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The Importance Of Epigenome And Microbiome In The Regulation Of Endocrine-Mediated Inflammation In Diet-Induced Obesity

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ABSTRACT

Microbiomes, also known as epigenomes, may have a role in metabolic health and the inflammation associated with diet-induced obesity (DIO), according to recent research. Examining the role of endocannabinoids in regulating inflammation in a mouse model, this work delves into the complex relationship between DIO, the epigenomic landscape, and the microbiome makeup of the digestive tract. To study the effects of a high-fat diet (HFD), researchers first made C57BL/6J mice overweight and then monitored their weight. Discovering alterations in metabolic parameters or inflammatory indicators, or both, was the aim. Researchers discovered changes in DNA methylation patterns linked to obesity by integrating genomic sequencing with epigenetic profiling. The most notable changes were seen in the genes that control inflammation and lipid metabolism. At the same time, scientists analyzed the gut microbiota using 16S rRNA sequencing and found that the HFD was associated with major changes in the variety and composition of microbes. The rise in inflammatory-promoting microbial taxa, linked to increased levels of endogenous THC, was the most striking finding. Researchers assessed the impact on inflammatory responses and metabolic repercussions after pharmaceutically modifying endocannabinoid signaling to identify the pathways. The results show that inflammation in DIO is influenced by both the microbiota and the epigenome. Endocannabinoid signaling is subsequently affected by this. This study demonstrates the complicated interaction between nutrition, microbiome, and epigenetic pathways in metabolic health and the possibility of addressing inflammation linked to obesity by targeting these pathways as a treatment strategy; however, further investigation is required to ascertain the precise mechanisms involved and their consequences for the prevention and treatment of obesity.

Keywords: *The endocannabinoid system, inflammation, changes in the microbiota and epigenome, and dietary factors all contribute to obesity.*

1. INTRODUCTION

Obesity caused by nutrition is a major contributor to the growing pandemic of chronic diseases and metabolic disorders (Zhang et al., 2019). This syndrome, which is basically produced by eating more calories than energy expended, is sometimes made worse by poor dietary choices (Yang et al., 2020). Two key biological systems, the microbiome and the epigenome, are involved in diet-induced obesity, according to recent studies. Both systems are essential for inflammatory regulation, but the endocannabinoid system is where they really shine. The epigenome modifies DNA and histone proteins chemically to regulate gene expression;

however, these modifications do not alter the genetic code itself. A person's food and other environmental factors could be contributing factors to these shifts. Metabolic changes caused by certain dietary components may influence inflammatory pathways and worsen illnesses associated with obesity. For instance, genes linked to inflammation and metabolism are impacted by methylation alterations brought about by a high-fat diet. The complex collection of bacteria that occupy the digestive system is known as the gut microbiome, and it has a substantial influence on metabolic health. Energy balance, chronic inflammation, microbiota makeup and function are all influenced by dietary choices. The endocannabinoid system has a role in several physiological functions, including inflammatory regulation, metabolism, and hunger regulation. It is possible that the microbiota influences this process. Studying the impact of diet-induced obesity on the microbiome, particularly the epigenome, and how these variables affect the regulation of inflammation by endocannabinoids may help scientists better understand obesity and its associated illnesses. states that this multimodal strategy might result in new approaches to improving metabolic health and reducing inflammation linked to obesity (Stapleton et al., 2020).

2. BACKGROUND OF THE STUDY

A dramatic change has occurred in the way scientists study diet-induced obesity and its mechanisms throughout the previous few decades. It was long believed that the primary cause of obesity was consuming more calories than one burned. Biochemical, environmental, and genetic factors all interact in complex ways to cause obesity, according to recent studies. The study of epigenetics began in earnest in the early 2000s when scientists began to ponder, beyond DNA, if dietary factors can impact gene expression. Dietary and environmental factors may modify genes via epigenetic pathways such as DNA methylation and histone modification, according to epigenetic research. These changes may have an even greater effect on inflammatory pathways, which in turn might worsen metabolic illnesses associated with obesity (Harsch & Konturek, 2021). At the same time, new findings from microbiome investigations have shown that gut bacteria play a pivotal role in determining health. The microbiome, which consists of billions of bacteria, plays a significant role in how the immune system, digestion, and metabolism work. 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. Metabolic dysregulation, inflammation, and an imbalanced microbiome are potential causes of obesity]], according to study. The endocannabinoid system is a complex network of receptors and signaling molecules that regulates several physiological functions, including inflammation and metabolism. According to studies, dietary and microbial alterations may set off endocannabinoid changes, which affect inflammatory responses, energy balance, and the control of hunger. Epigenetics, microbiome research, and endocannabinoid regulation are three promising areas. Studying the ways in which these systems are affected by diet-induced obesity and how they collaborate to control inflammation may lead to novel approaches to treating and preventing obesity and related disorders (Pinhel et al., 2020).

