Diabetes & Metabolism

Gutiérrez-Salmeán et al., J Diabetes Metab 2014, 5:9
http://dx.doi.org/10.4172/2155-6156.1000431

Research Article Open Access

Cardiometabolic Alterations in Wistar Rats Induced By an Obesogenic Paigen-Like Diet: Effects of (-) Epicatechin

Gabriela Gutiérrez-Salmeán[1], Elizabeth De Jesús-Torres[2], Pilar Ortiz-Vilchis[1], Claudia Vacaseydel[1], Leticia Garduño-Siciliano[2], Eduardo Meaney[1], Francisco Villarreal[3], Israel Ramírez-Sánchez[1], Alicia Ortiz[2], Germán Chamorro-Cevallos[2] and Guillermo Ceballos[1*]

[1]Integral Cardiometabolic Research Laboratory. Section of Graduate Studies and Research. School of Medicine, National Polytechnic Institute, Mexico
[2]National School of Biological Sciences, National Polytechnic Institute, Mexico
[3]University of California San Diego, Department of Medicine, Mexico

Abstract

Background and objective: The Metabolic Syndrome (MS) is suggested to develop from –among other factors- inadequate diet. To explore its pathophysiology, animal models of diet-induced obesity and its comorbidities are often used, although not all of them produce the same cardiometabolic alterations. Regarding novel therapeutic options, (-)-epicatechin (EPI), the most abundant polyphenol in cacao exerts several beneficial effects on MS features. Therefore, we aimed to test the effects of EPI in the cardiometabolic derangements of rats fed with a diet with added, sugar, saturated fat, added with cholesterol and cholate (Paigen-like diet, PD).

Methods: 4 groups of rats were assessed: normal diet (ND); normal diet + EPI (ND+E); Pagen-like diet (PD) and Paigen-like diet + EPI (PD+E, prevention group). EPI was administered by gavage (1 mg/kg daily) for 2 weeks. Body weight, Systolic Blood Pressure (SBP), glycemia, triglyceridemia, total and HDL cholesterol were measured at base, at week 5 and after 2-week period of treatment with EPI (treatment group).

Results: PD induced several markers of MS. EPI induced significative decreases in glycemia, triglyceridemia, and SBP. EPI raised HDL level without reaching the basal values. EPI treatment provided by 2 weeks after the MS markers develop (treatment group) induced a considerable weight lost.

Conclusion: The PD assayed in this work, effectively induced MS in rodents that are otherwise resistant to dietary modifications. EPI resulted in the attenuation of all cardiometabolic alteration previously induced by diet. These promising results obtained in a murine model with EPI indicate the possibility to begin testing it in human obesity and MS.

Keywords: Metabolic syndrome; Cardiometabolic alterations; Diet-induced; Flavonoids; Epicatechin

Background

In 1988, Reaven described a cluster of cardiometabolic traits, including hypertriglyceridemia, hypoalphalipoproteinemia, systemic arterial hypertension and glucose intolerance, associated to insulin resistance and hyperinsulinism [1]. Soon after, just in 1999, the World Health Organization (WHO) linked these abnormalities to abdominal obesity and microalbuminuria [2] and termed the aforementioned assemble conditions as "metabolic syndrome" (MS). These cardiometabolic anomalies, in humans, are associated with a significant increase in morbidity and all-cause mortality [3].

Although the precise etiology of MS has not been fully revealed, environmental factors such as diet and sedentary lifestyle may explain in part the surge of the abovementioned pathologic assemblage. A westernized diet, characterized by a high content of sugar, fat (particularly saturated), and cholesterol together with an excessive fructose intake [4,5] has been associated with the development of cardiometabolic alterations.

Nevertheless, the prevalence of such disruptions has risen worldwide over the last decades, mainly in low- and middle-income countries [6,7]. This fact points out that both first-line therapeutic approaches (i.e., "lifestyle modifications" as caloric restriction, weight-loss and increasing physical exercise) and pharmacologic treatments (including metformin, fibrates, statins and others) [8] have several limitations in effectiveness or compliance. Thereupon, it would be helpful to unearth new therapeutic interventions addressed to attenuate the magnitude of MS.

