

WEBVTT

NOTE duration:"00:21:22.3200000"

NOTE recognizability:0.772

NOTE language:en-us

NOTE Confidence: 0.970903116666667

00:00:00.000 --> 00:00:03.555 And next we're going to move to our speaker,

NOTE Confidence: 0.970903116666667

00:00:03.560 --> 00:00:06.440 Doctor Tamash Horvath. And Dr.

NOTE Confidence: 0.970903116666667

00:00:06.440 --> 00:00:08.659 Horvath is the Jane and David West

NOTE Confidence: 0.970903116666667

00:00:08.659 --> 00:00:10.842 Wallace Professor and chair of the

NOTE Confidence: 0.970903116666667

00:00:10.842 --> 00:00:12.398 Department of Comparative Medicine.

NOTE Confidence: 0.970903116666667

00:00:12.400 --> 00:00:15.610 He's also Professor of Neurosciences and

NOTE Confidence: 0.970903116666667

00:00:15.610 --> 00:00:18.799 OBGYN and Reproductive Sciences here at Yale.

NOTE Confidence: 0.970903116666667

00:00:18.800 --> 00:00:21.187 He was the founding director of the

NOTE Confidence: 0.970903116666667

00:00:21.187 --> 00:00:23.362 Yale Program and Integrative Cell

NOTE Confidence: 0.970903116666667

00:00:23.362 --> 00:00:26.077 Signaling and Neurobiology of Metabolism,

NOTE Confidence: 0.970903116666667

00:00:26.080 --> 00:00:27.880 which was the predecessor for

NOTE Confidence: 0.970903116666667

00:00:27.880 --> 00:00:30.091 the current Yale Center for

NOTE Confidence: 0.970903116666667

00:00:30.091 --> 00:00:32.079 Molecular and Systems Metabolism.

NOTE Confidence: 0.970903116666667

00:00:32.080 --> 00:00:35.440 He received a doctorate of veterinary  
NOTE Confidence: 0.970903116666667

00:00:35.440 --> 00:00:37.620 medicine from the Faculty of  
NOTE Confidence: 0.970903116666667

00:00:37.620 --> 00:00:39.240 Veterinary Sciences in Budapest,  
NOTE Confidence: 0.970903116666667

00:00:39.240 --> 00:00:42.439 Hungary, and and a PhD degree from  
NOTE Confidence: 0.970903116666667

00:00:42.439 --> 00:00:45.398 the University of Saged in Hungary.  
NOTE Confidence: 0.970903116666667

00:00:45.400 --> 00:00:47.836 His research has been focusing on  
NOTE Confidence: 0.970903116666667

00:00:47.836 --> 00:00:50.032 the body brain communication that  
NOTE Confidence: 0.970903116666667

00:00:50.032 --> 00:00:52.048 support physiological and pathological  
NOTE Confidence: 0.970903116666667

00:00:52.048 --> 00:00:54.568 homeostatic conditions as well as  
NOTE Confidence: 0.970903116666667

00:00:54.638 --> 00:00:56.798 aging and higher brain functions.  
NOTE Confidence: 0.970903116666667

00:00:56.800 --> 00:00:57.664 And with that,  
NOTE Confidence: 0.970903116666667

00:00:57.664 --> 00:00:58.240 Doctor Horvath,  
NOTE Confidence: 0.896088968

00:01:04.450 --> 00:01:06.210 thank you, Anya. Thank you,  
NOTE Confidence: 0.896088968

00:01:06.210 --> 00:01:07.458 Nancy, for the introduction.  
NOTE Confidence: 0.896088968

00:01:07.458 --> 00:01:09.150 It's, it's it's a little bit  
NOTE Confidence: 0.896088968

00:01:09.150 --> 00:01:11.607 of a tall task to follow this

NOTE Confidence: 0.896088968

00:01:11.607 --> 00:01:13.549 really remarkable talk of Anya.

NOTE Confidence: 0.896088968

00:01:13.549 --> 00:01:16.728 So I I'll give you more of a conceptual

NOTE Confidence: 0.896088968

00:01:16.728 --> 00:01:18.612 framework and and philosophical take

NOTE Confidence: 0.896088968

00:01:18.612 --> 00:01:20.556 on this coming from the research

NOTE Confidence: 0.896088968

00:01:20.556 --> 00:01:22.809 that started at Yale in 1990 and

NOTE Confidence: 0.896088968

00:01:22.809 --> 00:01:25.070 just going to repeat some of the

NOTE Confidence: 0.896088968

00:01:25.153 --> 00:01:27.259 slides that probably are redundant.

NOTE Confidence: 0.896088968

00:01:27.259 --> 00:01:29.632 And that is how obesity and diabetes

NOTE Confidence: 0.896088968

00:01:29.632 --> 00:01:31.797 have been growing and will be growing

NOTE Confidence: 0.896088968

00:01:31.797 --> 00:01:33.990 in the in the coming decades unless

NOTE Confidence: 0.896088968

00:01:33.990 --> 00:01:36.096 these medications really pan out and

NOTE Confidence: 0.896088968

00:01:36.096 --> 00:01:38.488 then we can end this trajectory.

NOTE Confidence: 0.896088968

00:01:38.488 --> 00:01:41.623 And of course diabetes is to great

NOTE Confidence: 0.896088968

00:01:41.623 --> 00:01:43.711 extent supported by increased

NOTE Confidence: 0.896088968

00:01:43.711 --> 00:01:45.799 body weight to obesity,

NOTE Confidence: 0.896088968

00:01:45.800 --> 00:01:47.780 which is also increasing  
NOTE Confidence: 0.896088968

00:01:47.780 --> 00:01:49.760 over the last decades.  
NOTE Confidence: 0.896088968

00:01:49.760 --> 00:01:51.559 If you look at the longevity of  
NOTE Confidence: 0.896088968

00:01:51.559 --> 00:01:52.560 individuals with different BMI,  
NOTE Confidence: 0.896088968

00:01:52.560 --> 00:01:54.835 you can see that BMI has some  
NOTE Confidence: 0.896088968

00:01:54.835 --> 00:01:57.386 predictive factor of how long we live.  
NOTE Confidence: 0.896088968

00:01:57.386 --> 00:01:59.893 And obviously all these various  
NOTE Confidence: 0.896088968

00:01:59.893 --> 00:02:02.558 metabolic impairments have impacts on  
NOTE Confidence: 0.896088968

00:02:02.560 --> 00:02:06.520 all tissues we have in our in our body.  
NOTE Confidence: 0.896088968

00:02:06.520 --> 00:02:07.880 And as Anya pointed out,  
NOTE Confidence: 0.896088968

00:02:07.880 --> 00:02:10.565 they have been medications over  
NOTE Confidence: 0.896088968

00:02:10.565 --> 00:02:12.672 the last almost 100 years.  
NOTE Confidence: 0.896088968

00:02:12.672 --> 00:02:14.392 They've been tried and some  
NOTE Confidence: 0.896088968

00:02:14.392 --> 00:02:16.520 of them successfully treated,  
NOTE Confidence: 0.896088968

00:02:16.520 --> 00:02:19.291 obviously including the one in 1933,  
NOTE Confidence: 0.896088968

00:02:19.291 --> 00:02:20.797 which is a mitochondria on coupler.

NOTE Confidence: 0.896088968

00:02:20.800 --> 00:02:22.960 You really were beautiful losing weight,

NOTE Confidence: 0.896088968

00:02:22.960 --> 00:02:24.087 but you ended up in the cough

NOTE Confidence: 0.896088968

00:02:24.087 --> 00:02:24.800 and then you died.

NOTE Confidence: 0.896088968

00:02:24.800 --> 00:02:26.720 So eventually that had to be

NOTE Confidence: 0.896088968

00:02:26.720 --> 00:02:28.268 stopped and and we are trying

NOTE Confidence: 0.896088968

00:02:28.268 --> 00:02:29.999 to go away from from those.

NOTE Confidence: 0.896088968

00:02:30.000 --> 00:02:32.135 But many of those issues that I

NOTE Confidence: 0.896088968

00:02:32.135 --> 00:02:34.000 will refer to actually relates

NOTE Confidence: 0.896088968

00:02:34.000 --> 00:02:35.560 to these conceptual frameworks.

NOTE Confidence: 0.896088968

00:02:35.560 --> 00:02:38.232 What it is to lose hunger and what

NOTE Confidence: 0.896088968

00:02:38.232 --> 00:02:41.075 it is to lose hunger and live with

NOTE Confidence: 0.896088968

00:02:41.075 --> 00:02:43.640 that for a prolonged period of time.

