Does Physical Activity In Athletes Affect The SCFA Production By Gut Microflora Influencing The Gut-Brain Axis?

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Abstract:

The microbiome in the gut contains over 100 trillion microbes (Rinninella et al., 2019), with a diversity of between 300 and 1000 bacterial species (Guinane and Cotter 2013). The anaerobic gut microflora can produce 500 to 600 mmols of short-chain fatty acids (SCFAs) daily in the lumen of the large intestine. SCFAs play a key role in gut homeostasis through communication with the central nervous system. Communication between these luminal metabolites and the nervous system - gut brain axis - is established through the vagus nerve. Vagal afferent and efferent nerves establish the bidirectional talk between the gut and the central nervous system. Among many parameters that can fluctuate the SCFA production in the gut, regular physical exercise has shown positive effect on the gut-brain axis through vagal afferent activation via free fatty acid receptors (FFA) The correlation between aerobic exercise with VO2 of 50% and the increased SCFA production has been analyzed in this review. 7 types of athletic activities have been considered to study the effect of SCFA production. Rugby players, competitive cyclists, female endurance runners, female athletes, elderly male athletes, elderly men subjected to 6 week exercise programs, and subjects participating in a 6 week endurance exercise program have been reviewed. The results of these studies suggest that strenuous physical activity leads to increased SCFA production in comparison to control groups. These SCFAs impact mood, behavior, as well as capability of muscle hypertrophy. This is highly relevant to athletes. This hormonal response is relayed to the central nervous system via the afferent vagus nerve.

Keywords: Gut microflora, exercise, gut-brain axis, bacteria, SCFAs

Introduction

The gastrointestinal system comprises of the mouth, esophagus, stomach, small intestine, large intestine, and anus. Inside the large intestine resides the gut microflora, containing about 400 anaerobic bacterial species (Quigley 2013). This microflora is sparse in the stomach and small intestine, but very apparent in the colon (large intestine). The small intestine contains anywhere from 10^3 to 10^7 total bacterial species, while the large intestine has about 10^12 bacterial species (Pérez-Reytor el al., 2021). All the species of gut microflora are collectively known as the gut microbiome. Some of these bacteria produce metabolites, which are necessary for tasks such as converting energy by breaking down sugars into ATP as well as signaling to the brain. The larger amount of bacteria in the microbiome of the large intestine leads to a greater amount of fatty acids produced, creating a significant impact on the gut brain axis. Some of these metabolites are fatty acids, namely three key short-chain fatty acids (SCFAs); acetate, propionate, and butyrate. In the peripheral nervous system, a system of nerves and neurons that controls involuntary behaviors, there is the vagus nerve, which is one of 12 cranial nerves whose purpose is to signal between the brain, face, and torso. The vagus nerve relays information between the gut and the brain. This communication is called the gut-brain-axis. The gut-brain axis contains key components of the peripheral nervous system, including the vagus nerve and enterochromaffin cells (ECCs). These ECCs, located in the epithelial layer of the gastrointestinal tract, secrete gut hormones, such as serotonin, in response to bacterial stimuli. They function as a two-way signaling system between the intestinal lumen (the gut) and the nervous system. This information from the intestinal lumen is relayed to the central nervous system via the vagus nerve. As the axis impacts mood, behavior, motility, nutrient balance, and many other measures that are important for athletes, the effects of strenuous exercise on the gut-brain axis are very relevant to athletes. Analysis was completed on data sets of various athletes, including rugby players and competitive cyclists analyzing the effect of exercise on the gut microflora. For the purpose of this review, strenuous exercise is defined as a vO2 max of 50-60%. The amount of short-chain fatty acids acetate, propionate, and butyrate, some of the metabolites involved in the gut-brain axis, was measured in the athletes. These effects are discussed in this review.

