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Research Article

Effect of the Administration of Ascorbic Acid on the Adiposity Index in Rats with Obesity Induced by Hypercaloric Diet or Hypercaloric Emulsion

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Abstract

Obesity is a prevalence metabolic and physiological disorder caused by host-environmental interaction, it is defined as the accumulation of adipose tissue. The animal models of obesity are an alternative for to evaluate therapeutics strategies for diminished this problem of public healthy, the recently development model of obesity without increased of weight is an alternative for to evaluate the efficacy of some therapies and discover differences in metabolic routes respect to traditional models of obesity with increased of weight. In this research we evaluated the effect of oral administration of ascorbic acid on the increased of adiposity index in Wistar rats with obesity induced for hypercaloric diet 60% fat (with elevated content of lard), a classical model of obesity with increased of weight; and rats with obesity induced by hypercaloric emulsion, a recent model of obesity in rats without increased of weight. The results shows that adiposity index is statistically minor with respect to obtained in rats with diet 60% fat (with elevated content of lard). This results suggest that oral consumption of ascorbic acid can will be efficient against obesity caused for edible vegetable oils and substitutes of glucose as fructose, but not against obesity induced by consumption of animal fat as lard in the food.

Keywords: *Obesity; Ascorbic Acid; Hypercaloric Diet; Adiposity Index; Metabolically Obesity with Normal Weight Animal Model*

Abbreviations

AA: Ascorbic Acid; AI: Adiposity Index; BMI: Body Mass Index; CVD: Cardiovascular Diseases; DM2: Diabetes Mellitus Type 2; FFA: Free Fatty Acids; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; MHO: Phenotype Metabolically Healthy but Obese; MONW: Phenotype Metabolically Obese but with Normal Weight; TG: Triglycerides; VLDL: Very Low Density Lipoproteins

Introduction

Obesity is a prevalence metabolic and physiological disorder caused by host-environmental interaction [1], it is defined as the accumulation of adipose tissue [2-4]. The main factor that induces it is a high consumption of fats and carbohydrates [5]. In 2008, a panel of experts on obesity concluded that it is a complex multi-causal condition, including factors foreign to individuals [6,7]. It is affirmed that, genetic, environmental factors, nutritional and metabolic disorders also contribute to the development of obesity, which is a consequence of the imbalance between energy intake and caloric expenditure; resulting in a progressive accumulation of unused energy in the form of triglycerides (TG) and cholesterol in adipocytes [8].

Overweight and obesity are defined based on the body mass index (BMI), these conditions in turn increase the prevalence of non-communicable chronic diseases such as diabetes mellitus type 2 (DM2), cardiovascular diseases (CVD) and metabolic diseases in the population, including metabolic syndrome [9-12].

Since 1980, the prevalence of obesity has more than doubled in the world, and more than 3.4 million people die each year due to this [13]. Obesity currently affects 5% of children and 12% of adults around the world [14], due to this, overweight and obesity are currently considered a global health problem as a result of the growth and development of large cities, and their consequent accumulation of food accompanied by a sedentary lifestyle [15]. In Mexico, According to the National Health and Nutrition Survey, 72.5% of adults between 20 - 59 years old have some degree of overweight and obesity, being higher in women (87.7%) than in men (65.4%) [16].

Adipose tissue is of special importance because it is predictive of metabolic diseases [17,18]. Abdominal obesity is the result of the consumption of diets high in carbohydrates and fats, as well as foods with low nutritional value, together with a considerable decrease in physical activity [14].

The increase of the intraabdominal or visceral adipose tissue causes an increase in the splanchnic circulation of free fatty acids (FFA), while the subcutaneous tissue and its derivatives prevent the hepatic circulation and its consequences (increase in the production of glucose, synthesis of lipids and secretion of prothrombotic proteins), fat is stored in abnormally long peripheral adipocytes. The effect of adipocyte dimensions on the risk of developing DM2 is independent and additive to the effect of insulin resistance [19].

Dyslipidemia in metabolic disorders is characterized by elevated TG and very low density lipoproteins (VLDL), as well as a decrease in high density lipoprotein (HDL) and low density lipoprotein (LDL), which has been called the atherogenic lipoprotein phenotype [20]. Normal lipid metabolism includes the release of free fatty acids from adipocytes into the bloodstream, liver and muscles. In the liver a part is oxidized and the rest re-esterified to TG. There is a continuous transport of free fatty acids between adipose tissue and the liver; however, if the re-esterification process is saturated, the accumulation of TG can induce fatty liver.

