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Editorial

Cardiac remodeling and vascular changes: Same music with a new instrument

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Raised blood pressure (BP) remains the world's leading mortality risk factor. A large part of the cardiovascular risk burden associated with elevated BP depends on the development of hypertensive heart disease, a constellation of abnormalities ultimately leading to symptomatic heart failure (HF). The potential sequence of structural changes accounting for the transition from cardiac remodeling to failure in hypertensive patients was firstly described more than 50 years ago. The underlying biological pathways that promote the natural evolution of the hypertensive heart disease, however, remain poorly characterised, although they seem to rely on the long-term BP overload, impaired autonomic function, and vascular senescence-related abnormalities.

The presence of an altered regulation of the central sympathetic nervous system (SNS) activity in hypertensive patients is a milestone discovery of the last century [1]. The paraventricular nucleus (PVN) is an important integrative site in the control of cardiovascular homeostasis and sympathetic outflow via its projections to the intermediolateral column of the spinal cord. In several experimental models of hypertension, including the spontaneously hypertensive rats (SHR), PVN inhibition dramatically reduces sympathetic vasomotor tone [2]. Thus, PVN provides a key contribution to the development and progression of hypertension in SHR, and sympathetic deactivation at this level has been considered an important therapeutic target for arresting the cardiac structural alterations related to the disease.

Salusin-β is a recently identified endogenous bioactive peptide detected in both the parvocellular and magnocellular parts of the PVN. It contributes to sympathetic activation and arginine vasopressin release, thus participating in the functional regulation of BP homeostasis [3]. Its pro-hypertensive effects are also attributed to the promotion of structural vascular changes in the periphery, as it stimulates vascular smooth muscle cell proliferation and vascular fibrosis via reactive oxygen species (ROS) generation, coupled with activation of downstream pro-inflammatory cytokines [4].

Given the overlap between the functions controlled by salusin β and the mechanisms involved in the development of the hypertension-related HF, in the present issue of this Journal, Li and colleagues [5] tested the hypothesis that increased salusin β at the level of PVN may contribute to the pathogenesis of HF in SHR-HF animals, an interesting rodent model that mimics the human condition of hypertension-related HF in older population.

The main results of this study are the demonstration that central salusin β silencing was able to ameliorate cardiac performances, and that these effects were achieved through a reduction of BP and SNS activity. They also demonstrated that the major mechanism accounting for the central activity of salusin β was the MAPK-NFκB-driven ROS generation. This study extends the authors' previous finding that silencing salusin β attenuates hypertension in SHR [6] and improves cardiac dysfunction, oxidative stress and inflammation in the diabetic cardiomyopathy [7]. The article by Li et al. provides novel insight into the role of central salusin β by showing that its overactivity is associated with increased oxidative stress and inflammatory exposure in the PVN, ultimately resulting in cardiac dysfunction due to an altered sympathetic drive.

Beyond these findings, another intriguing aspect of the present paper is the demonstration of a strict cross-talk between central and peripheral ROS detection. Indeed, following central salusin β knockdown, an attenuation of superoxide levels was detected not only in the PVN, but also in the heart and mesenteric vessels of the SHR. As a consequence of the reduced ROS production in peripheral arteries, the authors were able to document an improved endothelium-dependent relaxation of mesenteric arteries.

It is commonly accepted that the locally generated nitric oxide and vascular ROS exhibit their effects in an autocrine/paracrine manner. Such regulatory mechanisms make the vascular system an organ functionally heterogeneous, whose response may vary according to which stimulus is utilised and which vascular bed is investigated [8]. Despite these considerations, the unequivocal message given by Li et al. [5] is that a hierarchical relationship between myocardium and peripheral vasculature with central brain system occurs, leading to quiescent homeostasis. In several clinical circumstances, such as that occurring in hypertension-related HF, this equilibrium is unbalanced in favour of

