Lesson 15

Nutrition and the Nervous System

Video 3 Supplement

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About

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Overview

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In the following slides, you will learn about how the nervous system interacts with food. This is a fusion of neuroscience and nutrition that is extremely important to understand. Learning about the nervous system and its impact on food can help you to make better food choices, beyond the excitement of just learning fascinating new things about the human body.

Why This Topic?

Why This Topic?

- On May 19, 2021, Science Daily reported on a new paper published in *Nature Neuroscience*.[1,2] In this new paper, researchers from several hospitals and research institutes in Germany, Austria, and the United Kingdom report on their examination of several neurons in the brain's hippocampus and their impact on metabolism.
- The researchers found two different types of metabolism-regulating neurons in the hypothalamus: $POMC^{Lepr+}$ and $POMC^{Glp1r+}$, or pro-opiomelanocortin neurons with leptin (an energy balance hormone) or glucagon-like peptide (which regulates insulin release, among other functions) receptors respectively.

Neurons and Nutrition

Neurons and Nutrition

Many neurons impact how we eat and digest food. In this presentation, here are the neurons that we will cover in detail:

- POMC
- GABAergic
- AgRP/NPY
- D1

Neurons in Detail

POMC Neurons

- POMC neurons are the neurons that were examined in the recent *Nature Neuroscience* paper.[2] However, what role do they play in nutrition? Before we answer that question, let's learn what POMC neurons even are.
- POMC neurons, or pro-opiomelanocortin neurons, are neurons that are located in the brain's hypothalamus. These neurons are developed in a long, time-consuming process in the brain, although that can only be substantiated by mouse studies.[3]
- POMC neurons are regulated by several different types of modulators, including leptin, nicotine, etc.

Roles of POMC Neurons

- POMC neurons play several roles in the human body. For example, POMC neurons have been shown to play a role in the anti-inflammatory effects of certain cytokines (key immune cells), the function of the endoplasmic reticulum in cells, as well as autophagy.[3]
- First, POMC is related to inflammation. A 2016 paper in *Scientific Reports* found that POMC neurons that are improperly regulated result in inflammation in the hypothalamus, where the neurons are found, in obese individuals.[4] Further, a 2007 animal study in *Endocrinology* found that interleukin 1□ plays a role in increased inflammation because it stimulates POMC neurons specifically.[5]
- POMC neurons are thus responsible (indirectly) for regulating inflammation.

Roles of POMC Neurons

- So far, we know that POMC neurons regulate bodily inflammation, such as in the cytokines. However, how do POMC neurons regulate inflammation?
- A 2018 article in *eLife* reports on an animal study that shows that a molecule called leptin regulates the actions of POMC neurons.[6] Think of leptin as being similar to the role of an air traffic controller, who regulates when planes take off and land.
- Leptin, first found in 1994, is partially responsible for maintaining homeostasis (a state of bodily balance) in the brain. Leptin does this in a variety of ways, most notably through several types of neural circuits.[7] In fact, obesity is associated with leptin resistance, which explains why POMC neurons are partially dysfunctional in obesity.[8]

Roles of POMC Neurons

- POMC neurons have additional roles beyond regulating inflammation. The second role of POMC neurons is to regulate the endoplasmic reticulum (which works with proteins).[3]
- Previously, we learned that POMC neurons play a major role in inflammation in the hypothalamus and within the immune system (in regards to IL-1□). However, POMC neurons can also play a role in inflammation outside these areas, too.
- A study from 2014 in *Cell Metabolism* found that a protein called X-box binding protein 1 (Xbp1s), found in POMC neurons, is responsible for stress in the endoplasmic reticulum.[8] The paper also found that this stress was associated with leptin and insulin resistance in obese individuals.

Roles of POMC Neurons

- What this suggests is that POMC neurons are responsible for obesity in two ways: regulation of inflammation as well as regulation of the endoplasmic reticulum.
- The third role of POMC neurons is to be remade in autophagy, a biological process that eliminates contaminated cells and creates new ones.[3] Several studies have found that autophagy plays important roles in POMC neurons.[9-11]
- First, Atg12 (autophagy-related gene 12) proteins allow autophagy to occur in POMC neurons.[9] In fact, if autophagy does not occur, POMC neurons have reduced capacity to store energy as well as create new axons and maintain metabolic function.[10,11]

GABAergic Neurons

- GABAergic neurons are among the most important neurons in the brain. However, what role do they play in nutrition? Let's find out.
- To start, let's understand what GABAergic neurons even do. GABAergic neurons have several roles, including assisting in brain development, injury, and neuron regulation and creation.[12] However, in the next slides we will discuss what role GABAergic neurons play in nutrition.
- An April 2020 paper in the *Proceedings of the National Academy of Sciences* reported on an experiment involving both male and female mice.[13] The study researchers found that the GABAergic neurons present in the hypothalamus results in brain activity that causes mice to become hungry and want food.