NOTE Confidence: 0.896088968

00:02:43.640 --> 00:02:45.548 But definitely what happened in the

NOTE Confidence: 0.896088968

00:02:45.548 --> 00:02:47.639 last few years made a huge splash

NOTE Confidence: 0.896088968

00:02:47.640 --> 00:02:50.942 in in in every level, every medium.

NOTE Confidence: 0.896088968

00:02:50.942 --> 00:02:53.259 We do agree with the many of  
NOTE Confidence: 0.896088968

00:02:53.259 --> 00:02:55.359 us agree with the science.  
NOTE Confidence: 0.896088968

00:02:55.360 --> 00:02:58.512 Last issue of science that this was a  
NOTE Confidence: 0.896088968

00:02:58.512 --> 00:03:01.700 breakthrough that occurred in 2023.  
NOTE Confidence: 0.896088968

00:03:01.700 --> 00:03:04.017 So what's for me?  
NOTE Confidence: 0.896088968

00:03:04.017 --> 00:03:04.276 Again,  
NOTE Confidence: 0.896088968

00:03:04.276 --> 00:03:06.280 it's going to be my perspective on this.  
NOTE Confidence: 0.896088968

00:03:06.280 --> 00:03:07.935 What's for me it's remarkable  
NOTE Confidence: 0.896088968

00:03:07.935 --> 00:03:09.259 because these signaling molecules  
NOTE Confidence: 0.896088968

00:03:09.259 --> 00:03:10.958 that that Anya referred to and I  
NOTE Confidence: 0.896088968

00:03:10.958 --> 00:03:12.519 will come back to for a second,  
NOTE Confidence: 0.896088968

00:03:12.520 --> 00:03:14.140 they usually function for a couple  
NOTE Confidence: 0.896088968

00:03:14.140 --> 00:03:15.990 of minutes in our body when we  
NOTE Confidence: 0.896088968

00:03:15.990 --> 00:03:17.663 eat and they do not sustain their  
NOTE Confidence: 0.896088968

00:03:17.715 --> 00:03:19.375 functionality for the problem period  
NOTE Confidence: 0.896088968

00:03:19.375 --> 00:03:21.824 of time that the medication is taken.

NOTE Confidence: 0.896088968

00:03:21.824 --> 00:03:24.960 And and I will come back to what

NOTE Confidence: 0.896088968

00:03:24.960 --> 00:03:27.168 how the how our understanding of

NOTE Confidence: 0.896088968

00:03:27.168 --> 00:03:29.376 the control of feeding and and

NOTE Confidence: 0.896088968

00:03:29.376 --> 00:03:31.714 obesity evolved in the last 30 years.

NOTE Confidence: 0.896088968

00:03:31.720 --> 00:03:32.380 But how?

NOTE Confidence: 0.896088968

00:03:32.380 --> 00:03:34.030 Actually these drugs may not

NOTE Confidence: 0.896088968

00:03:34.030 --> 00:03:35.919 be coming from an evolution,

NOTE Confidence: 0.896088968

00:03:35.920 --> 00:03:38.512 but actually coming from a revolution

NOTE Confidence: 0.896088968

00:03:38.512 --> 00:03:41.520 of quasi serendipitous pharmacology.

NOTE Confidence: 0.896088968

00:03:41.520 --> 00:03:43.410 And I say that because when Dan

NOTE Confidence: 0.896088968

00:03:43.410 --> 00:03:45.333 Drucker was here a few weeks ago

NOTE Confidence: 0.896088968

00:03:45.333 --> 00:03:47.214 who gave a wonderful talk about GRP

NOTE Confidence: 0.896088968

00:03:47.214 --> 00:03:49.069 one and what came since mid 80s,

NOTE Confidence: 0.896088968

00:03:49.069 --> 00:03:51.190 when I asked him could you please

NOTE Confidence: 0.896088968

00:03:51.257 --> 00:03:53.267 tell me how these medications

NOTE Confidence: 0.896088968

00:03:53.267 --> 00:03:55.119 relate to Physiology, he said none,  
NOTE Confidence: 0.896088968

00:03:55.119 --> 00:03:55.758 not at all,  
NOTE Confidence: 0.896088968

00:03:55.760 --> 00:03:56.042 zero.  
NOTE Confidence: 0.896088968

00:03:56.042 --> 00:03:57.734 This is all pure pharmacology and  
NOTE Confidence: 0.896088968

00:03:57.734 --> 00:04:00.159 I think it's a very important conclusion.  
NOTE Confidence: 0.929064631428571

00:04:00.160 --> 00:04:02.596 It's a very important thing to consider  
NOTE Confidence: 0.929064631428571

00:04:02.600 --> 00:04:04.917 because it seems that in this case  
NOTE Confidence: 0.929064631428571

00:04:04.917 --> 00:04:06.736 and potentially many other diseases  
NOTE Confidence: 0.929064631428571

00:04:06.736 --> 00:04:09.034 that are undissolved for the moment,  
NOTE Confidence: 0.929064631428571

00:04:09.040 --> 00:04:12.672 the meticulous way of understanding  
NOTE Confidence: 0.929064631428571

00:04:12.672 --> 00:04:13.704 the physiological mechanism  
NOTE Confidence: 0.929064631428571

00:04:13.704 --> 00:04:15.680 may not lead to solutions.  
NOTE Confidence: 0.929064631428571

00:04:15.680 --> 00:04:17.600 However, such pharmacology as we've  
NOTE Confidence: 0.929064631428571

00:04:17.600 --> 00:04:19.968 been discussing or we'll be discussing  
NOTE Confidence: 0.929064631428571

00:04:19.968 --> 00:04:22.635 today may lead to solutions of disease.  
NOTE Confidence: 0.929064631428571

00:04:22.640 --> 00:04:25.196 And I think it may apply again for many,



NOTE Confidence: 0.929064631428571  
00:04:25.200 --> 00:04:27.040 many diseases for the future,  
NOTE Confidence: 0.929064631428571  
00:04:27.040 --> 00:04:28.447 including neurological disorders.  
NOTE Confidence: 0.929064631428571  
00:04:28.447 --> 00:04:30.792 So an evolution which was  
NOTE Confidence: 0.929064631428571  
00:04:30.792 --> 00:04:32.519 actually beautiful was insulin.  
NOTE Confidence: 0.929064631428571  
00:04:32.520 --> 00:04:33.976 When insulin was discovered,  
NOTE Confidence: 0.929064631428571  
00:04:33.976 --> 00:04:36.561 that really led to a fundamental change  
NOTE Confidence: 0.929064631428571  
00:04:36.561 --> 00:04:38.559 in how millions of people saved,  
NOTE Confidence: 0.929064631428571  
00:04:38.560 --> 00:04:40.960 millions of people's lives have been  
NOTE Confidence: 0.929064631428571  
00:04:40.960 --> 00:04:43.000 saved and continuously being saved.  
NOTE Confidence: 0.929064631428571  
00:04:43.000 --> 00:04:45.168 So that was a great example of how  
NOTE Confidence: 0.929064631428571  
00:04:45.168 --> 00:04:47.451 there is an evolution of science that  
NOTE Confidence: 0.929064631428571  
00:04:47.451 --> 00:04:49.077 leads to a medical intervention.  
NOTE Confidence: 0.929064631428571  
00:04:49.077 --> 00:04:52.102 I'm going to tell you a little bit about  
NOTE Confidence: 0.929064631428571  
00:04:52.102 --> 00:04:54.298 the evolution of our understanding of  
NOTE Confidence: 0.929064631428571  
00:04:54.298 --> 00:04:56.233 metabolism and obesity regulation from  
NOTE Confidence: 0.929064631428571

00:04:56.233 --> 00:04:58.513 from the perspective of the brain.  
NOTE Confidence: 0.929064631428571

00:04:58.520 --> 00:05:00.676 And indeed this is known by most,  
NOTE Confidence: 0.929064631428571

00:05:00.680 --> 00:05:03.640 that the main reason why we gain weight  
NOTE Confidence: 0.929064631428571

00:05:03.640 --> 00:05:06.675 is because we eat more and eating is  
NOTE Confidence: 0.929064631428571

00:05:06.675 --> 00:05:09.672 primarily governed by by the brain and  
NOTE Confidence: 0.929064631428571

00:05:09.672 --> 00:05:11.596 very specifically physiologically is  
NOTE Confidence: 0.929064631428571

00:05:11.596 --> 00:05:14.176 governed by by the by the hypothalamus.  
NOTE Confidence: 0.929064631428571

00:05:14.176 --> 00:05:16.479 And I was lucky enough to be involved  
NOTE Confidence: 0.929064631428571

00:05:16.479 --> 00:05:18.615 in one of the first studies here in  
NOTE Confidence: 0.929064631428571

00:05:18.680 --> 00:05:20.552 a year when I came to you in 1990  
NOTE Confidence: 0.929064631428571

00:05:20.560 --> 00:05:22.095 that described relationship between 2  
NOTE Confidence: 0.929064631428571

00:05:22.095 --> 00:05:24.320 subsets of neurons in the hypothalamus,  
NOTE Confidence: 0.929064631428571

00:05:24.320 --> 00:05:27.376 one for using MPY or now we know  
NOTE Confidence: 0.929064631428571

00:05:27.376 --> 00:05:29.794 AGRP and the other one that was  
NOTE Confidence: 0.929064631428571

00:05:29.794 --> 00:05:31.150 producing pro opioid metacortin  
NOTE Confidence: 0.929064631428571

00:05:31.211 --> 00:05:33.199 peptide including beta endorphins.

