Review Article

Cortistatin, a novel cardiovascular protective peptide

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Abstract: Cortistatin (CST) is a small molecule bioactive peptide containing an FWKT tetramer. It is widely distributed in nervous, immune and endocrine systems. Many studies have shown that CST can exert many biological effects, for example: regulating sleep, learning and memory processes, inducing immune tolerance, inhibiting inflammatory responses, and regulating endocrine metabolism. Notably, it is found that CST and its receptors are also widely distributed in the cardiovascular system, such as the aorta, coronary arteries and heart. In recent years, increasing studies have shown that CST played an important role in the development of cardiovascular diseases, such as reducing myocardial damage, inhibiting autoimmune myocarditis, alleviating vascular smooth muscle cell (VSMC) proliferation and migration, reducing vascular calcification (VC), and inhibiting atherosclerosis and aneurysm formation. Therefore, we reviewed the cardiovascular effects of CST in the heart and blood vessels, which will help to understand the role of CST and its receptors in the pathogenesis of cardiovascular diseases, and highlight novel strategies and targets for the prevention and treatment of cardiovascular diseases.

Keywords: Cortistatin (CST); heart; blood vessels; receptors; bioactive peptide

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Introduction

Cardiovascular disease is an important and urgent public health problem worldwide, leading to kinds of comorbidities and even mortality. The prevalence and mortality of cardiovascular diseases intend to decrease in Europe and the United States, but is still rising in China. In recent years, epidemiological data shows that cardiovascular disease is the leading cause of disease death in China, even higher than tumors and other diseases. Cardiovascular mortality varies between urban and rural areas, for example: 44.8% in rural areas and 41.9% in urban areas (1). Therefore, it is imperative to investigate the pathogenesis of cardiovascular disease and to identify the targets for prevention and treatment of cardiovascular disease, and further research is needed.

In recent years, bioactive peptides attracted increasing attention in preventing and treating cardiovascular diseases. Cortistatin (CST) is a novel small molecule bioactive peptide containing an FWKT (Phe-Trp-Lys-Thr) tetramer (2). It was once thought that CST was only expressed in the brain (cortex and hippocampus, etc.). However, as the research progressed, CST was found to be widely expressed in the nervous system, endocrine system and immune system (3). In recent years, CST was also found in the cardiovascular system, such as the aorta, coronary arteries and heart (4-6). CST contains an FWKT tetramer that is highly homologous to somatostatin (SST). Thus, CST could activate SST receptors (SSTRs) to exert similar biological effects as SST. Besides, CST can also activate growth hormone secretagogue receptor 1a (GHSR1a) and the Mas-related gene X-2 receptor (MrgX2) (7,8), with

different biological effect from SST. CST is becoming a new cardiovascular protective endogenous peptide due to its role in the pathophysiology of the heart and blood vessels. Therefore, we reviewed the recent advances of CST in the heart and blood vessels.

CST and heart

CST and ischemic myocardial injury

In 1999, Rauca *et al*. found that intraventricular administration of 10.0 mmol CST significantly reduced cerebral infarct size in rats with cerebral infarction caused by middle cerebral artery occlusion when compared with saline (9). Further studies found that the effect of CST on cerebral ischemic injury may be mediated by SSTR2 (10). Mastrodimou and his colleagues showed that CST could attenuate the retinal damage induced by chemical ischemia in a concentration-dependent manner (11). Similarly, CST also performed myocardial protection in a rat model of myocardial infarction caused by ligation of the left anterior descending artery. In the Wistar rat myocardial infarction model induced by left anterior descending ligation, CST was suggested to reduce acute myocardial infarction (AMI) area and improve cardiac function (12), as CST significantly increased left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS), decreased myocardial infarct size and serum level of cardiac troponin I (cTnI), when compared with the AMI group. Cardiomyocyte apoptosis plays an important role in myocardial infarction and the deterioration of cardiac function after myocardial infarction (13). Our study also found that CST significantly suppressed cardiomyocyte apoptosis in rat myocardial infarction model induced by left anterior descending ligation, as shown by a decrease in apoptotic bodies and vacuolar degeneration under electron microscopy, a decrease in the number of TUNEL-positive nuclear staining, a down-regulation of pro-apoptotic protein Bax, and an up-regulation of anti-apoptotic protein Bcl-2 (12). Our further study found that this protective effect of CST might be related to its inhibition of endoplasmic reticulum stress (12), but its specific molecular regulatory mechanisms and possible receptor signaling pathways remained to be elucidated.

