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During Obesity and Diabetes, Microbiota and Receptors that Resemble Nod keep Metabolism and Inflammation in Check

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Abstract

Obesity and metabolism are intertwined factors that significantly impact human health. Obesity, characterized by excess body fat, leads to metabolic dysregulation and increases the risk of chronic diseases, such as type 2 diabetes and cardiovascular disorders. Metabolism encompasses the complex set of chemical processes that convert food into energy and other essential substances within the body. Understanding the relationship between obesity and metabolism is crucial for unraveling the underlying mechanisms contributing to weight gain and its impact on overall health. Metabolic alterations observed in obesity include insulin resistance, dyslipidemia, and chronic inflammation. Adipose tissue, hormonal regulation, and the gut microbiota play pivotal roles in energy balance, appetite regulation, and metabolic homeostasis. Genetic factors influence obesity and metabolism, with numerous genes identified through genome-wide association studies. Lifestyle modifications, including diet and exercise, are crucial for managing obesity and improving metabolic health. Further research is needed to explore epigenetics, the gut-brain axis, and environmental influences. Addressing the obesity epidemic and promoting metabolic health require a multidisciplinary approach involving healthcare professionals, policymakers, and individuals themselves. By promoting healthy lifestyle habits and personalized interventions, we can mitigate the impact of obesity on individuals and societies, leading to improved health outcomes.

During obesity, the host's metabolism and immunity are affected by the gut microbiota. The innate immune system's bacterial sensors transmit signals from specific bacterial components, or postbiotics, that may have opposing effects on metabolic inflammation in the host. Although they both recruit receptor-interacting protein kinase 2 (RIPK2), NOD-like receptors (NLRs) like Nod1 and Nod2 have distinct effects on blood glucose control. Nod1 links metabolic inflammation and insulin resistance to signals from the bacterial cell wall, whereas Nod2 can boost immune tolerance, insulin sensitivity, and better control of blood glucose during obesity. Inflammasomes that contain a pyrin domain belonging to the NLR family (NLRP) can also produce distinct metabolic outcomes. NLRP3 appears to have a bias toward IL-1-mediated metabolic inflammation and insulin resistance, whereas NLRP1 protects against obesity and metabolic inflammation possibly due to a bias toward IL-18 regulation.

Introduction

Obesity and metabolism are two interconnected aspects of human health that play crucial roles in overall well-being. Obesity refers to the condition of having excessive body fat, often resulting from a combination of genetic, environmental, and lifestyle factors. Metabolism, on the other hand, refers to the complex set of chemical processes that occur within the body to convert food into energy and various other essential substances.

Obesity has become a global epidemic, with its prevalence increasing significantly over the past few decades. It poses a significant health risk and is associated with various chronic conditions such as type 2 diabetes, heart disease, certain cancers, and musculoskeletal disorders [1]. Understanding the relationship between obesity and metabolism is essential for comprehending the underlying mechanisms contributing to weight gain and its impact on overall health.

Metabolism plays a vital role in regulating body weight and composition. It encompasses two primary processes: anabolism and catabolism. Anabolism involves the synthesis of complex molecules from simpler ones, such as the production of new tissues and energy storage. Catabolism, on the other hand, is the breakdown of complex molecules into simpler forms, releasing energy that the body can utilize.

Basal metabolic rate (BMR) is a key factor in determining the energy expenditure of an individual at rest. It represents the number of calories required to sustain basic bodily functions such as breathing, circulating blood, and maintaining organ function. Factors such as age, sex, body composition, and genetics influence an individual's BMR. People with higher BMRs tend to burn more calories at rest, making it easier for them to maintain a healthy weight.

Obesity can disrupt the delicate balance of metabolism. Certain genetic factors can predispose individuals to obesity by affecting their metabolic rate and how their bodies process and store energy. Additionally, environmental factors, such as a sedentary lifestyle, poor dietary choices, and psychological factors, can contribute to weight gain and alter metabolic processes.

Furthermore, obesity can lead to metabolic dysregulation. Adipose tissue (body fat) is an active endocrine organ that produces hormones

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and signaling molecules [2]. Excessive adiposity can result in the release of pro-inflammatory substances and hormonal imbalances, leading to insulin resistance, dyslipidemia, and other metabolic abnormalities.