NOTE Confidence: 0.929064631428571

00:05:33.200 --> 00:05:35.498 And in 1992 we suggested that

NOTE Confidence: 0.929064631428571

00:05:35.498 --> 00:05:37.465 this interplay between these two

NOTE Confidence: 0.929064631428571

00:05:37.465 --> 00:05:39.679 subsets of neurons might be relevant

NOTE Confidence: 0.929064631428571

00:05:39.679 --> 00:05:41.520 for the control of hunger.

NOTE Confidence: 0.929064631428571

00:05:41.520 --> 00:05:44.160 And in fact with the subsequent

NOTE Confidence: 0.929064631428571

00:05:44.160 --> 00:05:47.050 discovery of leptin by Jeff Friedman's

NOTE Confidence: 0.929064631428571

00:05:47.050 --> 00:05:50.242 positional cloning of of leptin did

NOTE Confidence: 0.929064631428571

00:05:50.242 --> 00:05:52.414 lead to the conclusion that indeed

NOTE Confidence: 0.929064631428571

00:05:52.414 --> 00:05:54.806 this hormone that is secreted by the

NOTE Confidence: 0.929064631428571

00:05:54.806 --> 00:05:57.424 adipose tissue in the year of your body

NOTE Confidence: 0.929064631428571

00:05:57.424 --> 00:05:59.832 mass signals to the hypothalamus to to

NOTE Confidence: 0.929064631428571

00:05:59.840 --> 00:06:02.318 these two specific subset of neurons

NOTE Confidence: 0.929064631428571

00:06:02.320 --> 00:06:05.800 to control eating to promote satiety.

NOTE Confidence: 0.929064631428571

00:06:05.800 --> 00:06:06.946 Few years later,

NOTE Confidence: 0.929064631428571

00:06:06.946 --> 00:06:08.856 Matthias Chirp and eventually in

NOTE Confidence: 0.929064631428571

00:06:08.856 --> 00:06:10.519 collaboration with Matthias Chirp,  
NOTE Confidence: 0.929064631428571

00:06:10.520 --> 00:06:11.408 we showed the ghrelin,  
NOTE Confidence: 0.929064631428571

00:06:11.408 --> 00:06:12.518 A hormone that is sick,  
NOTE Confidence: 0.929064631428571

00:06:12.520 --> 00:06:14.837 secreting from the gut that is elevated  
NOTE Confidence: 0.929064631428571

00:06:14.837 --> 00:06:17.277 when you have less fuel available that  
NOTE Confidence: 0.929064631428571

00:06:17.277 --> 00:06:20.134 comes to the brain that's come to the  
NOTE Confidence: 0.929064631428571

00:06:20.134 --> 00:06:21.949 hypothalamus and again functions in  
NOTE Confidence: 0.929064631428571

00:06:21.949 --> 00:06:24.680 the same subset of neurons to control,  
NOTE Confidence: 0.929064631428571

00:06:24.680 --> 00:06:26.320 in this case hunger.  
NOTE Confidence: 0.929064631428571

00:06:26.320 --> 00:06:28.392 And the idea was that with these  
NOTE Confidence: 0.929064631428571

00:06:28.392 --> 00:06:29.920 two subsets of hormones,  
NOTE Confidence: 0.929064631428571

00:06:29.920 --> 00:06:31.204 ghelin and leptin,  
NOTE Confidence: 0.929064631428571

00:06:31.204 --> 00:06:34.200 eventually we would be able to control  
NOTE Confidence: 0.929064631428571

00:06:34.276 --> 00:06:37.276 obesity and find medications to obesity.  
NOTE Confidence: 0.929064631428571

00:06:37.280 --> 00:06:39.632 This was further supported by the by  
NOTE Confidence: 0.929064631428571

00:06:39.632 --> 00:06:42.153 the findings and discoveries of three

NOTE Confidence: 0.929064631428571

00:06:42.153 --> 00:06:44.918 very talented individuals in Cambridge,

NOTE Confidence: 0.929064631428571

00:06:44.920 --> 00:06:45.960 Sadaf, Farooqi,

NOTE Confidence: 0.929064631428571

00:06:45.960 --> 00:06:48.560 Jazeo and and Steve O'Reilly,

NOTE Confidence: 0.929064631428571

00:06:48.560 --> 00:06:51.120 who identified single mutations in

NOTE Confidence: 0.929064631428571

00:06:51.120 --> 00:06:53.680 this pathway of the hypothalamus

NOTE Confidence: 0.929064631428571

00:06:53.680 --> 00:06:55.063 that underlie obesity.

NOTE Confidence: 0.929064631428571

00:06:55.063 --> 00:06:59.080 Now these are few cases in the maximum,

NOTE Confidence: 0.929064631428571

00:06:59.080 --> 00:07:01.460 if you Add all these together may

NOTE Confidence: 0.929064631428571

00:07:01.460 --> 00:07:03.496 represent 1010% of of obesity.

NOTE Confidence: 0.929064631428571

00:07:03.496 --> 00:07:05.192 But nevertheless they suggested

NOTE Confidence: 0.929064631428571

00:07:05.192 --> 00:07:07.281 that genetic underpinning is the

NOTE Confidence: 0.929064631428571

00:07:07.281 --> 00:07:09.627 cause of obesity and perhaps finding

NOTE Confidence: 0.929064631428571

00:07:09.627 --> 00:07:11.885 the way to interfere with these

NOTE Confidence: 0.929064631428571

00:07:11.885 --> 00:07:13.680 pathways would help us deal

NOTE Confidence: 0.520070371111111

00:07:13.680 --> 00:07:14.992 with the with this,

NOTE Confidence: 0.520070371111111

00:07:14.992 --> 00:07:16.632 with the with the disease.  
NOTE Confidence: 0.5200703711111111

00:07:16.640 --> 00:07:18.596 Just to summarize the circuitry again,  
NOTE Confidence: 0.5200703711111111

00:07:18.600 --> 00:07:20.200 it's a very simple one.  
NOTE Confidence: 0.5200703711111111

00:07:20.200 --> 00:07:21.510 In this case I indicate  
NOTE Confidence: 0.5200703711111111

00:07:21.510 --> 00:07:22.558 you're the peripheral stomach,  
NOTE Confidence: 0.5200703711111111

00:07:22.560 --> 00:07:24.200 you have low energy availability.  
NOTE Confidence: 0.5200703711111111

00:07:24.200 --> 00:07:26.354 You have signals such as ghrelin  
NOTE Confidence: 0.5200703711111111

00:07:26.354 --> 00:07:28.655 coming to the hypothalamus and in this  
NOTE Confidence: 0.5200703711111111

00:07:28.655 --> 00:07:30.910 part of the brain you have these T2  
NOTE Confidence: 0.5200703711111111

00:07:30.910 --> 00:07:33.122 subsets of neurons that HGRP the MP1  
NOTE Confidence: 0.5200703711111111

00:07:33.122 --> 00:07:34.711 neurons when activated they promote  
NOTE Confidence: 0.5200703711111111

00:07:34.711 --> 00:07:36.930 hunger and then you eat they they  
NOTE Confidence: 0.5200703711111111

00:07:36.991 --> 00:07:39.133 get turned off and those neurons  
NOTE Confidence: 0.5200703711111111

00:07:39.133 --> 00:07:40.993 that produce menacordin active are  
NOTE Confidence: 0.5200703711111111

00:07:40.993 --> 00:07:42.863 activated and acting through the  
NOTE Confidence: 0.5200703711111111

00:07:42.863 --> 00:07:44.765 menacordin 4 receptor promote satiety.

