Cardiac Natriuretic Peptides, Their Receptors and Metabolism

Subjects: Cardiac & Cardiovascular Systems

Contributor: Riccardo Sarzani, Massimiliano Allevi, Chiara Di Pentima, Paola Schiavi, Francesco Spannella, Federico Giulietti

Cardiac natriuretic peptides (NPs), atrial NP (ANP) and B-type NP (BNP) are true hormones produced and released by cardiomyocytes, exerting several systemic effects. Together with C-type NP (CNP), mainly expressed by endothelial cells, they also exert several paracrine and autocrine activities on the heart itself, contributing to cardiovascular (CV) health. NPs prevent cardiac hypertrophy, fibrosis, arrhythmias and cardiomyopathies, counteracting the development and progression of heart failure (HF). Moreover, some studies revealed that a protein structurally similar to NPs mainly produced by skeletal muscles and osteoblasts called musclin/osteocrin is able to interact with the NPs clearance receptor, attenuating cardiac dysfunction and myocardial fibrosis and promoting heart protection during pathological overload.

Keywords: natriuretic peptides ; ANP ; BNP ; CNP ; osteocrin ; musclin

1. Introduction

Diseases of the heart and cardiovascular (CV) system are the main cause of disability and death worldwide. Several CV risk factors and conditions, such as hypertension, dyslipidemia, obesity and insulin resistance, lead to multiple organ damage. Together with the involvement of the small and large arterial vessels, these risk factors and conditions affect the heart through increased heart afterload, perivascular myocardial fibrosis, left ventricular remodeling and hypertrophy (LVH), myocardial ischemia and necrosis, leading to heart failure (HF) [1][2]. How can the heart defend itself from these common causative factors of myocardial damage?

In recent decades, evidence from multiple research groups has emphasized the crucial protective role of the natriuretic peptides (NPs) expressed by the heart [3][4][5][6][7][8]. Atrial NP (ANP) and brain (or B-type) NP (BNP) are true hormones produced and released by cardiomyocytes, exerting systemic effects that range from blood pressure (BP) regulation to both glucose and lipid metabolism, with a wide spectrum of cardio-metabolic properties, including vasodilation, natriuresis and inhibition of the renin–angiotensin–aldosterone system (RAAS), as well as lipid mobilization and oxidation, adipocyte browning and improved insulin sensitivity [9][10][11]. On the other hand, they also act locally on the heart, exerting both paracrine and autocrine activities, mainly preventing hypertrophy, fibrosis, arrhythmias and cardiomyopathies, counteracting the development and progression of HF [8][12][13][14].

2. Cardiac Natriuretic Peptides, Their Receptors and Metabolism: A Long History Made Short

Cardiac NPs are synthesized as precursor proteins (inactive preprohormones), undergo intracellular modification to prohormones (pro-ANP and pro-BNP) and are subsequently cleaved in their active forms [15][16]. Pro-ANP is mainly expressed by atrial tissue under physiological conditions. Pro-ANP is stored in secretory granules, mainly of cardiomyocytes, and cleaved into the 28 amino acid biologically active hormone (ANP) and the 98 amino acid N-terminal fragment (NT-proANP) by corin, a transmembrane serine protease, whose loss of function leads to a disease phenotype characterized by high BP with reduced ANP activity, in addition to contributing to the pathogenesis of HF [17][18]. Pro-BNP is synthesized mainly by ventricular myocytes; instead of being stored, it is produced and secreted in bursts. Whereas activation of pro-ANP occurs on the cell surface during secretion, pro-BNP is cleaved into the 32 amino acid active hormone (BNP) and the 76 amino acid N-terminal fragment (NT-proBNP) inside the cells by furin, an intracellular serine endopeptidase, and secreted in cleaved forms [19][20]. The expression and release of both ANP and BNP occurs in response to wall hemodynamic stress resulting from increased extracellular volume and cardiac transmural pressure in a context of augmented cardiac mechanical stress, such as in HF or myocardial ischemia [21]. Moreover, ANP is also released in response to elevated concentrations of sodium [22].