CST and septic myocardial injury

Sepsis is referred as a dysregulated host response to infection, which can lead to multiple organ dysfunction, accounting for more than 10% of the in-hospital mortality (14). The reason of septic shock involves serious infection complications related to dysregulation and high inflammation reactivity. In 2006, Gonzalez-Rey *et al.* found that CST could alleviate the pathological damage associated with septic shock in rodents and inhibit the expression of systemic and local inflammatory mediators, including cytokines, chemokines and acute phase proteins (15). Myocardial injury and dysfunction are common clinical manifestations of sepsis and septic shock, occurring in nearly 40–50% of patients (16). However, it is unclear what role CST plays in myocardial damage caused by septic shock. To investigate the effects of CST during sepsis, our team used a sepsis rat model induced by cecal ligation and puncture and found that CST could not only improve cardiac function and reduce cardiomyocyte apoptosis, but also significantly down-regulate the expression of glucose-regulated protein 94 (GRP94), caspase-12, and CCAAT/enhancer-binding proteins homologous protein (CHOP). Therefore, we speculate that inhibiting endoplasmic reticulum stress by CST may play an important role in protecting myocardium. We further used dithiothreitol (DDT) and lipopolysaccharide (LPS)-induced cardiomyocyte model and confirmed that CST could inhibit endoplasmic reticulum and reduce cardiomyocyte apoptosis, which can be reversed by GHSR1a receptor blockers (17). Since sepsis involves excessive production of inflammatory cytokines, and the NLRP3 inflammasome/interleukin 1β (IL-1β) signaling pathway plays a key role in cytokine secretion during sepsis (18), our team further examined whether CST reduced myocardial damage and myocardial fibrosis via NLRP3 inflammasome/caspase-1/IL-1β pathway. We observed that that CST could inhibit NLRP3 and caspase-1 activity, thereby reducing IL-1β secretion and ultimately myocardial damage (6). A recent clinical observation indicated CST was found to be elevated in plasma of patients with sepsis, indicating a possible marker of diagnosing sepsis. However, it still has a long way to go from the experimental and the clinical observational study of prevention and treatment of septic shock and its related myocardial injury to a tool of clinical treatment and diagnosis (19).

CST and experimental autoimmune myocarditis (EAM)

Since CST and its receptors (SSTR1-5 and GHSR1a) are widely distributed in the immune system, such as monocytes, macrophages, T lymphocytes (T cells),

etc., CST is showed to play a protective role in sepsis, arthritis, inflammatory bowel disease and autoimmune encephalomyelitis, through inhibiting the secretion of inflammatory factors and chemokines, T cell proliferation and T helper cell 1 (Th1) response (20,21). CST is considered as a key factor in the bidirectional communication between neuroendocrine and immune systems, which plays a pivotal role in immune regulation (22). Myocarditis is an autoimmune and inflammatory cardiomyopathy caused by infection, physical and chemical factors. Myocarditis and subsequent dilated cardiomyopathy are the main causes of heart failure in young patients (23). Specific immune response to the myocardium is a key process of the pathogenesis of myocarditis and is mediated by self-antibodies and T-cells (mainly Th17) (24). A mouse model of EAM induced by a fragment of cardiac myosin was used to investigate the therapeutic effect of CST on EAM. The results showed that CST could attenuate cardiac hypertrophy and myocardial injury, through inhibiting inflammatory infiltration of myocardial tissues and release of inflammatory cytokines by activating SSTRs and GHSR1a (25). Noteworthy, CST could significantly reduce the percentage of Th17 cells in peripheral lymphoid organs and hearts of EAM mice, without altering T-cell response (e.g., Th17-mediated responses). Therefore, we speculate that no suppression of immune response was caused by CST. These data suggest that CST may be a new treatment for autoimmune and inflammatory cardiovascular diseases, including myocarditis and dilated cardiomyopathy (25).