Within this interest, animal models have historically been tested in the characterization of human pathophysiology, including obesity and its comorbidities. Within this area of study, although murine models often include genetic mutations and/or knockouts, [9] these certainly do not resemble the human phenomenon since –as aforementioned- in clinical scenario, diet plays a crucial role. Thus different dietary protocols have been tested in rodents; however, not all have been effective in the development of MS components. The most common diet-induced metabolic disease models include: high-fat (30-60% of total energy value) diet for obesity, high-fructose or high sucrose (up to 70% of total kcal) for obesity/hyperglycemia/hypertrigliceridemia, high-saturated fat for atherosclerosis thus hypertension, high sodium for hypertension, and added cholesterol (up to 1.25% of weight) and cholate for atherogenesis; [10-12] however, each approach results in different cardiometabolic alterations and often are not able to develop all of the MS features simultaneously. Hence a mixture of the previous models –such as the one we present herein- are often capable to actually result more effective.

***Corresponding author:** Guillermo Ceballos, Integral Cardiometabolic Research Laboratory, Division of Graduate Studies and Research, School of Medicine of the National Polytechnic Institute, Mexico, Tel: (52) (55) 57296300; E-mail: gceballosr@ipn.mx

Received July 05, 2014; **Accepted** September 15, 2014; **Published** September 24, 2014

Citation: Gutiérrez-Salmeán G, De Jesús-Torres E, Ortiz-Vilchis P, Vacaseydel C, Garduño-Siciliano L, et al. (2014) Cardiometabolic Alterations in Wistar Rats Induced By an Obesogenic Paigen-Like Diet: Effects of (-) Epicatechin. J Diabetes Metab 5: 430 doi:10.4172/2155-6156.1000431

Once the dietary induction of MS has been successful, novel therapeutic are needed to be studied. In this context, chocolate (cacao) has traditionally been considered to exert health benefits [13]. But not until recently, epidemiological evidence had demonstrated that its consumption is associated with lower prevalence of cardiometabolic risk factors, including type 2 diabetes and hypertension; [14] moreover, experimental trials have shown that cacao and cacao-enriched products improve glucose tolerance, endothelial function, obesity and attenuate hypercholesterolemia [15-17]. The potential mechanisms involved in such beneficial effects include the effects of several bioactive compounds in cacao, including polyphenols. (-)-Epicatechin (EPI) is the most abundant polyphenol in cacao, representing nearly 35% of the total phenolic content [18]. Previous reports from our study group have shown that EPI exhibits the same effects than those observed with cacao intake, including decreases in hyperglycemia, hypertrigliceridemia and weight-gain within a high-fat diet-induced murine model of cardiometabolic risk factors [19] through the modulation of mitochondrial structure and metabolism.

Therefore, the present study was aimed to determine the effects of EPI in the treatment of each of the clustering components in an animal model of cardiometabolic abnormalities induced by a more aggressive –than the high-fat or high-sugars diet alone- Paigen-like diet, tested in murine atherosclerosis, composed mainly by saturated fatty acids derived from butter fat, cholate and cholesterol.

Materials and Methods

Animals were handled according to Institutional Guidelines and National Official Standards; protocol was approved by IRB. Male Wistar rats were individually housed under controlled temperature and humidity, with 12h light/dark cycles. All rats were provided with a standard pellet diet (Rat diet 5012, LabDiet®) and water *ad libitum* during acclimation period.