Gut microflora

The gut microflora resides in the large intestine, with the largest concentrations in the cecum and as a diverse community of anaerobic bacteria. Over 100 trillion microbial cells reside in the gut microflora, 99% of which are anaerobic bacteria (Guinane and Cotter 2013), bacteria which do not require oxygen to survive in their environment. The most commonly seen phyla in the microbiome are bacteroidetes, firmicutes, actinobacteria, and proteobacteria. These bacteria perform multiple tasks, including maintaining the intestinal barrier (Natividad and Verdu 2013), digestion of food and minerals, and aiding in enteric nerve function (Zhang et al., 2015), which is a complex system of about 600 million neurons, that moderate the motor, sensory, and absorptive functions in the GI tract (Fleming 2020). The small intestine is where the maximum amount of digestion and absorption of nutrients occur. Food that is undigested, including dietary fiber, then makes its way to the large intestine. The consumption of dietary fiber is one of the largest components of one's diet that affects the population of the gut microbiome, as anaerobic bacteria in the gut feed off the undigested dietary fiber in order to ferment and produce fatty acids, namely short-chain fatty acids (Clark and Mach 2016). As the amount of fiber consumed increases, the number of bacteria tends to increase as well. 3 key SCFAs that are produced, those that are the most abundant in the microbiome, are acetate, propionate, and butyrate (Portincasa et al., 2022). Each has large impacts on the gut-brain axis, and in turn is very relevant to athletes.

SCFA- key metabolites by gut microflora

Short-chain fatty acids (SCFAs) are the result of fermentation of dietary fibers. They are short chains of fatty acids, with a short chain of aliphatic carbon molecules at their core (den Besten et al., 2013). These SCFAs function as metabolites, substances which are necessary for metabolism.

SCFAs start by being generated by the gut microflora, within the lumen of the large intestine as seen in figure 1. Most SCFAs are absorbed by colonocytes and used as energy by being converted to ATP, the usable source of energy for all cells. However, not all SCFAs are used by the colonocytes. Some diffuse through the wall of the large intestine into the liver to be used by hepatocytes.

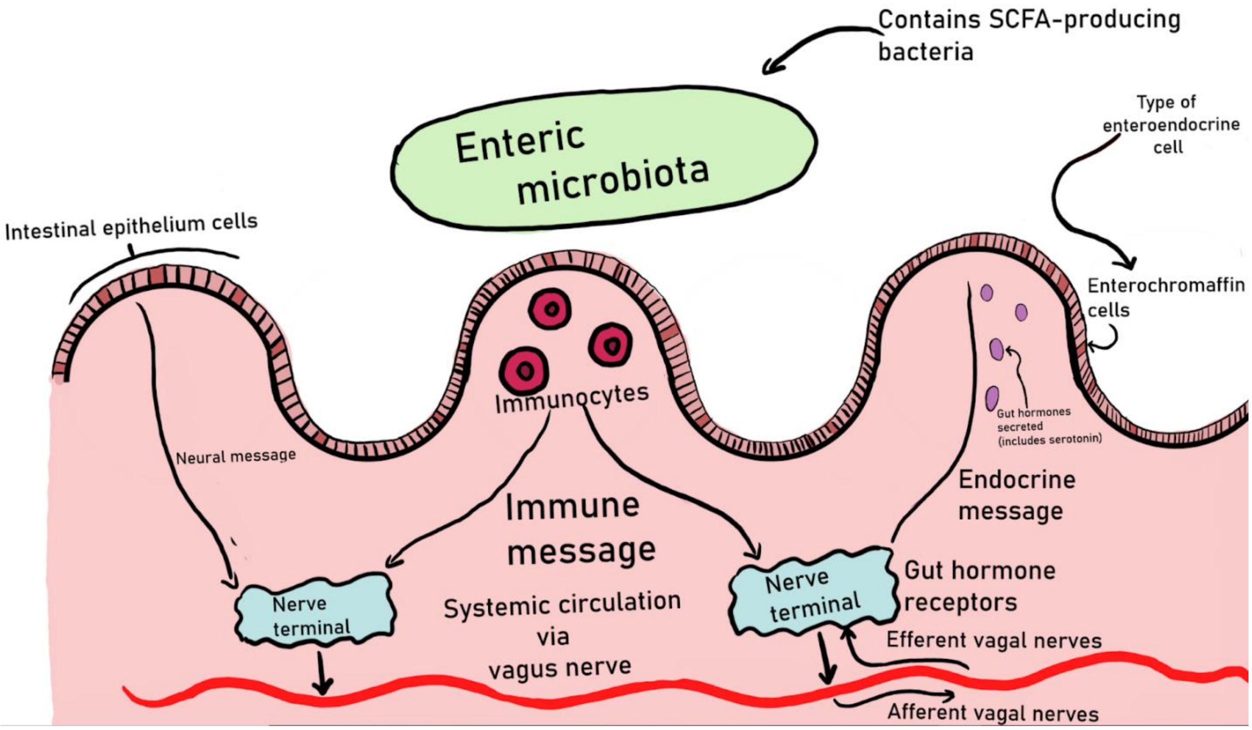

Figure 1. The diagram depicts the epithelial lining of the large intestine. Enteric microbiota in the lumen of the large intestine produce SCFAs. SCFAs in turn trigger enterochromaffin cells to secrete gut hormones such as GLP-1, peptide YY, GABA, and serotonin. Receptors are located along the vagus nerve, as well as on the plasma membranes of target cells (Mittal et al., 2017). This hormonal information, along with neural messages and immune messages via immunocytes are transmitted to nerve terminals, located in close proximity to gut hormone receptors. The information then reaches the nervous system via the afferent vagus nerve, and response from the brain is relayed back through efferent vagus nerves to the nerve terminals in the gut.

