

for a particular amount or calories – like the 100-calorie packs, but for all foods – would they choose the bigger portions of less calorically dense foods and eat less?

Dr. Rolls: I wish we could find a real world setting to do that, but that's part of what we try to educate people to do. If you go lower calorie density you are going to get more food for your calories. But if you ask most people how many calories they should eat in any one occasion they have no idea. You also have the economics of food choice – some people want the most calories for their money.

Dr. Rosenbaum: But forget about the economics for a second. If you just walk into a store and you pay by the calorie and you have to buy 500 calories for a meal, if you can see that you would get a lot more food if you choose apples rather than a calorie-dense sandwich, would you buy differently?

Dr. Rolls: There is a chain in Britain that has a 'bundled meal' where you pay a flat rate for 500 calories for lunch. They have all kinds of different packages where you can mix and match your sandwich, drink, and snack. This could provide a wonderful opportunity to do research because people could buy items that were different in value as well as energy density and portion size for their 500 calories. Wouldn't it be interesting to look at what they choose?

Dr. St. Jeor: I am curious about what your recommendations are regarding high-protein drinks, some of them with as much as 60 g of protein that promotes their satiety-enhancing properties.

Dr. Rolls: We will always have a lot of choices, but this goes back to where I began. We don't want people basing their choices on the hope that they will get a boost of satiety that will help them to eat less with little effort. We want people to be eating a diet with a balance of nutrients. We need to think more about how to show people that they can use regular food to enhance satiety and eat less.

Dr. Drewnowski: One trend in children's nutrition is to try and replace juices with intact whole fruits. Would that make a difference in satiety or energy density?

Dr. Rolls: We have done studies and so have others showing that whole fruit is more satiating than juice even if you add the fiber back into the juice. There is a lot of interesting work on texture and thickness of beverages and how these properties affect satiety. This takes us back to the functional ingredients approach to satiety, which we should continue to pursue, but in the context of a healthier diet overall.

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Obesity Treatment: Challenges and Opportunities

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Targeting Adipose Tissue Inflammation to Treat the Underlying Basis of the Metabolic Complications of Obesity

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Abstract

The prevalence of obesity has increased throughout the last three decades due to genetic, metabolic, behavioral, and environmental factors [1]. Obesity in turn increases risk for a number of metabolic diseases including type 2 diabetes, cardiovascular disease, fatty liver disease and some forms of cancer [1]. Despite the well-known link between obesity and increased morbidity, the mechanism of this remains elusive. Thus, the question 'why does increased body fat cause increased metabolic comorbidities' remains unanswered. By understanding the underlying basis of obesity-associated metabolic diseases, different therapies could be designed to target relevant pathways. Although we lack a full understanding of the underlying mechanisms that result in disease, several putative explanations exist for why fat affects metabolic health. One such theory is based on the anatomic location of fat deposition and ectopic fat accumulation [2]. Specifically, current literature suggests that visceral, liver and skeletal fat accumulation affects organ function and contributes to the development of insulin resistance, fatty liver, and the metabolic syndrome [3]. However, even in individuals matched for body fat and fat distribution, significant differences can exist in metabolic outcomes, and the phenomenon of metabolically healthy obese has been well described [4]. More recent data suggest the alternative hypothesis relating excess adipose tissue to disease risk based on the metabolic function and morphological properties of adipose tissue. In this scenario, excess adipose tissue is hypothesized to contribute to a state of chronic inflammation which promotes development of insulin resistance as well as other metabolic complications by stimulating nuclear factor- κ B and Jun N-terminal kinase pathways in adipocytes and the liver [5]. In this paper, we will review the hypothesis linking excess adipose tissue to increased disease risk through adipose tissue inflammation.

