

Role of three adipokines in metabolic syndrome

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Metabolic syndrome comprises a group of factors that represent a risk for heart diseases, in particular coronary artery disease.¹ Atherosclerosis, endothelial dysfunction, hypertension, obesity, insulin resistance, and diabetes are components of this syndrome, which underlies the high incidence of cardiovascular diseases in the industrialized world. The occurrence of metabolic syndrome is attributed to hormones released by adipose tissue, which is now also considered an endocrine organ.

In the current issue of the *Polish Archives of Internal Medicine* (Pol Arch Med Wewn), Skoczylas et al² report a study that investigated the role of 3 different adipokines in hypertension and obesity as well as their response to 4 different types of antihypertensive compounds. The references selected by the authors throw some light on the significance of the results obtained with adequate experimental protocols. Owing to the adequate selection of the references, the introduction and discussion sections are a sort of reviews that strongly underline the importance of the results.

The study focuses on the changes in plasma concentrations of apelin, resistin, and visfatin induced by antihypertensive treatment in patients with hypertension and obesity, compared with the changes occurring only in hypertensive non-obese or only non-hypertensive obese subjects.

Apelin is the ligand for the previously orphan APJ receptor.³ Although it is a ubiquitous peptide, apelin is classified as an adipokine because it is produced by adipocytes. Various fragments have been isolated as derived from the 77 aminoacid preproteins and classified according to the number of the aminoacids.³ Out of the various fragments, apelin-13 is considered the most active form for the cardiovascular system,⁴ where it exhibits a positive inotropic effect on the heart and a dilatatory effect on the vessels, the latter being the result of an increased nitric oxide production.

In addition to these basic effects, other important activities of apelin have been reported, such as protection of the myocardium against ischemia–reperfusion injury,⁵ inhibition of

the renin–angiotensin–aldosterone system, and cardiomyogenic differentiation of mesenchymal stem cells.⁶ Furthermore, a role in the control of food intake and stimulation of gastric, endothelial, and vascular smooth muscle cell proliferation have been reported.^{7–9}

An increase in plasma apelin concentrations in human and animal models has been observed in patients with metabolic syndrome.¹⁰ In this syndrome, apelin has a beneficial effect on the improvement of insulin sensitivity associated with an intervention both in glucose and lipid metabolism. The related antidiabetic and antiobesity roles suggest that apelin may be a promising therapeutic target in metabolic diseases.

Resistin is an adipocyte-derived hormone that has been reported to connect obesity with type 2 diabetes. Human resistin is a cysteine-rich peptide consisting of 108 aminoacids. Its name derives from the observation that it increases insulin resistance, although some doubts have been raised about the importance of this effect.¹¹ In addition to its activity on insulin resistance, resistin has been also reported to play a potent role in inflammation, either directly or through various compounds such as interleukin 6 (IL-6), tumor necrosis factor α (TNF- α), and NF- κ B. Interestingly, IL-6 and TNF- α can also regulate resistin gene expression. In particular, it has been observed that TNF- α strongly increases resistin mRNA in human blood mononuclear cells.¹² Resistin has also been reported to reduce the expression of endothelial nitric oxide synthase in the endothelial cells of human coronary arteries and to stimulate vascular smooth cell migration, thus inducing pathological alteration in the vessels.¹³

Visfatin is an adipocyte-derived hormone that shows a direct relationship between its plasma concentration and type 2 diabetes. Similarly to insulin, visfatin causes hypoglycemia. The effect depends on its binding to the site of the insulin receptor, which, although distinct from that of insulin, reduces glucose release from the liver and stimulates glucose utilization by muscle

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fibers and adipocytes. Human visfatin consists of 401 aminoacids.

An interesting study on visfatin¹⁴ showed that in heterozygous mice expressing visfatin, glucose plasma levels are higher than in wild-type animals in both normal conditions and under glucose tolerance test, indicating a role similar to that of insulin in lowering plasma glucose concentrations.

From the above description of the activities of the 3 different adipokines, it follows that while apelin and visfatin can have a beneficial effect in diabetes, resistin shows the opposite effect, which can also lead to vascular alterations, such as atherosclerosis.