The functions of SCFAs are as follows:

1] Absorbed by colonocytes to be converted into ATP as energy for cells of the large intestine

2] Use as substrate for hepatocytes, inducing the secretions of hormones such as GLP-1 in the liver

3] Maintaining protection of the intestinal barrier

4] Anti-inflammatory effects by regulating the production of immune cells

5] Reduced risk of colorectal cancer by regulating cell growth

6] SCFAs also lead to the secretion of gut hormones by binding to G protein-coupled receptors (GCPRs) such as FFA2, FFA3, GPR109a, and Olfr78 as viewed in table 1. The 3 key SCFAs that impact the gut-brain axis that are discussed in this review are acetate, propionate, and butyrate, each with unique beneficial effects on the brain as viewed in table 2

Table 1. [SCFA Receptors Table]

GPCR (g-protein-coupled receptors)	Gene	Name	Location of receptor
FFA2	Ffar2	Free fatty acid receptor 2	neutrophils
FFA3	Ffar3	Free fatty acid receptor 3	Enteroendocrine cells
GPR109a	Hcar2	Hydroxycarboxylic acid receptor 2	Colon
Olfr78	Olfr78	Olfactory receptor 78	Kidney, arterioles, colon, and prostate

Table 2. [Beneficial Impact of SCFAs Table]

SCFA	Beneficial impact of short chain fatty acid	Overall effect	References
Acetate	Acetate produced from acetyl-CoA derived from glycolysis can also be transformed into butyrate by the enzyme butyryl-CoA:acetyl-CoA transferase; also able to modulate inflammatory cytokines	Acetate was also able to modulate inflammatory cytokines and signaling pathways in astrocyte primary culture	(van de Wouw et al., 2018)

Propionate	Propionate exerts an influence on the intracellular potassium level, which implies the involvement of SCFAs in the operation of cell signaling systems	Propionate in the brain is responsible for controlling metabolic disorders including the activation of FFAR2 and FFAR3 receptors. It was shown that activation of these receptors leads to suppression of the activity of orexigenic neurons that express neuropeptide Y in the hypothalamus, and the modulation of the signaling mediate by the ghrelin receptor, contributing to circadian rhythm and appetite control.	(Hoyles et al., 2018)
Butyrate	Host energy metabolism and immune functions critically depend on butyrate as a potent regulator	Butyrate, has been implicated in various host physiological functions including energy homeostasis, obesity, immune system regulation, cancer, and even brain function	(Stilling et al., 2016)

There is an anaerobic condition in the lumen of the large intestine. Therefore, undigested food components reaching from the small intestine are subjected to anaerobic fermentation. This leads to SCFA production. There are a number of gut microflora species known to produce SCFAs. Within the gut microflora, there is a community of anaerobic bacteria that produce the SCFAs that play a significant role in communicating with the brain - utilized in the gut-brain axis. SCFA is specifically produced in the gut lumen inside the large intestine. Different bacteria produce one of the 3 key SCFAs: acetate (Louis and Flint 2017)*,* propionate (Louis and Flint 2017)*,* and butyrate as viewed in table 3. Some of the examples are *Eubacterium rectale*, a butyrate producing firmicute*, Bacteroides uniformis,* a propionate-producing bacteroidete, and *Roseburia, an* acetate-producing firmicute.

