Calcitonin gene-related peptide-mediated pharmacological effects in cardiovascular and gastrointestinal diseases (Review)

WAN-JUN MA[1,2*], YOU-CONG YIN[3,4*], BI-KUI ZHANG[1,2], YUAN-JIAN LI[4] and WEN-QUN LI[1,2]

[1]Department of Pharmacy, The Second Xiangya Hospital, Central South University; [2]Institute of Clinical Pharmacy, Central South University, Changsha, Hunan 410011; [3]Department of Pharmacy, Shaoyang Central Hospital, Shaoyang, Hunan 422000; [4]Department of Pharmacology, Xiangya School of Pharmaceutical Sciences, Central South University, Changsha, Hunan 410078, P.R. China

Received May 25, 2020; Accepted September 24, 2020

DOI: 10.3892/mmr.2020.11665

Abstract. Calcitonin gene-related peptide (CGRP) is the predominant neurotransmitter located in sensory nerves. This peptide is extensively distributed in central and peripheral tissues. CGRP causes relaxation of cardiovascular smooth muscle cells and confers protection against ischaemic myocardium and cardiac remodeling. The pharmacological effects of nitroglycerine and rutaecarpine have been demonstrated to be associated with an increase in the synthesis and release of CGRP. In the gastrointestinal tissues, CGRP participates in the regulation of gastrointestinal function, and exerts protective effects on gastric mucosa. Rutaecarpine, capsaicin and its derivatives, such as evodiamine, decrease gastric mucosal damage induced by several factors, including increased synthesis and release of CGRP. Taken together, this review focuses on the pharmacological effects of several CGRP related canonical drugs and suggests that synthesis and secretion of CGRP exhibit significant therapeutic effects in the occurrence and development of cardiovascular and gastrointestinal diseases.

Correspondence to: Dr Wen-Qun Li, Department of Pharmacy, The Second Xiangya Hospital, Central South University, 139 Renmin Road, Changsha, Hunan 410011, P.R. China
E-mail: liwq1204@csu.edu.cn

*Contributed equally

Abbreviations: CGRP, calcitonin gene-related peptide; ROS, reactive oxygen species; ALDH, aldehyde dehydrogenase; NO, nitric oxide; TRPV1, transient receptor potential channel vanilloid type 1; Ang-II, angiotensin II; AT1, angiotensin receptor 1; CaMK, camodulin dependent protein kinase; CREB, cAMP-response element binding protein

Key words: calcitonin gene-related peptide, nitroglycerine, rutaecarpine, sartans, capsaicin

Contents

1. Introduction

Calcitonin gene-related peptide (CGRP) is the first neuropeptide synthesized by gene recombination and biosynthesis that consists of 37 amino acids and is classified into two subtypes, α-CGRP and β-CGRP, which are encoded by the calcitonin/α-CGRP and β-CGRP genes, respectively (1,2). CGRP is a neurotransmitter of the capsaicin-sensitive sensory nerve, which is synthesized in neuronal cells and stored at the nerve endings (1). The transient receptor potential channel vanilloid type 1 (TRPV1), also known as vanilloid receptor subtype 1 (VR1), is a critical receptor that regulates the synthesis and release of CGRP (3). Given that the binding site of TRPV1 is located in the inner side of the cell membrane, its endogenous ligand anandamide is only active following intracellular transport (4). CGRP has exhibited extensive and complex biological activity. For example, in addition to its involvement in neuralgia and migraine, CGRP can regulate vascular tone, maintain the balance of circulation, attenuate ischaemic injury and inhibit cardiac fibroblast proliferation, as well as cardiac remodelling (5). Furthermore, CGRP plays a positive role in protecting the gastric mucosa in the gastrointestinal system (6,7). It has been reported that CGRP participates in the pathophysiological processes of several cardiovascular diseases, including hypertension, myocardial infarction, heart failure and pulmonary hypertension (5). Exogenous CGRP has been proven to be effective in the treatment of hypertension, pulmonary hypertension, acute lung injury, cerebral/cardiac ischaemia-reperfusion injury and chronic heart failure, suggesting that promoting endogenous synthesis and release of CGRP may be a novel direction of drug research and development (8-11). The present review

summarizes the existing studies focusing on CGRP-mediated pharmacological effects of drugs, as presented in Table I.

2. CGRP mediates the pharmacological effect of nitroglycerine

Nitroglycerine, a classic anti-angina drug that is extensively applied in clinical settings, can be used for treating and alleviating chronic cardiac insufficiency (12). Previous studies have demonstrated that CGRP is involved in nitroglycerine treatment of myocardial ischaemia and chronic cardiac insufficiency (13,14).

