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# Can the calcium-regulating hormones counteract the detrimental impact of pro-inflammatory damage-associated molecular patterns in the development of heart failure?

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## ABSTRACT

Growing evidence suggests an important role of the inflammatory component in heart failure (HF). Recent developments in this field indicate an ambiguous role that innate immunity plays in immune-driven HF. Damaged or stressed cells, cardiomyocytes, in particular, emit damage-associated molecular patterns (DAMPs) including HMGB1, S100 A8/A9, HSP70, and other molecules, unfolding paracrine mechanisms that induce an innate immune response. Designed as an adaptive, regenerative reaction, innate immunity may nevertheless become overactivated and thus contribute to the development of HF by altering the pacemaker rhythm, contraction, and electromechanical coupling, presumably by impairing the calcium homeostasis. The current review will explore a hypothesis of the involvement of the calcium-regulating hormones such as parathyroid hormone and parathyroid hormone-related protein in counteracting the detrimental impact of the excess of DAMPs and therefore improving the functional cardiac characteristics especially in the acute phase of the disease.

## HEART FAILURE AND INNATE IMMUNITY

Various cardiovascular pathologies often culminate in the complex condition, a heart failure (HF). HF is often associated with a variety of comorbid conditions. Common for such comorbidities is systemic inflammation, most frequently associated with oxidative stress and endothelial dysfunction.<sup>1</sup>

The broad range of cardiovascular disorders concluding in HF differs strongly in the timing and the extent of the immune activation. Thus, the ischemic injury, hypertension, and a variety of metabolic syndromes, as well as congenital cardiomyopathies, valve dysfunctions, and aortic stenosis are characterized by the secondary response of the immune system, whereas myocarditis of different origin, autoimmune and infectious (viral and bacterial) trigger primary activation of the innate and adaptive

immune systems.<sup>2</sup> The specific characteristics of the immune response in HF caused by different etiological triggers are widely discussed in the literature and presented in several excellent reviews.<sup>3–5</sup>

Until recently, it was considered that the heart muscle, being a highly differentiated tissue, has a limited capacity for regeneration. However, it is shown that tissue injury can result in the activation of the immune, regenerative processes in the myocardium. Starting as an adaptive reaction aimed at repairing the damaged tissue, inflammatory processes may, however, under certain circumstances convert into a chronic process contributing to the development of heart failure.

If, at the first, acute phase of the injury, the immune (primarily innate) response aiming at the tissue repair is mediated by mostly resident and infiltrating immune cells, later in the chronic phase of the disease the alarm signals released by the stressed or damaged cells initiate the second wave of the innate immune response.<sup>4</sup>

The heart tissues express all of the essential components of the signal transduction system responsible for the innate immunity in the heart tissue. They can be activated by both the exogenous and endogenous alarm signals, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs). Whereas PAMPs have exogenous, that is, bacterial or viral, origin (such as components of the bacterial wall, lipopolysaccharides (LPS)), DAMPs are endogenous molecules, most of which have important, non-immune-related intracellular functions. The key members of this group are the high mobility group box 1 (HMGB1), a ubiquitous structural component of the chromatin complex with multiple regulatory functions, molecular chaperone HSP70, cytokine S100 A8/A9, and others.<sup>6,7</sup>

The release of these molecules from the damaged cells into the extracellular space/circulation activates the defense apparatus of



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the innate immunity in a variety of tissues in a paracrine or endocrine fashion. Mechanistically, it occurs via the interaction of DAMPs with a group of pattern recognition receptors (PRRs), of which the most common is a family of toll-like receptors (TLR) with the TLR4 as a key member, and also the receptor for advanced glycation end products (RAGE).<sup>8,9</sup>

A growing body of evidence suggests the functional importance of these molecules for the development of chronic inflammation in HF. Activation of PRRs by HMGB1 and other DAMPs on the acute phase of heart tissue injury was found to have mostly beneficial, cytoprotective impact (reviewed in Mann<sup>10</sup>). For instance, the acute administration of HMGB1 into the peri-infarction zone (rodent model) mediates the regeneration of the tissue inducing proliferation and differentiation of cardiomyocytes.<sup>11</sup> Similarly, overexpression of HMGB1 in transgenic mice reduced necrosis and overall infarct size after myocardial infarction.<sup>12</sup>

