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EDITORIAL

Inside the pathophysiological mechanisms of cardiometabolic diseases: the other pandemic to fight

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Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in patient with metabolic disorders like type 2 diabetes, metabolic syndrome, and obesity [7]. Therefore, it is especially important not only to make an early diagnosis of this entity but even more relevant is to achieve an early prevention of cardiometabolic disease due to its impact on public health. A several numbers of reasons lead to cardiometabolic disease becoming more frequent worldwide, such as clinical inertia, poor therapeutic approach, adverse effects associated with intensive control, inefficient strategies with old drugs, or the lack of control of other risk factors. However, a key factor is the lack of knowledge of the pathophysiological mechanisms that lead to this malady. Elucidating these mechanisms will allow a better comprehensive as well as personalized approach to cardiometabolic disease.

In this special issue of Pflügers Archiv—European Journal of Physiology, a series of review articles will take a look on different key aspects of pathophysiological mechanism of cardiometabolic disease, such as the role of natriuretic peptide and renin angiotensin system [20, 22], the mitochondria as a fundamental organelle in cardiometabolic cell dysfunction [5, 11], as well as new and old actors (stromal interaction molecule 1, hyperuricemia, and chloride anion) [2, 10, 21], and some novel therapies approach [1, 6] (Fig. 1).

Besides bad lifestyle factors like high body mass index, bad food choice, smoking, and physical inactivity, obesity has now new thoughts due to its association with lifetime risk of CVD and early target organ damage [8]. In recent year, the role of natriuretic peptides as a linking actor between adipose tissue dysfunction and cardiovascular disease has been investigated [23]. A growing body of evidence demonstrated that natriuretic peptides are key component for energy metabolism regulation, thus interrelating the heart, as an endocrine organ, with various insulin-sensitive tissues and organs such as adipose tissue, muscle skeletal, and liver [20]. Thus, adipose tissue dysfunction is associated with altered regulation of the natriuretic peptide system, and vice versa. Although the causal relationship is not fully understood, natriuretic peptide dysfunction appears to induce the development of obesity, type 2 diabetes mellitus, and cardiometabolic complications [23]. Therefore, targeting the natriuretic peptide pathway could represent a promise strategy to improve metabolic health in obesity and type 2 diabetes mellitus patients.

Diabetic cardiomyopathy is one of the main causes of global morbidity and mortality and is on a rising trend with the increase in the prevalence of diabetes mellitus [15]. As a physiological antagonist of natriuretic peptides, the renin angiotensin system (RAS) has also been implicated in the pathophysiology of CVD and metabolic disorders. Although RAS inhibition is considered a golden treatment in heart failure, its role in diabetic cardiomyopathy remains unclear [9]. In diabetic cardiomyopathy, RAS could trigger different mechanisms like inflammation, oxidative stress, mitochondrial dysfunction, and autophagy that complicate the prognosis and treatment of diabetic cardiomyopathy [22]. Among the complex mechanisms involved, Ca^{2+} mishandling and mitochondrial dysfunction also represent crucial early processes. Jaquenod De Giusti et al. focus on these two processes and the molecular pathway that relates these two alterations to the development of diabetic cardiomyopathy [11]. Mitochondrion plays a key role in cell energy homeostasis and is the main source of reactive oxygen species [24]. Mitochondrial alterations together with inflammation

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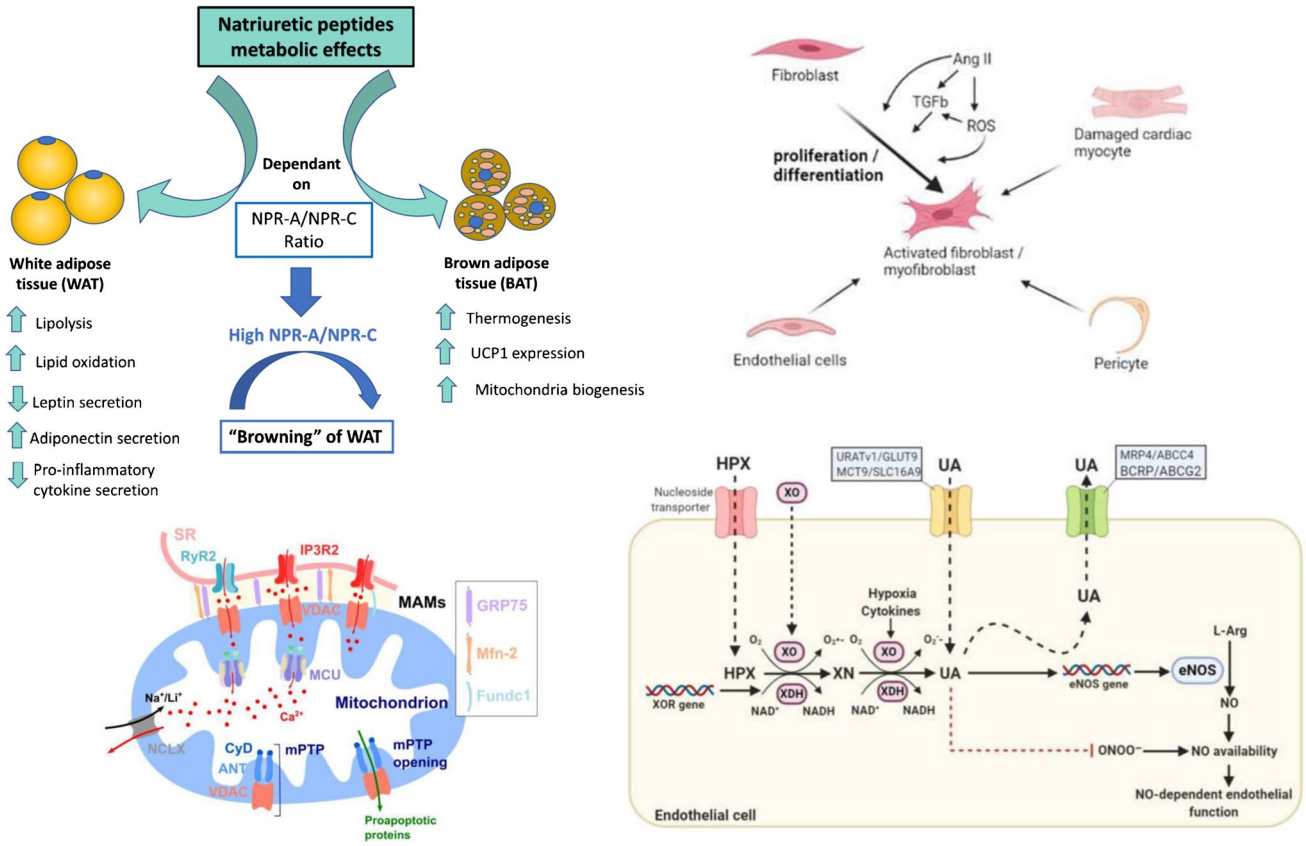