NOTE Confidence: 0.5200703711111111

00:07:44.765 --> 00:07:47.600 So there are interesting aspects of this

NOTE Confidence: 0.5200703711111111

00:07:47.600 --> 00:07:50.197 these these anatomy and that is that

NOTE Confidence: 0.5200703711111111

00:07:50.200 --> 00:07:52.798 the the default circuitry promotes hunger.

NOTE Confidence: 0.5200703711111111

00:07:52.800 --> 00:07:54.834 So this is one of the culprit of of

NOTE Confidence: 0.5200703711111111

00:07:54.834 --> 00:07:57.157 our our our life and that is our brain.

NOTE Confidence: 0.5200703711111111

00:07:57.160 --> 00:07:58.992 We always try to make an attempt to

NOTE Confidence: 0.5200703711111111

00:07:58.992 --> 00:08:00.701 drive us to eat and it's sensible

NOTE Confidence: 0.5200703711111111

00:08:00.701 --> 00:08:02.785 because if he was the other way around

NOTE Confidence: 0.5200703711111111

00:08:02.785 --> 00:08:04.717 then you would die soon after birth.

NOTE Confidence: 0.5200703711111111

00:08:04.720 --> 00:08:08.240 So you have to have the drive drive to eat.

NOTE Confidence: 0.5200703711111111

00:08:08.240 --> 00:08:08.540 However,

NOTE Confidence: 0.5200703711111111

00:08:08.540 --> 00:08:11.240 when you live in society such as we do,

NOTE Confidence: 0.5200703711111111

00:08:11.240 --> 00:08:12.965 and you have easily available

NOTE Confidence: 0.5200703711111111

00:08:12.965 --> 00:08:14.000 color dense foods,

NOTE Confidence: 0.5200703711111111

00:08:14.000 --> 00:08:16.260 then obviously this scenario

NOTE Confidence: 0.5200703711111111

00:08:16.260 --> 00:08:18.520 becomes becomes a burden.  
NOTE Confidence: 0.5200703711111111

00:08:18.520 --> 00:08:19.272 And many,  
NOTE Confidence: 0.5200703711111111

00:08:19.272 --> 00:08:21.528 many things that are associated with  
NOTE Confidence: 0.5200703711111111

00:08:21.528 --> 00:08:23.438 this circuitry indicates that it's  
NOTE Confidence: 0.5200703711111111

00:08:23.438 --> 00:08:25.986 enormously flexible and it will keep on  
NOTE Confidence: 0.5200703711111111

00:08:26.048 --> 00:08:28.640 trying to make you eat more because again,  
NOTE Confidence: 0.5200703711111111

00:08:28.640 --> 00:08:29.306 you don't know.  
NOTE Confidence: 0.5200703711111111

00:08:29.306 --> 00:08:31.490 We we evolved in a way that we don't  
NOTE Confidence: 0.5200703711111111

00:08:31.490 --> 00:08:33.200 know whether we have food tomorrow.  
NOTE Confidence: 0.5200703711111111

00:08:33.200 --> 00:08:35.513 So it's better to put it in today to  
NOTE Confidence: 0.5200703711111111

00:08:35.513 --> 00:08:37.717 make sure that tomorrow we survive.  
NOTE Confidence: 0.5200703711111111

00:08:37.720 --> 00:08:39.920 And perhaps because of this  
NOTE Confidence: 0.5200703711111111

00:08:39.920 --> 00:08:42.120 complicated flexibility of the system,  
NOTE Confidence: 0.5200703711111111

00:08:42.120 --> 00:08:44.496 despite all the advances that we had on  
NOTE Confidence: 0.5200703711111111

00:08:44.496 --> 00:08:46.932 on the circuitry on the physiological  
NOTE Confidence: 0.5200703711111111

00:08:46.932 --> 00:08:49.152 regulation of of of metabolism,



NOTE Confidence: 0.5200703711111111  
00:08:49.160 --> 00:08:51.070 we could not develop really  
NOTE Confidence: 0.5200703711111111  
00:08:51.070 --> 00:08:52.598 pharmacological treatments to obesity.  
NOTE Confidence: 0.5200703711111111  
00:08:52.600 --> 00:08:55.720 It's a few exceptional MC4 receptor  
NOTE Confidence: 0.5200703711111111  
00:08:55.720 --> 00:08:58.268 agonies but but I believe that those  
NOTE Confidence: 0.5200703711111111  
00:08:58.268 --> 00:09:01.405 are also not at the at the league of  
NOTE Confidence: 0.5200703711111111  
00:09:01.405 --> 00:09:03.460 of of these incretin based approaches.  
NOTE Confidence: 0.5200703711111111  
00:09:03.460 --> 00:09:06.929 So it seems at least in this case the  
NOTE Confidence: 0.5200703711111111  
00:09:06.929 --> 00:09:09.918 science and medicine may be less connected.  
NOTE Confidence: 0.5200703711111111  
00:09:09.920 --> 00:09:13.037 It's a question that that we ask and  
NOTE Confidence: 0.5200703711111111  
00:09:13.037 --> 00:09:15.032 then serendipitous sheer luck may  
NOTE Confidence: 0.5200703711111111  
00:09:15.032 --> 00:09:17.953 have more to do with the success of  
NOTE Confidence: 0.5200703711111111  
00:09:17.953 --> 00:09:19.898 of of development of medical advances.  
NOTE Confidence: 0.5200703711111111  
00:09:19.898 --> 00:09:22.210 And I believe and it's again it's my  
NOTE Confidence: 0.5200703711111111  
00:09:22.268 --> 00:09:23.972 personal view that to some degree  
NOTE Confidence: 0.5200703711111111  
00:09:23.972 --> 00:09:26.180 what we are dealing here with today  
NOTE Confidence: 0.5200703711111111

00:09:26.180 --> 00:09:27.197 on obesity medication,  
NOTE Confidence: 0.5200703711111111

00:09:27.200 --> 00:09:30.836 there is that potential relevance here.  
NOTE Confidence: 0.5200703711111111

00:09:30.840 --> 00:09:32.996 But it's also yes and no because  
NOTE Confidence: 0.5200703711111111

00:09:32.996 --> 00:09:34.838 obviously this system has been there.  
NOTE Confidence: 0.5200703711111111

00:09:34.840 --> 00:09:37.180 So those those peptide family that  
NOTE Confidence: 0.5200703711111111

00:09:37.180 --> 00:09:37.960 includes Glucagon,  
NOTE Confidence: 0.5200703711111111

00:09:37.960 --> 00:09:40.728 GRP one and \*\*\* one that Anya talked  
NOTE Confidence: 0.5200703711111111

00:09:40.728 --> 00:09:43.569 about had been known to be playing  
NOTE Confidence: 0.5200703711111111

00:09:43.569 --> 00:09:45.639 a role in systemic metabolism.  
NOTE Confidence: 0.5200703711111111

00:09:45.640 --> 00:09:48.529 \*\*\* One for example is a is an important  
NOTE Confidence: 0.5200703711111111

00:09:48.529 --> 00:09:50.198 controller of insulin release and  
NOTE Confidence: 0.5200703711111111

00:09:50.198 --> 00:09:52.440 it's all happening in in the gut.  
NOTE Confidence: 0.5200703711111111

00:09:52.440 --> 00:09:54.966 If you look at the relationship  
NOTE Confidence: 0.5200703711111111

00:09:54.966 --> 00:09:57.149 between \*\*\* one and \*\*\* One,  
NOTE Confidence: 0.5200703711111111

00:09:57.149 --> 00:09:59.243 they all have their own individual  
NOTE Confidence: 0.5200703711111111

00:09:59.243 --> 00:10:00.840 impacts on various tissues.

NOTE Confidence: 0.5200703711111111

00:10:00.840 --> 00:10:02.200 And if you look at how they work,

NOTE Confidence: 0.5200703711111111

00:10:02.200 --> 00:10:05.200 they they promote insulin secretion.

