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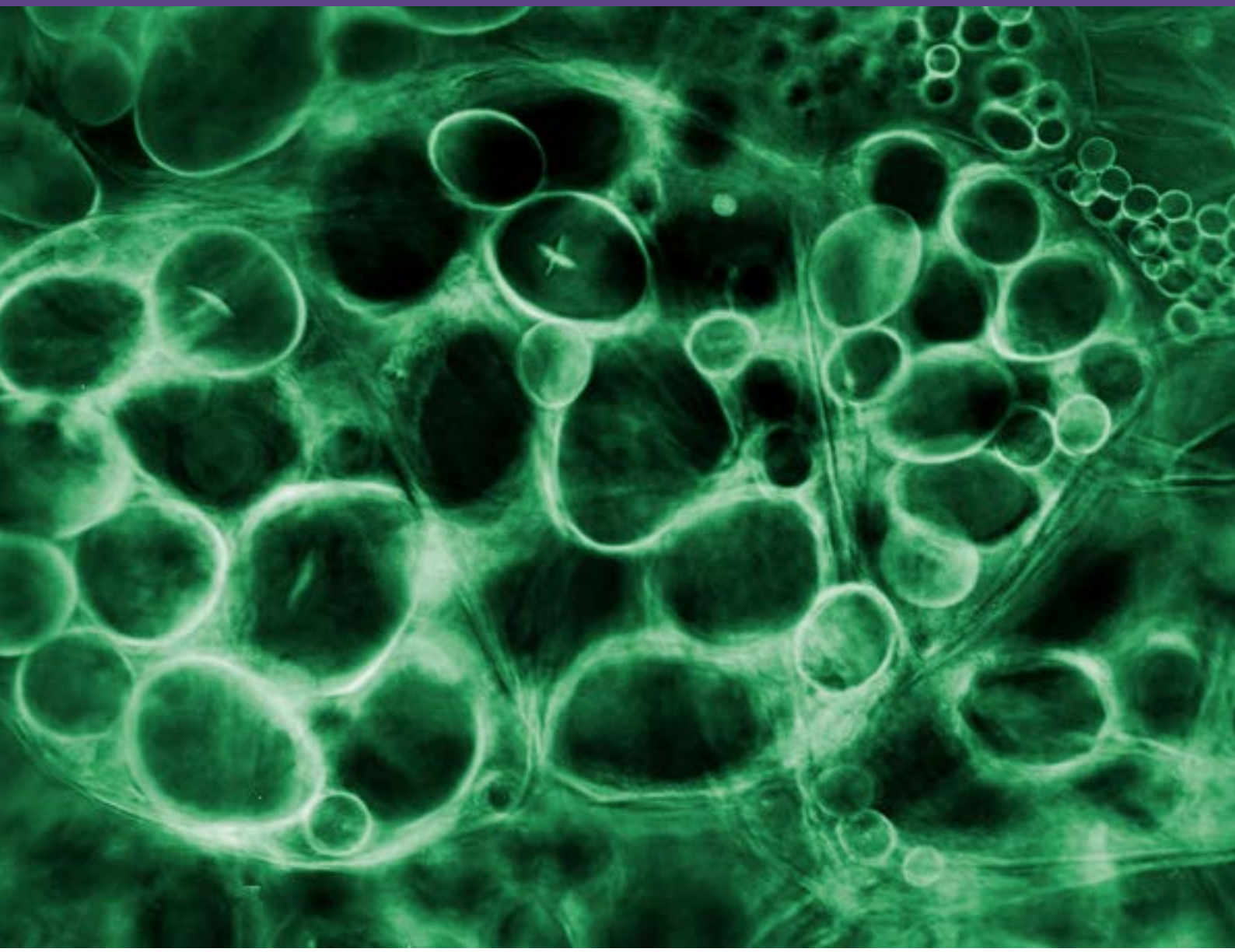

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Facultad de Ciencias Médicas; Universidad Nacional de La Plata;
La Plata, Buenos Aires, Argentina. Tel.-Fax: +54-211-4834833
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PAST, PRESENT AND FUTURE PERSPECTIVES OF ADIPOSE TISSUE, EXERCISE AND RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INTERACTIONS

F Cavalli[#], Claudia Caldiz[#]*

In memoriam of GE Chiappe de Cingolani

[#]Centro de Investigaciones Cardiovasculares "Dr. Horacio E. Cingolani", Facultad de Ciencias Médicas, Universidad Nacional de La Plata, Calle 60 y 120, (1900) La Plata, ARGENTINA.