Anti-angina effect of nitroglycerine. Nitroglycerine decreases cardiac blood volume, ventricular wall tension and myocardial oxygen consumption by dilating venules, which also dilates the coronary artery and increases the blood supply of the myocardial ischaemic area to attenuate angina pectoris (15). Nitroglycerine produces nitric oxide (NO) under the catalysis of aldehyde dehydrogenase (ALDH), and NO mediates the vasodilation of nitroglycerine (16). Previous studies have confirmed the key role of CGRP in mediating the inhibitory effect of nitroglycerine on angina. The results of the vessel ring *ex vivo* experiment demonstrated that the vasodilation effect of nitroglycerine can be reversed by CGRP receptor antagonists and capsaicin (17-19). *In vivo*, pre-treatment with capsaicin can also neutralize the hypotensive effect of nitroglycerine as it can deplete CGRP (20). An experiment was designed to assess whether the vasodilation effect associated with nitroglycerine was mediated by CGRP. Based on the polymorphisms of the ALDH gene, 40 unrelated male healthy volunteers with a mean age of 28 years (25 to 32 years) were enrolled, screened and stochastically divided into two groups according to their ALDH genotype, as follows: The ALDH2*1/*1 group (nine individuals, normal wild-type homozygote, ALDH 504 is glutamic acid, with high enzyme activity) and the ALDH2*2 group (nine individuals, carrying a mutant allele, ALDH 504 is lysine, resulting in reduced enzyme activity). Following treatment with nitroglycerine, the ALDH2*1/*1 group exhibited a distinct blood pressure drop and a significant increase in the concentration of CGRP in the blood, while the ALDH2*2 group displayed less changes in these two parameters (21). An additional study suggested that increased CGRP expression ultimately accelerates the antithrombotic effect of nitroglycerine (22). Collectively, these findings support the hypothesis that nitroglycerine releases NO to increase the concentration of CGRP, and subsequently plays an antagonistic role in the occurrence and development of angina (23).

Protective effects of nitroglycerine on ischaemic myocardium. Ischaemia-reperfusion injury is regarded as an aggravated injury in an ischaemic heart resulting from reperfusion following a period of ischaemia (24). Ischaemic preconditioning refers to the phenomenon by which transient ischaemia, prior to heart ischaemia, partially alleviates cardiac damage for 5-30 min (25). The protection of ischaemic preconditioning is mediated by endogenous active substances expressed due to ischaemic stimulation, such as adenosine and CGRP, which are also considered endogenous myocardial protective substances since they are released by the heart (26). It has been reported that transient cardiac ischaemia increases CGRP expression, while pretreatment with either a CGRP receptor blocker or capsaicin can offset cardiac defence mediated by ischaemic preconditioning, including the improvement of cardiac function, reduction in the myocardial infarction area and decreased creatine kinase release (27). The protective effect of CGRP on ischaemic myocardium may be associated with the repair of injured cardiomyocytes, the suppression of active oxygen species induced by hypoxia/reoxygenation and the balance of the mitochondrial membrane potential (28). CGRP induced by aerobic exercise has also been demonstrated to be protective in ischaemic myocardium (29). Considering that TRPV1 is temperature-sensitive, previous studies assessed whether the protection of ischaemic myocardium induced by high-temperature pre-adaptation was potentially associated with the induction of CGRP release. The experimental results demonstrated that both a CGRP receptor blocker and capsaicin can counteract the ischaemic myocardial protection associated with high-temperature pre-adaptation (19). Given that nitroglycerine can release GCRP, the hypothesis that pretreatment with nitroglycerine can imitate ischaemic preconditioning and serve a protective role in the ischaemic heart was investigated. These processes have only been demonstrated *in vivo* and *in vitro* (30). The results demonstrated that CGRP serum levels are significantly decreased in diabetic rats with acute myocardial ischaemia-reperfusion, and exogenous CGRP can recover myocardial cell damage from high glucose and ischaemia-reperfusion (31). Paeoniflorin, a pinane monoterpene glucoside extracted from the root of paeonia lactiflora pall, has been demonstrated to provide heart protection in diabetic mice by activating the TRPV1/calmodulin-dependent protein kinase/cAMP response element binding protein/CGRP signaling pathway (32).

Treatment of chronic cardiac insufficiency with nitroglycerine. Chronic cardiac insufficiency, also known as chronic heart failure, is a complicated syndrome induced by either ventricular filling or ejection capacity insufficiency, which stems from organic causes or functional cardiac diseases. Given that the pathological process of chronic cardiac insufficiency is partly associated with haemodynamic changes, drugs can improve cardiac function by dilating blood vessels (arteries and veins) and affecting haemodynamics (33). Nitrate esters currently play a significant role in the treatment of chronic cardiac insufficiency. By dilating the venules, nitroglycerine decreases the cardiac blood volume and ventricular wall tension, and strengthens the left ventricular compliance, myocardial contractility and cardiac output, ultimately improving cardiac function (17,34). A previous study demonstrated that nitroglycerine can be used in the treatment of chronic cardiac insufficiency by stimulating the CGRP signaling pathway. According to the gene type, patients were divided into two groups, as follows: The ALDH2*1/*1 group and the ALDH2*2 group. Following treatment with nitroglycerine, the experimental data indicated that the levels of CGRP in the ALDH2*1/*1 homozygote group were significantly increased, whereas the patients in this group exhibited apparent improvements in both blood pressure and left ventricular ejection fraction compared with those in the ALDH2*2 mutant group (34).

Table I. Pharmacological effects of drugs that regulate CGRP function.

Drug	Pharmacological effect	Molecular mechanism	(Refs.)
Nitroglycerine	Anti-angina	ALDH→ NO↑→ CGRP↑	(16,17,23)
	Anti-myocardial ischaemia		(30)
	Treatment for chronic cardiac insufficiency		(34)
	Tolerance of nitroglycerine	ROS→ALDH2↓→NO↓→CGRP↓	(36)
Sartan	Anti-hypertension	Ang-II activating AT1↓→CGRP↑	(45-47)
Rutaecarpine	Anti-hypertension	TRPV1→Ca^{2+}↑→CGRP↑	(52,54,55)
	Anti-pulmonary hypertension		(51)
	Anti-ventricular remodeling		(51,62)
	Protection of the gastric mucosa	TRPV1→CGRP↑→Gastric acid↓/K-ATP↑	(49,70,71)

ALDH, aldehyde dehydrogenase; NO, nitric oxide; CGRP, calcitonin gene-related peptide; ROS, reactive oxygen species; ALDH2, aldehyde dehydrogenase 2; Ang-II, angiotensin II; AT1, angiotensin receptor 1; TRPV1, transient receptor potential channel vanilloid type 1; K-ATP, ATP-sensitive potassium.

