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THE STRATEGIC ROLE OF EPIGENETIC AND MICROBIOME INTERACTIONS IN MANAGING INFLAMMATION-DRIVEN RISKS IN DIET-RELATED OBESITY

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Original Article

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Abstract

There is mounting evidence that microbiomes, also known as epigenomes, have a role in metabolic health and the inflammation linked to diet-induced obesity (DIO). This work examines the interaction between DIO, the epigenomic landscape, and the makeup of the microorganisms in the digestive tract within the setting of endocannabinoid-mediated inflammatory control in a mouse model. The negative effects of a high-fat diet (HFD) might be studied by first making C57BL/6J mice overweight and then monitoring their weight. Determining if there were alterations in metabolic parameters or inflammatory indicators was the primary objective. Researchers discovered changes in DNA methylation patterns linked to obesity by integrating genomic sequencing with epigenetic profiling. At the same time, scientists analysed the gut microbiota using 16S rRNA sequencing and found that the HFD was associated with major changes in the variety and composition of microbes. Researchers assessed the impact on inflammatory responses and metabolic repercussions after pharmaceutically modifying endocannabinoid signalling in order to identify the pathways. Inflammation in DIO is influenced by both the microbiota and the epigenome, as previously shown. Then, this influences the signalling of endogenous cannabinoids. While further study is required to clarify the precise processes at play and their relevance to obesity prevention and treatment, the present study does draw attention to the intricate relationship between the microbiome, nutrition, and epigenetic pathways as they pertain to metabolic health, as well as the possibility of using these pathways as therapeutic targets for the inflammation that accompanies obesity.

Keywords: Dietary Factors; Endocannabinoid System; Epigenome; Inflammation; Microbiota; Obesity

Introduction

Chronic diseases and metabolic disorders are increasing, with diet-induced obesity being a primary contributor to this pandemic. Suboptimal dietary selections often exacerbate this disease, which is fundamentally a result of caloric intake exceeding energy expenditure. Recent studies indicate that diet-induced obesity is affected by two significant biological systems: the microbiome and the epigenome [1]. These systems are crucial in regulating inflammation, particularly via the modulation of the endocannabinoid system. The epigenome regulates gene expression by inducing chemical modifications to DNA and histone proteins without altering the genetic code itself. Environmental factors, such as dietary habits, may influence these changes. Dietary modifications induced by certain dietary constituents may influence

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inflammatory pathways and aggravate obesity-related conditions. A high-fat diet alters the methylation landscape, impacting genes related to inflammation and metabolism [2]. The gut microbiome denotes the varied assemblage of microorganisms residing in the digestive system, which significantly influences metabolic health. Dietary choices influence energy equilibrium and chronic inflammation, thus affecting the microbiome's makeup and functionality. The endocannabinoid system regulates inflammation, metabolism, and hunger and is also implicated in several other physiological functions [3]. This pathway may be influenced by the microbiota. Researchers may get enhanced insights into obesity and its associated illnesses by examining the impact of diet-induced obesity on the microbiome, particularly the epigenome, and how these elements affect the regulation of inflammation by endocannabinoids. This multimodal strategy may provide innovative methods for reducing inflammation related to obesity and improving metabolic health [4].

Background of the Study

The way scientists study diet-induced obesity and its mechanisms has changed dramatically during the last several decades. It was long believed that the primary cause of obesity was consuming more calories than one burnt. Obesity is caused by a complex interaction of biochemical, environmental, and hereditary factors, according to recent studies. When scientists began to question if factors other than DNA may affect gene expression, such as food, in the early 2000s, the area of epigenetics was born. Epigenetic research has shown that environmental factors, such as food, may modify genes via processes including DNA methylation and histone modification. These changes may have an effect on inflammatory pathways, which might worsen metabolic disorders linked to obesity. Meanwhile, newly discovered information from microbiome investigations reveals that gut bacteria play a pivotal role in determining health status. Digestive health, metabolic rate, and immune system function are all profoundly affected by the billions of microorganisms that make up the human microbiome. Dietary changes may affect the microbiome's makeup and function, which in turn affects obesity and systemic inflammation; this theory gained widespread acceptance in the 2010s. According to studies, metabolic dysregulation, inflammation, and an imbalanced microbiome may all contribute to the development of obesity. The endocannabinoid system is a complex network of receptors and signalling molecules that regulates several physiological functions, including inflammation and metabolism [5]. Dietary and microbial alterations may alter endocannabinoid profiles, which affects inflammatory responses, energy homeostasis, and hunger control, according to the research. The intersection of epigenetics, microbiome research, and endocannabinoid regulation holds great promise. More research into the interplay between these systems and the ways in which diet-induced obesity affects their ability to control inflammation may lead to novel approaches to the treatment and prevention of obesity and related disorders [6].