CST and blood vessels

CST and vascular smooth muscle cells (VSMCs) proliferation and migration

Recent evidence indicates that proliferation and migration of VSMCs contribute to the development of vascular diseases, such as atherosclerosis, restenosis and transplant vasculopathy. Inflammatory cytokines and growth factors produced excessively after injury can promote the proliferation and migration of VSMCs and the formation of neointima, and then VSMCs promote the secretion of inflammatory factors, leading to a vicious circle (26). Platelet-derived growth factor (PDGF) plays an essential role in this vicious cycle (27). Aoki *et al.* demonstrated that isoquinoline-type CST attenuated vascular endothelial factor-induced human umbilical vein endothelial cells (HUVECs) migration and alkaline growth factor-induced renal tubular formation, and inhibiting the proliferation of HUVECs. The effects are independent of the ERK1/2 and p38 signaling pathways (28). Duran-Prado *et al.* found that CST was highly expressed in mouse carotid arteries, human aorta, and VSMCs derived from human atherosclerotic plaques, and correlated with progression of arterial intimal hyperplasia. It was shown that CST could inhibit PDGF-induced proliferation of human aorta, which might be mediated by SST2, SST5 and GHSR1a. Further studies demonstrated that anti-proliferation and anti-migration of VSMCs caused by CST were involved in activating intracellular cyclic adenosine monophosphate (cAMP) and p38-mitogen-activated protein kinase (P38-MAPK) and inhibiting of Akt (5). Interestingly, CST inhibited PDGF-induced SMC migration and lamellipodia formation by inactivating Rac1 through binding to GHSR1a (5). These data suggest that CST participates in vascular homeostasis in paracrine and autocrine manners, providing a new treatment for vascular diseases involving neointimal formation and intimal thickening, such as arteriosclerosis and restenosis.

CST and vascular calcification (VC)

VC is a common pathological phenomenon in hypertension, diabetes, chronic kidney disease, and atherosclerosis, thus increasing the risk of myocardial infarction and cardiovascular events (29). The pathogenesis of VC involves multiple mechanisms such as inflammation, oxidative stress, imbalance of calcium and phosphorus metabolism, imbalance of pro-/anti-calcification factors, and transformation of vascular wall cells into osteoblasts. VSMCs play an indispensable role in the pathogenesis of VC (30,31). Many pathogenic factors such as high phosphorus, inflammatory factors and oxidative stress could promote the transformation of VSMCs into osteoblast (31). In this process, vesicles and secreted pro-calcification factors are released by VSMCs to drive phenotypic transformation of VSMCs, ultimately resulting in VC (31).

Our team has demonstrated that CST could inhibit rat aortic calcification in rats *in vitro* and *in vivo*, which was mediated by GHSR1a rather than SSTR or MrgX2 receptors (32). To further elucidate the underlying mechanisms, we used β-glycerophosphoric acid (β-GP) to induce VSMCs calcification in humans and rats and confirmed that calcium deposition and phenotypic transformation of VMSCs induced by β-GP was attenuated by CST, which may be related to the inhibition of

endoplasmic reticulum stress (33). Moreover, we also found that CST might inhibit VC via phosphorylated glycogen synthase kinase 3 beta (p-GSK3β)/β-catenin and phosphorylated protein kinase C (p-PKC) but not phosphorylated c-Jun N-terminal kinase (p-JNK) signaling pathway (34). These data provide a theoretical and experimental basis for the clinical transformation of CST in the prevention and treatment of VC.