Adipose Tissue as an Endocrine Organ

It was once believed that adipocytes were only involved in the storage of triglycerides, but recent studies have demonstrated that they also act as endocrine organs. Hotamisligil et al. [6] and Karasik's group first showed that proinflammatory cytokine tumor necrosis factor (TNF)- α was produced by adipocytes, induced insulin resistance, and increased with expanding fat volume. The concept of adipose tissue as a site for the production of cytokines and other substances has expanded to include leptin, interleukin (IL)-6, resistin, monocyte chemoattractant protein-1 (MCP-1), plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, visfatin, retinol-binding protein-4, and serum amyloid A. Adiponectin is also produced by adipocytes, but its release decreases with increasing adiposity. Leptin and adiponectin are adipokines that are produced only by adipocytes; while TNF- α , IL-6, MCP-1, visfatin, and PAI-1 are also expressed at high levels in activated macrophages. TNF- α , IL-6, resistin, and other proinflammatory cytokines participate in the induction and maintenance of the acute inflammatory response associated with obesity. Additionally, MCP-1 and other chemokines recruit macrophages to adipose tissue. These cytokines and chemokines activate intracellular pathways that promote the development of insulin resistance, type 2 diabetes and other metabolic complications associated with obesity [5]. Therefore, adipose tissue and macrophages within adipose tissue have been shown to play important roles in the regulation of metabolic pathways through the excretion of adipokines and cytokines.

Metabolically Benign Adipose Tissue

Despite the observed link between body fat, non-alcoholic fatty liver disease, and type 2 diabetes, some individuals exhibit 'metabolically benign obesity' and are protected from the metabolic consequences of excess adiposity, possibly due to differences in adipocyte tissue metabolism and macrophage infiltration. In a study aimed at identifying insulin-resistant individuals, 17% of the overweight and obese participants were found to be insulin sensitive [7]. Additionally, a review by Karelis et al. [4] determined that approximately 20% of the general population can be categorized as obese but metabolically healthy. In contrast to this, 18% of the population were found to have a normal bodyweight but suffered from severe metabolic abnormalities. In other studies among obese adults, the degree of adipose tissue inflammation was closely associated with increased metabolic risk for type 2 diabetes, cardiovascular disease and fatty liver disease, whereas obese adults without adipose tissue inflammation have metabolic risk factors in the healthy range [8, 9]. Despite the fact that most human research has focused on the links between fat distribution and metabolic risk, these findings suggest a role for adipose tissue inflammation. In a previous study among

obese young minority adults, we found that approximately 40% of subjects had subcutaneous abdominal adipose tissue with crown-like structures, indicating inflammation, whereas approximately 60% of subjects had no signs of adipose tissue inflammation. Despite the two groups being identical for overall obesity and subcutaneous abdominal adipose tissue volume, those with inflamed adipose tissue had approximately 30% greater visceral adipose tissue and 41% greater liver fat; 53% greater fasting insulin and 23% lower β -cell function, and 22% higher TNF- α . Additionally, adipose tissue from those with inflamed adipose tissue had upregulated nuclear factor- κ B (NF- κ B) expression activity and downregulation of insulin signaling [9]. Another recent study by Br mer et al. [8] demonstrated that, among overweight and obese adults, those with metabolic syndrome have significantly higher levels of infiltrating macrophages/crown-like structures in their adipose tissue compared to those without the metabolic syndrome. Given these observations, the disparities in metabolic diseases among obese individuals may be explained by the degree of chronic low-grade inflammation of adipose tissue. Therefore, targeting adipose tissue inflammation has become an important new strategy in treating the metabolic conditions typically associated with obesity.

Weight Loss and Inflammation

One of the few effective anti-inflammatory treatments for these metabolic diseases is weight loss [10]. Studies in diet-induced obese mice have shown that reductions in adiposity result in decreases in macrophage infiltration of adipose tissue as well as gene expression of pro-inflammatory markers [11, 12]. Specifically, Kosteli et al. [11] found that the murine immune response to weight loss was dynamic. Caloric restriction of high-fat diet-fed mice resulted in an initial increase in adipose tissue macrophages; however, the number of adipose tissue macrophages decreased following an extended period of weight loss. Vieira et al. [12] examined the effects of diet and exercise on inflammation among high-fat diet-induced obese mice. This study examined the effects of weight loss via a low-fat diet, exercise training, or a combination of low-fat diet and exercise on inflammation. All methods of weight loss resulted in a significant attenuation of high-fat diet-induced increases in systemic and adipose tissue inflammation. Additionally, all three interventions improved insulin sensitivity, reduced adiposity, MCP-1, and TNF- α gene expression. Among obese humans, caloric restriction to achieve weight loss also decreases markers of inflammation. For example, a 28-day severe calorie-restrictive diet (800 kcal/day) among obese females was found to reduce bodyweight by an average of 13 pounds as well as significantly alter markers of inflammation. Specifically, weight loss resulted in a decreased expression of proinflammatory markers (e.g. IL-12a, matrix metalloproteinase-9) in white adipose tissue and increased the