Table 3. [SCFA-producing Bacteria Table]

SCFA	SCFA-producing bacteria	References
Butyrate	*Eubacterium rectale* *Roseburia inulinivorans* *Roseburia intestinalis* *Eubacterium hallii* *Anaerostipes hadrus* *Coprococcus eutactus* *Coprococcus catus* *Faecalibacterium prausnitzii* *Subdoligranulum variabile* *Eubacterium biforme* *R. hominis*	(Louis and Flint 2017)

Propionate	*Bacteroides uniformis* *Bacteroides vulgatus* *Prevotella copri* *Alistipes putredinis* *Roseburia inulinivorans* *Eubacterium hallii* *Blautia obeum* *Coprococcus catus* *Dialister invisus* *Phascolarctobacterium succinatutens* *Akkermansia muciniphila*	(Louis and Flint 2017)
Acetate	*Proteobacteria* *Verrucomicrobia* *Alistipes* *Blautia* *Ruminclostridium_9* *Roseburia*	(Zheng et al., 2021)

The gut-brain axis: SCFAs as an important mediator

The communication between the gut microbiome in the large intestine, the brain and the nervous system is labeled as the gut-brain axis. The communication in this system is bidirectional, meaning the gut relays information to the brain and central nervous system, and vice versa. Starting in the gut, indigestible fiber is fermented to create SCFAs. SCFAs influence the central nervous system, the enteric nervous system, and the immune system, connecting to the gut brain axis (Longo et al., 2023)*.* They are fermented by the bacteria residing in the large intestine. Within the epithelial lining of the large intestine are enterochromaffin cells, which are a type of enteroendocrine cell (EEC), a gastrointestinal cell that specializes in endocrine function (the facilitation of the secretion of hormones). The SCFAs that are produced interact with these enterochromaffin cells in order to secrete hormones. Glucagon-like peptide 1(GLP-1), y-aminobutyric acid (GABA), peptide YY (PYY), and serotonin are some of the hormones secreted. This hormonal information is relayed via the afferent vagus nerve, as shown in figure 2. The vagus nerve is the longest out of the 12 cranial nerves, and has been named the “wanderer” as it reaches organs in the abdomen, neck, and the brain. This information has an influence on neurotransmitters, stress and anxiety, and mood. Information from the brain can also be relayed to the gut microbiome via the efferent vagus nerve, such as information on motility (the action of transporting and evacuating waste), nutrient delivery to cells, as well as microbial balance which ensures the diversity of the microbiome. The nerve terminals of the vagus nerve are located very close to the ECCS in the gut, and contain the serotonin-specific receptor 5-HT3R, glucagon-like peptide receptor GLP1R, GABA-specific receptor GABAb, and the peptide YY receptor YR.