The relationship between weight and metabolic health is not applicable for some individuals. Different types of obesity phenotypes have been defined, or obesity variants in people based on weight variation and the accumulation of visceral adipose tissue with the consequent metabolic disorders that this implies. The most well-known condition of obesity is that of metabolically obese with overweight obese people; however, there are other types of obesity or phenotypes that have been recognized and described as “metabolically obese, but with normal weight” (MONW), and “metabolically healthy, but obese” (MHO) [6,21]. Individuals with the MONW phenotype are those who have a normal weight with an abnormal metabolic state. Whereas, individuals with the MHO phenotype are those with a normal metabolic profile who present obesity; that is, visceral fat accumulation [21]. Unlike the MHO phenotype, the MONW phenotype has gained interest because these patients are not obese according to BMI criteria, but they have a dysfunctional metabolic profile, as is often the case with obesity. The identification of possible risk factors associated with MONW will be important in deciding whether to modify health-related behaviors [21]. Likewise, the factors associated with MHO will indicate effective ways to prevent metabolic abnormalities related to obesity [21]. MONW people are a subgroup of individuals who have a normal weight and body mass index (BMI), but show a group of abnormalities related to obesity. Although for a long time there has been a clinical recognition of this group of individuals, this group was described for the first time in detail in the 1980s. As described, these individuals may be young and show early signs of insulin resistance, hyperinsulinemia and dyslipidemia, which may increase the risk of developing MD2 and CVD [6].

For the investigation of the aspects related to obesity, overweight and the metabolic syndrome, the use of animal models is widely used since these allow to investigate and know molecular and physiological aspects that, in most of the occasions are complicated or impossible to evaluate in clinical studies in which subjects voluntarily sign a consent but that must cover diverse inclusion criteria for the study and that by international agreements their participation is limited in the sense of type of tests or studies to which they can be submitted for aspects of bioethics. The most commonly used animal models of obesity are in rats and mice [22], with commercial hypercaloric diets or the so-called cafeteria diet, in both cases with a fat content that varies from 12% to 49% and varied fat content of animal or vegetable origin according to the manufacturer or who designs the diet [23,24]; however, there are commercial diets with a content of up to 60% fat, in addition to the high-calorie diet with a high fat content, solutions with a varied concentration of sugars of up to 30% are used [23-26], which are supplied along with the treatment with the selected diet. Genetically engineered animals can also be purchased, but in most cases they are costly and inaccessible to most researchers.

The previous models of obesity in rats are of phenotype metabolically obese with overweight, Garrido-Acosta., *et al.* in 2018 development of a metabolically obese model without weight gain, corresponding to the MONW phenotype in rat model of obesity, this is achieved through the intragastric administration of an emulsion based on edible vegetable oil and fructose syrup. 80%, (1:1) obtaining adiposity index (AI) of up to double with respect to the intact control group [27].

Obesity and diabetes are usually accompanied by a chronic state of oxidative stress and imbalance in the redox balance. Diet is the major factor in the lifestyle that can significantly influence the incidence and progression of type 2 diabetes and cardiovascular complications. Food can not only provide nutrition, they can also prevent diseases by ensuring optimal health status [28]. Some diets and lifestyle can be good prophylactic measures against the characteristic oxidative stress in complications due to diabesity (term commonly used to describe this epidemic or pandemic with dramatic worldwide exponential growth of obesity and diabetes comorbidity [28]). A significant benefit of phytochemicals such as polyphenols, vitamins (among which vitamin C is found) and some minerals is their ability to eliminate free radicals by decreasing the incidence of chronic diseases [28].

Vitamin C is a water soluble vitamin characterized by a 6-carbon monosaccharide structure, very structurally similar to glucose [4], it is an essential nutrient with critical participation in multiple hydroxylation reactions and in maintenance of redox homeostasis in organelles such as the mitochondria and the endoplasmic reticulum, is also one of the most important antioxidants present in human plasma. Ascorbic acid (reduced form of vitamin C) is an efficient physiological tracer of reactive oxygen and nitrogen species; in addition, it can induce the regeneration of other antioxidant molecules such as vitamin E [29].

Vitamin C is an electron donor (reducing agent), hence its antioxidant power is derived as it is able to reduce oxidized species or oxidative radicals [29], has anti-inflammatory, anti-cancer (against some types) of cancer due to its ability to regulate the epigenome), it is able to reinforce the cellular and humoral immune response, it has also shown some efficacy in the treatment of obesity in both animal models and clinical trials in humans; however, the results observed are contrasting among many of them [3,4,30-32].