Tolerance to nitroglycerine. The underlying molecular mechanism of the tolerance to nitroglycerine following its continuous application remains unclear. Previous studies have concluded that nitroglycerine tolerance is associated with thiol (-SH) consumption of tissue cells, since the application of drugs containing -SH, such as captopril or N-acetylcysteine, can partially reverse the tolerance to nitroglycerine (35). Previous studies have reported that the tolerance may be associated with nitroglycerine-induced oxidative stress (generation of active oxygen species), which restrains the activity of ALDH2, the release of NO and eventually attenuates the vasomotor effect (36). In addition, CGRP mediates the vasodilation effect of nitroglycerine, resulting in tolerance from a secondary decrease in CGRP caused by NO reduction (37). Previous *in vivo* and *in vitro* experiments have demonstrated that when nitroglycerine is tolerated, the levels of CGRP and the vasodilation effect decrease simultaneously, whereas pretreatment with drugs containing -SH can markedly increase the levels of NO and CGRP, partially reversing the tolerance (23,36,37). A recent study demonstrated that nitroglycerine tolerance may intensify the anti-ischaemic effect and cardiovascular mortality in rats, whereas exposure to a CGRP antagonist ($CGRP_{8-37}$) may improve this condition (38).

3. CGRP-mediated antihypertensive effect of sartans

It is widely accepted that the occurrence and development of hypertension is strongly associated with peripheral vascular resistance. CGRP induces vascular relaxation by decreasing the peripheral vascular resistance. Thus, suppressing CGRP synthesis and release can promote the development of hypertension (39). A previous study demonstrated that α-CGRP knockout animals exhibit higher basal blood pressure (40). In addition, both phenol-induced hypertension rats and spontaneous hypertension rats display lower levels of CGRP in the blood (4,41). Clinical studies have reported that CGRP levels in the blood of patients with essential hypertension and pregnancy hypertension are significantly lower than those in healthy subjects (4). Recently, it has been demonstrated that endogenous α-CGRP induced by physical activity can protect cardiac function during treatment of mice with chronic hypertension (42).

Released CGRP is regulated by several endogenous active substances, including NO, bradykinin, neuropeptide Y and angiotensin II (Ang II). Ang II inhibits CGRP release by activating anterior membrane angiotensin receptor 1 (AT1) (43). Sartans are AT1 receptor blockers, which can prevent Ang II from contracting blood vessels leading to the stimulation of aldosterone secretion. In addition, they can decrease peripheral vascular resistance and lower blood pressure (44). Thus, it was hypothesized that sartans can promote CGRP release by blocking the AT1 receptor since Ang II can activate the AT1 receptor and suppress the release of CGRP.

Previous studies have confirmed that while sartans decrease the blood pressure of spontaneously hypertensive rats, CGRP expression is significantly increased in the blood, heart, kidney and dorsal root ganglion (45,46). In addition, a clinical trial demonstrated that following treatment with the Ang II type 1 receptor blocker olmesartan, the systolic and diastolic blood pressure levels of patients with hypertension were normalized, and CGRP levels also increased (47). Taken together, these findings support the hypothesis that the molecular mechanism of blood pressure reduction of sartans may also be associated with the CGRP pathway.

4. CGRP-mediated pharmacological effect of rutaecarpine

Rutaecarpine is an active component extracted from the fruit of *Euodia rutaecarpa*, a traditional Chinese medicine used for the treatment of hypertension. It mediates an extensive range of pharmacological effects, including vasodilation, reduction in myocardial ischaemic injury, inhibition of thrombosis and protection of the gastric mucosa (48,49). A previous study suggested that rutaecarpine stimulates the synthesis and release of CGRP by activating the capsaicin receptor (50).

CGRP-mediated antihypertensive effect of rutaecarpine. A previous demonstrated that the CGRP receptor blocker, $CGRP_{8-37}$ can eliminate the positive inotropic force and the positive frequency effect of rutaecarpine in the isolated cavy

heart (51). In addition, it was indicated that rutaecarpine promotes the release of CGRP in a concentration-dependent manner and that exposure to capsazepine, a TRPV1 receptor antagonist, suppresses CGRP expression (52). TRPV1 receptor blockers have been demonstrated to counteract the vasodilation effects of rutaecarpine, suggesting that rutaecarpine protects the cardiovascular system by releasing CGRP through the activation of the TRPV1 receptor (3). As a vasodilator neurotransmitter, CGRP is tightly associated with the occurrence and development of hypertension (53). Thus, it is reasonable to assume that CGRP can mediate the antihypertensive effect of rutaecarpine since the latter promotes the release of CGRP and the stimulation of the TRPV1 receptor (52). Preclinical experiments have demonstrated that rutaecarpine elevates the synthesis and release of CGRP in both spontaneously hypertensive rats and phenol-induced hypertensive rats, whereas pretreatment with capsaicin eliminates the hypotensive effect of rutaecarpine by excessive binding to CGRP (54,55).