3. 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. The metabolic issues linked

to obesity include inflammation, and this study aims to investigate how these systems influence inflammation. By deciphering the intricate network of relationships between nutrition, genes, microorganisms, and endocannabinoid signaling, researchers want to discover strategies to aid individuals with diet-induced obesity in managing inflammation and improving their metabolic health. The main objective of this study is to address the knowledge gaps regarding the effects of diet-induced obesity on epigenetic alterations, changes in microbiome composition, and the role of endocannabinoid signaling in inflammatory regulation. Personalized treatments for obesity-related inflammatory illnesses may be possible with the use of this data.

4. LITERATURE REVIEW:

As a leading cause of metabolic diseases and inflammation, diet-induced obesity (DIO) is a major concern in modern public health (Maugeri & Barchitta, 2020). The complex interplay of inflammation, obeshave, and dietary factors has prompted investigations into the functions of the microbiome, epigenome, and endocannabinoid signaling. By regulating inflammatory processes and metabolic activity, the lipid-based neurotransmitters called endocannabinoids are crucial in the obesity environment. The complex relationship between the endocannabinoid system (ECS), microbiota, and the epigenome is becoming more and more linked to diet-induced obesity (DIO), a serious public health concern. 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 itself. These changes may exacerbate inflammation and metabolic imbalance circuits. The gut microbiota has a significant impact on the host's metabolism and immune responses. Dysbiosis, a prevalent complication of DIO, may have an effect on the ECS, a network of lipid signaling molecules that controls inflammation, appetite, and energy balance. The bioactive lipids called endocannabinoids within this system control inflammatory processes by interacting with immune cells and cytokine signaling. 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. A deeper comprehension of this intricate relationship may shed light on these concerns, since dietary therapy and microbiota change are two possible therapeutic targets for lowering the inflammatory consequences of obesity (Park et al., 2021).

5. RESEARCH QUESTIONS

- What is the impact of unhealthy dietary habits on the regulation of inflammation?

6. RESEARCH METHODOLOGY:

The research for this study was carried out using laboratory procedures. The investigation was carried out using a mouse as an animal model.

6.1 Research design:

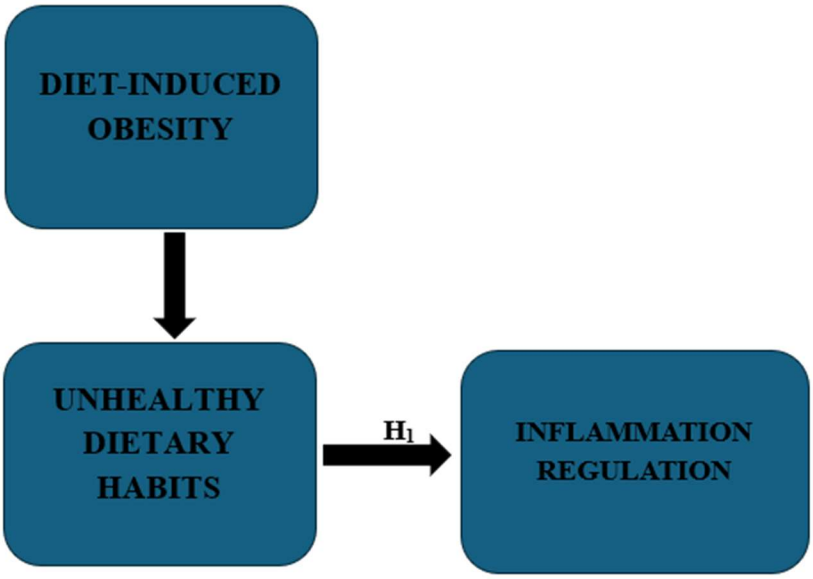
Obese mice on a high-fat diet may experience changes to the endocannabinoid system, which is crucial for the processing of pain signals and emotions. This study will examine the nociceptive response of obese mice as a model to learn about the effects of dietary modifications