The objective of this research was to evaluate the effect of ascorbic acid administration on the adiposity index in two rat obesity models with a different phenotype, one induced by the supply of a fat-calorie 60% fat diet and another by the administration of hypercaloric emulsion, models of metabolic obesity with weight gain; and the second of metabolic obesity without weight gain development by Garrido-Acosta., *et al.* in 2018 [27] for to elucidate the efficacy of vitamin C against obesity and control of weight.

Materials and Methods

Animals

In this research were used 18 adult male Wistar rats of ten months of age. The rats were bred and acclimated in the vivarium. All experiments complied with the requirements and guidelines established by law respect at proper use, care, and management of laboratory animals with light-dark cycle conditions 12 X 12 (7 - 19 hours).

Emulsion

The emulsion used was made with edible vegetable oil, the property for portion (15.2 ml) is 518 kJ of energetic content (5g of linoleic acid, 1.1g of linolenic acid, 5.9g of monounsaturated fat 1.9g of saturated fat). Also was used fructose syrup, the fructose syrup at 80% was prepared with fructose powder alimentary grade at hot water bath. 100 ml of emulsion were prepared with 1:1 proportion (edible vegetable oil: fructose syrup at 80%), the emulsificant agent used was Tween 80® (0.7 ml/ 100 ml).

Hypercaloric diet 60% fat (Rodent Purified Diet DIO w/60% Energy From Fat - Blue

The hypercaloric diet was commercially acquired (Rodent Purified Diet DIO w/60% Energy From Fat - Blue). The mainly properties of this diet is: 31.66% lard, 16.15% maltodextrin, 8.84% sucrose and 3.23% soybean oil as the main sources of fats and sugars (carbohydrates).

Standard diet

Was used Rodent Laboratory Chow 5001® *ad libitum* for groups that do not consume the 60% hypercaloric diet.

80% fructose syrup

In a water bath and under constant agitation 80g fructose alimentary grade in 100ml of purified water will be gradually added, was used at room temperature.

30% fructose solution as drinking water

300 g of fructose alimentary grade was diluted in 1 liter (final volume) of purified water and was used as drinking water in treated groups.

Ascorbic acid solution

800 mg of ascorbic acid (AA) was weighted and diluted in 10 ml of purified water (final volume) and administered 800 mg/kg at groups with ascorbic acid as treatment.

Groups of treatments

Three groups of 6 rats were formed and received treatment for 8 weeks.

Hypercaloric diet group 60% fat (60% fat): food 60% fat *ad libitum* and 30% fructose solution will be supplied as drinking water.

Group Hypercaloric diet 60% fat + Ascorbic acid (60% fat + AA): food was supplied 60% *ad libitum* fat, and 30% fructose solution as drinking water. Between 14 and 16 hours of day, he was administered v.o. the solution of vitamin C (800 mg/Kg weight/10 ml).

Hypercaloric emulsion group + Ascorbic acid (HE + AA): the rats of this group after being weighed between 7 and 9 hours of day were given a hypercaloric emulsion (edible vegetable oil, fructose syrup 80%, 1: 1) in a volume of 10 ml/kg of weight, and in the afternoon (between 14 and 16 hours of day) were administered the solution of vitamin C (800 mg/10 ml) with cannula for intragastric administration in volume of 10 ml/kg of weight.

In accordance with the recommendations of international research journals, national and international bioethics bodies and committees, the hypercaloric emulsion group without ascorbic acid treatment was omitted in this experimental design since it was recently published by Garrido-Acosta., *et al.* in October 2018 as a new model of metabolic obesity without overweight (Garrido-Acosta., *et al.* 2018).

Consumption of food and water

Every day was weighed the feed intake (Rat Chow 5001®) with bascule of 0.1 g precision. The consumption of fructose solution (30% as water drinking) was measured every day with probate of 2 ml precision.

Variation of weight

The rats was weighted daily in the morning with bascule of 1.0 g precision.

Oral glucose tolerance test (OGTT)

For the glucose tolerance test, the rats were fasted for 5 h prior to test [33]. A 20% glucose solution was prepared min [34], and this was administered v.o in the corresponding volume for a dose of 2.2 g/kg of weight [35]. The blood sample was collected from the base of the tail at 0, 30, 60, 90 and 120 min [34] and was recorded in mg/ dl by glucometer determination [33].

Blood serum glucose and lipid profile

The animals were sacrificed by decapitation and the blood was collected in tubes without anticoagulant (tubes with red cap). The sample was centrifuged at 3000 rpm and serum separated with micropipette. The lipid profile was determined with the Selectra Junior® machine.