Addressing obesity and metabolic disorders requires a multifaceted approach that involves lifestyle modifications, dietary changes, regular physical activity, and sometimes medical interventions. By understanding the intricate relationship between obesity and metabolism, researchers and healthcare professionals can develop targeted strategies to prevent and treat obesity-related complications, improve metabolic health, and promote overall well-being.

The accumulation of more fat on the body is the hallmark of obesity, a complicated condition. Diet, genetics, a sedentary lifestyle, and the environment are just a few of the many factors that increase the risk of obesity and accelerate its progression. Other metabolic diseases, such as type 2 diabetes (T2D), are more likely to occur in people who are obese. Obesity-induced changes in the immune system occur in a variety of metabolic tissues, including adipose tissue, the liver, skeletal muscle, the pancreas, and the intestine. Both obesity and T2D share a characteristic of chronic low-grade inflammation [3]. Compared to overt (bacterial or viral) infections, obesity-related inflammation has a smaller immune response, but metabolic inflammation can be chronic and compartmentalized. During the course of obesity, inflammation of white adipose tissue (WAT) can initiate and coordinate changes in metabolism throughout the body.

Obesity causes an increase in a wide variety of immune cells in metabolic tissues. For instance, macrophages invade hypertrophic WAT in obese people and animal models of obesity. Tumor necrosis factor (TNF) is a proinflammatory cytokine produced by macrophages that can alter insulin action. During obesity, macrophages and their inflammatory mediators participate in tissue and whole-body insulin resistance and the progression of type 2 diabetes. In both diet-induced and genetic models of obese mice, TNF- ablation lowers insulin resistance. During obesity, numerous immune pathways within metabolic and immune cells are active. IKK- and NF-B pathway inhibitors act as a bridge between inflammation and metabolism, including insulin resistance in obese individuals. During diet-induced obesity, mice can avoid developing insulin resistance by either pharmacologically inhibiting or genetically deleting IKK-/NF-B-dependent inflammatory signaling.

Although there aren't many well-defined sources or triggers for metabolic inflammation during obesity, several possibilities have been identified. One possible cause of obesity-related inflammation is the microbiota in the intestines. Studies have shown that metabolic endotoxemia, or an increase in circulating lipopolysaccharides (LPS) caused by eating a high-fat diet (HFD) for just four weeks raised LPS levels in the blood. Inflammation caused by obesity and insulin resistance are both caused by LPS, a membrane component of Gram-negative bacteria, according to this landmark study. A combination of HFD-induced changes in the composition of the gut microbiota and an increase in gut permeability could account for the elevated LPS. During obesity, supplementing the gut microbiota with antibiotics, probiotics, or prebiotics can alter the inflammation and metabolic endotoxemia as well as improve blood glucose control. This demonstrates that the gut microbiota can be targeted to alter the inflammation associated with obesity [4]. Numerous studies have attempted to link metabolic inflammation and changes in microbial taxonomy during obesity. Foods that are high in fat and low in fiber, for instance, have a negative impact on the ratio of bacteria to bacteria and reduce the diversity and abundance of the gut microbiota. Finding out how functional units of the microbiota interact with immune receptors to alter host metabolism and metabolic inflammation is an important next step.

It is well known that the host's immunity is influenced and programmed by the gut microbiota. The host-microbe relationship can be altered by obesity, which has an impact on metabolic inflammation and host metabolism. The epithelium and gut mucosal barrier are layers of defense that prevent microbial components from getting into the host. After one week of HFD feeding, increased levels of bacteria translocation into adipose tissue and blood are observed. Reduced epithelial tight-junction proteins cause an HFD-induced disruption in the integrity of the gut mucosal barrier. This makes it possible for more paracellular translocation of LPS, which in turn contributes to metabolic endotoxemia, inflammation, and metabolic dysfunction. Obesity has been linked to the development of an ethanolamine-poorly metabolizing microbiota in the upper intestine. By increasing the activity of the transcription factor ARID3 in the promoter region of miRNA-101a-3p, a miRNA that is capable of interacting and destabilizing the tight-junction protein zona occludens-1 mRNA, metabolic endotoxemia and inflammation were caused by decreased zona occludens-1 translation and consequently reduced its expression, high ethanolamine levels were associated with impaired intestinal permeability.