At the same time, prolonged effects of DAMPs are more negative.<sup>13</sup> Indirect evidence of that is the substantially reduced HMGB1 levels on the recovery of blood supply to the ischemic cardiomyocytes whereas the inhibition of HMGB1 release substantially dampens the intensity of the immune response.<sup>13</sup> In patients with HF, the increased HMGB1 levels were found associated with the disease severity.<sup>14–18</sup> The increased serum levels of HMGB1 in sepsis results in a negative inotropic effect.<sup>19</sup>

This has also been shown on many animal models of cardiac diseases. Thus, inhibition of HMGB1 accelerates cardiomyocyte re-modeling in the rat model of induced ischemic injury.<sup>20</sup> Administration of the heranilheranilacetone, a specific HMGB1 inhibitor, leads to the reduction of the infarction zone and decrease of lactate dehydrogenase and creatine kinase levels in the myocardium.<sup>21</sup> Treatment of wild-type mice with recombinant HMGB1 increased the infarct size murine model of I/R injury.<sup>22</sup>

## DAMPs AND CALCIUM REGULATION IN THE MYOCARDIUM

The molecular mechanisms of HMGB1 effects are very complex, depending on the redox state of HMGB1, the receptors it interacts with, and, most importantly, the effector tissue. However, it is widely accepted that in most of the tissues including myocardium, the HMGB1-triggered signal transduction pathway commences with the interaction with PRRs with the following activation of NF- $\kappa$ B nuclear receptor.<sup>23</sup> The latter transactivates promoters of several genes, in particular the pro-inflammatory cytokines and chemokines.

However, in addition to the pro-inflammatory effects of HMGB1, it appears that in the heart muscle HMGB1 can also interfere with the vital contractile function of cardiomyocytes, which is dependent primarily on the tightly regulated calcium homeostasis.

Calcium currents are of paramount importance for the formation of the action potential in the cardiac pacemaker myocytes, for the plateau phase of the action potential, and eventually for the cardiac excitation–contraction coupling.<sup>24–26</sup> Therefore, the impairments of calcium homeostasis may induce or aggravate the development of

cardiac pathology.<sup>27</sup> Hypocalcemia, for instance, might underlie the etiology of cardiomyopathies and HF whereas hypercalcemia results in calcification of the cardiac valves, vessels causing myocardium fibrosis.<sup>28–30</sup>

It appears that DAMPs might interfere with the calcium homeostasis in the cardiac muscle. Thus, ligand-mediated activation of a group of toll-like receptors in murine whole heart and cardiomyocytes in parallel with the inflammatory response (expression of IL6, various chemokines) was also associated with the decreased cardiomyocyte contractility.<sup>31</sup>

In vitro treatment of isolated feline cardiac myocytes with HMGB1 resulted in a 70% decrease of sarcomere shortening and a 50% decrease in the height of the peak Ca<sup>2+</sup> transient. It was concluded that HMGB1 negative inotropic effects are caused by decreasing calcium availability in cardiac myocytes via the modulation of the membrane calcium influx.<sup>32</sup>

It was also demonstrated that HMGB1 increases the frequency of Ca<sup>2+</sup> sparks, reduces the sarcoplasmic reticulum (SR) Ca<sup>2+</sup> content, and decreases the amplitude of systolic Ca<sup>2+</sup> transient and myocyte contractility (negative inotropic effect) in a dose-dependent manner in adult rat ventricular myocytes.<sup>33</sup> The authors suggest that these effects are connected with the previously demonstrated HMGB1/TLR4-dependent activation of NAD(P)H oxidase and increased reactive oxygen species (ROS) production with the redox modification of the cardiac ryanodine receptor (RyR2). The latter is known to play an essential role in cardiac excitation–contraction coupling by gating Ca<sup>2+</sup> release from the SR. Moreover, oxidative stress has also been shown to activate Ca<sup>2+</sup>/calmodulin-dependent protein kinase II by oxidizing the enzyme and consequently increasing the RyR activity. Overall, the authors conclude that such ROS-dependent HMGB1 effects on calcium leakage and consequently on contractility may contribute to various pathologies leading to HF.<sup>33</sup>