Body mass index and adiposity index

BMI was calculated with the weight (kg)/ square height (m^2). The adiposity index was used as an indicator of obesity because it enables the precise evaluation of body fat percentage [5]. This was evaluated with i.p fat calculated (this included epididimal fat + retroperitoneal fat + visceral fat) by X-ray with densitometer HOLOGYC® model DISCOVERY, the image was analyzed with HOLOGIC´s software. The adiposity index was obtained as (intraperitoneal fat calculated/body weight) X 100 [36].

Statistical analysis

Data was tested in normality and equal variances for parametric analysis, if any of this conditions not existed then was realized non parametric analysis.

Results and Discussion

Consumption of food and water

The table 1 and 2 shows weekly food and water consumption (fructose solution at 30% as drinking water). The oral administration of hypercaloric emulsion (edible vegetable oil and fructose syrup at 80%; 1:1) generate a tendency the highest reduction of consumption of balanced food and drinking water since the first week respect to diet with 60% fat.

	Week							
Group	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
60% fat	27±2	23±1	20±1	18±1	15±1	15±1	16±1	15±1
60% fat + AA	27±1	24±1	19±1	16±1	14±1	14±1	16±1	15±1
HE + AA	17±1	14±1	17±1	16±1	13±1	12±1	13±1	14±1

Table 1: *Median food weekly consumption (gr).*

Groups with n = 6. 60% fat: group with hypercaloric diet 60% fat; 60% fat + AA: group with diet 60% fat and ascorbic acid (800 mg/kg); HE + AA: group with hypercaloric emulsion (edible vegetable oil and fructose syrup 80%; 1:1) and ascorbic acid (800 mg/kg). Mean ± SEM. There is not a statistically significant difference between groups.

	Week							
Group	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
60% fat	39±2	45±1	41±2	42±3	37±2	35±2	37±4	37±3
60% fat + AA	43±3	45±3	42±3	46±4	48±5	37±3	44±5	52±4
HE + AA	38±3	42±2	50±5	51±4	41±3	36±3	44±4	48±4

Table 2: *Median weekly water consumption (ml).*

Groups with n = 6. 60% fat: group with hypercaloric diet 60% fat; 60% fat + AA: group with diet 60% fat and ascorbic acid (800 mg/kg); HE + AA: group with hypercaloric emulsion (edible vegetable oil and fructose syrup 80%; 1:1) and ascorbic acid (800 mg/kg). Mean ± SEM. There is not a statistically significant difference between groups.

The consumption of water is similar in the three groups, but the group with emulsion take around a half rations of feed respect to groups with diet 60% fat, the possible explication is the volume administered with the emulsion.

Variation of weight

The table 3 shows the effect of oral administration of emulsion with fructose solution (30%) and fructose solution (with oral administration of emulsion vehicle) on percentage of variation of weight. Both groups have a percentage weight reduction compared with intact control group, but without differences between them.

	Week								
Group	**Day 1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
60% fat	565±15	586±22	616±26	630±26	636±27	629±27	619±29	616±32	611±33
60% fat + AA	553±16	569±19	596±22	607±21	610±21	600±22	591±22	592±21	589±23
HE + AA*	546±23	535±22	527±21	526±20	528±20	522±19	511±18	506±18	505±18

Table 3: *Median weekly weight (gr).*

*Groups with n = 6. 60% fat: group with hypercaloric diet 60% fat; 60% fat + AA: group with diet 60% fat and ascorbic acid (800 mg/kg); HE + AA: group with hypercaloric emulsion (edible vegetable oil and fructose syrup 80%; 1:1) and ascorbic acid (800 mg/kg). Mean ± SEM. ANOVA on ranks. Tukey Post-Hock test. *P<0.05.*

Although there are different recognized obesity phenotypes, for the MONW phenotype there are no established criteria to define it. However, the study and understanding of it is important given that this subgroup is representative in obese population and understanding its response at some treatments as ascorbic acid administration as adjuvant against of obesity will allow developing appropriate therapies [6,7,21,37,38]. This treatment with emulsion was used previously to generate a model of MONW Wistar rats [27]. In this research not increased of weight the rats with co-administration of emulsion and ascorbic acid.

Oral glucose tolerance test (OGTT)

The figure 1 shows the results of OGTT. The results show a tendency to increase glucose in blood on this test but without significant difference in the evaluated time. The group with feed 60% fat without AA had the maximum concentration at 60 mins, the groups administered with AA 30 min after, but without statistical difference. The relevant aspect is the low concentration of basal glucose respect to others groups (fed 60% fat and fed 60% fat plus AA), inclusive with respect at group emulsion without AA reported to Garrido-Acosta., *et al.* 2018 [27].