***correspondence to:** clacaldiz@med.unlp.edu.ar

Abstract

In past decades, adipose tissue was considered as a mere fat deposit and therefore an energy storage. Nowadays, we know that, by secreting endocrine and paracrine factors, it plays a major role in regulating metabolism and homeostasis. Therefore, from the physiological point of view it is considered as an endocrine organ. Adipose tissue is target of insulin action, which promotes the uptake and storage of glucose in the form of fatty acids. In cardiovascular diseases such as high blood pressure, the response to insulin and the metabolism of adipose tissue are altered. It has been demonstrated that the blocking of the renin-angiotensin-aldosterone system (RAAS) is effective in counteracting those alterations. On the other hand, aerobic exercise has been shown to be a useful tool to modify the adipose tissue, alterations observed in cardiovascular diseases. Exercise changes the phenotype of adipose tissue from white to beige with the consequent improvement in the response to insulin at the systemic level. Recently, it has been proposed that the RAAS, through an increase in the hypotensive arm, could mediate the beneficial effects of exercise on adipose tissue, and favor the development of the beige phenotype of this tissue. In this review we will focus on the interaction of adipose tissue, RAAS and aerobic training in a context of arterial hypertension and insulin resistance.
Keywords: adipose tissue, insulin resistance, hypertension, Renin-Angiotensin-Aldosterone-System (RAAS)

Resumen

En décadas pasadas, el tejido adiposo ha sido considerado como un mero depósito de grasa y como un órgano de almacenamiento de energía. Hoy en día sabemos que, a través de la secreción de factores endócrinos y parácrinos, éste tejido juega un papel importante en la regulación del metabolismo y la homeostasis. Por lo tanto desde el punto de vista fisiológico se considera al tejido adiposo como un órgano endócrino. El tejido adiposo es blanco de acción de la insulina, promoviendo ésta la captación y el almacenamiento de glucosa en forma de ácidos grasos. En enfermedades cardiovasculares como hipertensión arterial la respuesta a insulina y el metabolismo del tejido adiposo se encuentran alterados. Se ha visto que el bloqueo del sistema renina-angiotensina-aldosterona (RAAS) resulta efectivo para contrarrestar estas alteraciones. Por otra parte, el ejercicio aeróbico ha demostrado ser una herramienta útil para modificar las alteraciones metabólicas del tejido adiposo que se observan en individuos con enfermedades cardiovasculares. Estas modificaciones involucran el cambio de fenotipo del tejido adiposo de blanco a beige con la consecuente mejora en la respuesta a la insulina a nivel sistémico. En este último tiempo se ha propuesto que el RAAS, a través de un aumento en la actividad del brazo hipotensor, podría mediar los efectos benéficos del ejercicio sobre el tejido adiposo, favoreciendo el desarrollo del fenotipo beige de este tejido. En esta revisión se abordará la relación entre tejido adiposo, RAAS y entrenamiento aeróbico en un contexto de hipertensión arterial y resistencia a la insulina.
Palabras claves: tejido adiposo, resistencia a la insulina, hipertensión, Sistema Renina, Angiotensina, Aldosterona (RAAS)

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Introduction

Cardiovascular diseases are the first cause of death in Argentina and worldwide, being hypertension (HTA) the main modifiable risk factor. Another cardiovascular risk factor that is closely related to hypertension is insulin resistance (IR). Adipose tissue is a target organ for insulin action. Interestingly results obtained from humans and experimental models demonstrated that hypertensive individuals not only have RAAS activation but also a decreased response to insulin. Both RAAS blockade and physical training are useful tools to delay the progression of cardiovascular disease and improve insulin sensitivity, possibly involving modifications in adipose tissue phenotype. Although the molecular mechanisms that are involved in these beneficial effects have not yet been fully elucidated, it has been postulated that an increase in the antihypertensive arm of the RAAS could mediate these effects.