NOTE Confidence: 0.5200703711111111

00:10:05.200 --> 00:10:07.810 Some of them \*\*\* 1 suppresses

NOTE Confidence: 0.5200703711111111

00:10:07.810 --> 00:10:08.680 Glucagon release,

NOTE Confidence: 0.66735123

00:10:08.680 --> 00:10:10.655 \*\*\* promotes Glucagon and Glucagon

NOTE Confidence: 0.66735123

00:10:10.655 --> 00:10:13.500 is one of those entities that were

NOTE Confidence: 0.66735123

00:10:13.500 --> 00:10:16.164 sort of dismissed in this area for

NOTE Confidence: 0.66735123

00:10:16.164 --> 00:10:18.138 a while as not something that you

NOTE Confidence: 0.66735123

00:10:18.138 --> 00:10:20.280 want to pursue in order to deal

NOTE Confidence: 0.66735123

00:10:20.280 --> 00:10:22.276 with the metabolism and to deal

NOTE Confidence: 0.66735123

00:10:22.276 --> 00:10:24.116 with the with obesity specifically.

NOTE Confidence: 0.66735123

00:10:24.120 --> 00:10:26.969 And the classical view was then during

NOTE Confidence: 0.66735123

00:10:26.969 --> 00:10:28.999 hyperglycemia from the artha cells

NOTE Confidence: 0.66735123

00:10:29.000 --> 00:10:32.213 you have the release of Glucagon and

NOTE Confidence: 0.66735123

00:10:32.213 --> 00:10:34.005 that promotes gluconalogenesis by

NOTE Confidence: 0.66735123

00:10:34.005 --> 00:10:36.780 delivery and that's how you sort of  
NOTE Confidence: 0.66735123

00:10:36.780 --> 00:10:39.960 survive in the under those conditions.  
NOTE Confidence: 0.66735123

00:10:39.960 --> 00:10:42.984 However, today we understand little more  
NOTE Confidence: 0.66735123

00:10:42.984 --> 00:10:45.920 about the about the Glucagon system.  
NOTE Confidence: 0.66735123

00:10:45.920 --> 00:10:49.600 So there are important roles of fatty acids,  
NOTE Confidence: 0.66735123

00:10:49.600 --> 00:10:52.600 metabolites, product in endocrine signals,  
NOTE Confidence: 0.66735123

00:10:52.600 --> 00:10:54.800 uterine signals and the overall  
NOTE Confidence: 0.66735123

00:10:54.800 --> 00:10:56.256 effect of Glucagon.  
NOTE Confidence: 0.66735123

00:10:56.256 --> 00:10:58.560 It goes beyond gluconeogenesis,  
NOTE Confidence: 0.66735123

00:10:58.560 --> 00:11:00.960 It also promotes life policies,  
NOTE Confidence: 0.66735123

00:11:00.960 --> 00:11:03.600 fatty acid oxidation, ketogenesis,  
NOTE Confidence: 0.66735123

00:11:03.600 --> 00:11:05.832 promotes satiety and thermogenesis  
NOTE Confidence: 0.66735123

00:11:05.832 --> 00:11:07.200 and energy expenditure.  
NOTE Confidence: 0.66735123

00:11:07.200 --> 00:11:09.372 So the newest version of these  
NOTE Confidence: 0.66735123

00:11:09.372 --> 00:11:11.732 drugs are actually a combination of  
NOTE Confidence: 0.66735123

00:11:11.732 --> 00:11:14.234 all these three peptide GLP one,

NOTE Confidence: 0.66735123

00:11:14.240 --> 00:11:17.522 \*\*\* one and and and Glucagon mimics.

NOTE Confidence: 0.66735123

00:11:17.522 --> 00:11:20.418 And this is going to be potentially the

NOTE Confidence: 0.66735123

00:11:20.418 --> 00:11:23.077 next generation of of of these drugs,

NOTE Confidence: 0.66735123

00:11:23.080 --> 00:11:25.235 semaglutide still being one of

NOTE Confidence: 0.66735123

00:11:25.235 --> 00:11:26.959 the most successful one.

NOTE Confidence: 0.66735123

00:11:26.960 --> 00:11:28.310 And then you have the combination

NOTE Confidence: 0.66735123

00:11:28.310 --> 00:11:30.712 of Glucagon, \*\*\* one, \*\*\* one,

NOTE Confidence: 0.66735123

00:11:30.712 --> 00:11:34.398 \*\*\* one and the triple triple agonist.

NOTE Confidence: 0.66735123

00:11:34.400 --> 00:11:36.549 And it's assumed that it probably will

NOTE Confidence: 0.66735123

00:11:36.549 --> 00:11:39.237 be the case that you will accomplish

NOTE Confidence: 0.66735123

00:11:39.237 --> 00:11:41.357 significant weight loss with the

NOTE Confidence: 0.66735123

00:11:41.357 --> 00:11:42.960 combination of of these drugs.

NOTE Confidence: 0.66735123

00:11:42.960 --> 00:11:44.634 Now he questions remain and these

NOTE Confidence: 0.66735123

00:11:44.634 --> 00:11:46.329 are the questions that I'm very

NOTE Confidence: 0.66735123

00:11:46.329 --> 00:11:47.913 much interested in and my laboratory

NOTE Confidence: 0.66735123

00:11:47.913 --> 00:11:49.438 is very much interested in.  
NOTE Confidence: 0.66735123

00:11:49.440 --> 00:11:51.869 Many of us in a comparative medicine  
NOTE Confidence: 0.66735123

00:11:51.869 --> 00:11:54.159 department are very much interested in.  
NOTE Confidence: 0.66735123

00:11:54.160 --> 00:11:56.192 So first of all despite of the fact  
NOTE Confidence: 0.66735123

00:11:56.192 --> 00:11:58.492 that this is a very fundamental  
NOTE Confidence: 0.66735123

00:11:58.492 --> 00:11:59.358 successful pharmacology,  
NOTE Confidence: 0.66735123

00:11:59.360 --> 00:12:01.508 we should really understand the mechanism  
NOTE Confidence: 0.66735123

00:12:01.508 --> 00:12:04.185 action and and how long term impact  
NOTE Confidence: 0.66735123

00:12:04.185 --> 00:12:05.761 of Physiology and pathophysiology  
NOTE Confidence: 0.66735123

00:12:05.761 --> 00:12:07.840 are affected by these actions.  
NOTE Confidence: 0.66735123

00:12:07.840 --> 00:12:10.717 And and people are working on these  
NOTE Confidence: 0.66735123

00:12:10.720 --> 00:12:13.205 and and hopefully in the near future  
NOTE Confidence: 0.66735123

00:12:13.205 --> 00:12:15.349 we will understand better what part  
NOTE Confidence: 0.66735123

00:12:15.349 --> 00:12:17.365 of the brain are mainly affected  
NOTE Confidence: 0.66735123

00:12:17.365 --> 00:12:19.319 by these various compounds.  
NOTE Confidence: 0.66735123

00:12:19.320 --> 00:12:21.485 There is indication from many

NOTE Confidence: 0.66735123

00:12:21.485 --> 00:12:23.650 laboratories that that the brainstem

NOTE Confidence: 0.66735123

00:12:23.719 --> 00:12:25.357 is a main site of action,

NOTE Confidence: 0.66735123

00:12:25.360 --> 00:12:27.280 how these drugs accomplish

NOTE Confidence: 0.66735123

00:12:27.280 --> 00:12:28.720 suppression of appetite.

NOTE Confidence: 0.66735123

00:12:28.720 --> 00:12:31.611 In the same time we also understand

NOTE Confidence: 0.66735123

00:12:31.611 --> 00:12:33.596 from from studies that they also

NOTE Confidence: 0.66735123

00:12:33.596 --> 00:12:35.720 impact many other parts of the brain.

NOTE Confidence: 0.66735123

00:12:35.720 --> 00:12:37.916 So they also impact the hypothalamus,

NOTE Confidence: 0.66735123

00:12:37.920 --> 00:12:40.034 the region I was telling you about,

NOTE Confidence: 0.66735123

00:12:40.040 --> 00:12:43.337 but that's not their main action through

NOTE Confidence: 0.66735123

00:12:43.337 --> 00:12:46.024 which they accomplish suppression of eating.

NOTE Confidence: 0.66735123

00:12:46.024 --> 00:12:49.360 But those parts going to be impacted.