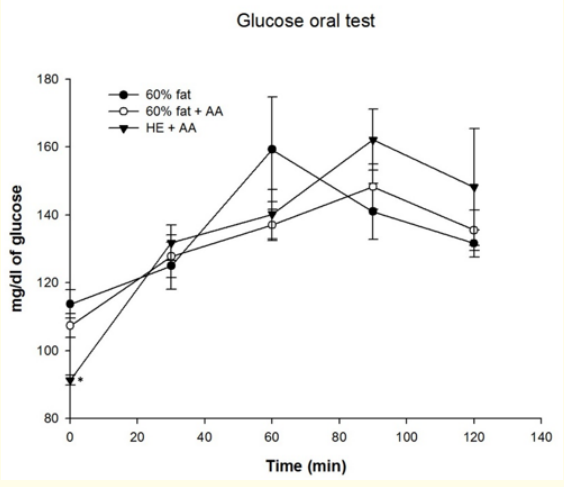

Figure 1: *Oral glucose tolerance test: n=6. 60% fat: group with hypercaloric diet 60% fat; 60% fat + AA: group with diet 60% fat and ascorbic acid (800 mg/kg); HE + AA: group with hypercaloric emulsion (edible vegetable oil and fructose syrup 80%; 1:1) and ascorbic acid (800 mg/kg). Mean + SME. ANOVA, Holm-Sidak Post-Hock test. *P < 0.05.*

Blood serum glucose and lipid profile

The table 4 shows the blood serum glucose and lipid profile (cholesterol, triglycerides and HDL cholesterol). Glucose present statistical differences respect to 60% fat and 60% fat+AA groups, and this in in concordance with results obtained on basal determination in OGTT.

	Glucose (mg/dl)	Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL (mg/dl)
Groups	**Mean ± SEM**	**Mean ± SEM**	**Mean ± SEM**	**Mean ± SEM**
60% fat	149.67 ± 4.15	63.00 ± 2.84	72.00 ± 7.76	23.67 ± 1.89
60% fat **±** AA	159.00 ± 2.49	66.83 ± 1.89	67.67 ± 7.61	23.50 ± 1.26
HE **±** AA	145.00 ± 2.46*	62.67 ± 1.45	67.17 ± 4.83	25.167 ± 1.81

Table 4: *Blood serum glucose, and lipid profile.*

*Groups with n = 6. *p < 0.05 by ANOVA with Post-Hoc test of SNK.*

Body mass index and adiposity index

The table 5 shows the body mass index and the adiposity index. The AI in HE+AA group present statistical difference with respect to 60% fat and 60% fat+AA groups.

Group	BMI	AI
60% fat	9.41 ± 0.56	13.62 ± 0.78
60% fat **±** AA	9.38 ± 0.97	14.35 ± 1.0
HE **±** AA	8.01 ± 0.89	6.93 ± 0.92*

Table 5: *Body mass index and adiposity index.*

*Groups with n = 4. BMI: Body mass index; AI: Adiposity index; 60% fat: group with hypercaloric diet 60% fat; 60% fat ± AA: group with diet 60% fat and ascorbic acid (800 mg/kg); HE ± AA: group with hypercaloric emulsion (edible vegetable oil and fructose syrup 80%; 1:1) and ascorbic acid (800 mg/kg). Mean ± SME. ANOVA, Holm-Sidak Post-Hock test. *P < 0.05.*

The traditional models of obesity induce overweight or obesity in rats or mice with increased weight, body mass index and visceral fat with increase in triglycerides, cholesterol and glucose serum [5,11,39-42], the AA not was a good adjuvant against obesity induced for diet 60% fat, with a great content of lard, but on the obesity induced for emulsion, with a great content of edible vegetable oil, the AA was efficient in diminished of AI. This results suggest that AA can be efficient against obesity induced by edible vegetable oils and carbon hydrates as fructose, used as substitute of glucose. Then the AA is an alternative in the therapeutic categories against some causes of obesity [1].

Conclusion

The AA can be an alternative in the therapeutic against some causes of obesity when this is caused by elevated consumption edible vegetables oils and substitutes of glucose as fructose, and the inconsistences in the results of AA against obesity can be for the content and class of fat used in prepared food. In this sense is necessary more studies with the model of obesity without increased of weight for to identify differences in metabolic routes and evaluated others substances that jointly with change of alimentary habits can going to be efficient against obesity.

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Conflict of Interest

None.

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