Purpose of the Research

Studying diet-induced obesity and the microbiome's role in endocannabinoid-mediated inflammatory control requires an examination of the complex interaction between the epigenome, the gut microbiota, and the endocannabinoid system. This study aims to investigate the manner in which these systems affect inflammation, which is a crucial aspect of metabolic issues linked to obesity. By deciphering the intricate network of relationships between nutrition, genes, microorganisms, and endocannabinoid signalling, researchers want to discover strategies to aid individuals with diet-induced obesity in managing inflammation and improving their metabolic health. Finding out how diet-induced obesity affects epigenetic alterations, microbiota composition changes, and the role of endocannabinoid signalling in inflammatory regulation is the main goal of this study. Personalised treatments for obesity-related inflammatory illnesses may be possible with the use of this data.

Literature Review

Inflammation and metabolic diseases are intimately associated with diet-induced obesity (DIO), making it one of the most critical public health issues of researchers' day. Research into the functions of the microbiome and epigenome, especially endocannabinoid signalling, has been prompted by the complicated link between inflammation, obesity, and food. Endocannabinoids, a class of lipid-based neurotransmitters, modulate inflammatory processes and metabolic activity, two key features of obesity. A growing body of evidence links diet-induced obesity (DIO), a serious public health issue, to the intricate interaction between the epigenome, microbiota, and endocannabinoid system (ECS) [7]. The inflammation and certain food components linked to obesity may alter the epigenome, which consists of changes in gene expression that are passed down through generations but do not change the DNA sequences themselves. These changes may exacerbate inflammation and metabolic imbalance circuits. The microbiota in the host's digestive tract has

a significant impact on the host's immune response and metabolism [5]. The ECS is a network of lipid signalling molecules that regulates inflammation, hunger, and energy balance; dysbiosis, which is common in DIO, may impact this network. In this system, bioactive lipids called endocannabinoids control inflammatory processes via their interactions with immune cells and cytokine signalling. The ECS may be affected by dietary changes that influence the microbiome and epigenome, according to new data. This, in turn, may lead to an increase in inflammation and metabolic disorders. Understanding this complicated interplay may provide insight on two possible treatment targets—dietary therapy and microbiota modification—that aim to reduce the inflammatory consequences of obesity [8].

Research Questions

- What is the effect of time restrictions on the regulation of inflammation control?

Research Methodology

Laboratory methods were used to conduct the research for this study. An animal model called a mouse was used to carry out the experiment.

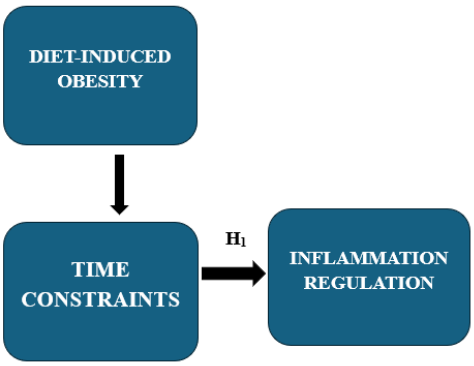
Research Design:

Nobody knows whether fat-fed obese mice experience changes in the endocannabinoid system, which is crucial for pain signals and emotion processing. In this study, obese mice will be used as a model to examine the nociceptive response and discover how dietary changes impact the endocannabinoid system. This project seeks to use a diet-induced obesity mice model to investigate the functions of the ECS in inflammation and metabolic control by genetic and pharmacological modification of the gut microbiota and cannabinoid receptors CB1 and CB2. Further testing of the CB1 antagonist was conducted on obese mice. The impact of HFD on leukocyte infiltration in the cecal-colonic lamina propria was better comprehended when CB1 and CB2 were studied. It is plausible to expect that alterations in the gut microbiota mediated by the ECS contribute to the obesity phenotype, given that inhibiting cannabinoid 1 (CB1) reduces intestinal inflammation. Researchers were looking at microbiota profiles using 16S rRNA gene sequencing to see whether CB1-/- or CB2-/- mice could withstand the effects of a high-fat diet on their gut flora.