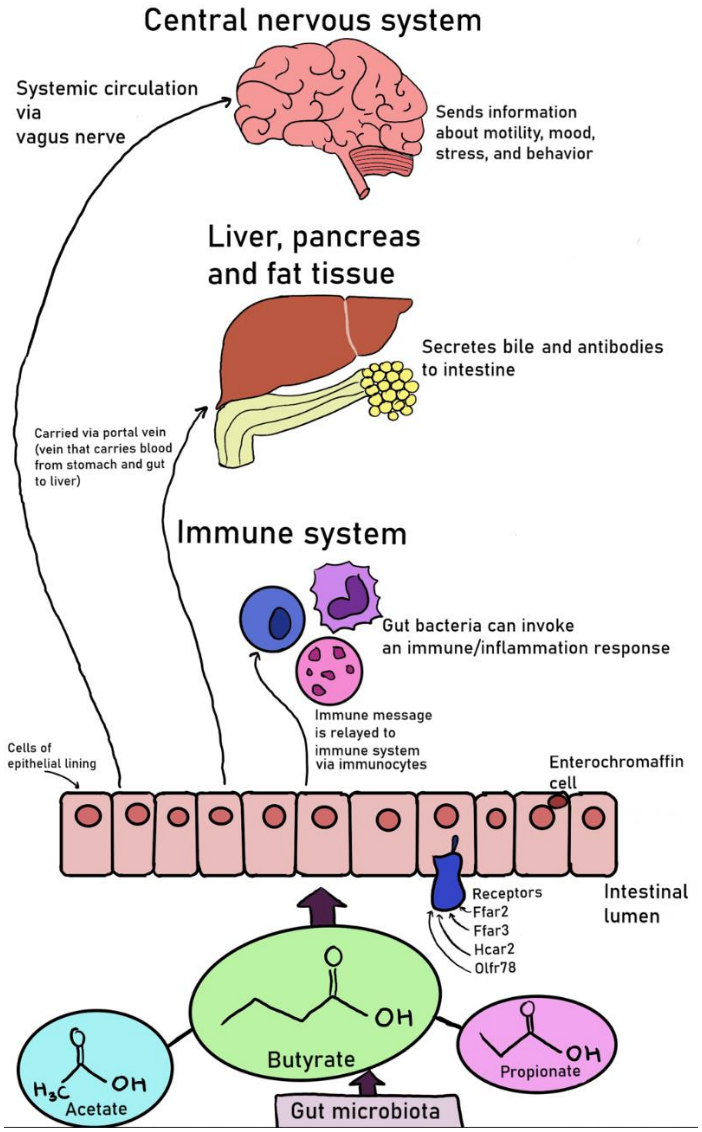

Figure 2. The diagram depicts the communication across the gut-brain axis. Bacteria in the gut produce the SCFAs acetate, butyrate, and propionate that make their way to the cells of the gut epithelial lining. The endocrine cells in the lining are involved in hormone stimulation. Receptors to the released hormones such as Ffar2, Ffar3, Hcar2, and Olfr78, located in close proximity to the enterochromaffin cells, transmit different messages to different systems of the body. Immune messages are relayed to the immune system via immunocytes in the gut microbiome. Messages to and from the liver are carried via the portal vein through SCFA receptors, which is a blood vessel that carries blood between the stomach and gut to the liver. Neural messages are carried through systemic circulation via the vagus nerve.

Athletic activities considered for this review

Rugby players, competitive cyclists, female endurance runners, female athletes, elderly male athletes, elderly men subjected to 6 weeks of endurance exercise, and subjects who participated in 6 weeks of supervised, endurance-based training. Athletes of multiple levels were considered, from beginner to elite.

For the purpose of this review, in the data sets of athletes below, strenuous or intensive exercise is defined as a vO2 max level of 50-60% (maximum rate of oxygen that one can absorb and use oxygen during an exercise period)

Results

In moderation, exercise has a beneficial effect on the gut-brain axis. Analysis was completed on datasets of different types of athletes, including rugby players (Barton et al., 2018), cyclists (Petersen et al., 2017), female endurance runners (Morishima et al., 2021), and elderly athletes (Šoltys et al., 2021). The effects of strenuous exercise were examined. In this review, strenuous exercise is defined as a vO2 max level of 50-60% and as an aerobic exercise. Results derived from fecal analysis show an increased population of butyrate-producing bacteria in athletes as shown in table 4.

Table 4

Physical Activity	Sample size	Method	Observation	References
Rugby players	40	mWGS analysis on the gut microbiomes	Microbiomes were enriched for SCFA synthesis	(Barton et al., 2018)

Competitive cyclists	33	metagenomic whole genome shotgun (mWGS) and metatranscriptomic (RNA-Seq) sequencing	High cardiorespiratory fitness also correlated with an increase in the SCFA butyrate	(Petersen et al., 2017)
Rugby players	-	performed metabolomic phenotyping of the microbiome	Reported higher activity of several pathways, including amino acid synthesis, and carbohydrate metabolism. As a result, athletes demonstrated an enriched profile of SCFAs	(Dalton et al., 2019)
Female endurance runners	15	Analyzed of fecal moisture content and putrefactive metabolites	abundances of butyrate-producing bacteria and concentrations of butyrate were observed to increase in humans after physical exercise.	(Morishima et al., 2021)
Female athletes	40	high-throughput sequencing of the 16s rRNA gene and quantitative PCR analysis	Increased population of R. hominis and F. prausnitzii have a beneficial effect on health as they produce butyrate	(Bressa et al., 2017)

Elderly male athletes	4	Microbiome analysis was performed on collected stool samples further subjected to 16S rRNA gene analysis. NMR-spectroscopic analysis was applied to determine and compare selected blood plasma metabolites mostly linked to energy metabolism	Found a higher relative abundance of bacteria characterized by an increased capacity to produce butyrate, such as Intestinimonas, in the group of lifetime endurance athletes.	(Šoltys et al., 2021)
Elderly men subjected to 6 weeks of endurance exercise	33	16S rRNA gene-based metagenomic analyses	Fecal concentrations of short-chain fatty acids (SCFAs) were increased by 6-week endurance exercise in lean subjects, and it was suggested that the microbial SCFAs influence blood pressure by interacting with host SCFA receptors	(Teniguchi et al., 2018)
Subjects participated in 6 wk. of supervised endurance-based exercise training	32	Fecal samples were collected, with beta-diversity analysis done on them	Exercise increased fecal concentrations of short-chain fatty acids in lean participants.	(Allen et al., 2018)

For the purpose of this review, in the data sets of athletes below, strenuous or intensive exercise is defined as a vO2 max level of 50-60% [maximum rate of oxygen that one can absorb and use oxygen during an exercise period]. Metagenomic analysis as well as fecal SCFA analysis were methods used to derive data.