CGRP-mediated anti-pulmonary hypertension effect of rutaecarpine. Pulmonary hypertension is a chronic respiratory disease characterized by persistent pulmonary hypertension caused by pulmonary capillary occlusion. Despite that the pathogenesis of pulmonary hypertension remains unclear, it is universally accepted that the vascular remodeling caused by smooth muscle cell proliferation and migration is the main contributing factor to the development of this disease (56). CGRP expression in the blood has been decrease in both mature and newborn rats suffering from pulmonary hypertension (57). It has been reported that continuous hypoxia for 3 weeks can cause persistent pulmonary hypertension in neonatal rats, with a decrease in plasma CGRP expression (58). In addition, targeted knockout of the CGRP receptor gene has been demonstrated to aggravate hypoxia-induced pulmonary hypertension (59). CGRP suppresses the extracellular signaling-regulated kinase 1/2 pathway, which contributes to the inhibition of vascular remodeling through a vasodilation effect, and the control of the proliferation of vascular smooth muscle cells (5). A previous study demonstrated that exogenous CGRP can inhibit the proliferation of smooth muscle cells induced by hypoxia in a concentration-dependent manner (60). Adenoviral transfection of the CGRP gene significantly decreases the pulmonary vascular resistance of rats with hypoxia-induced pulmonary hypertension, improving pulmonary vascular remodelling (53). It has also been reported that transfection of CGRP into endothelial progenitor cells mitigates pulmonary hypertension and vascular remodelling (57). Given that the release of CGRP alleviates pulmonary hypertension, rutaecarpine may also relieve pulmonary hypertension due to its activating effect on CGRP. It has been demonstrated that rutaecarpine inhibits the pulmonary hypertension induced by monocrotaline or hypoxia in rats by elevating CGRP levels in the blood (51). A recent study discovered that rutaecarpine inhibits the Notch1/eIF3a signaling pathway in order to improve the synthesis and release of CGRP, alleviating pulmonary fibrosis and the epithelial-to-mesenchymal transition process (61).

CGRP-mediated inhibitory effect of rutaecarpine on cardiac remodeling. As a compensatory response to the increase in ventricular pressure, cardiac remodeling is usually accompanied by pathological changes, including cardiac hypertrophy and cardiac fibroblast proliferation. Cardiac fibroblasts account for 60-70% of the total number of cardiac cells and play an important role in cardiac remodeling. Under pathological conditions, cardiac fibroblasts proliferate and differentiate into myofibroblasts (62). However, this process acts in an autocrine manner and several active substances, such as Ang II, endothelin and inflammatory factors can further promote the proliferation of cardiac fibroblasts (63). CGRP has been demonstrated to inhibit the proliferation of cardiac fibroblasts and cardiac remodelling (51). In addition, exogenous CGRP has been reported to inhibit the senescence of cardiac fibroblasts and the development of cardiac fibrosis by increasing the expression levels of klotho (64). A previous study demonstrated that pressure loading (coarctation of the aortic arch) aggravates the left ventricular hypertrophy and fibrosis of calcitonin/α-CGRP gene knockout mice (65). TRPV1 gene knockout also exacerbates cardiac remodeling in mice (66). Another study demonstrated that rutaecarpine alleviates left ventricular remodeling induced by isoproterenol by activating CGRP, which regulates the expression of apoptosis-related genes, including Bax and Bcl2 (62). To investigate whether the potential molecular mechanism of rutaecarpine-mediated inhibition of cardiac remodeling acts via the CGRP signaling pathway, an experiment was designed to construct a right ventricular remodeling model in rats with pulmonary hypertension induced by monocrotaline and hypoxia. The results demonstrated that rutaecarpine affects the eIF3a/p27 signaling pathway by promoting CGRP release, eventually suppressing cardiac remodelling (51).

Protective effects of rutaecarpine, curcumin and capsaicin derivatives on gastric mucosa are mediated via CGRP. Gastrointestinal function is regulated by visceral sensory nerves (67). CGRP may play an important role in protecting the gastric mucosa, and is considered an essential neurotransmitter among the dorsal root ganglion and vagal ganglion of the splanchnic nerves (6,7,68). A previous study indicated that CGRP can significantly inhibit gastric acid secretion induced by gastrin in rats (69). In addition, CGRP improves gastric mucosal blood flow, which is partially associated with the ATP-sensitive potassium channel (70,71). It has been reported that CGRP alleviates mucosal injury induced by ischaemia-reperfusion by decreasing inflammation and apoptosis (7). In addition, the CGRP receptor antagonist, $CGRP_{8-37}$ has been demonstrated to aggravate gastric mucosal injury induced by indomethacin (indomethacin) or ethanol (72,73). Notably, the increase in the healing time of gastric ulcer by the use of acetic acid and ethanol exacerbates gastric mucosal injury during stress in CGRP gene knockout animal models (74,75). Based on this evidence, TRPV1 may be used as a novel target to investigate drugs that can prevent and treat gastric mucosal injury, as demonstrated by the protective effect of CGRP on the gastric mucosa and the activation effect of TRPV1 on the synthesis and release of CGRP. Currently, several studies have reported that TRPV1 agonists, such as capsaicin, capsaicin ester, cannabinoid, curcumin and rutaecarpine can decrease gastric mucosal damage by promoting the release of CGRP (3,49,76-81). Indirect activation of CGRP induced by curcumin can mitigate gastrorrhagia in rats caused by