GABAergic Neurons

- Similar work in 2016 has also found that GABAergic neurons play an important role in nutrition and brain activity.[15-18]
- The *PNAS* paper mentioned earlier also found that GABAergic neurons in the hypothalamus pass through fibers to the ventral tegmental area (VTA) of the brain.[13] As a note, the VTA contains several neurons, including dopamine neurons, that play a vital role in the human body.[14]
- An experiment involving 21 mice whose results were published in *The Journal of Neuroscience* found a similar result to the *PNAS* paper, except that this time GABAergic neurons were projected neurons that set up a pathway to the VTA. This resulted in the rats feeling the need to eat.[15]

GABAergic Neurons

- Similar results were observed in another study in the journal *Neuron*, which found that dopamine neurons are disrupted by hypothalamic activity.[16]
- A 2015 article in the journal *Cell* also found that GABAergic neurons reduced sucrose consumption in the 12 mice tested.[17]
- Another article in the *Journal of Neuroscience*, published in 2017, found that specific GABAergic neurons can control the satisfaction that mice (and probably humans) feel from eating certain foods.[18]
- To wrap up our discussion of GABAergic neurons, fat can harm their function. A 2016 study in *Biological Research* found that high-fat diets result in rat obesity and high blood glucose, a precursor to diabetes.[19]

GABAergic Neurons

- Thus, from all of these studies across the past decade, we know that GABAergic neurons play a key role in regulating our food consumption and nutrition.[13-19]

AgRP/NPY Neurons

- The next neuron that we will explore is the AgRP neuron. Also found in the hypothalamus, the AgRP neuron is another important neuron in regards to nutrition and health. However, before delving into what AgRP neurons do in the body, let's first learn what AgRP neurons are and what they do in general.
- AgRP/NPY neurons are neurons that secrete agouti-related peptide, a neurotransmitter. These neurons play vital roles in food consumption and metabolism, as we will see.
- A 2011 experiment found that autophagy was responsible for regulating mouse food consumption and homeostasis in AgRP neurons.[20] In addition, later research has found that AgRP neurons regulate food consumption due to NPY (neuropeptide Y) signaling.[21,22]

AgRP/NPY Neurons

- Other research has found that AgRP neurons play many other roles in the body.
- AgRP neurons, for example, play a role in insulin sensitivity (how much the body reacts to insulin).
- A 2016 study whose results were published in the journal *Cell* examined whether AgRP neurons, POMC neurons (which we covered earlier), neither, or both impacted insulin sensitivity in mice. The researchers found that AgRP neurons increased insulin sensitivity, attributing the finding to an increase in melanocortin signaling (which regulates how much you eat).[23]

AgRP/NPY Neurons

- Further, this conclusion has been supported by reverse causality as well. A 2017 study in *Cell Reports* (a different journal) found that restricting a receptor of uridine diphosphate, a chemical that makes it easier to excrete toxins, can lead to weight loss and improve insulin sensitivity.[24,25] The researchers attribute this to the signaling of the uridine diphosphate receptor P2Y6 (purinergic receptor 6).
- Other studies have found that certain modifications to AgRP/NPY neurons results in changes to one's weight.[26,27] These include removing certain genes from the neurons in order to change their function, for example.[26,27]
- AgRP/NPY neurons thus play a major role in food consumption and obesity in the body, based on studies in mice and rats.[20-27]

D1 Neurons

- The third neuron that we will cover is the D1 neuron. D1 neurons have several different roles. A 2014 study in *Nature Neuroscience* found that, for example, D1 neurons play a role in regulating food intake through a neural circuit.[28]
- Further, a 2018 study in the *International Journal of Obesity* examined several male rats, finding that D1 neurons play a role in food rewards (how you feel after eating). In the experiment, the researchers examined rats whose protein intake was restricted. The researchers found that sensitivity to D1 neurons is a factor in determining whether or not one feels full.[29]
- Finally, a 2015 study in *Neuron* examined D1 neurons that stretch from the brain to other parts of the central nervous system in several mice.[30]