In addition to cardiac NPs (ANP and BNP), a third actor exists, the C-type natriuretic peptide (CNP), which has no natriuretic properties and is mostly produced by vascular cells [23]. There are three subtypes of NPs receptors: NP receptor A (NPR-A), also called GC-A; NP receptor B (NPR-B), also called GC-B; and NP receptor C (NPR-C). Both NPR-A and NPR-B are transmembrane receptors with guanylyl cyclase (GC) activity; NPR-A is the principal receptor for ANP and BNP, whereas NPR-B has high affinity for CNP [24]. Binding of ANP and BNP to NPR-A induces intracellular generation of the second messenger cyclic guanosine monophosphate (cGMP) which, in its downstream cascade, activates multiple targets, including cGMP-dependent protein kinases (PKGs), cGMP-gated ion channels and cGMP-regulated cyclic nucleotide phosphodiesterases. These mediators account most of the biological effects of NPs [7]. NPR-A is widely expressed in many tissues, especially in the vasculature, heart, adipose tissue, kidneys, lungs, adrenal glands, brain and liver [25][26], whereas NPR-B is expressed mostly in bone and fibroblasts [7]. The third receptor, NPR-C, exhibits no GC activity, resulting mainly a clearance receptor for cardiac NPs by incorporating them into cells for subsequent lysosomal breakdown [27]. NPR-C is also able to couple with inhibitory G proteins (Gi), causing inhibition of adenylyl cyclase and activation of phospholipase-C, providing some direct signaling functions that might contribute to effects in cardiac tissue [28][29]. NPR-C is highly expressed in endothelial cells [30], in addition to adipose tissue and kidneys, and binds all NPs, although the binding affinity is higher for ANP and CNP than for BNP, resulting in a longer plasma half-life of BNP compared to ANP [31]. Cardiac NPs are also silenced as a result of enzymatic degradation by neprilysin (NEP), a ubiquitous zinc-dependent membrane metalloendopeptidase that is expressed mainly in smooth muscle cells, endothelial cells, cardiac myocytes, fibroblasts and kidneys [32].

In this context, musclin, also called osteocrin (OSTN) because it was originally identified as a secretory peptide from muscle and bone [33][34], has become increasingly relevant in recent years [35]. The preprocessed mature form of mouse OSTN consists of 130 amino acids. Its carboxy terminus contains tandem NP-like sequences separated by polybasic amino acids that are presumably cleaved by peptidases [36].

Therefore, musclin can be considered a member of the NPs family without the “ring”, the common feature of ANP, BNP and CNP, and is mainly produced by skeletal muscles and osteoblasts [33][34]. It was also found to be expressed in the cardiomyocytes of animal models, and it is regulated by several conditions and molecules, such as physical activity, nutritional changes and fasting, hormones (especially insulin) and adiposity [33][37][38], although no direct evidence is currently available concerning the human heart. The main recent discovery is that this peptide binds NPR-C competitively and efficaciously inhibits NPR-C-mediated NPs degradation, therefore increasing NPs levels, with a consequent reduction in blood pressure and enhanced protective activities in many tissues, including the heart [36]. In skeletal muscle, musclin improves insulin-dependent glucose metabolism and enhances physical endurance by promoting mitochondrial biogenesis through NPs-induced cGMP production as a result of NPR-C blockade [38][39]. Musclin treatment prevents the worsening of congestive HF after myocardial infarction and doxorubicin-induced cardiotoxicity [40] in animal models. Musclin, by binding NPR-C and increasing ANP and CNP concentrations, leads to a consequent reduction in heart and lung weights, as well as reduced cardiac fibrosis [36]. Moreover, a recently published study showed that skeletal-muscle-derived musclin protects the heart during pathological overload [35]. Musclin was found to attenuate cardiac dysfunction and myocardial fibrosis by augmenting the CNP/NPR-B-stimulated crosstalk of cGMP and cAMP in cardiomyocytes and by inhibiting p38 MAP kinase (MAPK) signaling through the activation of PKG in cardiac fibroblasts. Furthermore, while musclin mRNA levels in skeletal muscle were increased by physical activity, on the contrary, they are markedly downregulated in biopsies from patients suffering from HF with sarcopenia or cachexia [35]. This evidence suggests that musclin could act as a possible bridge between sarcopenia and cachexia, which are highly prevalent in advanced states of HF [41], as well as the progression of HF itself. It could represent the biological basis of the vicious circle between reduced physical activity, reduced muscle mass and HF in older patients. Overall, these important recent findings highlight the critical role of NPR-C and its interaction with musclin in reducing the protecting activities of NPs in HF patients, suggesting possible new clinical therapeutic targets for this condition.