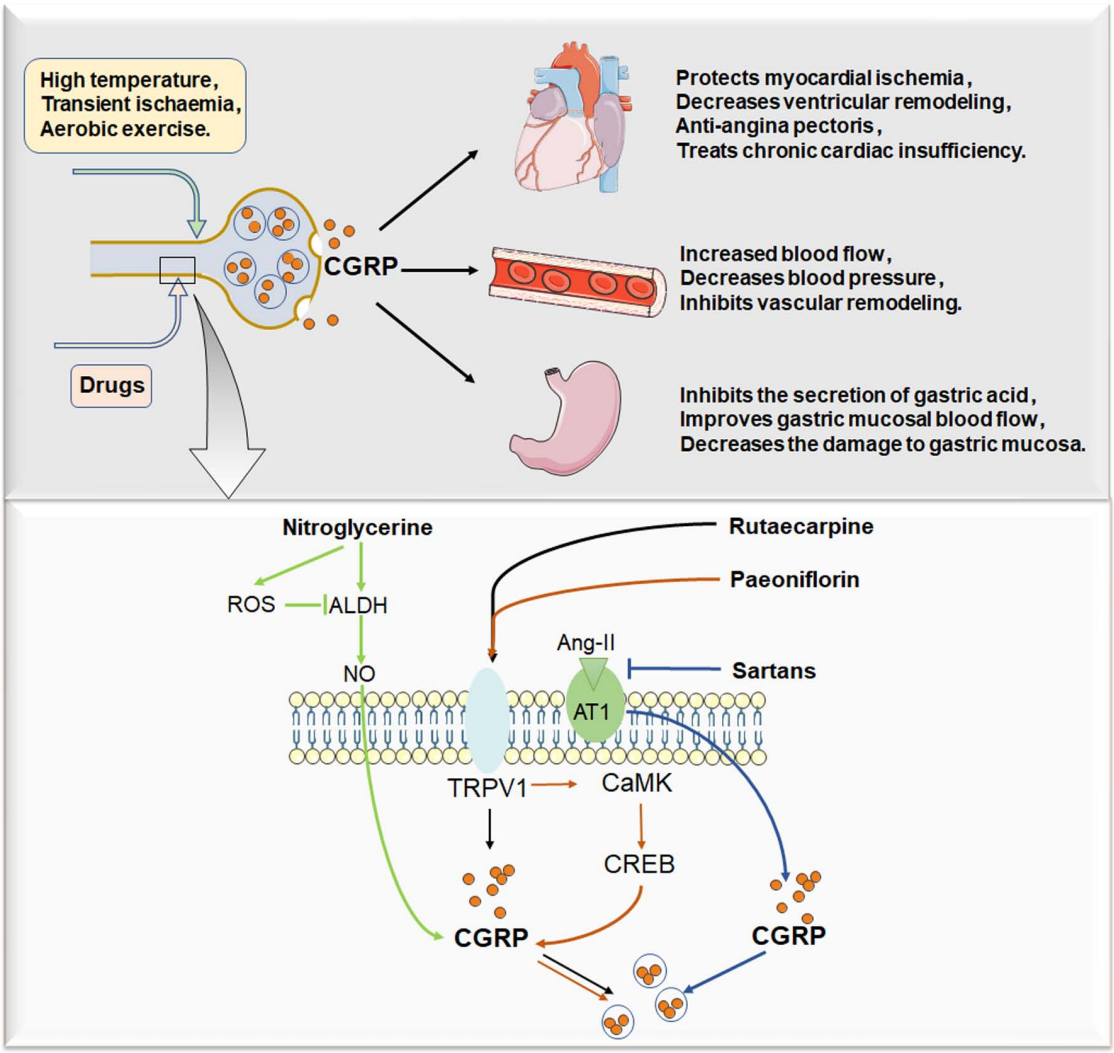

Figure 1. Schematic diagram describing the role of CGRP in the pharmacological effects of specific drugs. CGRP, calcitonin gene-related peptide; ROS, reactive oxygen species; ALDH, aldehyde dehydrogenase; NO, nitric oxide; TRPV1, transient receptor potential channel vanilloid type 1; Ang-II, angiotensin II; AT1, angiotensin receptor 1; CaMK, camodulin dependent protein kinase; CREB, cAMP-response element binding protein.

75% ethanol, which may be associated with the suppression of HIF-1α and Cdx-2, and the activation of HO-1 and SOD2 (82). A previous study demonstrated that pretreatment with rutaecarpine enhances both CGRP mRNA and protein expression, ameliorating ulcerative colitis in mice (83). An epidemiological study have demonstrated that Chinese subjects are three times more likely to suffer from gastric ulcers compared with Malaysian or Indian subjects, which may be associated with their habits of consuming higher amounts of pepper compared to those of other Asian populations (84). Rutaecarpine has been reported to upregulate endogenous CGRP expression by activating the VR1 signaling pathway, which results in the protection of rats with acute pancreatitis (85).

5. Discussion and perspective

Aforementioned studies have focused on neuronal CGRP, which acts as the transmitter of sensory nerves (Fig. 1) (39,43). However, it has been reported that CGRP also exists in non-nerve tissue cells, such as endothelial cells, endothelial progenitor cells, lymphocytes, bronchial epithelial cells and adipocytes, and plays an important role in regulating local tissues (86). The α- and β-subtypes of CGRP have been observed in endothelial cells and are regulated by TRPV1 to maintain physiological function of endothelial cells (87). A recent study suggested that cardiac fibroblasts synthesize and secrete CGRP, which suppresses their activation in an autocrine manner (88). Drugs such as clonidine, which is an α-receptor agonist regulating CGRP through a non-nerve pathway, have been demonstrated to influence the secretion of CGRP in endothelial cells by affecting its synthesis and secretion in local tissues (89). In addition, rutaecarpine delays cell senescence by promoting the expression and secretion of CGRP in endothelial progenitor cells (90). Thus, whether drugs can affect CGRP synthesis and secretion of other non-nerve cells remains to be investigated.