Dietary protocols, study groups and EPI treatment

After acclimation and upon reaching an initial weight of 200 ± 20 g, rats were randomly assigned to one of the following groups (n=8, for each): normal diet + vehicle (water) (ND), normal diet + EPI (ND+E), Paigen-like diet (PD), Paigen-like diet + EPI (PD+E) (prevention group). Each group was fed *ad libitum* with its corresponding diet for seven weeks; the nutritional value of each diet is described in Table 1 but, briefly, the PD included dietary modifications that have been reported to induce MS alterations; e.g., addition of cholesterol and cholic acid for atherosclerosis and fatty liver, butter (saturated fat) for hyperlipemia, sugar for hyperglycemia and hypertriglyceridemia as well as weight gain, etc. EPI (≥ 98%, from Sigma-Aldrich Co. LLC), was daily administered by gavage, in a 1mg/kg dose, and using water as vehicle. Further, rats fed with the Paigen-like diet for the aforementioned 7 weeks were afterwards treated with EPI for 2 weeks (treatment group); during this time, rats continued with their respective diet.

Diet	Composition (% from total weight)	Nutritional value (% of total kcal)	Energy density (kcal/g)
Normal (ND)	Commercially available: LabDiet's Rat diet 5012	Protein 27.09 Fat 13.13 Carbohydrate 59.78	3.43
Paigen-like (PD)	1% cholesterol 0.5% cholic acid 5% butter 30% powdered sugar 10% casein 53.5% standard chow (ND)	Protein 23.10 Fat 20.93 Carbohydrate 56.46	3.94

Table 1: Nutritional profiles of the dietary protocols.

Cardiometabolic assessment

Body weight was recorded weekly. Three blood samples were obtained via retro-orbital punction, in fasting conditions: just after acclimation, at week 7 of this period, and once the 2-week EPI treatment concluded. Serum was collected after blood clotting and centrifugation at 3500 r.p.m. for 15 minutes. Glucose, triglycerides, total- and HDL-cholesterol was determined using an automatic chemistry analyzer (Vitalab Selectra®, Rhode Island, USA) and the corresponding colorimetric kits (Randox S.A., Mexico). LDL-cholesterol was calculated using Friedewald's formula [20]. Insulin was determined through radioimmunoassay (Millipore®, Missouri, USA). Systolic blood pressure (SBP) was determined, via non-invasive tail-cuff method, [21] in times concurrent with the blood sampling.

Glucose tolerance test

An Oral Glucose Tolerance Test (OGTT) was performed once the experimental periods concluded, i.e, at week 7 and after 2 weeks of EPI administration (the latter for the PD group). In fasting conditions, glucose was determined in a drop of blood from the tail; it was immediately analyzed with glucometer and enzyme test strips (Dextrostix®, Indiana, USA). Following this, a glucose solution (3.5 g/kg) was administered by gavage. Blood tests were repeated at 30, 60, 120, and 150 minutes after such administration.

Statistical analysis

Results are expressed as means ± SEM, unless stated otherwise. Student's independent t-tests were used to evaluate two-group differences. Student's paired t-test was used for the differences within a same group. For such analyses, we used GraphPad Prism 5 (GraphPad® Software, California, USA). A $p<0.05$ value was considered statistically significant.