on the endocannabinoid system. By manipulating the gut microbiota and cannabinoid receptors CB1 and CB2 by genetic and pharmacological means, this work intends to ascertain the ECS's functions in inflammation and metabolic control in a diet-induced obesity mice model. The CB1 antagonist was also tested on obese mice. By studying CB1 and CB2, researchers were able to get a better understanding of how HFD affected leukocyte infiltration in the cecal-colonic lamina propria. Since inhibiting cannabinoid 1 (CB1) reduces inflammation in the intestines, it stands to reason those alterations in the gut microbiota, mediated by the ECS, contribute to the obesity phenotype. The purpose of analyzing microbiota profiles using 16S rRNA gene sequencing was to find out whether CB1-/- or CB2-/-mice were less likely to develop intestinal dysbiosis due to a high-fat diet.

6.2 Mice Model

This research made use of male C57Bl/6J mice that were procured from The University Laboratory. After 12 weeks, adult mice were randomly assigned to either a 60% kcal HFD or a 10% low-fat diet, with the findings showing which group performed better. The mice were given different diets when they were six to eight weeks old. The medical school at the University of South Carolina raised CB1-/-and CB2-/-mice in its animal facilities. The treatment group said that all the trials, except for the co-housing study, used cages with three to five mice each. The mice used in this investigation were from a wide range of litter and kept in different environments. Because of their hostile behavior, mice were sometimes housed in separate enclosures. The obese mice were split for the DIO intervention experiments based on their average DEXA fat mass after 12 weeks of an unhealthy feeding pattern. The experimental group took 10 milligrams of AM251 per kilogram orally with a 0.1% Tween 80 solution. Valve labels reading "Veh" were supplied to each of the other experimental groups. Researchers make sure that the Pair-fed group gets the same amount of HFD every day by monitoring their food intake as part of the PA feeding program. The mice were induced to sleep by administering an excessive amount of isoflurane as the experiment ended.