D1 Neurons

- Researchers found that D1 neurons are less active when one is eating and more active after one is completely done eating.[30]
- Thus, as we can see, D1 neurons have fairly interesting roles when it comes to nutrition and health. Their main roles (in regards to nutrition) are to regulate food intake. However, D1 neurons have been used for other purposes beyond nutrition.
- As an example, earlier this year a paper was published in the journal *eLife* that introduced a new technology for feeding mice, called the Feeding Experimentation Device (FED). The researchers targeted D1 neurons while developing the technology.[31]

The Brain and Nutrition

The Brain and Nutrition

- While it is true that nutrition affects the whole body, the impacts of nutrition on each part is different. This presentation is about the impact on the nervous system specifically. Now that we have examined the neurons, we will look at the brain, spinal cord, and the peripheral nervous system.
- A 2008 review article in *Nature Reviews Neuroscience* examined factors that affect brain health and found that healthy diet, exercise, and other lifestyle factors are important in maintaining one's health.[32]
- In this section of the presentation, we will look at nutrition in regards to the entirety of the brain and not just one part of it. Let's explore.

The Brain and Nutrition

- Dietary factors play a major role in brain function. A 2017 review article in *NPJ Food Science* found that certain signaling molecules play a role in the function of the food-brain axis, a biological interconnection between food consumption and brain health.[33]
- Further, a 2018 review article published in *Nutrition Reviews* found that gut bacteria play a key role in regulating brain function. This is because gut bacteria function within a microbiota-gut-brain axis, which allows the gut microbiota to regulate the brain and the gut (similar to checks and balances in the government, except for health this time).[34]
- What is the microbiota-gut-brain axis, however? We will find out in the next slide.

The Brain and Nutrition

- The gut-brain-microbiota axis is a biological construct that defines the idea that the brain and gut microbiota are connected to each other through biological mechanisms. The concept has been used to study several types of diseases in and beyond the brain.[35]
- In essence, the idea behind the gut-brain-microbiota axis is that the three are linked together and affect each other. For example, key signaling pathways that are part of the endocrine system link the gut microbiota to the brain and ensure proper function of the endocrine and nervous systems.[35]
- To summarize, the gut-brain-microbiota axis is an important part of brain function that plays a key role in proper nutrition.

The Brain and Nutrition

- The gut-brain-microbiota axis is the main food-brain axis that we currently know of. Regardless, this shows the importance of the brain in maintaining personal nutrition.
- Nutrition impacts a wide variety of parts of the body, including the nervous system. In future videos, we will look at the impact of nutrition on specific parts of the body. For now, however, we will move to the spinal cord.

The Spinal Cord and Nutrition

The Spine and Nutrition

- In the previous slides, we looked at the relationship between the brain and nutrition. Now, we will turn our attention to the spine, which is an important part of the nervous system.
- Before we continue, however, let's first understand why humans evolved to have a spine. A September 2018 research report published in the journal *Science* reported on an analysis of mammal fossils. Researchers found that fossil spines have evolved constantly and regularly across the class (biologically speaking).[36]
- Mammals are vertebrates, which means that they have a backbone. Generally, mammals have a spine (including humans). However, human evolution has led to some interesting problems with our spines.

The Spine and Nutrition

- Last year, *Science Daily* reported on new research in the open access journal *Evolution, Medicine, & Public Health*.[37,38] Researchers conducted a study in which they examined the lower spines of several human, gorilla, chimpanzee, and orangutan fossils from several different countries for fractures. The researchers found that lower spine fractures were common among those whose spine shape was at the higher end of the spectrum for humans.[37]
- One question, however, remains: what role does nutrition play in spinal health? In the following slides, we will answer that question.

The Spine and Nutrition

- The American Spinal Injury Association published guidelines last year for physicians about diet and nutrition for those whose spine is injured.[38] The ASIA recommends that those who have a spinal injury eat foods that have few calories but many nutrients, but emphasizes that this topic has not been adequately studied.[39]
- However, there are studies examining this exactly. For example, a 2009 study in *The Journal of Spinal Cord Medicine* examined 74 people with spinal problems. Researchers found that women were more likely to maintain healthy diets and that nutritional counseling would benefit the population with spinal injury.[40] Nevertheless, the small sample size and the age of the study must be noted.