Adipose tissue phenotypes and functions

The adipose tissue is a target organ for insulin; this hormone can translocate the glucose transporter 4 (Glut4) from an intracellular pool to the cellular membrane, mechanism that involves an auto phosphorylation of the receptor due to its intrinsic tyrosine protein kinase activity as well as downstream substrates.

In mammals, adipose tissue can be categorized in two main types, each one having different embryological origin and biological function. The white adipose tissue (WAT), traditionally considered as a lipid depot, is characterized by spherical shape cells, which represent the mature adipocytes. WAT depot is localized in different regions of the body, but mainly in the abdomen, the abdominal cavity (visceral fat) and under the skin (abdominal subcutaneous fat). The primary function of WAT is fuel storage. At present, it is known that this tissue is capable of secreting a large amount of cytokines and for these reason is considered as an endocrine organ that contributes to the functioning of several processes in the body such as, inflammatory and immune response [1]. Also, this variety of fat is associated with cardiovascular risk factors and contribute to IR and metabolic syndrome [2, 3].

The other type is the brown adipose tissue (BAT), which has de ability to dissipate energy in the form of heat, by a lipid and glucose oxidation through a mechanism called nonshivering thermogenesis. This process is mediated by uncoupling protein 1 (UCP-1), localized at the inner-mitochondrial membrane. BAT is characterized by a dark red tone due to the high vascularization; the cells cytoplasm contains small fat-filled droplets and a large number of mitochondria. In human, BAT depot is localized mainly in the interscapular and supraclavicular regions and is considered as a protector factor from cardiovascular events, since produces cytokines that counter regulates the cytokines from the WAT stores [4-6]. Recently a third type of fat, neither white nor brown was described, the beige or bright adipose tissue (BRAT) that shares almost all features of BAT except for the localization. It is found interspersed with WAT mainly in the inguinal subcutaneous tissue. Beige adipocytes and WAT have a common precursor originated from myogenic factor 5 negative cells, however, in the presence of certain stimuli such as low temperatures or sympathetic activation, they acquire characteristics of BAT [7]. They present a similar gene expression pattern, express UCP1, and have small lipid droplets and a high mitochondrial density [8]. Nevertheless the origin of beige adipocytes is still a matter of debate, since others authors suggest that BRAT may form either by interconversion from WAT or by proliferation and differentiation from specific precursor for each phenotype[9].

BRAT plays an essential role in regulating whole body metabolism because it can also uptake glucose and fatty acids. Since, activating BRAT may be a strategy for reversing insulin resistant states [10, 11], to elucidate the regulatory mechanisms of brown and beige adipose tissues may provide new targets for treating metabolic disorders as diabetes.

Exercise effect on adipose tissue

Physical exercise, particularly aerobic training (AT), offers protection against metabolic disorders such as obesity, diabetes, and HTA [12, 13]. AT, decreases adipose cell size, and lipid content and increases the number of mitochondria which leads to a healthier metabolic state. These results are in line with unpublished data from our lab where in Spontaneously Hypertensive Rats (SHR) an 8-week swimming routine, a decreased adipocyte size and increased citrate synthase activity, were observed. Additionally, AT has shown to be useful in producing the transformation of WAT, favoring the development of the beige phenotype. Exercise also increases the expression of the brown adipocyte marker uncoupling protein 1 (UCP1) in WAT depots, being this effect much more pronounced in the subcutaneous WAT [14]. Moreover exercise also favors the redox homeostasis, which is altered in hypertensive individuals [15], by diminishing NADPH oxidase activity and increasing antioxidant enzymes [16]

Hypertension and Insulin Resistance

Insulin is a peptide hormone which, when bound to its receptor, triggers a signaling cascade that involves glucose transporters translocation through a mechanism mediated by PI3Kinase and AKT. Although it has different effects on different target organs, the components involved on the signaling cascade are remarkably similar in all tissues. In WAT, insulin suppresses lipolysis and increases glucose transport and lipogenesis [17].