7. CONCEPTUAL FRAMEWORK

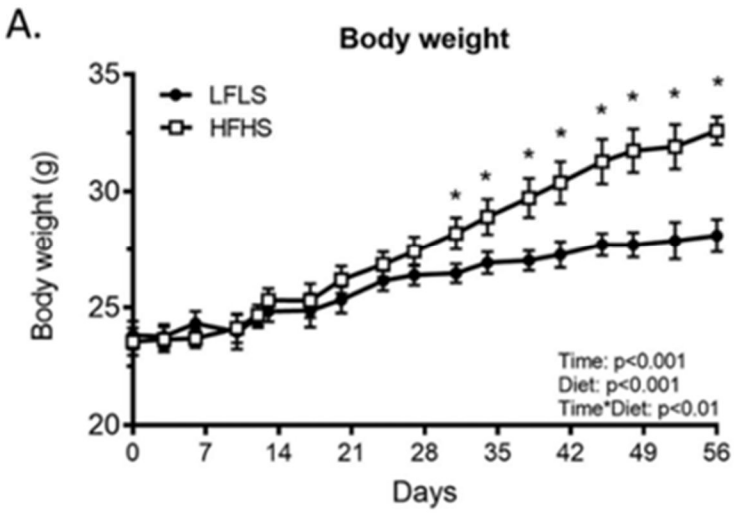


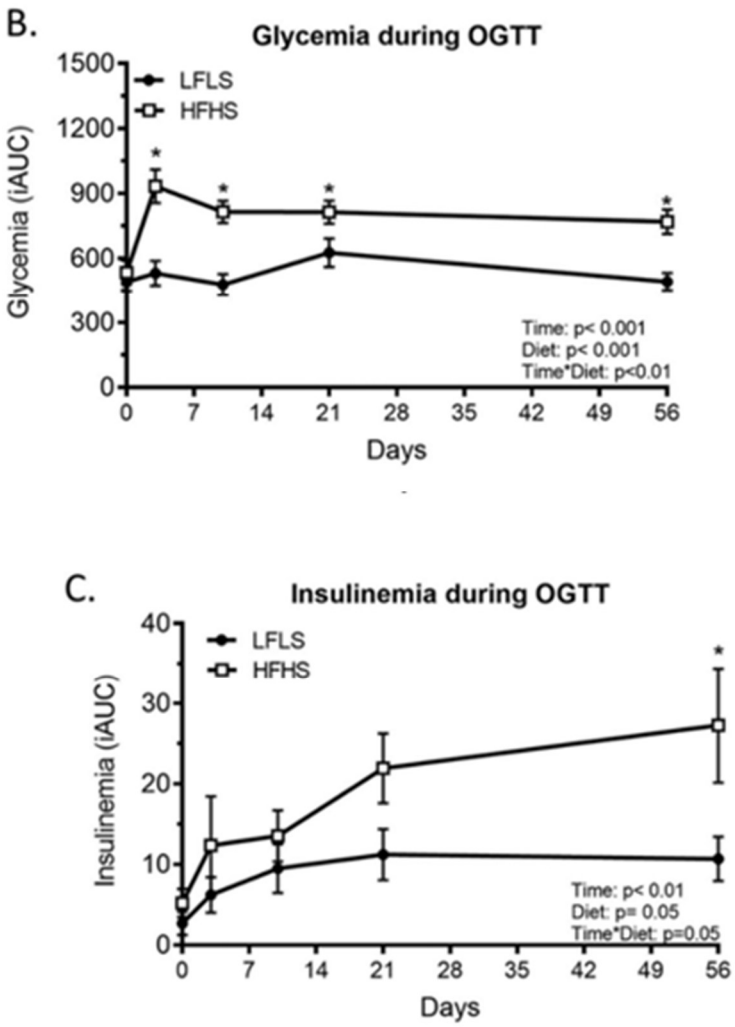
8. RESULTS

Weight gain was greater in the HFHS group compared to the LFLS group when fed varied diets.

As seen in Figure 1A, a significant difference emerged between the two groups starting from day 31. On average, the HFHS group put on 32.6 ± 1.8 g of weight, whereas the LFLS group put on 28.1 ± 1.6 g. Fig. 1B shows that the oral glucose tolerance test (OGTT) revealed a decrease in glucose tolerance, as shown by an increased glucose area under the curve. On the third day of HFHS feeding, these decreases started. An increase in body fat was linked to a decrease in this tolerance threshold. This supports the conclusion from Figure 1C that insulin sensitivity decreases with increasing body weight throughout treatment, as the insulin area beneath the OGTT curves did not show a meaningful improvement until day 56 of HFHS feeding.

Fig 1: The phenotypes of rats after 56 days of a low-fat diet high in sugar and fat. Eleven mice were administered LFLS or HFHS in a 56-day sequential manner. Here, three variables come into play: the individual's weight increase, the area under the oral glucose tolerance test (OGTT) curve for plasma glucose, and the area under the insulin OGTT curve for plasma (iAUC). To find the linkages and effects across time related to food, researchers used mixed linear regression and extended linear regression models. Mean ± SEM is shown for data (n = 9 to 12).The researchers found a significant result (*, P < 0.05) when researcher compared the LFLS and HFHS groups using a Tukey HSD post hoc test.





Segment-specific gut microbiome community reshaping during HFHS diet feeding

Before starting the HFHS diet, the gut flora was analyzed using principal component analysis (PCA). The cecum and small intestine were sliced (Fig. 2A). Their results lined up with those expected from gut flora populations. Aerobes and facultative anaerobes, such Bacillales, Erysipelotrichales, and Lactobacillales, do well in the small intestine segments, in contrast to obligatory anaerobes, which are shown in Figure 3 to fare poorly in the cecum. On top of that, Figure 4 shows the number of genera and the relative abundance of bacterial taxa at each location. The cecum, in comparison to the jejunum and ileum, showed a more diverse range of bacteria (3.2 [3.0-3.3]) (given as median [Q1-Q3]), indicating that different parts of the small intestine had different relative abundances of genera ($P < 0.01$). The cecum had a higher concentration of Bacteroidetes (1.46 [1.31-1.65]) than the ileum and jejunum (1.44 [1.40-1.64]), while Firmicutes were more numerous (1.46 [1.31-1.65]; p-value was less than 0.01). Considering these results, the researchers continued to test the HFHS diet on small intestinal portions to see what happened.