Fig. 1 Different actors involved in the cellular and molecular processes of cardiometabolic disease

have been reported to contribute to the development and progression of heart disease under insulin resistance conditions [25]. Furthermore, miRNAs may also regulate energy substrate metabolism, reactive oxygen species production, and apoptotic pathways within mitochondria, suggesting that epigenetic modifications could influence mitochondrial dysfunction [5].

The metabolic syndrome disorder is related with the etiology and progression of CVD. Cardiometabolic risk factors, like type 2 diabetes mellitus and features of metabolic syndrome (insulin resistance, dyslipidemia, hepatic steatosis, obesity, etc.), are associated with an increased risk of CVD due to increased oxidative stress, atherosclerosis, and chronic low-grade inflammation that led to different organ damage [4]. In addition to current pharmacological treatments, especially with the arrival of SGLT-2 cotransporter inhibitors, new pharmacological tools are still needed to counteract crucial pathophysiological mechanisms such as inflammation and oxidative stress and thereby improving the residual risk. In this way, substances with beneficial properties such as epicatechin have shown significant effects by regulating NADPH oxidase (NOX)-dependent oxidants production, nitric oxide production, and energy homeostasis (mitochondrial biogenesis and function) [6]. As essential micronutrients for cellular metabolism, vitamins consumed at pharmacological concentrations are also being recognized as modulators of genetic expression and signal transduction [17]. The etiology of cardiometabolic diseases includes a complex phenotype derived from interactions between genetic, environmental, and nutritional factors [14]. Although several evidences from experimental and clinical trials have evaluated the use of vitamin supplementation in the prevention and treatment of metabolic syndrome and cardiovascular disease, there is still controversy regarding its safety and efficacy [1].

Hypertension and hyperuricemia are two known risk factors for CVD. Hyperuricemia is a clear example of how inflammation and oxidative stress lead to CVD and metabolic dysfunction [12]. However, is still controversial, whether an increased circulating level of uric acid represents a causative factor for type 2 diabetes mellitus. Hyperuricemia causes endothelial dysfunction via induction of cell apoptosis, oxidative stress, and inflammation; the decrease in endothelial nitric oxide availability could lead to the development of endothelial insulin resistance, which seems to be a major underlying mechanism for hyperuricemia-induced endothelial dysfunction [2]. It remains to elucidate if uric acid-lowering drugs can improve endothelial function

in patients with hyperuricemia. On the other hand, hypertension is a main risk factor to induce stroke, an entity that represents a major cause of death and permanent disability worldwide [3]. In order to develop preventive and therapeutic strategies, several efforts have been made to identify molecular abnormalities that precede cerebral ischemia and neuronal death. Mitochondrial dysfunction, autophagy, and regulation of intracellular calcium homeostasis by the calcium sensor, stromal interaction molecule 1 (STIM1), appear to be important contributors to stroke development. Stanzione et al. discuss the relevant role of STIM1 in experimental stroke and the available evidence in the human disease [21]. Finally, it is well known that an elevated dietary sodium consumption is associated with hypertension and an increased risk of cardiovascular morbimortality [13, 16]. Also, excess of sodium intake promotes pro-inflammatory and pro-fibrotic effects on different target organs [18, 19]. These adverse effects have been attributed to the high consumption sodium as sodium chloride, but little is known about the contribution of chloride anion. Chloride anion is the predominant anion in the extracellular fluid and plays a variety of functions, such as regulation of cellular proliferation, differentiation, migration, apoptosis, intracellular pH, and cellular redox state. In this special issue, Kouyoumdzian et al. will discuss the relationship between dietary, serum, and intracellular chloride and how these different sources of chloride in the organism can be affected in hypertension and its relevance in CVD [10]. Non-pharmacological interventions by replacing chloride by another anion could represent a potential strategy for public health.

The mechanisms identified in these studies would permit to bring new evidence involved in this complex interaction between metabolic disorders and CVD as well as the future development of therapeutics that allow to reduce the residual risk in cardiometabolic patients.

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