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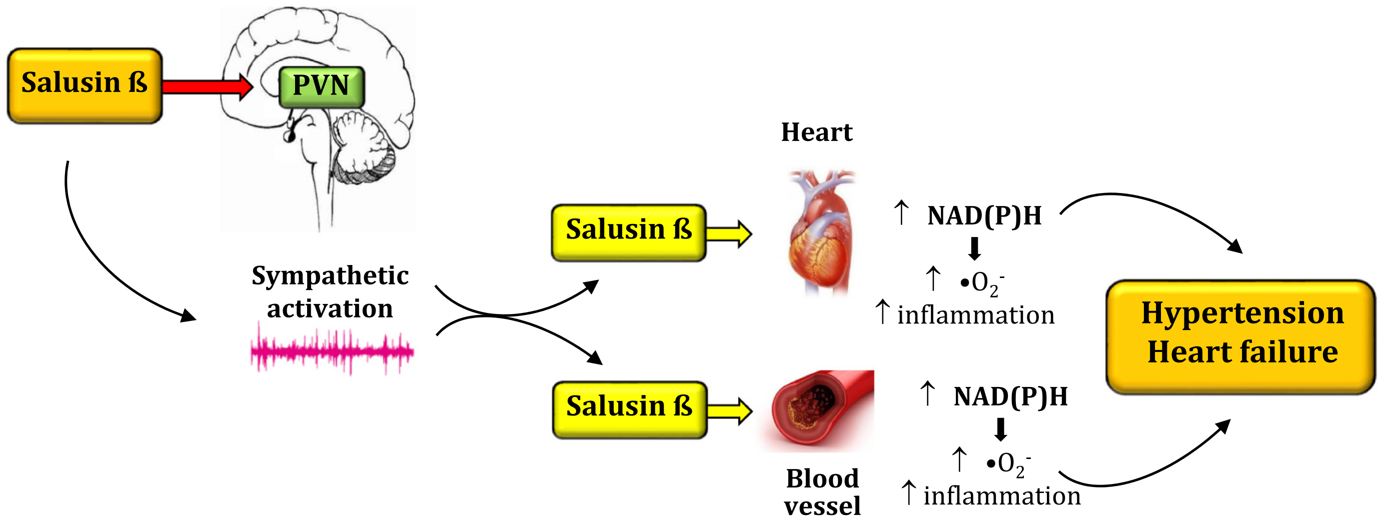

Fig. 1. Proposed mechanisms accounting for the impact of salusin β in the pathogenesis of cardiovascular disease. In this picture, hyperexpression of salusin β from paraventricular nucleus (PVN) favours a sympathetic activation, together with a stimulation of ROS generation and low-grade inflammation via NADPH oxidase activation, at the level of the heart and peripheral vasculature, finally promoting the hypertensive-related heart failure.

ROS-driven pro-remodeling and pro-atherosclerotic stimuli (Fig. 1). The finding that central knockdown of salusin β significantly decreased levels of oxidative stress also in myocardial and vascular tissues suggests that the hyperactivity of the SNS related to hyperexpression of PVN salusin β might account, at least in part, for the increased levels of peripheral oxidative stress. Increased vascular wall oxidative stress due to hyperproduction of ROS from different intracellular sources and/or reduced activity of antioxidant defences is considered a key mechanism leading to the age-dependent increase in the inflammatory exposure, alteration of the endothelial function and vascular remodeling. Importantly, the study by Li et al. documents a potential new mechanism regulating vascular levels of oxidative stress in ageing, which is a hyperexpression of salusin β. Remarkably, this central alteration will involve not only the vascular structure but also, more generally, all peripheral tissues influenced by the activity of the SNS, including the myocardium.

Thus, the development of an assay enabling the determination of salusin β in the peripheral circulation (not available at present) could provide a useful tool to monitor the age-related dysregulation of the sympathetic activity and its clinical manifestations.

The study by Li et al. might also have important implications for future research, given the demonstration of a selective control of the p38MAPK, ERK1/2, JNK and NFκB pathways by salusin β. Indeed, experimental studies have documented a potential role of ERK1/2, JNK1/2 and p38α MAPK in the cardiac remodeling which follows myocardial infarction [9]. Furthermore, animal experiments have suggested that ERK1/2, JNK1/2 and p38α MAPK are involved in the neointima formation and smooth muscle cell proliferation after vascular injury [10]. This evidence should stimulate research in exploring the potential role of the hyperexpression of salusin β also in these cardiovascular conditions. What is more, because a hyperexpression of MAPKs and NFκB and their downstream targets are commonly detected during physiological ageing and are essential signalling modules that convert environmental inputs into a plethora of cellular programmes, their control by salusin β might be relevant also to other diseases, including the ageing process. Thus, if the role of salusin β in controlling these important pathways will be extended to other "age-related" diseases, the results of the present study might represent the first to identify salusin β as a new important instrument playing in the complex symphony biological ageing.

Conflict of interest

None.

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