It is well known that insulin response is altered in different pathologies such as HTA and others cardiovascular diseases. A strong association between HTA and IR has been described, although the mechanisms that lead to IR in HTA have not yet been elucidated (6). Moreover, there is a discussion regarding if IR could induce HTA[18], [19], [20].

Human studies as well as experimental data support the notion that resistance to insulin-stimulated glucose uptake and hyperinsulinemia play a significant role in the etiology of HTA [21]. In this context, Mondon and Reaven showed an impaired insulin-mediated glucose metabolism, at organ and cellular level, in SHR compared to normotensive control rats [22, 23]. Interestingly, working with the same experimental model, we have shown that, at cellular level, there is a decrease in the response to insulin of these animals, compared to their normotensive controls WKY (Fig 1, panel A). This alteration was reversed when the animals were treated with antihypertensive drugs. In particular, enalapril an Angiotensin Converting Enzyme (ACE) inhibitor was capable of reversing the IR state in SHR, effect that was not observed when we used the AT1 receptor blocker, losartan (Fig1panel B) [24]. In other studies, we verified that SHR metabolic alterations also involved the GLUT4 glucose transporters whose translocation to the membrane as well as their phosphorylation, were decreased, suggesting that both events could be the cause of IR observed in this experimental model. [25]

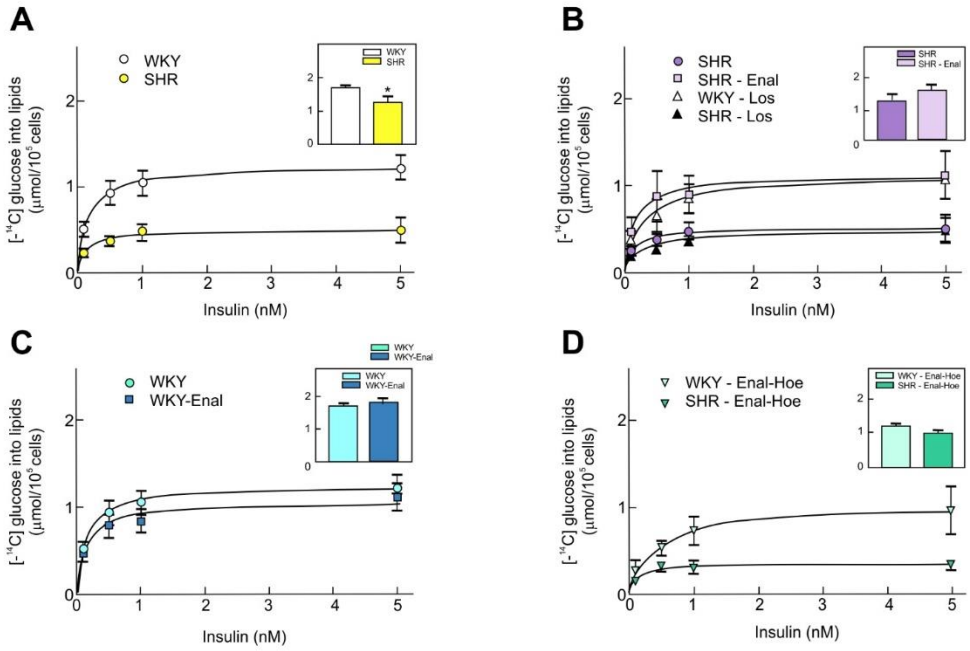


Fig 1 Panel A: Effect of insulin on lipogenesis from glucose in isolated adipocytes from SHR and WKY rats. Basal lipogenesis (inset) was subtracted from each value obtained in the presence of insulin. **Panel B and C:**Effect of long-term treatment with enalapril (Enal) and Losartan (Los). **Panel D:** Effect of long-term treatment with Enal and the bradikynin B2-receptor antagonist Hoe 140. The B2-receptor antagonist suppressed the improvement of insulin resistance induced by Enal. *(Modified from Caldiz, C.I. and G.E. de Cingolani Metabolism 1999)*

