HHS Public Access

Author manuscript

J Cardiovasc Pharmacol. Author manuscript; available in PMC 2024 November 01.

Published in final edited form as:

J Cardiovasc Pharmacol. ; 82(5): 347–349. doi:10.1097/FJC.0000000000001457.

The Potential Role of Visfatin in Mediating Vascular Dysfunction and Hypertension

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Visfatin/nicotinamide phosphoribosyltransferase (NAMPT) was first discovered as a cytokine named pre-B-cell colony-enhancing factor, and later rediscovered as an important enzyme in nicotinamide adenine dinucleotide generation, which has considerably widened its potential biological activities (1). While visfatin/NAMPT was originally thought to be produced exclusively by the adipose tissue (adipocytes and infiltrating macrophages), other tissues such as skeletal muscle, liver, and brain as well as cardiomyocytes and immune cells are also able to synthetize it (1). Noteworthy, both the cytokine-like (extracellular) and enzymatic (intracellular) functions seem to be responsible for its relevance in immunity, metabolism, and stress responses in both physiological and pathological conditions (1). Several studies have shown that the extracellular NAMPT (eNAMPT) participates in various cellular functions such as apoptosis, inflammation, and extracellular matrix degradation; however, there is debate regarding the underlying mechanisms for these effects, as reviewed elsewhere (1).

Growing evidence indicates that the circulating levels of visfatin are altered in cardiovascular diseases, including atherosclerosis, essential hypertension, and preeclampsia (2). Curiously, the association between visfatin levels with circulating markers of endothelial dysfunction and with systolic and diastolic blood pressure levels seems to be independent of the degree of adiposity (3, 4). However, the role of visfatin in mediating vascular dysfunction and hypertension are still controversial.

In this context, Bayram and collaborators have recently published a study aiming to investigate the effects of visfatin on vascular responses in the human left internal mammary artery, the gold standard vessel for coronary artery bypass grafting, with the possible underlying mechanisms (5). They reported that visfatin did not significantly affect

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Conflict of Interest Disclosure: The authors declare absence of any commercial or financial relationships that could be interpreted as a potential conflict of interest.

the contractile responses of internal mammary artery rings to several vasoconstrictors. However, visfatin induced relaxation of internal mammary artery rings preconstricted by phenylephrine in an endothelium-dependent manner, and this vasodilatory response was attenuated by incubation with a selective guanylate cyclase inhibitor and with a NAMPT enzymatic inhibitor FK866 (5). While we agree that these findings may have a substantial importance for new therapeutic approaches toward coronary artery disease, we would like to further discuss the results regarding the effects of visfatin on endothelium-dependent vasorelaxation. We do not agree with the authors when they interpreted that incubation of internal mammary artery rings preconstricted by phenylephrine with visfatin in the 10^{-9} and 10^{-8} M concentrations for 30 min decreased the relaxant responses to cumulatively applied concentrations of acetylcholine. Figure 6 and Table 1 in this study from Bayram et al. actually show that the control and visfatin at 10^{-10} M groups relaxed around 70% in response to acetylcholine, and the incubation with visfatin at 10^{-9} and 10^{-8} M increased acetylcholine-induced maximal relaxation to around 90% (5). These observations are in line with a prior study demonstrating a vasodilatory effect of visfatin (100 ng/mL) in noradrenaline-preconstricted aorta of male Wistar rats via endothelium-derived nitric oxide (NO) (6).

Conversely, several studies point to visfatin as a factor associated with endothelial dysfunction. Indeed, the same research group has previously performed a similar set of experiments but using small mesenteric arteries isolated from male Wistar rats instead (7). They found that visfatin incubation (at doses ranging from 1 to 100 ng/mL) reduced the relaxation responses to acetylcholine in phenylephrine-preconstricted endothelium-intact mesenteric rings, and this effect was reverted by the incubation with NAMPT enzymatic inhibitor FK866 or superoxide dismutase (7). In addition, visfatin was shown to impair endothelium-dependent vasodilation in these vessels through a reduction in NO bioavailability caused by increased formation of superoxide anions (7). Similar results were observed in bovine small coronary arteries precontracted with phenylephrine (8). Moreover, visfatin is also able to decrease endothelium-dependent vasorelaxation partially by nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase stimulation in rat (male Sprague-Dawley) and human (female) mesenteric vessels (9). Further evidence in humans (male) for the detrimental actions of visfatin in the endothelium is that obese individuals present lower quantity of endothelial progenitor cells along with higher visfatin and oxidative stress products in the circulation than controls (10). Taken together, these reports suggest that NADPH oxidase-induced release of superoxide anions may play a role in visfatin-induced impaired NO-mediated vasodilation, especially under obesity conditions.