Results

Body weight

Figure 1 shows that the Paigen-like diet induced significantly more

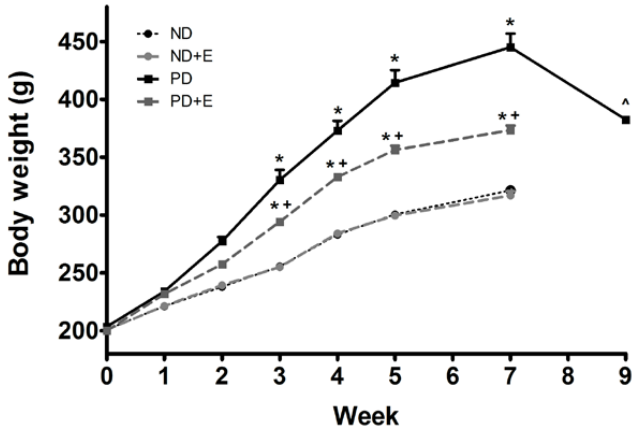

Figure 1: Cumulative body weight during the dietary induction and after the EPI treatment. Results represent the mean ± SEM of the cumulative weekly body weight for each group (n = 8, in each), where ND = normal diet, ND+E = normal diet concomitant with 1 mg/kg EPI, PD = Paigen-like diet, PD+E = Paigen-like diet concomitant with 1 mg/kg EPI, and PD+E2 = Paigen-like diet after 2 weeks of EPI treatment. *$p<0.05$, vs. ND after Student's *t* test for independent samples, $^{+}p<0.05$, vs. PD after Student's *t* test for independent samples, $^{\wedge}p<0.05$, vs. PD after Student's *t* test for paired samples.

weight gain as compared with the ND (443.56 ± 31.38 g vs. 321.36 ± 5.25 g, respectively at week 7). EPI did not affect weight gain in the ND+E (316.90 ± 10.41 g) group; EPI treatment significantly attenuated the excessive weight-gain when it was concomitantly administered with the experimental diet (443.56 ± 31.38 g vs. 373.40 ± 10.80 g respectively). The administration of EPI following the dietary induction period resulted in a significantly decrease in the rats' body weight: from 443.56 ± 31.38 g by week-7, to 384.14 ± 7.63 g after 2 weeks of treatment.

Cardiometabolic endpoints

As shown in Table 2, at the end of the dietary-induction period (i.e., week 7), the PD group showed significantly higher levels of glucose, triglycerides, total- and LDL-cholesterol as compared to their own basal values and vs. the ND-fed rats. The same phenomenon was observed for Systolic Blood Pressure (SBP). In addition, HDL-cholesterol was significantly decreased in rats that received the Paigen-like diet.

Group	Basal	Week 7	+10 days with EPI
	Glucose (mg/dL)		
ND	76.8 ± 0.78	77.7 ± 1.01	
ND+E	82.6 ± 2.31	83.1 ± 3.82	
PD	84.1 ± 2.04	141.1 ± 0.92 [a,b]	105.6 ± 1.08b [a,c]
PD+E	82.4 ± 2.49	95.3 ± 1.14 [a,b,c]	
	Triglycerides (mmol/L)		
ND	0.7 ± 0.08	0.8 ± 0.04	
ND+E	0.7 ± 0.05	0.80 ± 0.02	
PD	0.8 ± 0.06	3.0 ± 0.05 [a,b]	1.9 ± 0.05 [a,c]
PD+E	0.8 ± 0.06	1.3 ± 0.07 [a,b,c]	
	Total colesterol (mmol/L)		
ND	18.5 ± 0.34	19.1 ± 0.37	
ND+E	18.7 ± 0.37	19.0 ± 0.46	
PD	18.8 ± 0.41	59.8 ± 0.81 [a,b]	30.2 ± 0.94 [a,c]
PD+E	18.6 ± 0.56	25.78 ± 0.92 [a,b,c]	
	HDL colesterol (mmol/L)		
ND	13.4 ± 0.07	13.6 ± 0.08	
ND+E	13.7 ± 0.02	13.7 ± 0.07	
PD	13.6 ± 0.05	8.3 ± 0.03 [a,b]	10.6 ± 0.08 [a,c]
PD+E	13.7 ± 0.05	12.4 ± 0.03 [a,b,c]	
	LDL colesterol (mmol/L)		
ND	4.61 ± 0.43	5.2 ± 0.37	
ND+E	4.7 ± 0.53	4.9 ± 0.57	
PD	4.8 ± 0.38	50.1 ± 0.62 [a,b]	18.73 ± 0.34 [a,c]
PD+E	4.5 ± 0.56	12.8 ± 0.79 [a,b,c]	
	Blood pressure (mmHg)		
ND	111.9 ± 0.51	111.9 ± 0.42	
ND+E	111.7 ± 0.43	112.5 ± 0.61	
PD	112.3 ± 0.64	144.7 ± 0.76 [a,b]	126.8 ± 0.74 [a,c]
PD+E	113.9 ± 0.48	119.5 ± 0.29 [a,b,c]	