CST and atherosclerosis

Chronic inflammation and autoimmune abnormalities play an important role in the pathogenesis of atherosclerosis (35). As the described above, CST and its receptors were expressed in the heart, vascular endothelial cells and smooth muscle cells. Furthermore, CST participates in the development of inflammatory cardiovascular diseases such as septic shock-related myocardial damage, myocarditis, and atherosclerosis. In 2009, Tian *et al.* found that the plasma CST levels before and 1 day after percutaneous coronary intervention (PCI) in patients with coronary heart disease were both significantly higher than healthy subjects, which correlated negatively with triglycerides and cholesterol (36). In the acute and chronic atherosclerotic model of ApoE knockout mouse induced by western diet, Delgado-Maroto *et al.* has found that CST inhibited the formation of atherosclerotic plaque, and reduced plaque area and number, which might be caused by down-regulation of Th1/Th17 cell-mediated inflammatory response and restoration of the ratio of Th1/regulatory T cells (37). Notably, CST impaired the formation of foam cells by enhancing cholesterol efflux from macrophages (37). These evidence supports that CST may be a new marker for the diagnosis of coronary heart disease and a new potential target for the treatment of atherosclerotic disease, but further clinical and experimental research is needed.

CST and abdominal aortic aneurysm (AAA)

AAA is a fatal cardiovascular disease characterized by chronic inflammation of the arteries and tumor-like dilatation (usually referred to as an increase in vessel diameter greater than 50%) (38). One study indicated that CST reduced the incidence and severity of AAA and reserved arterial remodeling in mice. There are several possible reasons for this phenomenon: (I) inhibiting the expression of inflammatory factors [tumor necrosis factor α (TNFα); interleukin 6 (IL-6) and monocyte chemotactic protein 1 (MCP1)]; (II) reducing aortic inflammatory cell infiltration, inhibiting matrix metalloproteinase activation and expression; and (III) reducing reactive oxygen species production and apoptosis (39). Moreover, the authors also found that the inhibitory effect of CST on AAA could be achieved by phosphorylation of ERK1/2 rather than phosphorylation of JNK and p38-MAPK (39), however, its specific molecular signal regulation mechanism remained to be further studied.

Summary

CST is a novel circular small molecule bioactive polypeptide. CST and its receptors (SSTRs, GHSR1a) are widely expressed in the cardiovascular system, such as the aorta, coronary artery and heart. Thus, CST exerts diverse cardiovascular protective effects, such as alleviating myocardial damage, inhibiting autoimmune myocarditis, suppressing VSMC proliferation and migration, reducing VC, inhibiting atherosclerosis and aneurysms formation and so on. These data show that CST has a potential prospect in the diagnosis and treatment of cardiovascular diseases. When CST is considered as a diagnostic marker, wide expression of CST in multiple systems can possess the advantages of high-sensitivity and shortcoming of low-specificity. However, the change of CST expression depends on different disease conditions, for example: plasma level of CST in patients with coronary heart disease was significantly higher than those in healthy subjects (36); plasma CST levels were obviously reduced in newly diagnosed T2DM patients compared to healthy subjects (40). Expression difference of CST in different disease condition need further studied, which contributes to find best diagnostic cutoff value for some kind of cardiovascular disease.

A low-level inflammation plays an important role in many diseases such as coronary heart disease, atherosclerosis and restenosis, AAA, myocarditis and so on. As mentioned above, CST exerts the regulation of immunity and suppression of inflammation in multiple levels, suggesting that CST can be a promising therapeutic drug for immune disorders and inflammatory diseases of heart and blood vessel. However, the results of animal experiments cannot be completely copied into clinical practice because of the differences in species, anatomy and pathophysiology between animals and humans. Several studies showed CST could be regarded as effective and safe when applied to Cushing's syndrome, acromegaly and

prolactinoma in human trials (41,42). Excitingly, studies have shown that chemically synthesized analogs of CST have been successfully synthesized and confirmed in animal experiments to inhibit the formation of retinal blood vessels in mice, which brings a light to the clinical application of CST (43). Even so, there is still a long way to extend CST to clinical treatment, like the transformation of B-type natriuretic peptide from laboratory to clinic. It is believed that under the unremitting efforts of researchers, these help to understand the role and its specific mechanism of CST in the pathogenesis of cardiovascular disease, and describe the possibility of CST in the diagnosis and treatment of cardiovascular diseases, which can open up a vast new world in the application of CST in cardiovascular disease.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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