalent of living in small villages with very few suitable mates versus online dating, for instance. - I'm not going to make a judgment call there because they do serve an important purpose. - I like restaurants too. - And so do supermarkets, thank God. I think they're not the culprits. I think the culprits of course are our reliance on foods that are not necessarily healthy. Now, going back to the supermarket, don't fall in love with the first, they need to work. You know, you take a tangerine, and you take an extract of tangerine that you used to cook that spiked, let's say with sugar and you equalize in both where they both provide the same amount of calories. If you eat them both, they're going to have a very different effect in your gut brain axis on your system. Once you make the extract and you process it and you add processed sugar to use it now to cook, to add, to make it really sweet tangerine thing. Now you're providing now fully ready to use broken down source of sugar, in the tangerine that sugar's mixed in the complexity of a whole set of other chemical components, fiber, long chains of sugar molecules that need a huge amount of work by your stomach, your gut system, to break it down. So you are using a huge amount of energy to extract energy and the balance it's very different that when I take this process highly extracted tangerine, by the way I use tangerines because I had a tangerine just before I came here. - Delicious, they are delicious. - And so this goes back to the issue of supermarkets. And to some degree, given a choice, you don't want to eat highly processed foods because everything's already been broken down for you. And so your system has no work. And so you are, co-opting hijacking the circuits in a way that they're being activated at a time scale that normally wouldn't happen. - Well, this is why I often feel that, and I think a lot of data are now starting to support the idea that while indeed the laws of thermodynamics apply calories ingested versus calories burned is a very real thing, right? That the appetite for certain foods and the wanting and the liking are phenomena of the nervous system, brain and gut as you've beautifully described. And that changes over time, depending on how we are receiving these nutrients. - Absolutely. Look, we have a lot of work to do. I'm talking as society. I'm not talking about you and I. - We also have a lot of work to do. - Now. I think understanding the circuits is giving us important insights in how ultimately, and hopefully we can improve human health and make a meaningful difference. Now, it's very easy to try to connect the dots A to B, B to C, C to D. And I think there's a lot more complexity to it, but I do think that the lessons that are emerging out of understanding how these circuits operate, can ultimately inform how we deal with our diets in a way that we avoid what we're facing now as a society. I mean it's nuts that over-nutrition happens to be such a prevalent problem. And I also think the training of people who are thinking about metabolic science and metabolic disease is largely divorced from the training of the neuroscientist and vice versa. No one field is to blame, but I fully agree that the brain is the key over, or the nervous system to be more accurate is one of the key overlooked features.

02:10:38 Favorite Foods: Enjoyment, Sensation & Context

- Is the arbiter, ultimately is the arbiter of many of these pathways. - As a final question. And one which is simply to entertain my curiosity and the curiosity of the listeners. What is your absolute favorite food? - Oh, my goodness. - Taste, I should say. Taste to distinguish between taste and the nutritive value or lack thereof. - Look, we, unlike every animal and every animal species eat for the enjoyment of it, it doesn't happen in the wild, most animals eat when they need to eat. Doesn't mean they don't enjoy it, but it's a completely different story. I have too many favorite foods because I enjoy the sensory experience rather than the food itself to me is the whole thing, is from the presentation, look, there've been these experiments done in psycho physics, I'm going to take a salad, made out of 11 components and I'm going to mix them all up in potpourri greens and other things here. And in the other one, I'm going to present it in a beautiful arrangement. And I'm going to put them behind a glass cabinet and I'm going to sell them. And I'm going to sell one for $2 and one for $8, precisely the same ingredient. Exactly the same amount of each. Ultimately you're going to mix them, they're all going to be the same, and people will pay the $8 because you know what, it evokes a different person. It gives you the feel that, oh my goodness, I'm going to enjoy that salad. So going back to, what is my favorite food, to me eating is really a sensory journey. I don't mean the every day, let me have some chicken wings, because I'm hungry it, but eh, every piece I think has an important evoking sensory role. And so in terms of categories of food I grew up in Chile. So meat has always been, but I eat it so seldom now. - Is that right? - Yeah, because I know that it's not necessarily the healthiest thing, red meat I'm talking about. And so I grew up eating it every day. I'm talking seven days a week, Chile, Argentina, that's the mainstay of our diet. Now maybe I have red meat. I don't know, once every four weeks. - And you enjoy it? - Oh, I love it. Part of it is because I haven't had it in four weeks. But you know, I love sushi, but I love the art of sushi, the whole thing, the way it's presented, it changes the way you taste it. I love ethnic food in particular. - You're in the right place. - You got it, that was the main reason I wanted to come to New York. No, I'm just kidding. - There's also that Columbia University that's- - And I came here because I wanted to be with people that are thinking about the brain, the same way that I like to think, which can we solve this big problem, this big question. - - And certainly you're making amazing strides in that direction. And I love your answer because it really brings together the many features of the circuitries and the phenomena we've been talking about today, which is that while it begins with sensation and perception, ultimately it's the context. And that context is highly individual to person, place and time, and many, many other things on behalf of myself. And certainly on behalf of all the listeners, I want to thank you, first of all, for the incredible work that you've been doing now for decades, in vision, in taste and in this bigger issue of how we perceive and experience life, it's truly pioneering and incredible work. And I feel quite lucky to have been on the sidelines, seeing this over the years and hearing the talks and reading the countless beautiful papers, but also for your time today to come down here and talk to us about what drives you and the discoveries you've made. Thank you ever so much. - It was great fun. Thank you for having me. - We'll do it again. - We shall. - Thank you for joining me today for my discussion about perception and in particular, the perception of taste with Dr. Charles Zuker. If you're learning from, and or enjoying this podcast, please subscribe to our YouTube channel. That's a terrific zero cost way to support us. In addition, please subscribe to the podcast on Spotify and Apple and on Spotify and Apple, you can leave us up to a five star review. If you have feedback for us in terms

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