Mice Model

All the male C57Bl/6J mice used in this investigation came from The University Laboratory. Adult mice were randomly assigned to either a 60% kcal HFD for 12 weeks or a 10% low-fat diet solely for 12 weeks, based on the findings. A variety of meals were introduced to the six- to eight-week-old mice. Experimental CB1-/- and CB2-/- mice were generated at the medical school of the University of South Carolina. From what the treatment group could tell, every experiment that wasn't the co-housing trial had cages with three or five mice each. Various litters and living conditions provided the mice used in this investigation. The aggressive behaviour of mice led to their occasional isolation. To conduct the DIO intervention experiments, obese mice were split according to their average DEXA fat mass after 12 weeks of an unhealthy diet. The AM251 dosage for the treatment group was 10 mg/kg given orally in a 0.1% Tween 80 solution. They gave "Veh" valves to all the other experimental groups. When it comes to the PA feeding programme, researchers make sure that the Pair-fed group gets the same amount of HFD every day by watching what they eat. Mice were induced to sleep by inhaling an excess of isoflurane once the experiment was complete.

Conceptual Framework

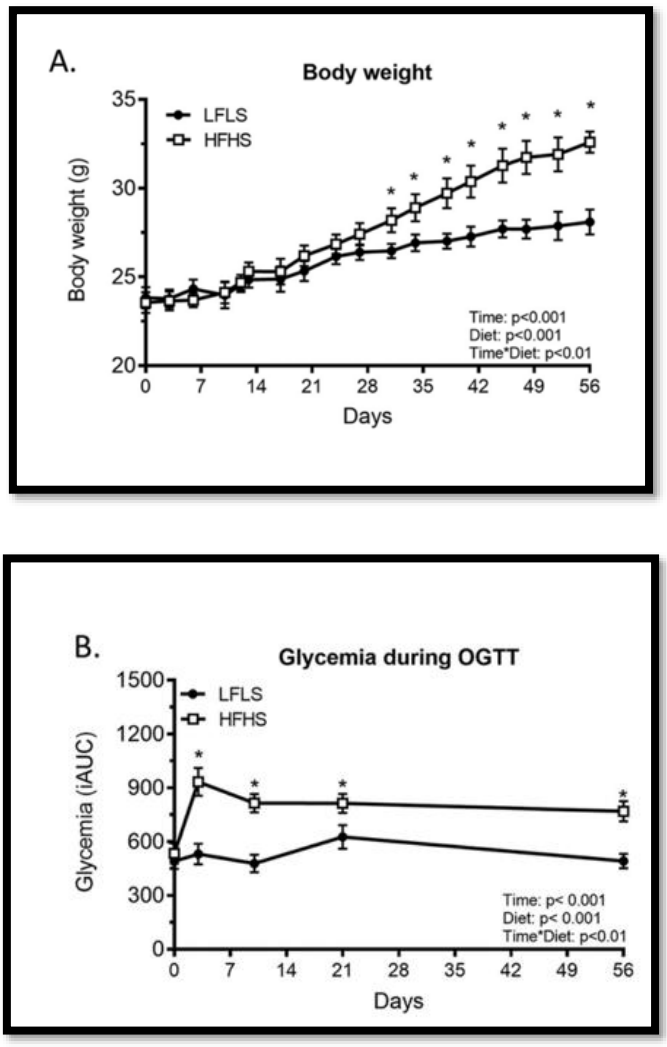


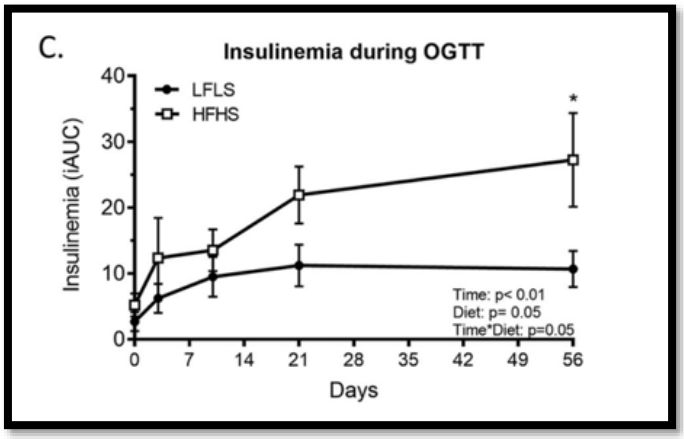
Results

The HFHS group of mice gained greater weight compared to the LFLS group when fed varied diets. The difference between the two groups became apparent as early as day 31, as seen in Figure 1A. The average weight increase for the HFHS group was 32.6 ± 1.8 g, whereas the LFLS group only managed 28.1 ± 1.6 g. As seen by a higher glucose area under the curve (Fig. 1B), the oral glucose tolerance test (OGTT) demonstrated a decrease in glucose tolerance. They started dropping on the third day of HFHS feeding. Loss of this tolerance threshold was linked to a rise in body fat percentage. If the insulin area beneath the OGTT curves only showed a substantial improvement on day 56 of HFHS feeding, then the results in Figure 1C indicating insulin sensitivity decreases with increasing body weight throughout treatment must be believed.