Fig 2: Gut microbiota composition due to HFHS diet. The researchers examined the microbiota

composition in each part of the intestines (A) using "principal component analysis (PCA)" prior to beginning the HFHS diet. Influence of HFHS on the composition of the jejunum, ileum, and cecum microbiota (n= 6-12 per time point) (A–D).

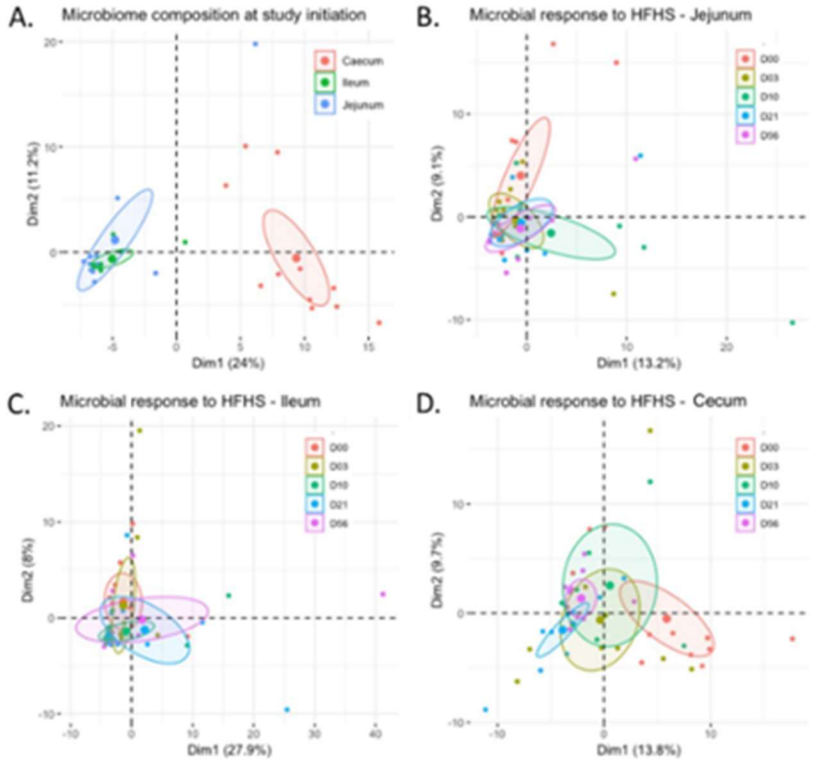
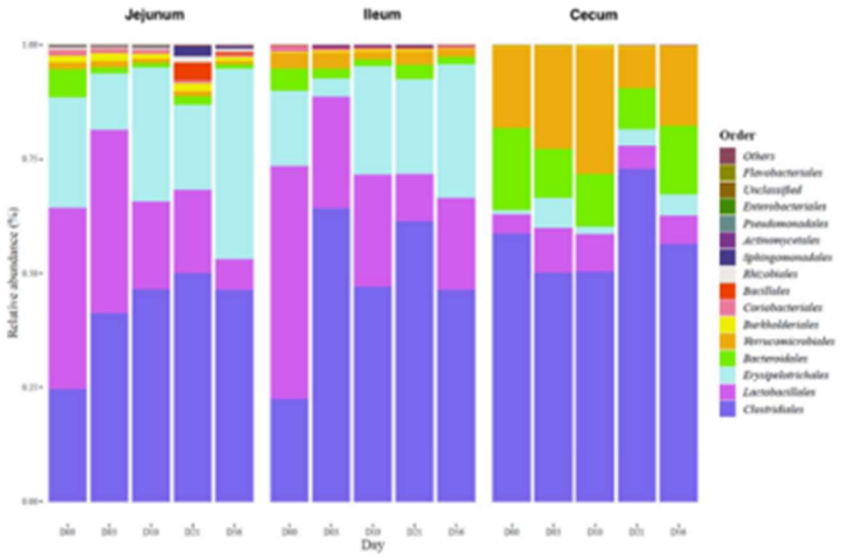


Fig 3: The way HFHS affects the relative abundance of microorganisms at the order level. The bacterial orders were mixed up in several places, even though they only accounted for 1% of the total.