References

1. Kokubo, Y.; Matsumoto, C. Hypertension Is a Risk Factor for Several Types of Heart Disease: Review of Prospective St udies. Adv. Exp. Med. Biol. 2017, 956, 419–426.
2. Gjesdal, O.; Bluemke, D.A.; Lima, J.A. Cardiac remodeling at the population level—Risk factors, screening, and outco mes. Nat. Rev. Cardiol. 2011, 8, 673–685.
3. Nishikimi, T.; Maeda, N.; Matsuoka, H. The role of natriuretic peptides in cardioprotection. Cardiovasc. Res. 2006, 69, 3 18–328.

4. Cannone, V.; Cabassi, A.; Volpi, R.; Burnett, J.C. Atrial Natriuretic Peptide: A Molecular Target of Novel Therapeutic App roaches to Cardio-Metabolic Disease. Int. J. Mol. Sci. 2019, 20, 3265.
5. Forte, M.; Madonna, M.; Schiavon, S.; Valenti, V.; Versaci, F.; Zoccai, G.B.; Frati, G.; Sciarretta, S. Cardiovascular Pleio tropic Effects of Natriuretic Peptides. Int. J. Mol. Sci. 2019, 20, 3874.
6. Nakagawa, H.; Saito, Y. Roles of Natriuretic Peptides and the Significance of Neprilysin in Cardiovascular Diseases. Bi ology 2022, 11, 1017.
7. Goetze, J.P.; Bruneau, B.G.; Ramos, H.R.; Ogawa, T.; de Bold, M.K.; de Bold, A.J. Cardiac natriuretic peptides. Nat. Re v. Cardiol. 2020, 17, 698–717.
8. Volpe, M.; Rubattu, S.; Burnett, J.J. Natriuretic peptides in cardiovascular diseases: Current use and perspectives. Eur. Heart J. 2014, 35, 419–425.
9. Sarzani, R.; Salvi, F.; Dessì-Fulgheri, P.; Rappelli, A. Renin-angiotensin system, natriuretic peptides, obesity, metabolic syndrome, and hypertension: An integrated view in humans. J. Hypertens. 2008, 26, 831–843.
10. Sarzani, R.; Spannella, F.; Giulietti, F.; Balietti, P.; Cocci, G.; Bordicchia, M. Cardiac Natriuretic Peptides, Hypertension and Cardiovascular Risk. High Blood Press. Cardiovasc. Prev. 2017, 24, 115–126.
11. Spannella, F.; Giulietti, F.; Bordicchia, M.; Burnett, J.C.J.; Sarzani, R. Association Between Cardiac Natriuretic Peptides and Lipid Profile: A Systematic Review and Meta-Analysis. Sci. Rep. 2019, 9, 19178.
12. Calvieri, C.; Rubattu, S.; Volpe, M. Molecular mechanisms underlying cardiac antihypertrophic and antifibrotic effects of natriuretic peptides. J. Mol. Med. 2012, 90, 5–13.
13. Rubattu, S.; Sciarretta, S.; Valenti, V.; Stanzione, R.; Volpe, M. Natriuretic peptides: An update on bioactivity, potential t herapeutic use, and implication in cardiovascular diseases. Am. J. Hypertens. 2008, 21, 733–741.
14. Rubattu, S.; Forte, M.; Marchitti, S.; Volpe, M. Molecular Implications of Natriuretic Peptides in the Protection from Hyp ertension and Target Organ Damage Development. Int. J. Mol. Sci. 2019, 20, 798.