As the pivotal receptor affecting the release of CGRP, the TRP receptor contains several subtypes, including TRPC, TRPV, TRPM, TRPML, TRPP, TRPA and TRPN (91). Previous studies that assessed the regulation of CGRP synthesis and release focused on TRPV1, which is considered

a significant target for drug discovery (54,91). Transient receptor potential ankyrin 1 (TRPA1) is localized in primary sensory dorsal root ganglion neurons. It was confirmed that H2S induced NO production and the subsequent activation of the neuroendocrine HNO-TRPA1-CGRP signaling pathway is the main cause of vasodilatory effects (92). A previous study demonstrated that cinnamaldehyde activates TRPA1 and inhibits hypoxia-induced cardiac fibrosis through a molecular mechanism that involves the upregulation of cardiac fibroblast-derived CGRP . Collectively, these studies suggest that TRPA1 may also be considered a novel target for drug discovery.

The data reported in the present review demonstrates that CGRP participates in the regulation of the function of multiple organs. It also mediates the pharmacological effects of marketed drugs, such as nitroglycerine and sartans. These studies not only improve our understanding on the therapeutic effects of marketed drugs, but also provide novel targets for drug discovery. Thus, targeting endogenous CGRP synthesis and release may be considered a novel direction for drug research and development.

Acknowledgements

Not applicable.

Funding

The present study was supported by grants from the National Natural Scientific Foundation of China (grant nos. 81703518 and 81973406), the Hunan Provincial Natural Scientific Foundation (grant nos. 2019JJ50849 and 2020JJ4823), the Scientific Research Project of Hunan Provincial Health and Family Planning Commission (grant no. B20180253) and the Fundamental Research Funds for the Central Universities of Central South University (grant no. 2020zzts822).

Availability of data and materials

Not applicable.

Authors' contributions

WJM and YCY contributed equally in classifying the literature and drafting the manuscript. BKZ and YJL collected and analyzed the literature. WQL designed the framework of this article and critically revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patients consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Rosenfeld MG, Mermod JJ, Amara SG, Swanson LW, Sawchenko PE, Rivier J, Vale WW and Evans RM: Production of a novel neuropeptide encoded by the calcitonin gene via tissue-specific RNA processing. Nature 304: 129-135, 1983.
2. Wimalawansa SJ, Morris HR, Etienne A, Blench I, Panico M and MacIntyre I: Isolation, purification and characterization of beta-hCGRP from human spinal cord. Biochem Biophys Res Commun 167: 993-1000, 1990.
3. Peng J and Li YJ: The vanilloid receptor TRPV1: Role in cardiovascular and gastrointestinal protection. Eur J Pharmacol 627: 1-7, 2010.
4. Li D, Chen BM, Peng J, Zhang YS, Li XH, Yuan Q, Hu CP, Deng HW and Li YJ: Role of anandamide transporter in regulating calcitonin gene-related peptide production and blood pressure in hypertension. J Hypertens 27: 1224-1232, 2009.
5. Li XW, Hu CP, Wu WH, Zhang WF, Zou XZ and Li YJ: Inhibitory effect of calcitonin gene-related peptide on hypoxia-induced rat pulmonary artery smooth muscle cells proliferation: Role of ERK1/2 and p27. Eur J Pharmacol 679: 117-126, 2012.
6. Evangelista S: Role of calcitonin gene-related Peptide in gastric mucosal defence and healing. Curr Pharm Des 15: 3571-3576, 2009.
7. Feng G, Wang Q, Xu X, Liu Z, Li Z and Liu G: The protective effects of calcitonin gene-related peptide on gastric mucosa injury of gastric ischemia reperfusion in rats. Immunopharmacol Immunotoxicol 33: 84-89, 2011.
8. Sukhishvili E, Bekaia G and Kvachadze I: Effect of exogenous calcitonin gene-related Peptide on systemic arterial blood pressure in pregnant and non-pregnant rats. Georgian Med News: 71-75, 2011 (In Russian).
9. Yang W, Xv M, Yang WC, Wang N, Zhang XZ and Li WZ: Exogenous α-calcitonin gene-related peptide attenuates lipopolysaccharide-induced acute lung injury in rats. Mol Med Rep 12: 2181-2188, 2015.
10. Yang SI, Yuan Y, Jiao S, Luo QI and Yu J: Calcitonin gene-related peptide protects rats from cerebral ischemia/reperfusion injury via a mechanism of action in the MAPK pathway. Biomed Rep 4: 699-703, 2016.
11. Chai W, Mehrotra S, Jan Danser AH and Schoemaker RG: The role of calcitonin gene-related peptide (CGRP) in ischemic preconditioning in isolated rat hearts. Eur J Pharmacol 531: 246-253, 2006.
12. Scardi S, Pandullo C, Pivotti F, Ceschia G and Pollavini G: Hemodynamic and anti-angina effects of transdermal nitroglycerin after acute and chronic administration. Additive effect of sublingual isosorbide dinitrate. G Ital Cardiol 16: 895-903, 1986 (In Italian).
13. Li YJ and Du YH: CGRP-mediated cardiovascular effect of nitroglycerin. Med Hypotheses 60: 693-698, 2003.
14. Zhou ZH, Peng J, Ye F, Li NS, Deng HW and Li YJ: Delayed cardioprotection induced by nitroglycerin is mediated by alpha-calcitonin gene-related peptide. Naunyn Schmiedebergs Arch Pharmacol 365: 253-259, 2002.
15. Glyceryl trinitrate and angina. Br Med J 4: 252, 1969.
16. Munzel T, Daiber A and Mulsch A: Explaining the phenomenon of nitrate tolerance. Circ Res 97: 618-628, 2005.
17. Booth BP, Tabrizi-Fard MA and Fung H: Calcitonin gene-related peptide-dependent vascular relaxation of rat aorta. An additional mechanism for nitroglycerin. Biochem Pharmacol 59: 1603-1609, 2000.
18. Wei EP, Moskowitz MA, Boccalini P and Kontos HA: Calcitonin gene-related peptide mediates nitroglycerin and sodium nitroprusside-induced vasodilation in feline cerebral arterioles. Circ Res 70: 1313-1319, 1992.
19. Song QJ, Li YJ and Deng HW: Early and delayed cardioprotection by heat stress is mediated by calcitonin gene-related peptide. Naunyn Schmiedebergs Arch Pharmacol 359: 477-483, 1999.
20. Zhou ZH, Deng HW and Li YJ: The depressor effect of nitroglycerin is mediated by calcitonin gene-related peptide. Life Sci 69: 1313-1320, 2001.
21. Guo R, Chen XP, Guo X, Chen L, Li D, Peng J and Li YJ: Evidence for involvement of calcitonin gene-related peptide in nitroglycerin response and association with mitochondrial aldehyde dehydrogenase-2 (ALDH2) Glu504Lys polymorphism. J Am Coll Cardiol 52: 953-960, 2008.
22. Booth BP, Nolan TD and Fung HL: Nitroglycerin-inhibited whole blood aggregation is partially mediated by calcitonin gene-related peptide-a neurogenic mechanism. Br J Pharmacol 122: 577-583, 1997.