Methods and Materials

Studying obesity and metabolism involves a wide range of research methodologies and tools. Here are some common methods and materials used in the field:

Human studies: Human studies play a crucial role in understanding the relationship between obesity and metabolism. These studies often involve participants of various ages, genders, and body compositions. Researchers may measure body weight, body composition (e.g., using dual-energy X-ray absorptiometry or bioelectrical impedance analysis), and metabolic parameters such as basal metabolic rate (BMR), insulin sensitivity, lipid profiles, and hormone levels. These studies can include cross-sectional analyses, longitudinal studies, and clinical trials to assess the impact of interventions.

Animal models: Animal models, such as rodents (mice and rats), are commonly used in obesity and metabolism research. Researchers can manipulate the genetics or diets of these animals to study the effects on metabolism and obesity-related factors [5]. Animal studies allow for more controlled experiments, enabling researchers to examine specific molecular and physiological mechanisms underlying obesity and metabolism. Techniques like calorimetry, glucose tolerance tests, and gene expression analysis are often employed in these studies.

Dietary and exercise interventions: Conducting controlled dietary and exercise interventions is crucial in investigating the impact of lifestyle modifications on obesity and metabolism. Researchers design and implement intervention studies where participants are assigned to specific dietary regimens (e.g., low-fat, low-carbohydrate, or calorie-restricted diets) or exercise programs (e.g., aerobic or resistance training). Changes in body weight, body composition, metabolic parameters, and other relevant factors are measured before and after the interventions.

Metabolic phenotyping: Metabolic phenotyping involves assessing metabolic parameters to gain insights into obesity and metabolism. Techniques like indirect calorimetry can measure oxygen consumption and carbon dioxide production to estimate energy expenditure and metabolic rates. Glucose tolerance tests, insulin sensitivity tests (e.g.,

euglycemic clamp), and lipid profiling can provide information about glucose and lipid metabolism. Metabolomics, a field that analyzes small molecule metabolites in biological samples, can also be employed to identify metabolic signatures associated with obesity and related disorders.

Molecular and genetic analysis: Molecular and genetic techniques help uncover the underlying mechanisms involved in obesity and metabolism. Researchers may analyze gene expression patterns using techniques like microarrays or quantitative polymerase chain reaction (qPCR) [6]. Genetic variants associated with obesity or metabolic disorders can be identified through genome-wide association studies (GWAS) or targeted sequencing approaches. Additionally, techniques such as Western blotting, enzyme assays, and immunohistochemistry allow the assessment of specific proteins and molecular pathways involved in metabolism.

Bioinformatics and statistical analysis: Analyzing complex data sets is an integral part of obesity and metabolism research. Bioinformatics tools and databases help researchers interpret genomic, transcriptomic, proteomic, and metabolomic data. Statistical analysis is employed to identify significant associations, correlations, and differences between variables, as well as to assess the effectiveness of interventions and identify biomarkers related to obesity and metabolism.

These methods and materials are continually evolving as new technologies and techniques emerge. Researchers employ a multidisciplinary approach to gain a comprehensive understanding of the complex interactions between obesity and metabolism, contributing to the development of effective prevention and treatment strategies.

Results and Discussion

Obesity and metabolism research have yielded numerous important findings that have deepened our understanding of the complex relationship between these two factors. Here are some key results and discussions pertaining to obesity and metabolism:

Metabolic alterations in obesity: Studies have consistently shown that obesity is associated with metabolic dysregulation [7]. Obesity is often accompanied by insulin resistance, impaired glucose tolerance, dyslipidemia (elevated triglycerides and decreased high-density lipoprotein cholesterol), and increased levels of inflammatory markers such as C-reactive protein. These metabolic changes contribute to an increased risk of developing type 2 diabetes, cardiovascular disease, and other obesity-related complications.

Adipose tissue and hormonal regulation: Adipose tissue, particularly visceral adipose tissue (fat around internal organs), plays a crucial role in metabolic regulation. It secretes various hormones and signaling molecules collectively referred to as adipokines, including leptin, adiponectin, and resistin. Leptin, for example, helps regulate appetite and energy balance by signaling satiety to the brain. In obesity, adipose tissue dysfunction leads to abnormal adipokine secretion, contributing to metabolic disturbances and systemic inflammation.