Table 2: Results are presented as mean ± EEM for each group (n = 8). ND = normal diet, ND+E = normal diet concomitant with 1 mg/kg EPI during dietary induction, PD = Paigen-like diet, PD+E = Paigen-like diet concomitant with 1 mg/kg EPI during dietary induction, PD+E10 = Paigen-like diet receiving 1 mg/kg EPI for 10 days after dietary induction.
[a]$p<0.05$ vs. own basal level after Student's *t* test for paired samples. [b]$p<0.05$ vs. control (ND) group at the same timeline after Student's *t* test for independent samples. [c]$p<0.05$ vs. Paigen-like (PD) group at 7-weeks after Student's *t* test for paired samples.

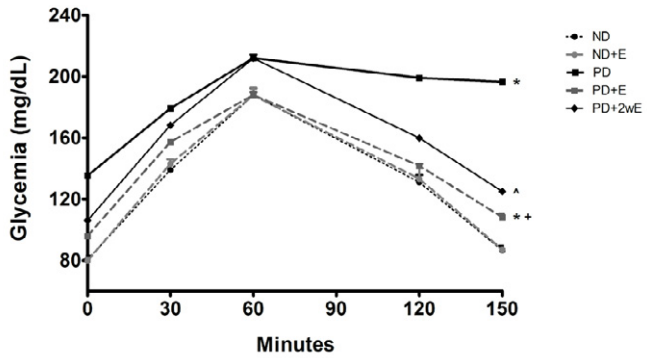

Figure 2: Oral glucose tolerance tests. Results represent the mean ± SEM of glycemia for each group (n = 8, in each) at 0, 30, 60, 120 ad 150 minutes after 3.5 g/kg glucose load, by gavage. ND = normal diet, ND+E = normal diet concomitant with 1 mg/kg EPI, PD = Paigen-like diet, PD+E = Paigen-like diet concomitant with 1 mg/kg EPI, and PD+E2 = Paigen-like diet after 2 weeks of EPI treatment. *$p<0.05$, vs. ND after Student's *t* test for independent samples, +$p<0.05$, vs. PD after Student's *t* test for independent samples, ^$p<0.05$, vs. PD after Student's *t* test for paired samples.

Even though the experimental diet induced significant alterations in all cardiometabolic endpoints, the simultaneous administration of EPI attenuated such distortions since values in the PD+E group were significantly lower (or higher, for HDL-cholesterol), at week 7, than those observed in the PD rats.

Moreover, EPI ameliorated all endpoints in the already altered PD group as values at the end of the 2 weeks of EPI administration were significantly lower (or higher, for HDL-cholesterol) than those from the same group at week 7.

Finally, EPI did not induce any change among the normal diet-fed rats.

OGTT

Figure 2 shows that ND+E presented no significant differences vs. the ND group in the glucose tolerance test. On the other hand, we observed a significant increase in glucose levels among PD-fed animals as glycemia remained in high levels during the course of the test. Concomitant treatment with EPI (i.e., PD+E group) significantly enhances glucose tolerance values are lower than those of the PD group. Moreover, after the PD rats were treated with EPI for two weeks, they showed an improved glycemic in course.

Discussion

All together, the findings herein presented support the conclusion that the Paigen-like diet is an effective approach for the induction of cardiometabolic alterations although it is a "forced" model and does not mimic the more attenuated phenomenon observed in the clinical setting. Nevertheless, EPI significantly impacts all disruptions by either alleviating them from the beginning or by reversing them once they have developed. These promising results in rodents, altogether with other evidences that many research groups (including our own) have produced indicate the real possibility to test the beneficial actions of epicatechin in human beings.

Dietary interventions have been widely used for provoke obesity and

its comorbidities in murine models; however, no general agreement has been reached in regard of which modifications are the most effective.