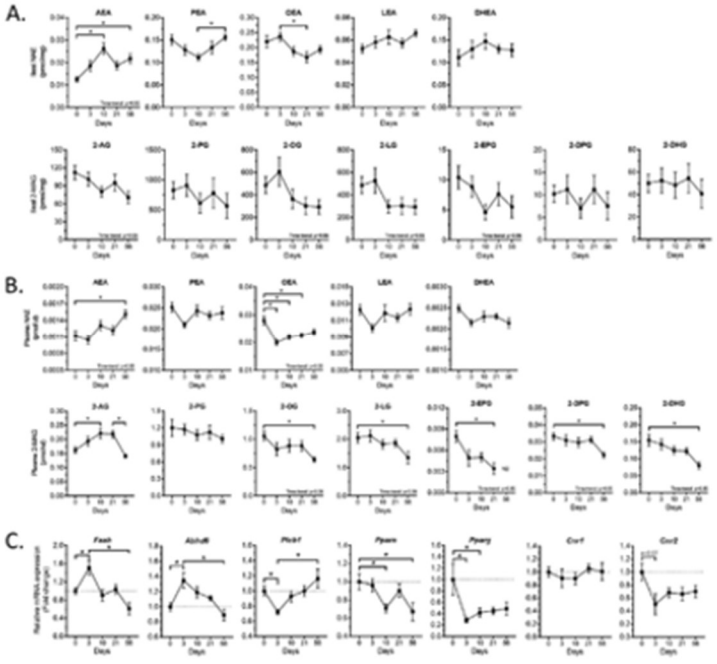


Become mediators are modified in response to the HFHS diet

Controlling the behavior of target molecules intricately linked to metabolic processes, such as

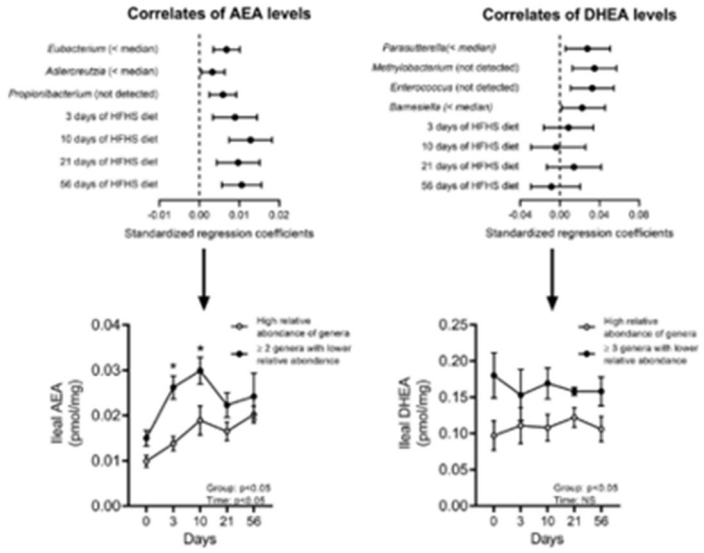
CB1 (AEA and 2-AG), PPARα (N-oleoyl ethanolamine [OEA] or N-palmitoyl ethanolamine [PEA]), TRPV1 (including long-chain non-saturated N-acylethanolamines and 2-monoacylglycerols), the GPR technique (OEA, N-linoleoyl ethanolamine [LEA], 2-oleoyl-glycerol [2-OG], and 2-linoleoyl-glycerol [2-LG]), or GPR55 (PEA), has 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 percent after 10 days, $P < 0.05$). Although PEA levels normalized 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, a negligible decrease was seen 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: An endocannabinoidome response occurs in response to high-fat and sugary diets. A and B are both the endocannabinoidome mediator in the ileum (A) and plasma (B) is shown in this line chart at every point after HFHS feeding commences. Those N-acylethanolamines (NAEs) are up there in the header. The student could come across 2-monoacylglycerols (2-MAGs) a few rows down the page. The activation response threshold (ACT) for ileum mRNA expression of the endocannabinoidome-related gene was determined. Day 0 percentages were used to display the data after they were adjusted to Tbp. The researcher provides the data as the mean plus or minus the average error of the mean for each time point when there are 9-12 observations. The P values from the post hoc nonlinear contrast analysis are shown in the bottom right corner when the findings are statistically significant. At a significance threshold of $P < 0.05$, the Tukey HSD post hoc test is executed for each time point. This is represented by the label "not determined" (ND).