23. Hu R, Li XH and Li YJ: Nitroglycerin-induced myocardial protection and tolerance: Role for CGRP. Trends Pharmacol Sci 35: 369-370, 2014.
24. Binder A, Ali A, Chawla R, Aziz HA, Abbate A and Jovin IS: Myocardial protection from ischemia-reperfusion injury post coronary revascularization. Expert Rev Cardiovasc Ther 13: 1045-1057, 2015.
25. Zhou FW, Li YJ, Lu R and Deng HW: Protection of calcitonin gene-related peptide-mediated preconditioning against coronary endothelial dysfunction induced by reperfusion in the isolated rat heart. Life Sci 64: 1091-1097, 1999.
26. Li J, Zhang M, Yang C, Dun Y, Zhang Y and Hao Y: Nitroglycerin protects small intestine from ischemia-reperfusion injury via NO-cGMP pathway and upregulation of alpha-CGRP. J Gastrointest Surg 13: 478-485, 2009.
27. Li YJ, Song QJ and Xiao J: Calcitonin gene-related peptide: An endogenous mediator of preconditioning. Acta Pharmacol Sin 21: 865-869, 2000.
28. Guo Z, Liu N, Chen L, Zhao X and Li MR: Independent roles of CGRP in cardioprotection and hemodynamic regulation in ischemic postconditioning. Eur J Pharmacol 828: 18-25, 2018.
29. Wang Y, Zhang L, Jia L, Liu J, Liu K, Feng Q and Wang Q: Calcitonin gene-related peptide in aerobic exercise induces collateral circulation development in rat ischemia myocardium. Biomed Pharmacother 82: 561-567, 2016.
30. Hu CP, Li YJ and Deng HW: The cardioprotective effects of nitroglycerin-induced preconditioning are mediated by calcitonin gene-related peptide. Eur J Pharmacol 369: 189-194, 1999.
31. Li TP, Guo Z, Liu CJ, Sun T, Chen L and Zhao X: Association of down-regulation of calcitonin gene-related peptide and substance P with increase of myocardial vulnerability in diabetic neuropathic rats. Peptides 96: 1-7, 2017.
32. Han F, Zhou D, Yin X, Sun Z, Han J, Ye L, Zhao W, Zhang Y, Wang Z and Zheng L: Paeoniflorin protects diabetic mice against myocardial ischemic injury via the transient receptor potential vanilloid 1/calcitonin gene-related peptide pathway. Cell Biosci 6: 37, 2016.
33. Kosarev MM, Obrezan AG, Strel'nikov AA and Gur'ianov AV: Modern principles of diagnostics of chronic cardiac insufficiency. Klin Med (Mosk) 89: 8-13, 2011 (In Russian).
34. Peng LM, Chen XP, Sun J, Guo YJ, Li L, Mo L, Xie W, Li YJ, Yang TL and Li CC: Influence of ALDH2 Glu504Lys polymorphism on nitroglycerin response in chronic heart failure and involvement of calcitonin gene related peptide (CGRP). Int J Clin Pharmacol Ther 50: 701-711, 2012.
35. Zhou ZH, Jiang JL, Peng J, Deng HW and Li YJ: Reversal of tolerance to nitroglycerin with N-acetylcysteine or captopril: A role of calcitonin gene-related peptide. Eur J Pharmacol 439: 129-134, 2002.
36. Chen YR, Nie SD, Shan W, Jiang DJ, Shi RZ, Zhou Z, Guo R, Zhang Z and Li YJ: Decrease in endogenous CGRP release in nitroglycerin tolerance: Role of ALDH-2. Eur J Pharmacol 571: 44-50, 2007.
37. Zhou ZH, Deng HW and Li YJ: Involvement of calcitonin gene-related peptide in the development of tolerance to nitroglycerin in the rat. Eur J Pharmacol 427: 137-141, 2001.
38. Kezeli T, Rukhadze T, Gongadze N, Sukoyan G, Dolidze N, Chipashvili M and Mirziashvili M: Effect of calcitonin gene-related peptide antagonist on the cardiovascular events, mortality, and prostaglandin E2 production by nitrate-induced tolerant rats with acute myocardial infarction. EPMA J 7: 6, 2016.
39. Márquez-Rodas I, Longo F, Rothlin RP and Balfagón G: Pathophysiology and therapeutic possibilities of calcitonin gene-related peptide in hypertension. J Physiol Biochem 62: 45-56, 2006.