Fig 1: A low-fat diet rich in sugar and fat affects the phenotypic of rats after 56 days. Eleven mice had 56 days of sequential dosing with LFLS or HFHS. Here, the researchers have three variables: the individual's weight increase, their oral glucose tolerance test (OGTT) curve, and their insulin area under the plasma OGTT curve (iAUC). For this study, the researchers utilised mixed linear regression and extended linear regression models to find the correlations and effects of diet and time. Shown as mean ± SEM is the data (n = 9 to 12). A significant result was found, with a p-value of less than 0.05, when comparing the LFLS and HFHS groups using a Tukey HSD post hoc test.

Figure 1: Effects of LFLS and HFHS Diets on Weight Gain, Glucose Tolerance, and Insulin Response in Rats Over 56 Days





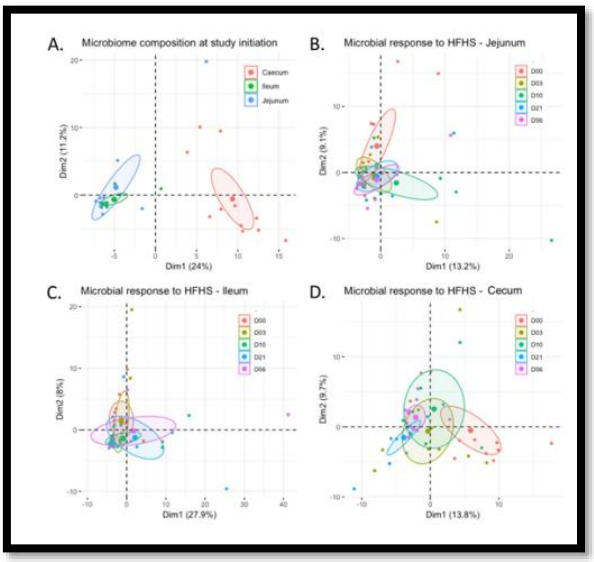
Source: Source: Lacroix et al. (2019) [11]

Segment-specific gut microbiome community reshaping during HFHS diet feeding

Prior to starting the HFHS diet, a principal component analysis (PCA) was conducted on the gut flora, which included segmenting the cecum and small intestine (Fig. 2A). These results agreed with projections made for gut flora populations. As shown in Figure 3, aerobes and facultative anaerobes, including Bacillales, Erysipelotrichales, and Lactobacillales, do better in the small intestine segments than obligatory anaerobes, such as Clostridiales, Bacteroidales, and Verrucomicrobiales, who do poorly in the cecum. There is a breakdown of the relative abundance of bacterial taxa and the number of genera for each location in Figure 4. There was a greater diversity of bacteria in the cecum (3.2 [3.0-3.3]) (represented as median [Q1-Q3]), indicating that different parts of the small intestine had different relative abundances of genera, in contrast to the jejunum (2.1 [1.8-2.8]) and ileum (2.2 [1.9-2.5], $P < 0.01$). While Bacteroidetes were more numerous in the cecum (1.46 [1.31-1.65] and 1.44 [1.40-1.64], respectively; p-value was less than 0.01), Firmicutes were more numerous in the ileum and jejunum. These results supported the researchers' decision to continue examining the HFHS diet on isolated intestinal sections.