Role of genetics: Genetic factors significantly influence both obesity and metabolism [8]. Numerous genes have been identified through genome-wide association studies (GWAS) that are associated with obesity and metabolic traits. For instance, variations in genes involved in appetite regulation (e.g., FTO and MC4R) and energy expenditure (e.g., UCP1 and PPARγ) have been linked to obesity susceptibility and metabolic alterations. Understanding the genetic basis of obesity and metabolism can help identify individuals at risk and develop personalized interventions.

Energy expenditure and basal metabolic rate (BMR): Obesity is often attributed to an energy imbalance, where energy intake exceeds energy expenditure. Basal metabolic rate (BMR) is a key determinant of energy expenditure at rest. Studies have shown that individuals with obesity tend to have lower BMRs compared to lean individuals, even after adjusting for differences in body composition. This suggests that metabolic adaptations may contribute to weight gain and difficulties in weight loss among individuals with obesity.

Gut microbiota and metabolism: The gut microbiota, the collection of microorganisms residing in the gastrointestinal tract, has emerged as a key player in metabolism. Studies have demonstrated that alterations in the composition and diversity of the gut microbiota, often observed in obesity, can impact energy metabolism and contribute to weight gain [9]. Certain gut bacteria are involved in the fermentation of dietary fibers, producing short-chain fatty acids that influence appetite, energy expenditure, and glucose metabolism.

Lifestyle interventions and metabolic health: Lifestyle modifications, including dietary changes and increased physical activity, play a central role in managing obesity and improving metabolic health. Caloric restriction, adoption of a balanced and nutrient-dense diet, and regular exercise have been shown to promote weight loss, reduce insulin resistance, improve lipid profiles, and enhance overall metabolic function. These interventions are crucial for preventing obesity-related complications and improving long-term health outcomes.

Role of inflammation: Chronic low-grade inflammation is a hallmark of obesity and is believed to contribute to metabolic disturbances [10]. Adipose tissue inflammation, driven by the infiltration of immune cells, can impair insulin signaling, disrupt lipid metabolism, and promote insulin resistance. Inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), are elevated in obesity and have been implicated in the development of metabolic abnormalities.

Personalized approaches: The field of obesity and metabolism research is moving towards personalized approaches that consider individual variations in genetics, metabolism, and response to interventions.

Conclusion

Obesity and metabolism are intricately linked and have profound implications for overall health and well-being. Obesity, characterized by excessive body fat, disrupts the delicate balance of metabolic processes, leading to metabolic dysregulation and an increased risk of chronic diseases such as type 2 diabetes and cardiovascular disorders.

Research in the field of obesity and metabolism has provided valuable insights into the underlying mechanisms and interplay between genetic, environmental, and lifestyle factors. Metabolic alterations in obesity, including insulin resistance, dyslipidemia, and chronic inflammation, contribute to the development of metabolic syndrome and related complications.

Understanding the role of adipose tissue, hormonal regulation, and the gut microbiota has shed light on the complex interactions that influence energy balance, appetite regulation, and metabolic homeostasis. Genetic studies have identified numerous gene variants associated with obesity and metabolic traits, providing potential targets for personalized interventions and treatments.

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Lifestyle modifications, such as adopting a healthy diet and engaging in regular physical activity, play a pivotal role in managing obesity and improving metabolic health. These interventions can lead to weight loss, improved insulin sensitivity, and favorable changes in lipid profiles, thereby reducing the risk of obesity-related diseases.

Further research is needed to unravel the intricate mechanisms underlying obesity and metabolism, including the role of epigenetics, the gut-brain axis, and the influence of environmental factors. Advances in technologies and data analysis methods will continue to enhance our understanding of these complex interactions and facilitate the development of personalized approaches to prevent and treat obesity and metabolic disorders.

Addressing the obesity epidemic and promoting metabolic health require a comprehensive, multidisciplinary approach involving healthcare professionals, policymakers, and individuals themselves. By promoting healthy lifestyle habits, early detection of metabolic abnormalities, and personalized interventions, we can mitigate the impact of obesity on individuals and societies and improve overall health outcomes.

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Conflict of Interest

None

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