Nonetheless, in agreement with a possible dilatory effect of visfatin on the vasculature, Zhou and colleagues have recently assessed visfatin levels in aorta of patients undergoing aortic replacement surgery due to acute aortic dissection (11). In this study, NAMPT expression was found to be reduced in the aortic tissue of patients with hypertension compared to those with normal blood pressure levels. Moreover, NAMPT male knockout mice exhibited higher blood pressure and reactive oxygen species (ROS) levels after continuous infusion of angiotensin II for 4 weeks compared to wild-type counterparts, and administration of recombinant human NAMPT prevented these effects of angiotensin II on blood pressure and ROS levels. Treatment with recombinant human NAMPT also improved angiotensin

II-induced abnormal vascular remodelling in NAMPT knockout mice, suggesting NAMPT as a potential therapeutic target for hypertension (11).

However, another recent in vivo study stands against these findings by showing that small mesenteric arteries of male C57BL/6 mice continuously infused with visfatin/eNAMPT for 7 days (100 ng/kg/day) presented reduced endothelium-dependent relaxation in noradrenaline precontracted rings (12). The co-infusion of visfatin/eNAMPT with NAMPT inhibitor FK866 or toll-like receptor (TLR)-4 blocker CLI095 attenuated this vasoconstrictor effect, supporting a role for NAMPT enzymatic activity and TLR4 activation in endothelial dysfunction induced by visfatin/eNAMPT. Furthermore, visfatin/eNAMPT-induced endothelial dysfunction was improved by the nod-like receptor protein 3 (P3)-inflammasome inhibitor MCC950 as well as by the interleukin (IL)-1-receptor antagonist anakinra, suggesting that IL-1β released by NLRP3-inflammasome may also mediate endothelial damage caused by visfatin/eNAMPT.

Interestingly, the potential interaction among eNAMPT, TLR-4, and cytokines including NLRP3 in the pathophysiology of preeclampsia has been reviewed elsewhere (13). Thus, we would like to close this commentary by discussing the potential role of visfatin on endothelial dysfunction associated to preeclampsia. Placental ischemia/hypoxia leads to the release of antiangiogenic factors into maternal circulation, including the soluble fms-like tyrosine kinase (sFLT)-1, which is an important mediator of widespread maternal endothelial dysfunction in preeclampsia by blocking the effects of vascular endothelial growth factor (VEGF) on angiogenesis and vascular health (14). Moreover, preeclampsia is characterized by decreased circulating levels of NO, which was shown to be inversely related to sFLT-1 (15). Although most studies provide evidence for increased circulating levels of visfatin in preeclampsia, there are few reports of similar or even decreased visfatin levels in preeclampsia as compared to normotensive pregnant women (16). Nevertheless, visfatin/NAMPT levels were shown to be inversely related to NO, but positively related to sFLT-1 levels in the circulation of pregnant women with preeclampsia (17). Similar relationships between visfatin/NAMPT levels with NO and soluble sFLT-1 were observed in the subgroup of patients with preeclampsia classified as nonresponsive to antihypertensive therapy, who exhibited higher levels of sFLT-1 and the worst clinical outcomes as compared to the subgroup of patients with preeclampsia classified as responsive to antihypertensive therapy (18). While these findings may suggest that visfatin/NAMPT inhibits NO formation and upregulates the production of sFLT-1 in preeclampsia, the potential contribution of visfatin/NAMPT to endothelial dysfunction in this hypertensive disorder of pregnancy needs to be confirmed by additional studies.

Other relevant variables related to experimental design that should be considered when evaluating results of vasocontractility studies is concentration of substances/drugs, as they frequently use concentrations that are different from those found/used in human diseases, and exposure time, as vessels are incubated with these substances/drugs acutely (usually 1 to 2 h), which also differs from the chronic exposure that vessels undergo during the course of chronic syndromes (months to years). Ex vivo studies are important to guide the vasoactive role of a substance, but do not exactly reflect what happens in vivo most of the time.

In conclusion, while the mechanisms underlying the possible beneficial and detrimental actions of visfatin on the vasculature are still being uncovered, visfatin definitely plays a role in inflammation and endothelial function (Figure 1). It seems that the contribution of visfatin to the development or attenuation of pathological processes implicated in coronary artery disease and hypertension depend on its concentration (low versus high), exposure time (acute versus chronic), and the vascular bed (resistant versus complaint, healthy versus sick) being examined; however, these questions still need to be addressed by further studies.

Declaration of Funding Source:

This work was supported by the National Council for Scientific and Technological Development (CNPq/Brazil; grants 312599/2019-6 and 302076/2022-0], Minas Gerais Research Foundation (FAPEMIG/Brazil; grant APQ-01960-18], and The National Institutes of Health (NIH/USA; grants K01HL159032, R01HL148191, and U54GM115428).