Fig 2: Gut microbiota composition because of the HFHS diet. Using "principal component analysis (PCA)" before starting the HFHS diet, the researchers investigated the microbiota makeup in each section of the intestines (A). Impact of HFHS on microbiota structure in the jejunum (from A to D), ileum, and cecum (n= 6-12 for each time point).

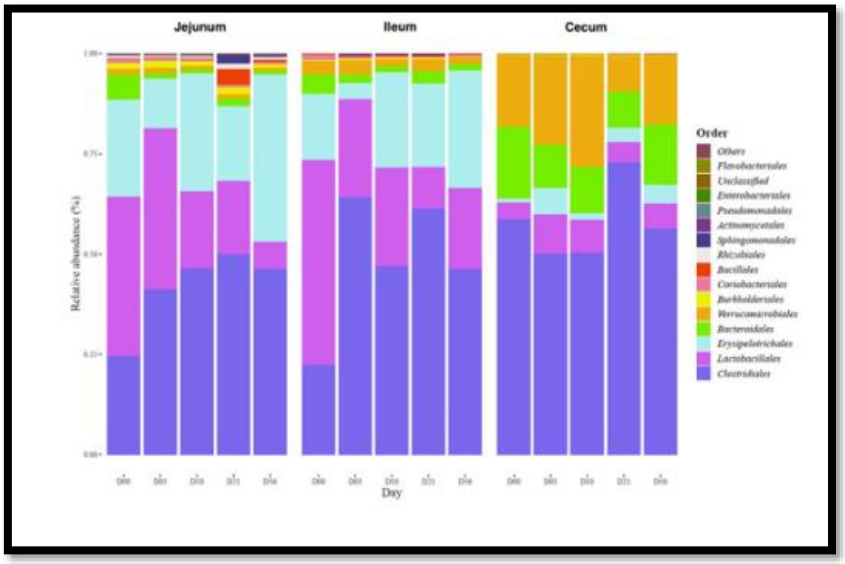
Figure 2: Alterations in Gut Microbiota Composition Induced by the HFHS Diet



Source: Source: Lacroix et al. (2019) [11]

Fig 3: Influence of HFHS on the order-level relative abundance of microbes. In certain parts, the orders that made up the bacteria were jumbled up, even though they only made up 1% of the total.

Figure 3: Effect of HFHS Diet on Order-Level Relative Abundance of Gut Microbes



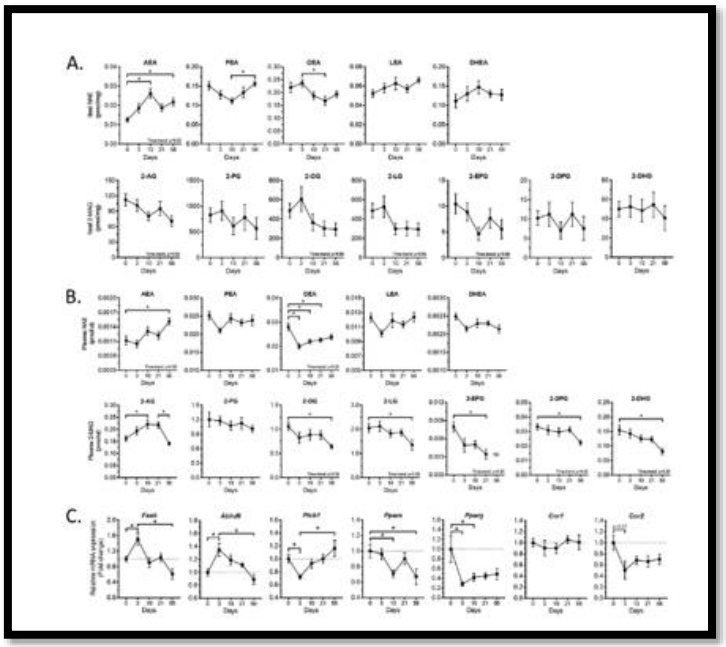
Source: Lacroix et al. (2019) [11]