expression of anti-inflammatory molecules (e.g. IL-10 and IL-1 receptor antagonist) [13]. Studies using surgical methods to achieve weight loss also improve inflammation among obese patients. A study by Aron-Wisniewsky et al. [10] demonstrated that weight loss following gastric bypass surgery resulted in a mean weight loss of 44 pounds at 3 months. Among the 16 obese females in this study, the activation state of adipose tissue macrophages switched from mostly proinflammatory to anti-inflammatory after weight loss. However, since weight loss is difficult to achieve and maintain, alternative strategies aimed at adipocyte inflammation present a unique target in which to modify metabolic health.

Diet and Inflammation

Diets high in sugar and fat have been shown to increase systemic markers of inflammation [14, 15]. Given the link between diet and inflammation, it is not surprising that dietary alterations have been used to examine obesity and obesity-associated inflammation among obese humans [12]. Specifically, healthy adult males given fructose (40 or 80 g/day) or glucose (40 or 80 g/day) sugar-sweetened beverages for 2 weeks demonstrated significant increases in high-sensitivity CRP [14]. In addition to sugar intake, trans fat consumption is related to markers of inflammation. A cross-sectional analysis of 730 women from the Nurse's Health Study found that CRP levels were 73% higher and IL-6 levels were 17% higher among those in the highest quintile of trans fat intake compared to those in the lowest [15]. Among humans, a diet high in fiber (30 g/day), either through diet or fiber supplementation, has been shown to significantly reduce CRP levels [16]. Baseline examination of data from 406 participants from the Finnish Diabetes Prevention Study found that increases in fiber predicted decreases in CRP and IL-6. They also found that changes in fat and carbohydrate intake were either weakly or not related to reductions in CRP and IL-6 [17].

Studies using obese mice have found differing effects of diet composition on inflammation. For example, Wang et al. [18] used mice with high-fat diet-induced obesity to examine the effects of weight loss achieved by switching from high-fat diet to: (1) an ad libitum low-fat normal diet or (2) restricting the high-fat diet intake to match bodyweight of mice with low-fat normal-diet-induced weight loss. Weight loss by either of the two methods resulted in decreased fat mass and liver steatosis; however, effects were greatest among the low-fat normal-diet-induced weight loss than the high-fat diet restriction-induced weight loss. Interestingly, weight loss with the low-fat normal diet, but not the restricted high-fat diet, normalized blood CD11c⁺ monocytes and attenuated hepatic inflammation. In contrast, the calorie-restricted high-fat diet significantly reduced chemokine levels and CD11c⁺ cells in adipose tissue when compared to low-fat diet-induced weight loss and obese controls. Although

these studies demonstrate that changes in diet can affect systemic inflammation associated with obesity, the direct mechanism and critical dietary components are not known. Additionally, the dietary changes necessary to elicit weight loss and decreases in inflammation are likely to be too drastic to sustain over time.

Anti-Inflammatory Treatments

In addition to dietary interventions, studies have examined the effects of anti-inflammatory treatments on systemic markers of inflammation. For example, human studies examining omega-3 polyunsaturated fatty acid (n-3 PUFA) supplementation have shown mixed results in its ability to target systemic inflammation [19], while high-dose aspirin treatments have decreased plasma markers of inflammation [20]. Among adult men and women, a placebo-controlled, double-blind study used 3.5 g/day of fish oil (1.5 g/day n-3 PUFA) for 12 weeks to examine change in plasma markers of inflammation. Compared to placebo, the treatment group did not differ in the median CRP change over the course of the study. In fact, results suggested an increase, not a decrease, in CRP with n-3 PUFA supplementation compared to placebo [19]. Given the disparate findings among animal models and humans, it is not surprising that the potential therapeutic role of n-3 PUFA supplementation to target inflammation has been, for the most part, abandoned. Despite these lackluster findings, researchers have begun examining other potential anti-inflammatory treatments that directly target adipose tissue inflammation.