The administration of a high-fat diet does not always show consistent and reproducible results, as some rodent species significantly increased their weight, while others are resistant to such dietary induction [22]. Moreover, it has been found that caloric intake is not the only determinant in the development of obesity, but also the type of fat within the chow. E.g., a study administered two isoenergetic diets, but qualitatively different in the lipid fraction: one, made from fish oil (i.e., mainly unsaturated fatty acids), the other from lard (i.e., saturated fatty acids). Rodents fed with the latter gained significantly more weight and developed insulin resistance and dyslipidemia [23]. In modified chow we used, the lipid fraction came mainly from butter, i.e., saturated fat, which has been proven to induce obesity as it increases palatability, [24] thus favors food intake and positive energy balance which, in turn, contributes to the development of obesity. It is worth mentioning that the feed also included sucrose. Sweet food has been associated to overconsumption as it is linked to reward-related circuits, [25, 26] e.g., dopamine, that are critical in feeding behaviors [27]. This fact complements the suggestion that rats are sensitive to the palatability of the food, [28] as shown in a study that exposed rats to a palatable liquid diet; such rats became obese due to an overeating pattern and then reduced their intake when switched to standard chow [29].

High saturated fat diets have also been reported to induce atherogenesis by increasing total and LDL-cholesterol; [30,31] however, the attainment of hypoalphalipoproteinemia in rats is usually ineffective. It is proposed that rodents have a highly efficient lipoprotein metabolism, which allow them to maintain healthy lipoprotein levels in spite of the modified chow [32]. For this reason, experimental murine models –such as the Paigen diet- often "force" the atherosclerotic phenotype through the addition of cholic acid and cholesterol within the feed (in a 0.5 and 1.25%, respectively, weight/weight). This results in atherosclerotic lesions in otherwise resistant rodent strains [33]. Although our model implemented such strategy with success, it does not resemble the human-like natural evolution as cholic acid causes a direct injure to the liver thus other plasmatic lipids (triglycerides and HDL-cholesterol) are also affected [34].

From our findings, we can infer that the modified diet was effective in the induction of MS cardiometabolic distortions including obesity, hyperglycemia, hypertriglyceridemia, hypercholesterolemia, hypoalphalipo proteinemia, insulin resistance and systolic hypertension. Nevertheless, such dietary approach does not resemble the human-like natural evolution.

On behalf of EPI treatment, the results herein presented show a significant decrease in all cardiometabolic endpoints: SBP, glycemia, plasmatic triglycerides, total- and LDL-cholesterol levels, and cumulative body weight; simultaneously, HDL levels were raised. Similar results have been reported, e.g., with the administration of apple juice, by gavage, inducing a significant descent of total, LDL-cholesterol, and triglycerides, while at the same time HDL-cholesterol levels were increased. Such effect was attributed to the flavonoid content in apples [35]. Another study showed that hesperidin –a flavonoid isolated from citrus fruits- decreased blood glucose, triglycerides, total- and LDL-cholesterol, together with an increase in HDL-cholesterol in rats [36].

The mechanisms by which EPI is capable of improving the cardiometabolic profile are not yet clear. Although it has been suggested that flavonoids inhibit intestinal lipid and carbohydrate absorption, [37] we have previously demonstrated that these are not the predominant mechanisms by which EPI exerts its beneficial effects. Instead, we have reported that EPI enhances mitochondrial function and structure which, in turn, promotes oxidative metabolism that further attenuates both weight gain and lipid and glucose disturbances [19]. In addition we have also shown that EPI enhances mitochondrial biogenesis [19]. Moreover, as the flavonoid amends insulin resistance, it may also contribute to improve high blood pressure, because in the endothelial cell, insulin binds to its receptor and promotes the activation of nitric oxide sinthase (eNOS) increasing nitric oxide bioavailability, [38,39] which ultimately leads to a decrease in blood pressure [40].

Regardless that more studies are certainly needed in both humans and rodents, EPI should be considered as a potential new therapeutic approach for obesity and its comorbidities.