NOTE Confidence: 0.66735123

00:12:49.360 --> 00:12:51.712 In fact one would argue that and the

NOTE Confidence: 0.66735123

00:12:51.712 --> 00:12:53.800 entire brain is going to be impacted,

NOTE Confidence: 0.66735123

00:12:53.800 --> 00:12:55.312 not only all parts of the brain

NOTE Confidence: 0.66735123

00:12:55.312 --> 00:12:55.960 will be impacted.  
NOTE Confidence: 0.66735123

00:12:55.960 --> 00:12:58.501 And and and Anya showed this interesting  
NOTE Confidence: 0.66735123

00:12:58.501 --> 00:13:00.000 combination of various drugs,  
NOTE Confidence: 0.66735123

00:13:00.000 --> 00:13:02.148 most of which have important action  
NOTE Confidence: 0.66735123

00:13:02.148 --> 00:13:03.580 on various neurotransmitters so  
NOTE Confidence: 0.66735123

00:13:03.640 --> 00:13:05.728 that the brain will be massively  
NOTE Confidence: 0.66735123

00:13:05.728 --> 00:13:07.120 impacted by these interventions.  
NOTE Confidence: 0.66735123

00:13:07.120 --> 00:13:09.850 And the question is to what extent  
NOTE Confidence: 0.66735123

00:13:09.850 --> 00:13:11.531 those interventions and operational  
NOTE Confidence: 0.66735123

00:13:11.531 --> 00:13:14.189 brain functions will have impact on  
NOTE Confidence: 0.66735123

00:13:14.189 --> 00:13:16.661 behaviors and also how these brain  
NOTE Confidence: 0.66735123

00:13:16.661 --> 00:13:18.044 regions eventually communicating  
NOTE Confidence: 0.66735123

00:13:18.044 --> 00:13:20.349 downwards to the periphery through  
NOTE Confidence: 0.66735123

00:13:20.349 --> 00:13:22.595 the autonomic nervous system and  
NOTE Confidence: 0.66735123

00:13:22.595 --> 00:13:24.319 the endocrine hypothalamus will  
NOTE Confidence: 0.66735123

00:13:24.319 --> 00:13:25.181 have impact



NOTE Confidence: 0.845027820416667  
00:13:25.243 --> 00:13:26.559 on on tissue function.  
NOTE Confidence: 0.845027820416667  
00:13:26.560 --> 00:13:28.396 And I'm talking about long term.  
NOTE Confidence: 0.845027820416667  
00:13:28.400 --> 00:13:30.500 So we are talking about here using  
NOTE Confidence: 0.845027820416667  
00:13:30.500 --> 00:13:32.000 these medications not for a day,  
NOTE Confidence: 0.845027820416667  
00:13:32.000 --> 00:13:33.360 not for two days,  
NOTE Confidence: 0.845027820416667  
00:13:33.360 --> 00:13:34.720 but for decades potentially.  
NOTE Confidence: 0.845027820416667  
00:13:34.720 --> 00:13:35.985 And what will be the  
NOTE Confidence: 0.845027820416667  
00:13:35.985 --> 00:13:36.997 outcome of that eventually?  
NOTE Confidence: 0.845027820416667  
00:13:37.000 --> 00:13:38.950 I think these are very important  
NOTE Confidence: 0.845027820416667  
00:13:38.950 --> 00:13:40.250 and very intriguing questions  
NOTE Confidence: 0.845027820416667  
00:13:40.305 --> 00:13:41.811 and I think this is something  
NOTE Confidence: 0.845027820416667  
00:13:41.811 --> 00:13:43.399 that we would like to pursue.  
NOTE Confidence: 0.845027820416667  
00:13:43.400 --> 00:13:45.240 Now one interesting thing that  
NOTE Confidence: 0.845027820416667  
00:13:45.240 --> 00:13:47.452 I believe is also triggering me  
NOTE Confidence: 0.845027820416667  
00:13:47.452 --> 00:13:49.594 specifically to pursue these is if you  
NOTE Confidence: 0.845027820416667

00:13:49.594 --> 00:13:51.953 look at the profile of these various  
NOTE Confidence: 0.845027820416667

00:13:51.953 --> 00:13:54.017 scenarios that I show you here,  
NOTE Confidence: 0.845027820416667

00:13:54.017 --> 00:13:55.902 color restriction which has been  
NOTE Confidence: 0.845027820416667

00:13:55.902 --> 00:13:58.509 known and promoted to be one of  
NOTE Confidence: 0.845027820416667

00:13:58.509 --> 00:14:00.234 the main interventions that you  
NOTE Confidence: 0.845027820416667

00:14:00.234 --> 00:14:01.958 can propagate healthspan and  
NOTE Confidence: 0.845027820416667

00:14:01.958 --> 00:14:04.456 lifespan incase in analogs and  
NOTE Confidence: 0.845027820416667

00:14:04.456 --> 00:14:06.960 a situation that we all consider  
NOTE Confidence: 0.845027820416667

00:14:06.960 --> 00:14:08.560 negative which is cachexia.  
NOTE Confidence: 0.845027820416667

00:14:08.560 --> 00:14:10.375 So hunger is suppressed by  
NOTE Confidence: 0.845027820416667

00:14:10.375 --> 00:14:11.827 interacting analogues as well  
NOTE Confidence: 0.845027820416667

00:14:11.827 --> 00:14:14.510 as during cachexia and hunger is  
NOTE Confidence: 0.845027820416667

00:14:14.510 --> 00:14:16.314 elevated during calorie restriction.  
NOTE Confidence: 0.845027820416667

00:14:16.320 --> 00:14:18.574 Now there are many other changes here  
NOTE Confidence: 0.845027820416667

00:14:18.574 --> 00:14:20.997 that may be similar or dissimilar  
NOTE Confidence: 0.845027820416667

00:14:20.997 --> 00:14:23.126 between these situations but one

NOTE Confidence: 0.845027820416667  
00:14:23.126 --> 00:14:25.538 question for me which is very  
NOTE Confidence: 0.845027820416667  
00:14:25.538 --> 00:14:27.771 intriguing is what might be the long  
NOTE Confidence: 0.845027820416667  
00:14:27.771 --> 00:14:30.051 term effect of of interfering with  
NOTE Confidence: 0.845027820416667  
00:14:30.051 --> 00:14:32.123 hunger through these interacting  
NOTE Confidence: 0.845027820416667  
00:14:32.123 --> 00:14:34.195 analogues on on longevity.  
NOTE Confidence: 0.845027820416667  
00:14:34.200 --> 00:14:36.312 And I think it's very intriguing  
NOTE Confidence: 0.845027820416667  
00:14:36.312 --> 00:14:38.916 to ask the question whether color  
NOTE Confidence: 0.845027820416667  
00:14:38.916 --> 00:14:41.590 restriction that of course comes with  
NOTE Confidence: 0.845027820416667  
00:14:41.590 --> 00:14:45.120 the lower food intake and increased appetite.  
NOTE Confidence: 0.845027820416667  
00:14:45.120 --> 00:14:47.444 But is it the decreased food intake  
NOTE Confidence: 0.845027820416667  
00:14:47.444 --> 00:14:49.734 that prolongs your life or it is  
NOTE Confidence: 0.845027820416667  
00:14:49.734 --> 00:14:51.269 the altered metabolic profile of  
NOTE Confidence: 0.845027820416667  
00:14:51.269 --> 00:14:53.121 the individual or the subject  
NOTE Confidence: 0.845027820416667  
00:14:53.121 --> 00:14:54.841 that makes you survive longer?  
NOTE Confidence: 0.845027820416667  
00:14:54.841 --> 00:14:57.010 And I think it would be cool to see  
NOTE Confidence: 0.845027820416667

00:14:57.066 --> 00:14:58.546 whether actually it's sufficient  
NOTE Confidence: 0.845027820416667

00:14:58.546 --> 00:15:00.766 to suppress appetite in order for  
NOTE Confidence: 0.845027820416667

00:15:00.822 --> 00:15:02.654 you to really have a long and and  
NOTE Confidence: 0.845027820416667

00:15:02.654 --> 00:15:03.846 and and and healthy life.  
NOTE Confidence: 0.845027820416667

00:15:03.846 --> 00:15:05.540 And this is something we are very  
NOTE Confidence: 0.845027820416667

00:15:05.590 --> 00:15:06.918 much interested in pursuing.  
NOTE Confidence: 0.845027820416667

00:15:06.920 --> 00:15:09.560 We are also interested in understanding  
NOTE Confidence: 0.845027820416667

00:15:09.560 --> 00:15:11.685 how these seemingly counter intuitive  
NOTE Confidence: 0.845027820416667

00:15:11.685 --> 00:15:14.590 ideas such as the use of Semaglutat  
NOTE Confidence: 0.845027820416667