Studies using mice models have successfully used anti-inflammatory treatments, such as n-3 PUFA and resolvin D1 to target adipose tissue inflammation [21, 22]. Todoric et al. [22] treated diabetic mice with a low-fat or a high-fat diet [rich in either saturated/monounsaturated fatty acids (HF/S) or n-3 PUFA] and found that adipose tissue macrophage infiltration was increased and genes involved in inflammation were upregulated in mice fed HF/S compared with the low fat diet. The high-fat diet containing n-3 PUFA completely prevented macrophage infiltration induced by the high-fat diet as well as changes in inflammatory gene expression. Most notably, a recent study has demonstrated the therapeutic potential of resolvins. Resolvins are a newly discovered family of lipid mediators that are generated from n-3 PUFA eicosapentaenoic acid and docosahexaenoic acid. Resolvins have an anti-inflammatory affect by blocking leukocyte infiltration into tissues and decreasing the expression of proinflammatory cytokines. A recent study found that resolvin D1 significantly decreased adipose tissue macrophage accumulation and improved insulin sensitivity in male leptin-deficient mice [21]. Despite these promising results, to our knowledge, this is the only study examining the effects of resolvin D1 on adipose tissue inflammation. Further studies aimed at using resolvin D1 in humans are needed to fully understand the therapeutic potential of this agent.

Among animal models and humans, aspirin has shown promise for decreasing inflammation and improving type 2 diabetes. Aspirin is a non-steroidal anti-inflammatory drug that inhibits COX enzymes through the modification of the enzyme's active sites and inhibits prostaglandin synthesis in a similar manner [23]. Specifically, high-dose aspirin studies in Caucasian adults have shown that aspirin inhibits JNK, I κ B kinase, and the key enzyme of inflammatory transcription, NF- κ B. Additionally, high-doses of aspirin (7 g/day) have been shown to improve peripheral insulin sensitivity and CRP [20]. In obese humans and mice, low-dose aspirin therapy was shown to inhibit systemic IL-6 and reduce IL-6 release from subcutaneous white adipose tissue [24]. In addition to aspirin, statin therapy attenuated increased mRNA expression of pro-inflammatory genes, MCP-1 and IL-6, in adipose tissue of obese mice [25]. Of these treatments, aspirin shows the most promise with regard to reducing adipose tissue inflammation associated with obesity; however, the therapeutic potential of high-dose aspirin is limited by bleeding risk.

Several recent studies, mostly in Caucasian adults, used the anti-inflammatory drug salsalate to address its efficacy and tolerability as a new treatment for insulin resistance and glucose control. Salsalate, unlike aspirin, lacks an acetyl group and does not effectively inhibit COX enzymes [23]; however, salsalate has been shown to inhibit NF- κ B [26]. Four trials have examined the effects of salsalate treatment among obese adults. Studies by Fleischman et al. [27], Koska et al. [28], and Goldfine et al. [29–30], have demonstrated the viability of salsalate treatment as a means to decrease markers of inflammation and improve glucose control. Specifically, Fleischman et al. [27] used a double-masked, placebo-controlled trial of salsalate (4 g/day) for 4 weeks to examine inflammation and metabolic indices among 20 obese adults who were at risk for type 2 diabetes. After treatment, they found that salsalate reduced fasting glucose by 13%, glycemic response after oral glucose challenge by 20%, glycosylated albumin by 17%, and CRP by 34% [27]. Koska et al. [28] examined 54 obese adults using a randomized, double-blind, placebo controlled trial of 3 g/day of salsalate for 7 days. This shorter study found a reduction in fasting plasma glucose concentration and glucose area under the curve during an oral glucose tolerance test. Lastly, Goldfine et al. [29–30] completed two fundamental studies demonstrating the effects of a moderate and high-dose salsalate on insulin sensitivity as well as the effects of a longer-term clinical trial of salsalate [29, 30]. The first trial consisted of three arms: 4.5 g/day for 2 weeks, 3 g/day for 2 weeks, and 4.5 g/day for 4 weeks. The 4.5 and 3 g/day treatment lasting 2 weeks reduced fasting and post-challenge glucose, while the 4.5 g/day for 4 weeks improved fasting and post-challenge glucose levels and decreased NF- κ B activity in peripheral blood mononuclear cells by approximately 65%. The second study by Goldfine et al. [30] included 108 obese adults in a randomized, double-masked placebo controlled trial using 3, 3.5, and 4 g/day of salsalate treatment for 14 weeks [29]. Hemoglobin A1c levels decreased and glycemic