References

1. Reaven GM (1988) Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 37: 1595-1607.
2. Parikh RM, Mohan V (2012) Changing definitions of metabolic syndrome. Indian J Endocrinol Metab 16: 7-12.
3. Sundström J, Risérus U, Byberg L, Zethelius B, Lithell H, et al. (2006) Clinical value of the metabolic syndrome for long term prediction of total and cardiovascular mortality: prospective, population based cohort study. BMJ 332: 878-882.
4. Popkin BM, Adair LS, Ng SW (2012) Global nutrition transition and the pandemic of obesity in developing countries. Nutr Rev 70: 3-21.
5. Ferder L, Ferder MD, Inserra F (2010) The role of high-fructose corn syrup in metabolic syndrome and hypertension. Curr Hypertens Rep 12: 105-112.
6. Batsis JA, Nieto-Martinez RE, Lopez-Jimenez F (2007) Metabolic syndrome: from global epidemiology to individualized medicine. Clin Pharmacol Ther 82: 509-524.
7. Kaur J (2014) A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014: 943162.
8. Tenenbaum A, Fisman EZ (2011) "The metabolic syndrome... is dead": these reports are an exaggeration. Cardiovasc Diabetol 10: 11.
9. Kennedy AJ, Ellacott KL, King VL, Hasty AH (2010) Mouse models of the metabolic syndrome. Dis Model Mech 3: 156-166.
10. Panchal SK, Brown L (2011) Rodent models for metabolic syndrome research. J Biomed Biotechnol 2011: 351982.
11. Cakar M, Balta S, Demirkol S, Kucuk U, Demirbas S (2013) Differences in the mechanisms that induce obesity and metabolic syndrome in experimental animal models and humans may cause treatment failure. Clinics (Sao Paulo) 68: 119.
12. Abraham KM (2007) Animal models of obesity and metabolic syndrome: potential tools for Alzheimer's disease research. Curr Alzheimer Res 4: 145-146.
13. Dillinger TL, Barriga P, Escárcega S, Jimenez M, Salazar Lowe D, et al. (2000) Food of the gods: cure for humanity? A cultural history of the medicinal and ritual use of chocolate. J Nutr 130: 2057S-72S.
14. Latif R (2013) Chocolate/cocoa and human health: a review. Neth J Med 71: 63-68.
15. Hooper L, Kay C, Abdelhamid A, Kroon PA, Cohn JS, et al. (2012) Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr 95: 740-751.
16. Belz GG, Mohr-Kahaly S (2011) [Cacoa and dark chocolate in cardiovascular prevention?]. Dtsch Med Wochenschr 136: 2657-2663.
17. Matsui N, Ito R, Nishimura E, Yoshikawa M, Kato M, et al. (2005) Ingested cocoa can prevent high-fat diet-induced obesity by regulating the expression of genes for fatty acid metabolism. Nutrition 21: 594-601.
18. Andres-Lacueva C, Monagas M, Khan N, Izquierdo-Pulido M, Urpi-Sarda M, et al. (2008) Flavanol and flavonol contents of cocoa powder products: influence of the manufacturing process. J Agric Food Chem 56: 3111-3117.

19. Gutiérrez-Salmeán G, Ortiz-Vilchis P1, Vacaseydel CM1, Garduño-Siciliano L2, Chamorro-Cevallos G2, et al. (2014) Effects of (-)-epicatechin on a diet-induced rat model of cardiometabolic risk factors. Eur J Pharmacol 728: 24-30.

20. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18: 499-502.

21. Kubota Y, Umegaki K, Kagota S, Tanaka N, Nakamura K, et al. (2006) Evaluation of blood pressure measured by tail-cuff methods (without heating) in spontaneously hypertensive rats. Biol Pharm Bull 29: 1756-1758.