Rugby players were examined. A sample size of 40 rugby players was used to conduct this experiment. Metagenomic analysis was performed on the gut microbiomes through stool samples. In the rugby players, using targeted gas chromatography–mass spectrometry, it was found that SCFAs butyrate, acetate, and propionate are found to have increased in comparison to the control group.

Competitive cyclists were also examined. A sample size of 33 was used for this experiment, and metagenomic analysis was used as well, along with 16s rRNA sequencing. The high cardiorespiratory fitness that the cyclists demonstrated was correlated with an increase in the SCFA such as butyrate.

Data of female athletes was also analyzed. In a sample size of 40, a method of high-throughout sequencing of the 16s rRNA gene and quantitative PCR analysis in stool samples was used. In the gut microbiome of these athletes, there was an increased population of *R. hominis* and *F. prausnitzii.* These two bacteria have a beneficial effect on health, as they produce SCFAs. This increased population of the bacteria led to an increased production of butyrate, acetate, and propionate.

Female endurance runners were also viewed. In a sample set of 15 athletes, analysis of fecal moisture content and concentration of metabolites was examined. There was an abundance of butyrate-producing bacteria, and concentrations of butyrate increased after physical exercise.

Elderly male athletes were examined. In a sample set of 4, Microbiome analysis was performed on collected stool samples, and the samples were later subjected to 16S rRNA gene analysis. A higher abundance of bacteria was found with an increased ability to produce acetate, butyrate, and propionate in this group of lifetime endurance athletes.

A group of people subjected to a 6 week program of supervised, endurance-based exercise training was examined as well. In a sample set of 32, fecal samples were collected, and beta-diversity analysis was performed. Exercise was found to increase concentrations of short-chain fatty acids in the stool of participants.

The SCFAs that were found to have increased in athletes signal for the release of gut hormones GLP-1, peptide YY, and GABA, which have many significant functions when secreted. GLP-1 plays a very important role in glucose homeostasis. It inhibits the secretion of glucagon, and augments glucose-induced insulin secretion. It has an effect of reduced appetite for athletes, which is significant for athletes, as it is necessary to consume an adequate amount of calories to meet their goal of maintenance, fat loss, or muscle gain. GABA is an aminobutyric acid that lessens a nerve cell’s ability to send and receive signals. For this reason, it’s been known to produce a calming effect, and supplementation may aid in increasing training-induced muscle hypertrophy. This is of high relevance to athletes as it can be used to increase muscle mass, reduce body fat percentage, the maintenance of muscle mass, muscle recovery, or to calm nerves during a high-intensity competition or game. Peptide YY, similar to GLP-1, is also anorexigenic, meaning it causes a loss of appetite. It creates the sensations of “fullness”, which is why it limits calorie intake. Obesity has been observed to be associated with reduced peptide YY levels, which is relevant to athletes as it may contribute to weight gain.

Conclusion

This review demonstrates how aerobic exercise with a VO2 max of 50-60% has shown a positive effect on SCFA production. SCFA production is an important measure to consider due to the fact that it modulates the gut-brain axis, as well as plays an important role in gut homeostasis. Therefore, along with positive effects, it is important to analyze if strenuous physical activities in athletes have a negative impact on SCFA production.

SCFAs aid in the communication of the gut brain axis. They trigger the secretion of vital gut hormones, meaning they have a big role in controlling mood, hunger, weight control, immunity, muscle recovery and hypertrophy. The studies considered in this review have indicated an increase in SCFA production correlates with exercise, So, no negative effect is observed.

SCFA production is the outcome of the digestion of fibers and indigestible carbohydrates. Athletes normally pay attention to diet for better performance. So food rich in components that will stimulate SCFA production should be included in one's diet.

Physical and mental stress can also take a large toll on an athlete, as well as hinder performance. Many athletes take supplements containing the gut hormone GABA, which, as discussed in this review, has a calming effect that is vital to muscle recovery. As GABA is also a hormone produced by gut SCFAs, an increase in dietary fibers could also potentially produce a calming effect, as well as increase the capability for muscular hypertrophy.

As mentioned, peptide YY is an anorexigenic gut hormone secreted, meaning an increase in dietary fiber consumed will lead to a greater population of the bacteria that lead to peptide YY being secreted. Due to the fact that the hormone leads to a loss in appetite, less calories are consumed. So in turn, making dietary fiber a larger proportion of one's diet could lead to a caloric deficit and aid in weight loss.

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