The RAAS in adipose tissue

The classical systemic RAAS generates hormones that are key regulators of blood pressure, hydrosaline balance and plays a role in the pathogenesis of cardiovascular diseases. The RAAS is composed by renin enzyme secreted in the kidney, at the juxtaglomerular level, which function is to transform angiotensinogen into angiotensin 1 (Ang I). Ang I is converted to angiotensin II (Ang II) by an enzyme located in the membrane of endothelial cells, called ACE. Ang II is the main actor of the system since its interaction with the Ang II type 1 receptor (AT1) induces vasoconstriction, hypertrophy and increases oxidative stress. It is well established that hypertensive individuals have an increase in the expression and activity of the components of this system [26, 27]. RAAS components are locally produced in adipose tissue, both in humans and animal models, where up-regulation of the classical arm promotes lipogenesis and reduces lipolysis and adipogenesis, leading to adipocyte hypertrophy and increased lipid storage. [28, 29] Information from both clinical and basic research has shown that RAAS inhibition beneficial effects not only by lowering blood pressure but also by decreasing target organ damage [30-32].

As mentioned above, in the 1990s, in our laboratory, we demonstrated that adipocytes from SHR have a decreased response to insulin and that chronic treatment with enalapril, an ACE inhibitor, reversed this effect (Fig. 1, panel C). ACE not only promotes the formation of Ang II but also inhibits the formation of a potent vasodilator, bradykinin (BK), therefore ACE inhibitors increase the half-life of BK and prevent the formation of Ang II. Interestingly, we observed that the improvement in the response to insulin obtained with enalapril was reversed when we administered a BK-B2 receptor blocker, Hoe 140 [24](Fig 1 panel D). Simultaneously, and in agreement with these results, other research groups reported that BK can enhance insulin stimulated glucose uptake [33, 34]

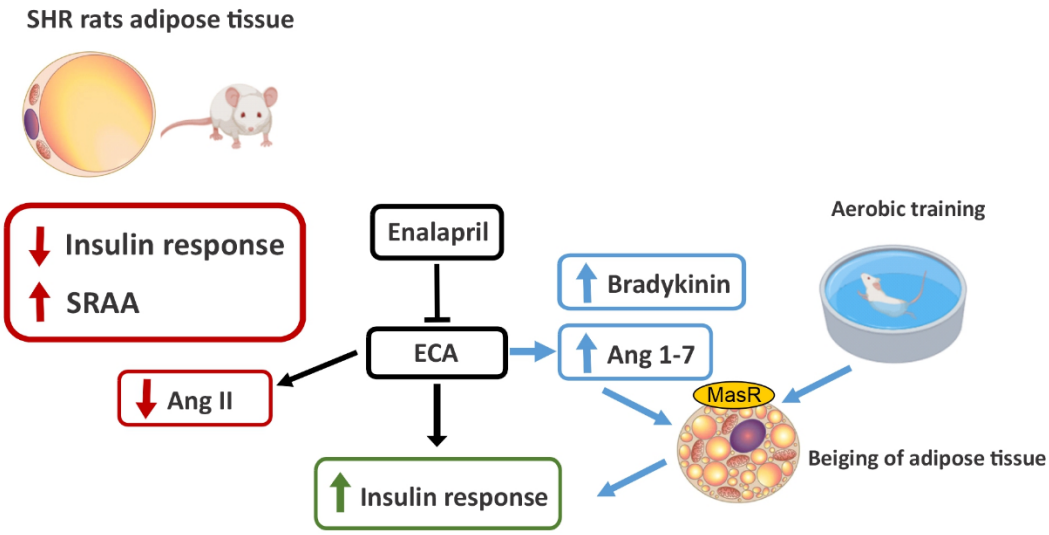
Currently, through the contributions of Santos and others, [35-37] the understanding of the RAAS system has improved and today it is known that its function is far more complex. The modern concept of the RAAS includes, in addition to the deleterious arm already mentioned, a protective arm which counteracts the effects of the previous one. In the production of protective effects, angiotensin–