Become mediators are modified in response to the HFHS diet

The ability to regulate the behaviour of target molecules is intricately linked to the modulation of metabolic processes, including CB1 (AEA and 2-AG), PPARα (N-oleoyl ethanolamine [OEA] and N-palmitoyl ethanolamine [PEA]), TRPV1 (which encompasses long-chain non-saturated N-acylethanolamines and 2-monoacylglycerols), the GPR technique (OEA, N-linoleoyl ethanolamine [LEA], 2-oleoyl-glycerol [2-OG], and 2-linoleoyl-glycerol [2-LG]), and GPR55 (PEA). Advances in the eCBome intermediary have been associated with the development of metabolic syndrome, obesity, and type 2 diabetes, as well as their potential interactions with gut microbiota. Researchers investigated ileal or plasma eCBome concentrations to determine the mediating influence of a high-fat, high-sugar meal. Upon evaluating AEA using analysis of variance (ANOVA) and linear comparability post hoc analysis, researchers identified a significant increase in the ileum 10 days after the initiation of the HFHS diet (+109 per cent after 10 days, $P < 0.05$). Although PEA levels had reverted to baseline by day 56 of HFHS feeding, OEA and PEA, two AEA congeners, exhibited a decline after 10 days of HFHS feeding. The concentrations of the anti-inflammatory AEA congener N-Docosahexaenoylethanolamine (DHEA) were unchanged by the HFHS diet. On day 56, there was a negligible decrease in the secondary principal endocannabinoid, 2-AG, which had been decreasing consistently throughout the period. GPR119 and TRPV1 activators, 2-OG and 2-LG, two congeners of 2-AG, have a distinct diminishing pattern in Figure 4A.

Fig 4: A reaction in the endocannabinoidome is triggered by consuming excessive amounts of sugar and fat. In addition to A and B For each time point after the onset of HFHS feeding, this line chart displays the endocannabinoidome mediator in the ileum (A) and plasma (B). Notice the N-acylethanolamines (NAEs) in the upper row. In the next rows, the researchers could see 2-monoacylglycerols (2-MAGs). With the act approach, the FC of the ileum mRNA expression of the endocannabinoidome-related gene was recognised. With Tbp applied, the data were transformed into percentages as of day 0. There are 9–12 observations at each time point, and the data is presented as the mean plus or minus the average error of the mean. Statistically significant findings are shown in the bottom right corner by the *P* values from the post hoc nonlinear contrast analysis. Per time point, the Tukey HSD post hoc test is executed with a significance threshold of $P < 0.05$. Here, "not determined" (ND) is the designation.

Figure 4: HFHS Diet Induces Endocannabinoidome Responses in Ileum and Plasma Over Time



Source: Lacroix et al. (2019) [11]

As seen in Figure 4B, there were also noticeable alterations to the eCBome mediators in the plasma. There was a 31% rise in ECBs containing arachidonic acid (+AG) and a 50% increase in 2-AG (+31%; $P < 0.05$). Plasma 2-AG levels peaked on days 10 and 21 and then declined significantly by day 56. Most eCBome mediators, including oleoyl "(OEA and 2-OG), linoleoyl (2-LG), and omega-3 [2-EPG, 2-DPG and 2-DHG]," were decreased when HFHS was administered, as shown in Figure 4B. Although the two diets were nutritionally identical, the HFHS diet purposefully consumed 4.5 times more total lipids than the LFLS diet. This made it possible to execute these changes in a controlled manner.