00:15:14.658 --> 00:15:16.238 for example in anorexia,  
NOTE Confidence: 0.845027820416667

00:15:16.240 --> 00:15:18.375 narrow setting might actually benefit  
NOTE Confidence: 0.845027820416667

00:15:18.375 --> 00:15:21.120 certain subpopulation of of of subjects.  
NOTE Confidence: 0.845027820416667

00:15:21.120 --> 00:15:22.080 And we've been doing that.  
NOTE Confidence: 0.845027820416667

00:15:22.080 --> 00:15:23.862 We were working on that in  
NOTE Confidence: 0.845027820416667

00:15:23.862 --> 00:15:26.200 my lab in in animal models.  
NOTE Confidence: 0.845027820416667

00:15:26.200 --> 00:15:26.476 Overall,

NOTE Confidence: 0.845027820416667  
00:15:26.476 --> 00:15:28.684 I think and I would like to finish  
NOTE Confidence: 0.845027820416667  
00:15:28.684 --> 00:15:30.796 with that that I believe that Why  
NOTE Confidence: 0.845027820416667  
00:15:30.796 --> 00:15:32.776 Weight is an amazing organization  
NOTE Confidence: 0.845027820416667  
00:15:32.776 --> 00:15:36.080 and it has an intellectual capacity  
NOTE Confidence: 0.845027820416667  
00:15:36.080 --> 00:15:38.488 and that has the ability to push  
NOTE Confidence: 0.845027820416667  
00:15:38.488 --> 00:15:39.994 forward the understanding of  
NOTE Confidence: 0.845027820416667  
00:15:39.994 --> 00:15:42.072 these upcoming challenges of this  
NOTE Confidence: 0.845027820416667  
00:15:42.072 --> 00:15:43.742 remarkable new pharmaco therapeutics.  
NOTE Confidence: 0.845027820416667  
00:15:43.742 --> 00:15:46.696 So obviously both at the pre clinical  
NOTE Confidence: 0.845027820416667  
00:15:46.696 --> 00:15:49.376 and and the clinical arena and I would  
NOTE Confidence: 0.845027820416667  
00:15:49.376 --> 00:15:51.280 like to thank you for your attention.  
NOTE Confidence: 0.830522006  
00:15:59.760 --> 00:16:02.448 Perfect on timing too.  
NOTE Confidence: 0.830522006  
00:16:02.448 --> 00:16:06.840 So questions for Doctor Horvath, Yes.  
NOTE Confidence: 0.810483131666667  
00:16:18.240 --> 00:16:20.576 So we use a model where where it's  
NOTE Confidence: 0.810483131666667  
00:16:20.576 --> 00:16:22.892 an animal model where we put the  
NOTE Confidence: 0.810483131666667

00:16:22.892 --> 00:16:24.968 animals in a scenario where they  
NOTE Confidence: 0.810483131666667

00:16:24.968 --> 00:16:27.383 have access to wheel and we restrict  
NOTE Confidence: 0.810483131666667

00:16:27.383 --> 00:16:29.315 their food intake and and what you  
NOTE Confidence: 0.810483131666667

00:16:29.315 --> 00:16:31.269 find is that most of the animals  
NOTE Confidence: 0.810483131666667

00:16:31.269 --> 00:16:32.924 have an addiction eventually to  
NOTE Confidence: 0.810483131666667

00:16:32.924 --> 00:16:34.772 the way running and frequently the  
NOTE Confidence: 0.810483131666667

00:16:34.772 --> 00:16:36.760 cause of death is because of the  
NOTE Confidence: 0.810483131666667

00:16:36.822 --> 00:16:38.718 exhaustion on on the real running.  
NOTE Confidence: 0.810483131666667

00:16:38.720 --> 00:16:40.940 And we are interested in understanding  
NOTE Confidence: 0.810483131666667

00:16:40.940 --> 00:16:43.330 how this addiction to the wheel might  
NOTE Confidence: 0.810483131666667

00:16:43.330 --> 00:16:45.759 be affected by some of the and how  
NOTE Confidence: 0.810483131666667

00:16:45.760 --> 00:16:47.325 the various metabolic profiles of  
NOTE Confidence: 0.810483131666667

00:16:47.325 --> 00:16:48.890 these animals during those things  
NOTE Confidence: 0.810483131666667

00:16:48.937 --> 00:16:50.365 could be affected or might be  
NOTE Confidence: 0.810483131666667

00:16:50.365 --> 00:16:51.880 affected which may be beneficial.  
NOTE Confidence: 0.810483131666667

00:16:51.880 --> 00:16:54.295 And also look at the long term

NOTE Confidence: 0.810483131666667  
00:16:54.295 --> 00:16:57.496 impact of such an intervention on on  
NOTE Confidence: 0.810483131666667  
00:16:57.496 --> 00:16:59.923 stereotypic behaviors and some long  
NOTE Confidence: 0.810483131666667  
00:16:59.923 --> 00:17:02.160 longer acting negative outcomes.  
NOTE Confidence: 0.627791075  
00:17:41.090 --> 00:17:41.810 know you want to answer that  
NOTE Confidence: 0.790147864761905  
00:17:41.810 --> 00:17:43.871 question. How can I say if you can repeat  
NOTE Confidence: 0.790147864761905  
00:17:43.871 --> 00:17:45.896 the question because I realized I did  
NOTE Confidence: 0.790147864761905  
00:17:45.896 --> 00:17:47.858 not say my housekeeping that, yeah.  
NOTE Confidence: 0.790147864761905  
00:17:47.858 --> 00:17:51.274 So the question was how does this  
NOTE Confidence: 0.790147864761905  
00:17:51.274 --> 00:17:52.970 potentially impact, you know,  
NOTE Confidence: 0.790147864761905  
00:17:52.970 --> 00:17:54.770 insulin resistance or glucose metabolism,  
NOTE Confidence: 0.790147864761905  
00:17:54.770 --> 00:17:56.726 whether a patient has insulin resistance  
NOTE Confidence: 0.790147864761905  
00:17:56.726 --> 00:17:58.667 at baseline or potentially they have  
NOTE Confidence: 0.790147864761905  
00:17:58.667 --> 00:18:00.127 obesity and don't have diabetes.  
NOTE Confidence: 0.790147864761905  
00:18:00.130 --> 00:18:02.090 Well, I I  
NOTE Confidence: 0.6970606  
00:18:04.730 --> 00:18:07.450 don't have with taking these drugs.  
NOTE Confidence: 0.575351277

00:18:08.520 --> 00:18:09.696 I think Anya you are the  
NOTE Confidence: 0.575351277

00:18:09.696 --> 00:18:10.480 right person to answer.  
NOTE Confidence: 0.575351277

00:18:10.480 --> 00:18:13.080 No, no, no, you are the clinician.  
NOTE Confidence: 0.577668384

00:18:13.480 --> 00:18:14.152 I'm the clinician.  
NOTE Confidence: 0.577668384

00:18:14.152 --> 00:18:15.557 OK, fine, I'm the clinician.  
NOTE Confidence: 0.577668384

00:18:15.557 --> 00:18:18.294 So you know what we see is in  
NOTE Confidence: 0.577668384

00:18:18.294 --> 00:18:19.998 terms of obesity treatment,  
NOTE Confidence: 0.577668384

00:18:20.000 --> 00:18:21.680 what happens with these drugs  
NOTE Confidence: 0.577668384

00:18:21.680 --> 00:18:23.360 is as people lose weight,  
NOTE Confidence: 0.577668384

00:18:23.360 --> 00:18:25.760 the insulin levels actually come down.  
NOTE Confidence: 0.577668384

00:18:25.760 --> 00:18:29.160 So, so the insulin release in terms of,  
NOTE Confidence: 0.577668384

00:18:29.160 --> 00:18:31.554 you know, the to glucose response is  
NOTE Confidence: 0.577668384

00:18:31.554 --> 00:18:33.320 more robust, but as they lose weight,  
NOTE Confidence: 0.577668384

00:18:33.320 --> 00:18:34.840 their insulin levels actually  
NOTE Confidence: 0.577668384

00:18:34.840 --> 00:18:36.080 come down long term.  
NOTE Confidence: 0.577668384

00:18:36.080 --> 00:18:37.280 You know, we don't know.



NOTE Confidence: 0.577668384

00:18:37.280 --> 00:18:38.960 We have data in, you know,

NOTE Confidence: 0.577668384

00:18:38.960 --> 00:18:40.870 individuals with type 2 diabetes

NOTE Confidence: 0.577668384

00:18:40.870 --> 00:18:42.398 who take these medications.