As antihypertensive drugs, Skoczylas et al² used a β -blocker (bisoprolol), calcium antagonist (amlodipine), thiazide-like diuretic (indapamide), and AT1 receptor blocker (candesartan).

The effect of bisoprolol deserves a comment, based on the role of body fat in the activity of the sympathetic system. It has been suggested that aging-related accumulation of body fat results in the chronic stimulation of the sympathetic system¹⁵ via adiposity-sensitive humoral signals, such as leptin and insulin, which can cross the blood-brain barrier. The activation of the sympathetic system should lead to an increased β -adrenergic thermogenesis aimed at turning into heat the energy that otherwise would be stored as adipose tissue. Unfortunately, adipogenesis replaces thermogenesis when tissue responsiveness is reduced, as it may occur in aged subjects. Seals and Bell¹⁵ reported that also the reduction of β -adrenergic signaling contributes to the prevalence of adipogenesis with respect to thermogenesis. As a matter of fact, these authors suggested that an increase of sympathetic activity, initiated by the accumulation of adipose tissue and aimed at preventing enhancement of this accumulation, may paradoxically lead to the development of obesity with aging.

Amlodipine is a dihydropyridine-type calcium antagonist commonly used in the treatment of hypertension. Due to the closure of calcium channels of vascular smooth muscle cells and cardiomyocytes, it is expected not only to produce vasodilatation but also to exert a negative inotropic effect on the heart. However, since amlodipine displays its activity more on smooth muscle cells than on cardiomyocytes, the reduction of blood pressure is mainly due to vasodilation rather than to reduction of cardiac contractility.

Indapamide is a thiazide-like diuretic that limits sodium reabsorption from the renal distal convoluted tubule. As a consequence, its antihypertensive effect is the result of a reduction of the fluid circulating volume and not of vasodilatation. Skoczylas et al² emphasized that the use of thiazide diuretics may have a negative effect on carbohydrate and lipid metabolism and may be responsible for diabetes or lipid disturbances.

Finally, candesartan reduces blood pressure by blocking the AI receptors of angiotensin II. Since sartans are known to induce the production of

apelin, it cannot be excluded that an antihypertensive effect may depend on the activation of the angiotensin converting enzyme-2, which converts angiotensin I and angiotensin II into the non-vasoconstrictor angiotensin 1-7 and angiotensin 1-9, respectively.

After 6 weeks of treatment, the authors observed a nonsignificant decrease in plasma apelin concentrations in nonobese hypertensive patients, while an increase was observed in all obese hypertensive patients. In these patients, however, only the treatment with amlodipine induced a significant increase in apelin plasma levels.

In the discussion section, the authors suggested that the decreased apelin plasma level caused by indapamide may represent the reason why a prolonged hypotensive therapy may become less effective with time. This point of view suggests that the effectiveness of the antihypertensive treatments depend at least in part on the availability of apelin.

After 6 weeks of treatment with amlodipine, bisoprolol, and indapamide, the authors observed a significant reduction of plasma resistin concentrations, while no effect was obtained with candesartan. Bisoprolol reduced also plasma visfatin concentrations, which was not affected by the other compounds.

The differences between the 3 antihypertensive compounds studied by Skoczylas et al² can be seen in their effect on blood pressure. In fact, while apelin is considered to act as a vasodilator that contributes to maintaining normal blood pressure, resistin has been demonstrated to favor the increase of blood pressure in patients with metabolic syndrome and to enhance vascular responsiveness to other hypertensive compounds.¹⁶ Unlike the other 2 adipokines, visfatin does not seem to produce any effect on blood pressure. These differences must be kept in mind when the effects of various antihypertensive drugs are studied with regard to the concentration and function of endogenous compounds that act with different mechanisms in the control of blood pressure.

If we refer to the specific compounds examined in the present study, we see that also other aspects characterize apelin, resistin, and visfatin. In fact, the opposite effects on diabetes, shown by apelin and visfatin on one side and by resistin on the other, are part of broader effects on the syndrome that comprise various metabolic and cardiovascular alterations.

In general, when a topic is relatively new and still poorly explored, an experimental study must give precise answers to some emerging questions without confusing the reader. This is what Skoczylas et al² have done successfully in their study in that the comparison between the responses of different endogenous compounds to some selected stimuli represents an important step towards a better understanding of these compounds.

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