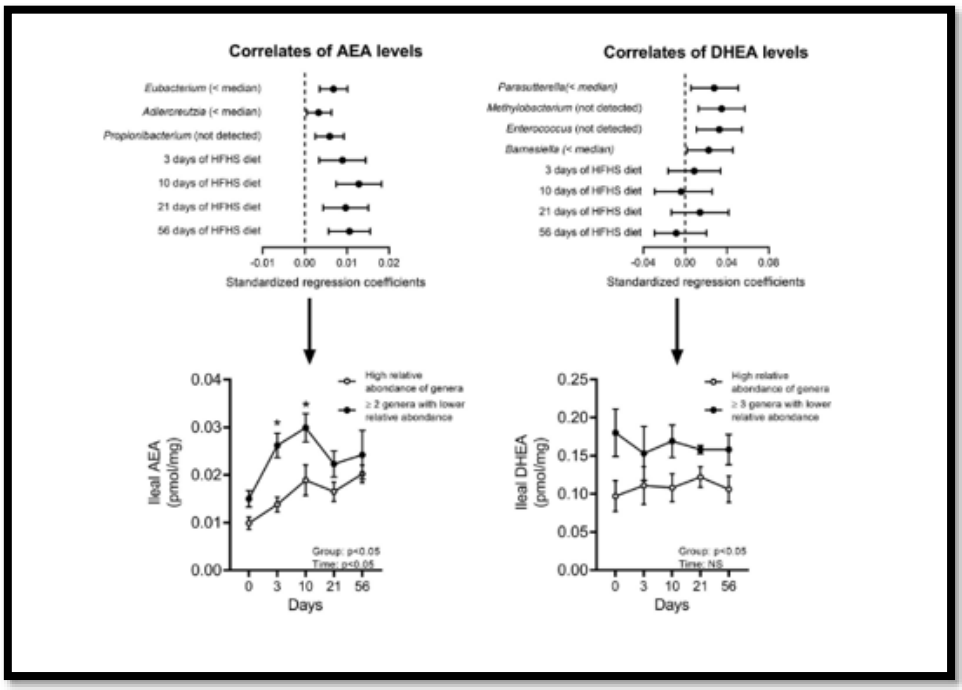
They were able to detect changes in the intestinal microbiome-eCBome axis by identifying the smallest collection of ileal microbiome taxa that adequately reflects the levels of each ileal eCBome mediator following HFHS consumption (Fig. 5). Changes in the ileal levels of the ECB AEA and the PPARα/γ agonist DHEA prompted that

The regression models that were created showed that some bacterial species were either undetectable or had low levels, irrespective of the increased weight. The relative concentrations of Eubacterium, Adlercreutzia, and Propionibacterium in the ileum were either undetectable or very low. Subsequently, there was a distinct and considerable correlation between early HFHS feeding intervals and higher AEA levels (Fig. 5). On the third and tenth days, when glucose intolerance first began, the AEA levels were significantly higher in the mice whose ileum microbiota had decreased the relative abundance of two of these species, according to the findings of the analysis using this model (Fig. 5). Elevated ileal DHEA was independently and strongly correlated with undetectable levels and low relative numbers of Parasutterella, Methylobacterium, Enterococcus, or Barnesiella (Fig. 5). Ileal DHEA levels were typically highest at zero hours and lowest at the beginning of glucose intolerance. It was also not possible to adequately imitate the other eCBome mediators, such as 2-AG.

Fig 5: The ileum endocannabinoid mediator engages in interactions with the gut flora in response to HFHS. The standardised regression coefficients of the intestinal flora are associated with the ileum's AEA and DHEA levels (top). The ileum microbiota profile was used to filter the AEA and DHEA levels at each time point. Species that have been shown to have strong ties to the eCBome as intermediaries were not included, nor were those with relative abundance

levels that could not be detected. In this study, researchers looked at every species that may be affected by HFHS feeding as well as every species that was strongly linked to the mediator. The time spent HFHS feeding is taken into consideration by all models. The final models were computed using a stepwise selection technique. With n ranging from 3 to 8 per group at each point, the data is shown as an average with or without the standard error of the mean in parentheses. A significance threshold of $P < 0.05$ was used to conduct a Tukey HSD post hoc test at each time point.

Figure 5: Interaction Between Ileal Endocannabinoid Mediators and Gut Microbiota in Response to HFHS Feeding



Source: Lacroix, et al. (2019) [11]

Discussion

Changes in the gut microbiota and eCBome signalling might impact how the host's metabolism reacts to food and environmental factors. Whether endogenous or symbiotic, the interdependent "omes" are still in their formative years. In the end, the goal of this research was to find out if diet-induced obesity is associated with metabolic repercussions. Alterations in the relative abundance of certain genera in the gut microbiota and specific amounts of eCBome mediators in the ileum or plasma are associated with the development of glucose intolerance, obesity, and hyperinsulinemia caused by the HFHS diet [9]. Obesogenic diets may alter the makeup of the gut microbiome by influencing the concentrations of eCBome mediators in the blood and the gut, according to previous research. Variations in segmentation and time of day affect the specifics. Furthermore, independent of changes in body weight, researchers discovered a correlation between certain bacterial species in the cecum and small intestine and eCBome mediator levels in blood and tissues. Adlercreutzia, Barnesiella, Parasutterella, Propionibacterium, Enterococcus, and Methylobacterium are all genera that belong to this class. Multiple simultaneous alterations to the gut microbiota or eCBome were seen as early as three days into the HFHS diet, suggesting that the gut microbiome-eCBome axis is involved in the first host adaptation to the diet. Dietary changes that cause obesity cause certain commensal bacterial populations to shift and levels of 2-monoacylglycerol and N-acylethanolamine to alter as well. Obesity, produced by a high-fat diet, is a known contributor to a decrease in stool quantity in several species. So, it is not surprising that the current discovery of decreased