The Spine and Nutrition

- On the more recent side of the spectrum, a 2019 systematic review and meta-analysis in *Spinal Cord* found that those with a spinal cord injury ate more than those without, and often skipped necessary nutrients.[41]
- Finally, a case series analysis published in *The Journal of Spinal Cord Medicine* examined 10 people who were advised virtually to consume a healthy diet (eat fruits and vegetables; limit fat, salt, and sugar, etc.) Researchers found that “tele-nutrition” can improve diets of individuals with spinal cord injuries.[42]
- To conclude, the ASIA recommends a DASH- or Mediterranean-style dietary pattern based on existing evidence, especially if the person has cardiometabolic issues.[39]

Nutrients for the Nervous System

Nutrients

- There are several nutrients that benefit the nervous system. In the final section of the presentation, I will cover some of these nutrients and why they are important.
- We will cover the following nutrients:
  - ➔ B Vitamins
  - ➔ Vitamin K
  - ➔ Omega-3 fatty acids

B Vitamins

- A recently published article in *CNS Neuroscience & Therapies* found that the B vitamins – specifically Vitamins B1, B6, and B12 – all play important roles in the function and structure of the nervous system.[43]
- Vitamin B1, found most notably in brown rice, plays an important role in providing energy to neurons to allow their function.[43] Further, a 2019 paper published in *Cell Cycle* found that Vitamins B1 and B12 prevented neuron death (apoptosis) in mice due to signaling processes that these vitamins activate.[44]
- Vitamin B6 plays a key role in the function of dopamine, a crucial neurotransmitter in the brain, and protects the brain as well.[43] Other research has found that Vitamin B6 can protect against DNA damage

B Vitamins

and that taking a tablet with B6, tryptophan, and nicotinamide can benefit young adults with depression. (I will not comment on the accuracy or strength of these studies; this is just general information.)[45-46]

- Finally, vitamin B12, which is perhaps the most important B vitamin, is responsible for creating the myelin sheath that protects neural signals while they travel.[43] This is important because it means that Vitamin B12 deficiency can impair one's ability to respond to threats of any kind, leaving them vulnerable to harm.
- Thus, in summary, B vitamins play a key role in maintaining the health of one's nervous system, especially the neurons.

Vitamin K

- Vitamin K, like the B vitamins, plays a key role in nervous system function. A 2012 article published in *Advances in Nutrition*, an official journal of the American Society for Nutrition, examined these roles.[47]
- First, Vitamin K in the brain depends on how much Vitamin K you consume. The more that you consume, the more that ends up in your brain. This means that consumption of Vitamin K is absolutely crucial.[47]
- Second, Vitamin K has two proteins dependent on it: Gas6 and Protein S. These proteins are important in regulating cell growth and protecting the brain, among other functions.[47] Gas6 is responsible for regulating myelin sheath production as well.[48]

Omega-3 Fatty Acids

- The final nutrient that we will cover is omega-3 fatty acids. A review article published in *Current Medical Chemistry* found that omega-3 fatty acids play a key role in the function of the central nervous system. Let's explore in more detail.[49]
- Omega-3 fatty acids play a role in homeostasis and the function of the central nervous system. Specifically, omega-3, as a healthy fat, increases ALA and DHA levels in the brain, which is beneficial for its function.[49]
- Further, a 2017 study found that omega-3 fatty acids benefit myelin sheath productions in mice tested.[50] However, this study was small (5 mice per group), so that must be considered in context.

Omega-3 Fatty Acids

- Further, a study from last year in *Nature Communications* found that pregnant individuals with an omega-3 and omega-6 deficiency have children with reduced synapse connections.[51]
- Thus, omega-3 fatty acids can play a key role in the health and well-being of everyone's nervous systems. It is important to consume an adequate amount of them.

Summary

Summary

- In this presentation, we learned about the nervous system and the role that nutrition plays in maintaining it.
- We looked at how the nervous system impacts neurons, the brain, and the spine, and what role specific nutrients played in maintaining the health of the nervous system.
- I hope that this presentation was helpful, informative, and fun, and that you learned something new from this video. Thank you for your viewership.

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