control improved in all treatment groups. It is interesting to note that mild hypoglycemic events occurred in 22% of the 3 g/day, 30% of the 3.5 g/day, and 22% in the 4 g/day groups [29].

Overall, these trials noted improvements in insulin sensitivity, fasting glucose, CRP, and NF- κ B activity with a 2- and 4-week high-dose salsalate treatment of 4.0 and 4.5 g/day [27, 28, 30]. These data support the hypothesis that utilizing a non-steroidal anti-inflammatory drug, such as salsalate, to target adipose tissue inflammation may provide a therapeutic route for treating obesity-related diseases. Coupled with the above-mentioned findings, and due to the fact that non-acetylated salicylates do not prolong bleeding times, salsalate may offer a relatively safe and effective treatment for the low-grade inflammation associated with obesity. However, it is important to note the limitations of salsalate treatment. Specifically, the moderately high dose needed to elicit improvements in inflammation has potential side effects that warrant concern. Participants in these trials experienced ringing in the ears, alterations in liver function tests, as well as hypoglycemia. These adverse effects highlight the need to understand the mechanism in which salsalate targets inflammation and improves metabolic indices.

Previous studies in obese individuals show that salsalate decreases plasma markers of inflammation and improves glucose control under conditions of weight stability. However, the mechanism of these effects is not known, and no prior clinical study has examined whether the improvement of metabolic complications is due to reduction in adipose tissue inflammation. Currently, our group is initiating a double-blind, randomized control trial, among obese Hispanic young adults, aimed at determining the effects of 4 weeks of salsalate treatment (4 g/day) on the number of macrophages in adipose tissue. This study will be the first to examine the effects of salsalate therapy, without weight loss, on subcutaneous adipose tissue inflammation. In particular, we will examine the notion that the improvement of metabolic risk after salsalate intervention occurs due to its effect on suppressing adipose tissue inflammation, and that without an improvement in adipose tissue inflammation there will be limited improvement in other metabolic risk factors. Findings from this study have the potential to elucidate the mechanism in which salsalate improves glucose control and decreases inflammation. Once the mechanism(s) is identified, safer and more effective therapies could be designed to target inflammation, and thereby treat the metabolic complications, associated with obesity.

Conclusions

Given the known link between chronic low-grade inflammation and metabolic health, it is becoming increasingly important to understand the biological processes that contribute to inflammation in adipose tissue. We have reviewed the

evidence linking dietary composition, physical activity, bodyweight, and possibly race/ethnicity to the inflammatory profile that is observed in most overweight and obese individuals. The effects of dietary interventions, dietary supplements, and weight loss have demonstrated mixed results in their ability to effectively treat the inflammation associated with obesity. Nonsteroidal anti-inflammatory drugs have been found to successfully target markers of inflammation and improve glucose control among obese participants. Studies in animal models, as well as humans, have highlighted the potential contribution of adipose tissue inflammation to metabolic disease risk. These studies underscore the need to examine treatments that have shown success in alleviating the metabolic complications associated with obesity, such as nonsteroidal anti-inflammatory drugs, in order to determine their effects on adipose tissue inflammation. Studies such as these would shed light on the mechanism in which these therapies improve systemic inflammation and metabolic health. By understanding the development of obesity-induced inflammation, as well as potential therapeutic targets, drugs can be engineered to alter the inflammatory process that occurs during obesity. These kinds of treatments may offer important clinical methods that can be used to prevent/treat insulin resistance, type 2 diabetes, non-alcoholic fatty liver disease, and other metabolic conditions associated with obesity and inflammation.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the chapter.