15. Potter, L.R.; Yoder, A.R.; Flora, D.R.; Antos, L.K.; Dickey, D.M. Natriuretic peptides: Their structures, receptors, physiol ogic functions and therapeutic applications. In cGMP: Generators, Effectors and Therapeutic Implications; Handbook of Experimental Pharmacology; Springer: Berlin/Heidelberg, Germany, 2009; pp. 341–366.
16. Pandey, K.N. Biology of natriuretic peptides and their receptors. Peptides 2005, 26, 901–932.
17. Dries, D.L.; Victor, R.G.; Rame, J.E.; Cooper, R.S.; Wu, X.; Zhu, X.; Leonard, D.; Ho, S.-I.; Wu, Q.; Post, W.; et al. Cori n gene minor allele defined by 2 missense mutations is common in blacks and associated with high blood pressure and hypertension. Circulation 2005, 112, 2403–2410.
18. Dong, N.; Chen, S.; Yang, J.; He, L.; Liu, P.; Zheng, D.; Li, L.; Zhou, Y.; Ruan, C.; Plow, E.; et al. Plasma soluble corin i n patients with heart failure. Circ. Heart Fail. 2010, 3, 207–211.
19. Sudoh, T.; Kangawa, K.; Minamino, N.; Matsuo, H. A new natriuretic peptide in porcine brain. Nature 1988, 332, 78–81.
20. Nishikimi, T.; Nakagawa, Y.; Minamino, N.; Ikeda, M.; Tabei, K.; Fujishima, A.; Takayama, K.; Akimoto, K.; Yamada, C.; Nakao, K.; et al. Pro-B-type natriuretic peptide is cleaved intracellularly: Impact of distance between O-glycosylation an d cleavage sites. Am. J. Physiol. Regul. Integr. Comp. Physiol. 2015, 309, R639–R649.
21. Kuwahara, K.; Nakao, K. Regulation and significance of atrial and brain natriuretic peptides as cardiac hormones. Endo cr. J. 2010, 57, 555–565.
22. Ferri, C.; Bellini, C.; Coassin, S.; Baldoncini, R.; Luparini, R.L.; Perrone, A.; Santucci, A. Abnormal atrial natriuretic pepti de and renal responses to saline infusion in nonmodulating essential hypertensive patients. Circulation 1994, 90, 2859 –2869.
23. Suga, S.; Nakao, K.; Itoh, H.; Komatsu, Y.; Ogawa, Y.; Hama, N.; Imura, H. Endothelial production of C-type natriuretic peptide and its marked augmentation by transforming growth factor-beta. Possible existence of “vascular natriuretic pe ptide system”. J. Clin. Investig. 1992, 90, 1145–1149.
24. Bennett, B.D.; Bennett, G.L.; Vitangcol, R.V.; Jewett, J.R.; Burnier, J.; Henzel, W.; Lowe, D.G. Extracellular domain-IgG fusion proteins for three human natriuretic peptide receptors. Hormone pharmacology and application to solid phase sc reening of synthetic peptide antisera. J. Biol. Chem. 1991, 266, 23060–23067.
25. Sarzani, P.; Dessì-Fulgheri, P.; Paci, V.M.; Espinosa, E.; Rappelli, A. Expression of natriuretic peptide receptors in hum an adipose and other tissues. J. Endocrinol. Investig. 1996, 19, 581–585.
26. Nagase, M.; Katafuchi, T.; Hirose, S.; Fujita, T. Tissue distribution and localization of natriuretic peptide receptor subtyp es in stroke-prone spontaneously hypertensive rats. J. Hypertens. 1997, 15, 1235–1243.