HMGB1 can also be upregulated in rat cardiac myocytes on LPS administration, with the ensuing decrease in cardiac function. The HMGB1 specificity of this effect was corroborated by the perfusion with recombinant HMGB1 with the resulting negative inotropic effect on the left ventricle.<sup>34</sup>

Interestingly, the incubation of yet another DAMP, HSP70, with the primary mouse cardiomyocytes also leads to the decrease of contractility; however, authors connect this with NF- $\kappa$ B-mediated upregulation of pro-inflammatory mediators and hence with the cardiomyocyte inflammation rather than with altered calcium homeostasis.<sup>3</sup>

## CALCIUM-REGULATING FACTORS AND CARDIOVASCULAR DISEASES

What are the main factors regulating calcium homeostasis and are they potentially involved in the innate immunity-mediated calcium disturbances?

The blood levels of calcium are regulated predominantly by the calcium-regulating hormonal system that includes parathyroid hormone (PTH), parathyroid hormone-related protein (PTHrP), vitamin D, and calcitonin. The main target organs for all these hormones/vitamins are the kidney, bone marrow, and gastrointestinal tract. PTH, PTHrP, and vitamin D stimulate an increase in blood calcium levels, whereas calcitonin has the opposite effect.<sup>35</sup>

Due to their important role in calcium homeostasis, the mechanisms of action of calcium-regulating hormones were studied mostly in application to bone physiology. However, the PTH/PTHrP effects are also documented for several other organs and tissues including the heart.

PTH, as well as PTHrP, are considered as mostly cardioprotective as they facilitate an increase in heart rate, positive inotropic and chronotropic effects, and coronary vasodilation.<sup>36–41</sup> Interestingly, our unpublished data demonstrate increased levels of circulating PTH in patients with cardiomyopathies, and this shift correlated with the elevated levels of HMGB1.

Although the PTH-mediated changes in the blood calcium levels may indirectly affect the cardiac conduction, growing evidence indicates also a direct PTH/PTHrP impact on cardiomyocytes (Palmeri and Walker<sup>42</sup> and references therein). This is supported by the discovery of the PTH/PTHrP receptor, PTH1R, expression in cardiomyocytes. Thus, mRNA of PTH1R was detected in the mouse heart tissue and also in the human ventricular myocytes, which appeared to be elevated after the ischemic injury.<sup>43 44</sup>

Positive inotropic effects of PTH in cardiomyocytes are mediated by PTH1R and associated G-proteins with subsequent activation of L-type calcium channels that increases the intracellular calcium.<sup>45–47</sup> Chronotropic effects were shown to be dependent on the activation of adenylate cyclase and downstream cAMP signaling that increases the  $I_f$  pacemaker currents, specifically in the sinoatrial node of the heart.<sup>48 49</sup>

Summarizing the calcium-regulating properties of the PTH/PTHrP system and calcium dysregulation accompanied with overactivation of the elements of the innate immune system in the course of many cardiac disorders, it can be hypothesized that the presumed cardioprotective features of calcium-regulating hormones might play an important role in the recovery of heart muscle function.

## CALCIUM-REGULATING HORMONES AND OVERACTIVATED INNATE IMMUNE RESPONSE IN HEART

Among various calcium-regulating factors, PTHrP appears to be the most interesting candidate molecule. Unlike PTH, PTHrP is not secreted by the parathyroid gland; however, it is expressed and secreted in/from many different cell types under physiological as well as pathological conditions and is believed to act in a mostly paracrine or autocrine manner.<sup>50</sup> Although the physiological function of PTHrP is not fully understood, the primary molecular mechanisms of its action resemble, at least in part, the PTH, as both hormones are activating ligands of PTH1R,<sup>51</sup> a G-protein coupled receptor that can activate both adenylyl cyclase and phospholipase C with the initiation of the signal transduction pathways culminating in the expression of various target genes.<sup>52</sup> PTHrP-mediated activation of phospholipase C results in the formation of inositol 1,4,5-trisphosphate (IP3) that initiates the release of calcium from the endoplasmic reticulum.