NOTE Confidence: 0.577668384

00:18:42.400 --> 00:18:44.040 But in in obesity in and of itself,

NOTE Confidence: 0.577668384

00:18:44.040 --> 00:18:46.200 we don't have 20 years of data yet.

NOTE Confidence: 0.577668384

00:18:46.200 --> 00:18:46.400 Yeah,

NOTE Confidence: 0.801631494

00:18:49.520 --> 00:18:51.440 yeah, too much I think great

NOTE Confidence: 0.801631494

00:18:51.440 --> 00:18:52.720 point about the pharmacology.

NOTE Confidence: 0.801631494

00:18:52.720 --> 00:18:54.736 And so one of the approaches I think

NOTE Confidence: 0.801631494

00:18:54.736 --> 00:18:56.156 everybody had been thinking about

NOTE Confidence: 0.801631494

00:18:56.156 --> 00:18:57.878 was that maybe obesity is whether

NOTE Confidence: 0.801631494

00:18:57.878 --> 00:18:59.839 the cause of obesity is hyperphagia,

NOTE Confidence: 0.801631494

00:18:59.840 --> 00:19:02.464 which is only there in a few models

NOTE Confidence: 0.801631494

00:19:02.464 --> 00:19:04.940 of genetic mutations that have this.

NOTE Confidence: 0.801631494

00:19:04.940 --> 00:19:07.342 So my question is, you know,

NOTE Confidence: 0.801631494

00:19:07.342 --> 00:19:09.862 over the period of court, you know,  
NOTE Confidence: 0.801631494

00:19:09.862 --> 00:19:13.048 long usage of these drugs that  
NOTE Confidence: 0.801631494

00:19:13.048 --> 00:19:15.959 inhibit the hedonic pathways,  
NOTE Confidence: 0.801631494

00:19:15.960 --> 00:19:18.571 they are fundamental in many ways for  
NOTE Confidence: 0.801631494

00:19:18.571 --> 00:19:20.520 some multiple species like hunger.  
NOTE Confidence: 0.801631494

00:19:20.520 --> 00:19:24.228 Where do you see these interactions  
NOTE Confidence: 0.801631494

00:19:24.228 --> 00:19:25.164 in Physiology,  
NOTE Confidence: 0.801631494

00:19:25.164 --> 00:19:27.036 in this case pharmacology  
NOTE Confidence: 0.801631494

00:19:27.040 --> 00:19:28.240 impacting individuals.  
NOTE Confidence: 0.855671173571428

00:19:28.400 --> 00:19:29.792 So I think it's a very good question  
NOTE Confidence: 0.855671173571428

00:19:29.792 --> 00:19:31.158 and we are interested in these.  
NOTE Confidence: 0.855671173571428

00:19:31.160 --> 00:19:33.293 The The fact of the matter is that the  
NOTE Confidence: 0.855671173571428

00:19:33.293 --> 00:19:34.983 actual trial is going on with humans  
NOTE Confidence: 0.855671173571428

00:19:34.983 --> 00:19:37.078 going to go on for a couple decades.  
NOTE Confidence: 0.855671173571428

00:19:37.080 --> 00:19:39.560 But I think we can ask these questions  
NOTE Confidence: 0.855671173571428

00:19:39.560 --> 00:19:41.518 very specifically in in in animal models,

NOTE Confidence: 0.855671173571428  
00:19:41.520 --> 00:19:43.080 let it be mouse red,  
NOTE Confidence: 0.855671173571428  
00:19:43.080 --> 00:19:44.080 the non human primate.  
NOTE Confidence: 0.855671173571428  
00:19:44.080 --> 00:19:46.370 And I think that can inform to some degree  
NOTE Confidence: 0.855671173571428  
00:19:46.370 --> 00:19:48.440 what's going on in the human human trial.  
NOTE Confidence: 0.855671173571428  
00:19:48.440 --> 00:19:51.520 But I don't think we can really  
NOTE Confidence: 0.855671173571428  
00:19:51.520 --> 00:19:53.240 declaratively conclude that until we  
NOTE Confidence: 0.855671173571428  
00:19:53.240 --> 00:19:55.520 understand more about the human situation.  
NOTE Confidence: 0.870666304  
00:19:59.960 --> 00:20:01.898 Yes, John, and we'll try and  
NOTE Confidence: 0.870666304  
00:20:01.898 --> 00:20:03.570 repeat the question unless somebody  
NOTE Confidence: 0.870666304  
00:20:03.570 --> 00:20:05.560 hands you the mic, OK shout. That  
NOTE Confidence: 0.557246277777778  
00:20:06.400 --> 00:20:10.024 was a great summon to get at the  
NOTE Confidence: 0.557246277777778  
00:20:10.024 --> 00:20:12.280 question following up on this question.  
NOTE Confidence: 0.557246277777778  
00:20:12.280 --> 00:20:14.555 So if it's the hindbrain  
NOTE Confidence: 0.557246277777778  
00:20:14.555 --> 00:20:16.426 part that's driving it,  
NOTE Confidence: 0.557246277777778  
00:20:16.426 --> 00:20:20.012 those centers are associated with the kind  
NOTE Confidence: 0.557246277777778

00:20:20.012 --> 00:20:23.779 of dangerous signal and put it forward.  
NOTE Confidence: 0.557246277777778

00:20:23.779 --> 00:20:26.620 So is there interactivating those,  
NOTE Confidence: 0.557246277777778

00:20:26.620 --> 00:20:30.160 those kind of tumour suppression athletes?  
NOTE Confidence: 0.557246277777778

00:20:30.160 --> 00:20:35.439 Is there a basically sympathetic notice?  
NOTE Confidence: 0.557246277777778

00:20:35.440 --> 00:20:37.997 Is there a difference between any?  
NOTE Confidence: 0.557246277777778

00:20:37.997 --> 00:20:39.899 I have a question about food  
NOTE Confidence: 0.557246277777778

00:20:39.899 --> 00:20:41.320 restriction would be hungry,  
NOTE Confidence: 0.557246277777778

00:20:41.320 --> 00:20:42.972 which is the stress.  
NOTE Confidence: 0.557246277777778

00:20:42.972 --> 00:20:45.450 Is the stress of that different  
NOTE Confidence: 0.557246277777778

00:20:45.530 --> 00:20:48.400 than the stress of being told that's  
NOTE Confidence: 0.52209723

00:20:50.680 --> 00:20:52.124 I think there's some great  
NOTE Confidence: 0.52209723

00:20:52.124 --> 00:20:53.870 work being done right now and  
NOTE Confidence: 0.872467843636364

00:20:53.927 --> 00:20:56.063 hopefully soon published that makes the  
NOTE Confidence: 0.872467843636364

00:20:56.063 --> 00:20:58.079 distinction between in the hind vein,  
NOTE Confidence: 0.872467843636364

00:20:58.080 --> 00:21:00.846 between those pathways that promote sickness  
NOTE Confidence: 0.872467843636364

00:21:00.846 --> 00:21:03.639 type of behavior versus pure satiety,

NOTE Confidence: 0.872467843636364  
00:21:03.640 --> 00:21:04.772 whatever that might mean.  
NOTE Confidence: 0.872467843636364  
00:21:04.772 --> 00:21:06.846 And I think that will answer your  
NOTE Confidence: 0.872467843636364  
00:21:06.846 --> 00:21:08.736 question whether that can be actually  
NOTE Confidence: 0.872467843636364  
00:21:08.736 --> 00:21:10.840 segregated with a pharmacological tool,  
NOTE Confidence: 0.872467843636364  
00:21:10.840 --> 00:21:11.884 that's a different question.  
NOTE Confidence: 0.872467843636364  
00:21:11.884 --> 00:21:14.074 But I think there is a reason to  
NOTE Confidence: 0.872467843636364  
00:21:14.074 --> 00:21:16.540 believe that you have pathways that  
NOTE Confidence: 0.872467843636364  
00:21:16.540 --> 00:21:18.440 are promoting sickness behaviour,  
NOTE Confidence: 0.872467843636364  
00:21:18.440 --> 00:21:19.946 but those are that are not  
NOTE Confidence: 0.872467843636364  
00:21:19.946 --> 00:21:20.950 promoting sickness behaviour and  
NOTE Confidence: 0.872467843636364  
00:21:20.998 --> 00:21:22.318 nevertheless suppress appetite.