Barnesiella counts in the intestines during HFHS lends credence to this. Peritoneal and jejunal parasutterella levels are decreased in obese individuals. The decrease of Akkermansia populations in this location during HFHS feeding is inversely connected to the metabolic mayhem, inflammation, obesity, and Acinetobacter baumannii that follow. Finally, research on overweight pigs has indicated that although the jejunum stays the same, the ileum has an increased population of Intestinimonas and Sphingomonas. Prior research has connected these two bacteria to obesity and poor leptin signalling. These and other alterations in gut flora might be explained by reactions to changes in nutrition availability. This study used HFHS and LFLS diets that were very comparable in terms of fatty acid composition, fibre sources, and amounts to assess the effects of increasing sugar and fatty acid intake on weight gain, dysmetabolism, and gut microbiota. Scientists found that HFHS increased plasma AEA and 2-AG levels, which is in line with the abundant evidence showing that these compounds are more prominent in fat people and animals with obesity. This trend of falling plasma 2-OG and 2-LG levels is consistent with an inverse association between body mass index and other 2-monoacylglycerol levels. There may be a correlation between the composition of the gut microbiome and the presence of eCBome mediators [8]. The fact that both systems react similarly to dietary changes provides a plausible explanation. This could be true in certain settings; even accounting for variations in BMI, researchers still found a number of associations. Changes in the same tissue that lead to obesity may initiate interactions between commensal bacteria and eCBome mediators long before the onset of obesity. Ileal AEA levels showed a significant temporal variation, ruling out the hypothesised protective effects of the ileal genera Parasutterella, Coprobacillus, Akkermansia, and Barnesiella against diet-induced dysmetabolism in mice. It seems plausible to infer a relationship between the two effects from these findings. Other research has connected circumstances producing elevated AEA levels to a reduction in the predominance of A. muciniphila, and reintroducing this beneficial species by probiotic use quickly decreases AEA levels [10]. The ileum's n-3 polyunsaturated fatty acid eCBome mediators affect certain genera irrespective of weight. These mediators have the potential to reduce inflammation to some extent. There was also a correlation between plasma levels of eCBome mediators and the relative number of bacterial species in the intestines' three sections. To further understand the relevance of these associations, more study is needed to uncover the origins of plasma eCBome mediators. There seems to be little evidence linking the genera found in the ileal microbiome to these compounds; therefore, it's worth contemplating that the small intestine might not be the primary source of plasma mediators or becomes.

Scientists found that ileum levels of many metabolically beneficial species were reduced in HFHS-fed mice, but AEA and DHEA levels were greater. This might suggest that CB1 and PPARα/γ are activated. These findings are linked to inflammation in certain areas and glucose intolerance [5]. researchers found that exploring these linkages as a community, rather than focusing on particular genera, would be the most beneficial method, given the metabolic importance of the gut microbiota and eCBome interactions. Based on the results, it should be possible to conduct more studies investigating the impact of gut colonisation on eCBome targets and mediators and how eCBome alterations relate to these aspects. Shockingly, the results suggest that the HFHS diet sets off time- and segment-specific bacterial responses. This emphasises the need for investigating different parts of the intestines, preferably using easier-to-handle animal models [7].

Conclusion

By tracking the eCBome in various sections of the intestines over time, this study maps out the HFHS-related complications like hyperinsulinemia, glucose intolerance, obesity, and others. Metabolic problems brought on by the HFHS diet and host-microbiome imbalance may have their origins in an endogenous signalling system, according to the study's authors. At this stage, the gut microbiome interacts with the online community's biome. Lastly, the current results should pave the way for future studies to investigate the molecular bases of the gut microbiome-eCBome axis.

Conflict of Interests

The authors declare that they have no conflict of interests.

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