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Discussion

Dr. Lovejoy: I question the accuracy of the term 'healthy obesity'. If we take a diabetes-centric view, it might be possible, as you have shown here, to talk about individuals who are metabolically healthy versus those who aren't. But when we look broadly, a big part of the public health burden of obesity are things like osteoarthritis and sleep apnea which require weight loss to reverse. So, there are other consequences of obesity in addition to metabolic ones. Furthermore, recent studies suggest that even 'metabolically healthy obesity' may be a temporary condition, as these obese individuals develop metabolic abnormalities over time at a higher rate than non-obese [1, 2]. The risk of using the term is the backlash we saw a few years ago when there was a lot of media attention around the notion of 'healthy obesity' that led many people to erroneously conclude that obesity is not a problem.

Dr. Goran: Good points, thank you for highlighting that. Most of what I have talked about relates to the metabolic dysfunction of obesity. The more correct term to use would be 'metabolically healthy obesity'. The other aspects that you mention probably fall outside of the metabolic consequences of obesity.

Dr. Oppert: I have two quick questions. First, could it be that inflammation at the beginning is something beneficial or a normal reaction to enlarge the adipocytes? Second, could it be that there is a point of no return? For example, when there is inflammation and then fibrosis in the liver? Perhaps strategies to reduce inflammation would not be so beneficial at the beginning, and perhaps could be difficult to put in place when it's fibrosis.

Dr. Goran: I think that's a potentially very interesting point, and we don't know a lot about the time course of when the process is established relative to the accumulation of body fat. It's unclear whether this is an intrinsic property of adipose tissue or that it's a normal reaction to adipocytes growth. I think those are questions that remain.

Dr. Rosenbaum: At the beginning, you are showing that adipocytes attract macrophages or macrophages come to adipocytes. I was wondering if you go back and look at the healthy versus the unhealthy obese, do you think the major difference is in whatever the adipocytes put out there to attract the macrophages, or in the macrophages themselves and in their aggressiveness in pursuing the adipocytes. Where is the original difference between those groups?

Dr. Goran: I don't know who is calling whom, I think that's a good question as to who is attracting whom. I don't think we really know the answer to that.

Dr. Finegood: Is it not about the death of the cells themselves?

Dr. Goran: It is – but then what causes the death of the cells?

Dr. Finegood: Yes, but the point is that the macrophages are called to wall off the triglyceride that is sitting around presumably because the cells had died. What causes the difference in the death of the cells I think is important.

Dr. Ochoa: A recent paper showed that M2 responses prevented the insulin resistance and the hyperglycemia in mice from M1 responses. Do you know if when we do interventions, we are promoting M2 responses instead of just quieting down the whole system? Has anyone studied that?

Dr. Goran: I showed the surgical weight loss study where the M1 and M2 responses were different.

Dr. Ochoa: It's interesting that any surgical intervention promotes M2 responses dramatically, and those in severe traumas may last for a month or more; so, it's really fascinating that we are seeing that M2 response predominate in our patients.

Dr. Jakicic: When you look at this cascade and when you throw activity or fitness into this mix, what makes this pathway healthy? Can you really have a healthier obese person if you put activity into the mix? Is it necessary? And I guess you are thinking about at least doing some of that.

Dr. Goran: I wasn't.

Dr. Jakicic: Are you sure? Have you thought about the issue when you talk about the GLP-1 and the blocking of the insulin that obesity may be blocking that if you are increasing insulin sensitivity on the other side with activity? Where does activity fit into this cascade?

Dr. Goran: We have published a few studies showing that exercise, or strength training can have variable effects on insulin and circulating cytokines for example, and there are some other studies like that, but I don't really know what the mechanism is. It's an interesting point, and I should probably think about it a bit more. Mostly, I have been disappointed with our studies with exercise as we have found mixed results. This was not just in different people but also in different studies that were done in the same way. We found one effect versus another, so our most consistent observation is that we can't get a consistent effect of exercise.

Dr. Drewnowski: I have a question about sugar consumption. The consumption of added sugar in its many forms, whether solid or liquid, is often associated with lower incomes. Are there any racial or ethnic groups for whom this combination is particularly devastating? Can you answer that based on your research? I am saying the consumption of sugar varies as a function of socioeconomic status and is higher among lower income people than among the upper income people. Are there some low-income groups for whom sugar-fat mixtures would be particularly damaging?