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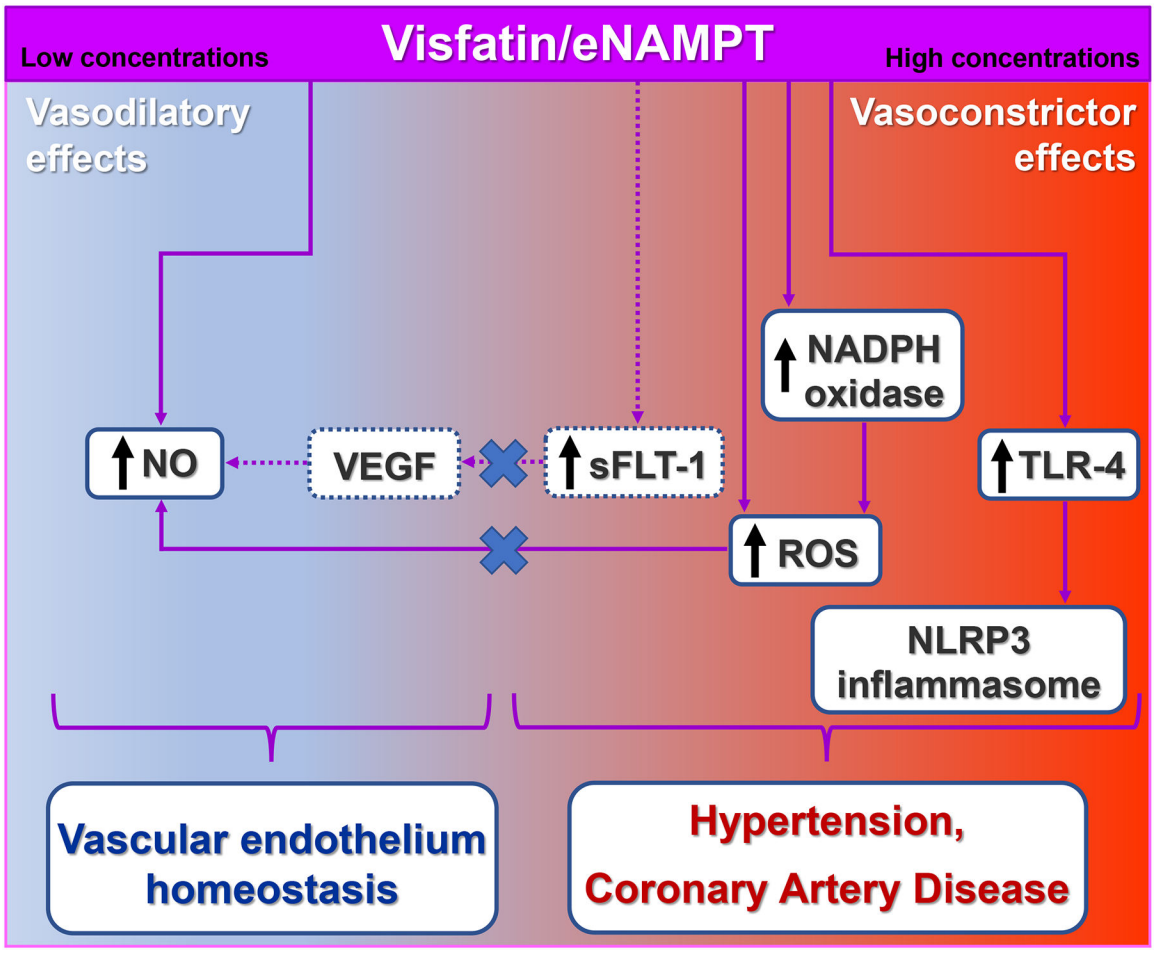

Figure 1.

Vascular mechanisms underlying the effects of visfatin/extracellular NAMPT (eNAMPT) on endothelium in normal vascular homeostasis (blue shaded area), and the potential detrimental actions of visfatin/eNAMPT on vascular function (red shaded area), such as stimulation of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase (9), exaggerated reactive oxygen species (ROS) levels (11), reduction in nitric oxide (NO) bioavailability caused by oxidative stress (7), and activation of toll-like receptor (TLR)-4 with downstream formation of nod-like receptor protein 3 (NLRP3)-inflammasome (12). These visfatin/eNAMPT-stimulated mechanisms may contribute to amelioration or development of pathological processes implicated in coronary artery disease and hypertension. Dotted arrows were used to illustrate the potential visfatin/eNAMPT stimulation of soluble fms-like tyrosine kinase (sFLT)-1 synthesis, with subsequent reductions in vascular endothelial growth factor (VEGF) and NO levels; however, this pathway of visfatin/eNAMPT on mediating vascular dysfunction and hypertension during pregnancy needs to be confirmed by further studies.