PTHrP is the only calcium-regulating hormone expressed in the heart tissues. PTHrP protein was detected in both developing and adult human hearts.<sup>53 54</sup> More specifically, the expression was found in the endothelial cells and the

atrial myocytes.<sup>55</sup> However, it was also detected in the ventricular cardiomyocytes.<sup>56</sup>

Functionally, PTHrP was suggested to act as a mechanosensitive regulatory molecule that participates in the control of vascular tone (and thus blood pressure), chronotropy, and inotropy, leading to the concept of PTHrP as an endocrine cardioprotective “conditioning mimetic”.<sup>50 57</sup>

Indeed, its expression was shown to be induced under ischemic injury<sup>56</sup> and congestive heart failure,<sup>54</sup> and the contractile function of stunned myocardium in rats and pigs was improved on administration of recombinant PTHrP.<sup>58</sup> Similarly, PTHrP improved the contractile responsiveness of the adult rat cardiomyocytes.<sup>59</sup>

As it was shown previously, the inflammatory component of many cardiac disorders is, at least in part, responsible for dysregulation of calcium homeostasis, which makes it tempting to speculate that the adaptive acute response might include the induction of the PTHrP to restore the contractile function of cardiomyocytes.

What is the evidence supporting this hypothesis? The immune system activation as driven by the LPS was shown to induce mRNA of PTHrP in different organs, including the heart, after the increased local expression of pro-inflammatory cytokines, TNF- $\alpha$ , and IL-1 $\beta$ . It was suggested that the local paracrine or autocrine actions of these cytokines may be responsible for the inducible PTHrP expression during the host response.<sup>60</sup>

Another example of the cytokine-induced PTHrP overexpression was demonstrated in the mouse mesangial cells. It was suggested that PTHrP may act as a survival factor via the negative feedback loop mechanism that includes the upregulation of cyclooxygenase-2.<sup>61</sup> Moreover, PTHrP gene expression can be activated by NF- $\kappa$ B, which is a main nuclear receptor orchestrating various downstream effects of DAMPs. Thus, it was shown that one of the two distinct PTHrP gene promoters, P2, contains NF- $\kappa$ B binding sites. Chromatin immunoprecipitation assays confirmed the *in vivo* binding of p50 and c-Rel subunits of NF- $\kappa$ B to the P2 promoter whereas the gene reporter approach demonstrated the NF- $\kappa$ B-driven upregulation of the P2 promoter of PTHrP.<sup>62</sup>

A common motif in such signal transduction pathways culminating in the transcriptional gene activation/repression is a strictly limited temporal window, which is usually regulated by the negative feedback loops.<sup>63</sup> This is an evolutionarily conserved mechanism that prevents overaccumulation of the target gene products that can often have a detrimental impact on the normal cell physiology. Immune-mediated upregulation of PTHrP expression in the heart appears to follow such temporal pattern, for instance, PTHrP mRNA levels peak 1–2 hours after the endotoxin injection with a subsequent return to the baseline levels.<sup>60</sup> Moreover, the intracellular downstream effects of PTHrP are similarly short-lived.<sup>50</sup>

All of these data speak in favor of the hypothesis that one of the consequences of the innate immunity overactivation in cardiac pathologies can be the induction of PTHrP expression triggering a spectrum of intracellular effects that would limit the detrimental impact of various immunomodulators such as PAMPs and DAMPs on the calcium homeostasis and therefore restore the contractile properties of cardiomyocytes. It can be also suggested that due

to the specific temporal pattern of the PTHrP-initiated signaling cascade, such cardioprotective effects might play an important role in the early (acute) stages of immune-driven cardiac pathologies. Given the sheer wealth of data supporting this hypothesis, it certainly merits further rigorous studies that could aid in the development of novel therapeutical approaches using the calcium-regulating factors for the prophylaxis and/or therapy of the immune-driven complications of heart failure.

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