Dr. Goran: Yes, in fact we have a paper in our Hispanic cohort, and this is a very specific example but it answers your question. There is some evidence to suggest that Hispanics have an increased liking for sugars. They have an increased prevalence of the PNPLA3 gene, though I don't know why. The prevalence of this gene is almost 50% in Hispanics versus 20% in Caucasians. This gene promotes fatty liver disease. The substrate for fatty liver disease is sugar, possibly fructose, because fructose is lipogenic and promotes lipogenesis in the liver. So, I think this is a perfect storm among Hispanics who have a genetic predisposition and a liking for sugar. The issue of economics comes into the equation as well. If you consider the whole story of high fructose corn syrup, you see that the exports of corn sweeteners by the US are increasing dramatically as a result of a recent policy shift by the World Trade Organization. So, I think this is a very clear example of a specific subgroup of the population which is susceptible to the damaging effects of sugar.

Dr. Ard: How much of this has to do with energy balance in the context of intake of sugar or other things? Adipocyte biology can change with a bout of exercise or with the institution of calorie restriction or even bringing people into energy balance; so, how much of this do you think is related to that milieu of excess caloric intake that then continues to foster the inflammation?

Dr. Goran: There are limited data to answer this question, especially in humans which would require a fat biopsy. There are some animal studies that have looked at the

effects of positive overfeeding on the development of adipose tissue and the creation of adipose tissue inflammation.

Dr. Rolls: We would hypothesize that a low energy dense eating pattern would be a low inflammatory eating pattern, but I don't know of specific data on that. Do you know of studies or do you agree with that hypothesis?

Dr. Goran: Yes I would. I think that's a very interesting idea. The Zone diet for example has an anti-inflammatory element, and there are other diets that are promoted as anti-inflammatory. I would agree that the low energy density diet is also anti-inflammatory, but there is a lack of studies to show effectiveness in this regard.

Dr. Finegood: Did you characterize the subjects that you had in terms of their food intake and exercise levels? Do you know about differences in their eating patterns or exercise?

Dr. Goran: In our study that I showed you, the groups were quite small, and unfortunately we don't have good dietary or activity data.

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Summary Discussion on Obesity Treatment: Challenges and Opportunities

Dr. Lovejoy: I would like to ask a controversial question that ties to what most of the speakers have talked about. Are there specific foods, for example those high in sugar or fat, that have effects on the brain or body that are parallel to those of addictive drugs? If that is the case, do we need to consider this in relation to obesity treatment and strategies for a healthy diet?

Dr. Rolls: I presume you are talking about addiction in a stringent way using a formal definition that includes withdrawal symptoms.

Dr. Lovejoy: I think that has been a part of the controversy. There are those who would argue that the stringent definition of addiction applies to food, including withdrawal. But others disagree and say that it's not truly addiction with food. But obviously certain foods are stimulating the same areas in the brain as addictive drugs. How do we come to grips with that as a field in a way that makes sense to the public?

Dr. Rosenbaum: Some of the brain areas that are more active in individuals following weight loss and are sensitive to leptin are the same ones that are more active in individuals who are addictive, so there are certain parallels between addiction and the inability to sustain weight loss. I don't know if anyone has looked prospectively at who is going to gain weight along those lines. Could you identify someone early and say that he is going to be a food junky down the line? I don't know the answer.

Dr. Drewnowski: France Bellisle and I published a review entitled 'Is sweetness addictive?' in the *British Nutrition Bulletin* some years ago. It is worth noting that the former definition of addiction, as featured in the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, is now gone. It used to be based on the criteria of tolerance and withdrawal. What we have now is something called substance dependence and the inclusion criteria are very soft. Just about anything fits. Substance use behaviors that are performed in private, that take precedence over other activities are now part of the definitions. So, conceivably, eating chocolate would fit the bill. We need to pay attention to the fact that the definitions of food addiction are changing. Our studies need to keep pace with the definitions. And then there are very few studies on food addiction or on the potential underlying mechanisms. Dr. David Kessler in his book, *The End of Overeating*, was referring to some studies performed by us at the University of Michigan.