22. Speakman J, Hambly C, Mitchell S, Król E (2007) Animal models of obesity. Obes Rev 8 Suppl 1: 55-61.

23. Buettner R, Parhofer KG, Woenckhaus M, Wrede CE, Kunz-Schughart LA, et al. (2006) Defining high-fat-diet rat models: metabolic and molecular effects of different fat types. J Mol Endocrinol 36: 485-501.

24. Rolland V, Roseau S, Fromentin G, Nicolaidis S, Tomé D, et al. (2002) Body weight, body composition, and energy metabolism in lean and obese Zucker rats fed soybean oil or butter. Am J Clin Nutr 75: 21-30.

25. de Araujo IE (2011) Sweet taste signaling and the formation of memories of energy sources. Front Syst Neurosci 5: 99.

26. McCaughey SA (2008) The taste of sugars. Neurosci Biobehav Rev 32: 1024-1043.

27. Kelley AE, Schiltz CA, Landry CF (2005) Neural systems recruited by drug- and food-related cues: studies of gene activation in corticolimbic regions. Physiol Behav 86: 11-14.

28. Gale SK, Van Itallie TB, Faust IM (1981) Effects of palatable diets on body weight and adipose tissue cellularity in the adult obese female Zucker rat (fa/fa). Metabolism 30: 105-110.

29. Levin BE, Dunn-Meynell AA (2002) Defense of body weight depends on dietary composition and palatability in rats with diet-induced obesity. Am J Physiol Regul Integr Comp Physiol 282: R46-54.

30. Hegsted DM, Ausman LM, Johnson JA, Dallal GE (1993) Dietary fat and serum lipids: an evaluation of the experimental data. Am J Clin Nutr 57: 875-883.

31. Mensink RP, Katan MB (1992) Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. Arterioscler Thromb 12: 911-919.

32. Witztum JL (1993) Murine models for study of lipoprotein metabolism and atherosclerosis. J Clin Invest 92: 536-537.

33. Hsueh W, Abel ED, Breslow JL, Maeda N, Davis RC, et al. (2007) Recipes for creating animal models of diabetic cardiovascular disease. Circ Res 100: 1415-1427.

34. Getz GS, Reardon CA (2006) Diet and murine atherosclerosis. Arterioscler Thromb Vasc Biol 26: 242-249.

35. Setorki M, Asgary S, Eidi A, Rohani AH, Esmaeil N (2009) Effects of apple juice on risk factors of lipid profile, inflammation and coagulation, endothelial markers and atherosclerotic lesions in high cholesterolemic rabbits. Lipids Health Dis 8: 39.

36. de Oliveira DM, Dourado GK, Cesar TB (2013) Hesperidin associated with continuous and interval swimming improved biochemical and oxidative biomarkers in rats. J Int Soc Sports Nutr 10: 27.

37. Wang T, An Y, Zhao C, Han L, Boakye-Yiadom M, et al. (2011) Regulation effects of Crataegus pinnatifida leaf on glucose and lipids metabolism. J Agric Food Chem 59: 4987-4994.

38. Ramirez-Sanchez I, Maya L, Ceballos G, Villarreal F (2010) (-)-epicatechin activation of endothelial cell endothelial nitric oxide synthase, nitric oxide, and related signaling pathways. Hypertension 55: 1398-1405.

39. Muniyappa R, Montagnani M, Koh KK, Quon MJ (2007) Cardiovascular actions of insulin. Endocr Rev 28: 463-491.

40. Grassi D, Necozione S, Lippi C, Croce G, Valeri L, et al. (2005) Cocoa reduces blood pressure and insulin resistance and improves endothelium-dependent vasodilation in hypertensives. Hypertension 46: 398-405.

Citation: Gutiérrez-Salmeán G, De Jesús-Torres E, Ortiz-Vilchis P, Vacaseydel C, Garduño-Siciliano L, et al. (2014) Cardiometabolic Alterations in Wistar Rats Induced By an Obesogenic Paigen-Like Diet: Effects of (-) Epicatechin. J Diabetes Metab 5: 430 doi:10.4172/2155-6156.1000431