Changes to the plasma eCBome mediators were also evident, as seen in Figure 4B. The arachidonic acid content of ECBs increased by 31% and the 2-AG content by 50% (+31%; $P < 0.05$). On days 10 and 21, plasma 2-AG levels were at their highest, and by day 56, they had dropped considerably. Figure 4B shows that feeding HFHS lowered levels of most eCBome mediators, including oleoyl "(OEA and 2-OG)-, linoleoyl (2-LG)-, and omega-3 [2-EPG, 2-DPG and 2-DHG]". The HFHS diet purposefully consumed 4.5 times more total lipids than the LFLS diet, while maintaining the same composition and omega-3 to omega-6 ratio. This allowed for the gradual introduction of these changes under supervision. By determining the minimal set of ileal microbiome taxa that adequately represents the amounts of each ileal eCBome mediator after HFHS consumption, they were able to detect changes in the axis between the intestinal microbiome and eCBome (Table 5). The regression models that were developed revealed that some bacterial species were either not detectable or had low levels, regardless of the rise in weight, in reaction to changes in the ileal levels of the ECB AEA and the PPARα/γ agonist DHEA. The ileum did not contain any measurable or very low relative amounts of Eubacterium, Adlercreutzia, or Pro bacterium. There was a clear and significant relationship between greater AEA levels and earlier HFHS feeding intervals (Fig. 5). Fig. 5 shows that the mice whose ileum microbiota had reduced the relative abundance of two of these species had considerably higher AEA levels on the third and tenth days, when glucose intolerance initially appeared. The presence of undetectable amounts of Parasutterella, Methylobacterium, Enterococcus, or Barnesiella, as well as low relative numbers of these bacteria, were significantly and independently associated with elevated ileal DHEA (Fig. 5). Normally, ileal DHEA levels were greatest at 0 hours and lowest when glucose intolerance first started. Inadequate imitation of other eCBome mediators, such 2-AG, was also not achievable.

Fig 5: Interactions between the gut flora and the ileum endocannabinoid me mediator occur in response to HFHS. Ileum AEA and DHEA levels are related to the intestinal flora's standardized regression coefficients (top). The amounts of AEA and DHEA were filtered at each time point based on the ileum microbiota profile. The researcher did not consider species with undetectable relative abundance levels or those with demonstrably significant links to the eCBome as intermediates. In this investigation, the researcher examined all species that were highly associated with the mediator and all species that may be impacted by HFHS feeding. Every model encompasses the duration of HFHS feeding. Using a stepwise selection procedure, the final models were generated. In each point, n ranges from 3 to 8, and the findings are given as the average plus or minus the standard error of the mean. *, A significance threshold of $P < 0.05$ was used to conduct a Tukey HSD post hoc test at each time point.



9. DISCUSSION

According to research (Choi et al., 2020), alterations in the gut microbiota and eCBome signaling may influence the host's metabolic response to environmental and dietary inputs. The intricate web of interactions between endogenous and exogenous/symbiotic "omes" is an ongoing process. In this study, the researcher aimed to determine if diet-induced obesity and its metabolic consequences are causally related. While the HFHS diet is beginning to promote glucose intolerance, obesity, and hyperinsulinemia, there is a correlation between changes in the relative abundance of certain genera in the gut microbiota and specific amounts of eCBome mediators in the ileum or plasma. Research suggests that obesogenic meals may change the gut microbiome composition by affecting blood and gut levels of eCBome mediators. Day of the week and segmentation influence the specific variations. Certainnally, they found that certain bacterial species in the cecum and small intestine correlated with eCBome mediator levels in blood and tissues; this link was unaffected by changes in body weight. Some genera that fall within this umbrella include Adlercreutzia, Barnesiella, Parasutterella, Propionibacterium, Enterococcus, and Methylobacterium. Hosts began to adjust to the HFHS diet at three days in, with several concurrent changes to the gut microbiota or eCBome. This indicates that the gut microbiome-eCBome axis plays a role in this early adaptation. In addition to alterations in the number of certain commensal bacteria, alterations in 2-monoacylglycerol and N-acylethanolamine levels have been associated with dietary-induced obesity. One example is the correlation between obesity and a decrease in the quantity of some species' excrement, as shown in earlier research on the effects of a high-fat diet. Subsequently, this is consistent with the present finding of reduced Barnesiella populations throughout the intestines during HFHS. Less Parasutterella is found in the ileum and jejunum of overweight people. The HFHS-induced decline in Akkermansia populations in this area is inversely related to the subsequent metabolic mayhem, inflammation, obesity, and Acinetobacter baumannii. The ileum of overweight mice exhibits an increase in Intestinimonas and Sphingomonas, but the jejunum remains unchanged,