27. Nussenzveig, D.R.; Lewicki, J.A.; Maack, T. Cellular mechanisms of the clearance function of type C receptors of atrial natriuretic factor. J. Biol. Chem. 1990, 265, 20952–20958.
28. Rose, R.A.; Giles, W.R. Natriuretic peptide C receptor signalling in the heart and vasculature. J. Physiol. 2008, 586, 353–366.
29. Moyes, A.J.; Hobbs, A.J. C-type Natriuretic Peptide: A Multifaceted Paracrine Regulator in the Heart and Vasculature. Int. J. Mol. Sci. 2019, 20, 2281.
30. Leitman, D.C.; Andresen, J.W.; Kuno, T.; Kamisaki, Y.; Chang, J.K.; Murad, F. Identification of multiple binding sites for atrial natriuretic factor by affinity cross-linking in cultured endothelial cells. J. Biol. Chem. 1986, 261, 11650–11655.
31. Mukoyama, M.; Nakao, K.; Hosoda, K.; Suga, S.; Saito, Y.; Ogawa, Y.; Shirakami, G.; Jougasaki, M.; Obata, K.; Yasue, H. Brain natriuretic peptide as a novel cardiac hormone in humans. Evidence for an exquisite dual natriuretic peptide system, atrial natriuretic peptide and brain natriuretic peptide. J. Clin. Investig. 1991, 87, 1402–1412.
32. Kenny, A.J.; Bourne, A.; Ingram, J. Hydrolysis of human and pig brain natriuretic peptides, urodilatin, C-type natriuretic peptide and some C-receptor ligands by endopeptidase-24.11. Biochem. J. 1993, 291 Pt 1, 83–88.
33. Nishizawa, H.; Matsuda, M.; Yamada, Y.; Kawai, K.; Suzuki, E.; Makishima, M.; Kitamura, T.; Shimomura, I. Musclin, a novel skeletal muscle-derived secretory factor. J. Biol. Chem. 2004, 279, 19391–19395.
34. Thomas, G.; Moffatt, P.; Salois, P.; Gaumond, M.-H.; Gingras, R.; Godin, E.; Miao, D.; Goltzman, D.; Lanctôt, C. Osteocrin, a novel bone-specific secreted protein that modulates the osteoblast phenotype. J. Biol. Chem. 2003, 278, 50563–50571.
35. Szaroszyk, M.; Kattih, B.; Martin-Garrido, A.; Trogisch, F.A.; Dittrich, G.M.; Grund, A.; Abouissa, A.; Derlin, K.; Meier, M.; Holler, T.; et al. Skeletal muscle derived Musclin protects the heart during pathological overload. Nat. Commun. 2022, 13, 149.
36. Miyazaki, T.; Otani, K.; Chiba, A.; Nishimura, H.; Tokudome, T.; Takano-Watanabe, H.; Matsuo, A.; Ishikawa, H.; Shimamoto, K.; Fukui, H.; et al. A New Secretory Peptide of Natriuretic Peptide Family, Osteocrin, Suppresses the Progression of Congestive Heart Failure after Myocardial Infarction. Circ. Res. 2018, 122, 742–751.
37. Chiba, A.; Watanabe-Takano, H.; Terai, K.; Fukui, H.; Miyazaki, T.; Uemura, M.; Hashimoto, H.; Hibi, M.; Fukuhara, S.; Mochizuki, N. Osteocrin, a peptide secreted from the heart and other tissues, contributes to cranial osteogenesis and chondrogenesis in zebrafish. Development 2017, 144, 334–344.
38. Subbotina, E.; Sierra, A.; Zhu, Z.; Gao, Z.; Koganti, S.R.K.; Reyes, S.; Stepniak, E.; Walsh, S.A.; Acevedo, M.R.; Perez-Terzic, C.M.; et al. Musclin is an activity-stimulated myokine that enhances physical endurance. Proc. Natl. Acad. Sci. USA 2015, 112, 16042–16047.
39. Chen, W.-J.; Liu, Y.; Sui, Y.-B.; Yang, H.-T.; Chang, J.-R.; Tang, C.-S.; Qi, Y.-F.; Zhang, J.; Yin, X.-H. Positive association between musclin and insulin resistance in obesity: Evidence of a human study and an animal experiment. Nutr. Metab. 2017, 14, 46.
40. Hu, C.; Zhang, X.; Zhang, N.; Wei, W.-Y.; Li, L.-L.; Ma, Z.-G.; Tang, Q.-Z. Osteocrin attenuates inflammation, oxidative stress, apoptosis, and cardiac dysfunction in doxorubicin-induced cardiotoxicity. Clin. Transl. Med. 2020, 10, e124.
41. Zhang, Y.; Zhang, J.; Ni, W.; Yuan, X.; Zhang, H.; Li, P.; Xu, J.; Zhao, Z. Sarcopenia in heart failure: A systematic review and meta-analysis. ESC Heart Fail. 2021, 8, 1007–1017.