converting enzyme 2 (ACE2) is a key factor which generates Ang 1–7 by hydrolysis of Ang II. The interaction with its receptor, Mas, mediates 'the beneficial effects'' of Ang1–7 such as vasodilatation, inhibition of proliferation and anti-fibrosis. Regarding to cardiovascular effects the works of Fernandes and Silva have shown that both, AT and swimming routine increased increased Ang 1-7 levels and Mas receptors expression in aorta of SHR rats [38, 39].Therefore the possibility of using Ang 1-7 or other Mas agonists as therapeutics agents is being explored. This strategy represents an important shift in the concept of intervention on the RAAS since it implies not only the benefits obtained by blocking the hypertensive arm of the system, but also the ones achieved by stimulating the protective axis. This beneficial axis is expressed in the WAT and, when activated, it induces metabolic actions such as an increase in glucose uptake and reduction in oxidative stress [40, 41]

The aim of this review was to give a brief description about the relationship among adipose tissue, RAAS and exercise. We summarize the links reported:

1. RAAS an exercise: the antihypertensive arm of RAAS participates in some exercise-induced beneficial effects. AT also reduces the Ang II /AT1 axis activation.
2. RAAS and adipose tissue: Ang-(1-7) increase the expression of beige markers in incubated adipocytes, and this effect is mediated through the Mas receptor.

Based in our results and in light of new reports we can speculate that, ECA inhibitors like enalapril and perhaps some others, exert not only antihypertensive effects by blocking Ang II formation and increasing BK levels but also could favor the beneficial arm of RAAS on adipose tissue. Concomitantly a recent study "in vivo" demonstrated that both, the administration of enalapril or AT, increased the expression of ECA 2, B2, and Mas receptors in adipose tissue [42] favoring the development of beige phenotype.
However, the effect of AT on RAAS and on the WAT and the repercussions preventing IR and other metabolic alterations still need investigation. A combined therapy involving pharmacological strategies and AT should open a new door for the treatment of metabolic disorders associated with hypertension and other cardiovascular diseases.



Graphic Abstract Adipose tissue of SHR rats present insulin resistance (red arrows). This pathological condition can be reverted by chronic treatment with ACE inhibitor enalapril (black arrows), which by increasing Ang 1-7 levels would favor the beige phenotype. AT was proposed to be a potential beiging mechanism (blue arrows). In light of available literature, both mechanisms increase insulin sensitivity (green box) and could have ANG 1-7 as a common mediator triggering the change from WAT to BAT phenotype.

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ABOUT AUTHORS

Dr. Claudia Caldiz is Assistant Professor of Physiology and Biophysics of Facultad de Ciencias Médicas de La Plata (Universidad Nacional de La Plata) and Professor of Physiology and Biophysics of Facultad de Humanidades y Ciencias de la Educación (Universidad Nacional de La Plata) She has published 28 papers on this and other topics related with Cardiovascular Pathophysiology and Adipose Tissue Metabolism. I began my research career under the direction of Dr. Gladys Chiappe who directed my doctoral thesis and introduced me to the study of adipose tissue.

Lic. Fiorella A Cavalli is a doctoral fellow of CONICET, Laboratory Instructor of Physiology and Biophysics of Facultad de Ciencias Médicas (Universidad Nacional de La Plata).