according to the study. Past studies have linked these two bacteria to an increased risk of obesity and impaired leptin signaling. This, along with other changes in gut flora, might be a reaction to changes in the food supply. In order to determine how increasing sugar and fatty acid consumption affected weight gain, dysmetabolism, and gut microbiota, this research used HFHS and LFLS diets that were very similar in terms of fatty acid content, fiber sources, and percentages. Research has shown that plasma AEA and 2-AG levels are higher after HFHS eating, which is consistent with the large literature demonstrating that these intermediates are amplified in obese individuals and animal models of obesity. Other 2-monoacylglycerol levels were shown to be negatively correlated with body mass index, which is in line with the reduction in plasma 2-OG and 2-LG levels. A possible relationship exists between the gut microbiome's makeup and the existence of eCBome mediators. The fact that the two systems react similarly to changes in food weight could be the explanation. Several connections persisted even when researchers controlled for differences in body mass index, suggesting this could be the case in certain contexts. Obesity may not develop until after commensal bacteria and eCBome mediators have begun interacting in the same tissue. The expected preventive benefits of the ileal genera Barnesiella, Parasutterella, Akkermansia, and Coprobacillus against diet-induced dysmetabolism in mice were disproven by a considerable temporal adjustment of ileal AEA levels. These results provide sufficient evidence to suggest a causal relationship between the two effects. A. muciniphila prevalence decreases under circumstances causing increased AEA levels, and the rapid lowering of AEA levels is a direct result of reintroducing this beneficial species via probiotic therapy. A relationship between weight and certain genera is not reliant on the ileum's n-3 polyunsaturated fatty acid eCBome mediators. Inflammation may be mitigated to a certain degree by these mediators. Further, it was shown that the relative abundance of bacterial species in all three parts of the intestines was linked with plasma concentrations of eCBome mediators. The significance of these relationships needs more exploration from researchers since the sources of plasma eCBome mediators are yet unclear. Little is known about the relationships between the genera identified in the ileal microbiome and plasma mediators or eCBomes; hence, it is possible that the small intestine is not the main source for these compounds.

In the ileum of mice given the HFHS diet, researchers discovered that higher amounts of AEA and DHEA were associated with a deficiency of several species that promote metabolic health. The activation of CB1 and PPARα/γ might be suggested by this evidence. Some of the results include glucose intolerance and inflammation in the affected area. Based on these findings, it would be wise to investigate potential interactions between the gut microbiota and the eCBome, rather than concentrating on individual genera, as these interactions might have metabolic implications. Given these findings, it should be feasible to conduct more research into the relationship between eCBome changes and the effect of gut colonization on eCBome targets and mediators. The data indicate that the HFHS diet triggers bacterial responses that are unique to time and segments, which is somewhat strange. This highlights the importance of studying various sections of the intestines, ideally in conducive animal models (Barron-Cabrera et al., 2019).

10.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. This study's findings suggest that metabolic problems brought on by the HFHS diet and host-microbiota dysbiosis may originate in an endogenous signaling system that is crucial for metabolic homeostasis. During this process, there is an interaction between the biome of the online community and the gut microbiome. Finally, further research into the molecular underpinnings of the gut microbiome-eCBome axis should be made possible by the present findings (Ali et al., 2021).

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