40. Li J, Zhao H, Supowit SC, DiPette DJ and Wang DH: Activation of the renin-angiotensin system in alpha-calcitonin gene-related peptide/calcitonin gene knockout mice. J Hypertens 22: 1345-1349, 2004.
41. Deng PY, Ye F, Cai WJ, Deng HW and Li YJ: Role of calcitonin gene-related peptide in the phenol-induced neurogenic hypertension in rats. Regul Pept 119: 155-161, 2004.
42. Skaria T, Mitchell KJ, Vogel O, Walchli T, Gassmann M and Vogel J: Blood pressure normalization-independent cardioprotective effects of endogenous, physical activity-induced αCGRP (α calcitonin gene-related peptide) in chronically hypertensive mice. Circ Res 125: 1124-1140, 2019.
43. Russell FA, King R, Smillie SJ, Kodji X and Brain SD: Calcitonin gene-related peptide: Physiology and pathophysiology. Physiol Rev 94: 1099-1142, 2014.
44. Hobara N, Gessei-Tsutsumi N, Goda M, Takayama F, Akiyama S, Kurosaki Y and Kawasaki H: Long-term inhibition of angiotensin prevents reduction of periarterial innervation of calcitonin gene-related peptide (CGRP)-containing nerves in spontaneously hypertensive rats. Hypertens Res 28: 465-474, 2005.
45. Harada N, Shimozawa N and Okajima K: AT(1) receptor blockers increase insulin-like growth factor-I production by stimulating sensory neurons in spontaneously hypertensive rats. Transl Res 154: 142-152, 2009.
46. Shi RZ, Hu CP, Luo D, Li D, Pan W, Li SX, Yang TL, Li YJ and Zhang GG: Decreased anandamide transporter activity and calcitonin gene-related peptide production in spontaneously hypertensive rats: Role of angiotensin II. Eur J Pharmacol 680: 81-87, 2012.
47. Ravarotto V, Pagnin E, Maiolino G, Fragasso A, Carraro G, Rossi B and Calò LA: The blocking of angiotensin II type 1 receptor and RhoA/Rho kinase activity in hypertensive patients: Effect of olmesartan medoxomil and implication with cardiovascular-renal remodeling. J Renin Angiotensin Aldosterone Syst 16: 1245-1250, 2015.
48. Jia S and Hu C: Pharmacological effects of rutaecarpine as a cardiovascular protective agent. Molecules 15: 1873-1881, 2010.
49. Wang L, Hu CP, Deng PY, Shen SS, Zhu HQ, Ding JS, Tan GS and Li YJ: The protective effects of rutaecarpine on gastric mucosa injury in rats. Planta Med 71: 416-419, 2005.
50. Hu CP, Li NS, Xiao L, Deng HW and Li YJ: Involvement of capsaicin-sensitive sensory nerves in cardioprotection of rutaecarpine in rats. Regul Pept 114: 45-49, 2003.
51. Li WQ, Li XH, Du J, Zhang W, Li D, Xiong XM and Li YJ: Rutaecarpine attenuates hypoxia-induced right ventricular remodeling in rats. Naunyn Schmiedebergs Arch Pharmacol 389: 757-767, 2016.
52. Yang Y, Chen Q, Jia S, He L, Wang A, Li D, Li Y and Li X: Involvement of TRPV1 in the expression and release of calcitonin gene-related peptide induced by rutaecarpine. Mol Med Rep 17: 5168-5174, 2018.
53. Bivalacqua TJ, Hyman AL, Kadowitz PJ, Paolocci N, Kass DA and Champion HC: Role of calcitonin gene-related peptide (CGRP) in chronic hypoxia-induced pulmonary hypertension in the mouse. Influence of gene transfer in vivo. Regul Pept 108: 129-133, 2002.
54. Deng PY and Li YJ: Calcitonin gene-related peptide and hypertension. Peptides 26: 1676-1685, 2005.
55. Deng PY, Ye F, Cai WJ, Tan GS, Hu CP, Deng HW and Li YJ: Stimulation of calcitonin gene-related peptide synthesis and release: Mechanisms for a novel antihypertensive drug, rutaecarpine. J Hypertens 22: 1819-1829, 2004.
56. Gumusel B, Hao Q, Hyman AL, Kadowitz PJ, Champion HC, Chang JK, Mehta JL and Lippton H: Analysis of responses to adrenomedullin-(13-52) in the pulmonary vascular bed of rats. Am J Physiol 274: H1255-H1263, 1998.
57. Zhao Q, Liu Z, Wang Z, Yang C, Liu J and Lu J: Effect of prepro-calcitonin gene-related peptide-expressing endothelial progenitor cells on pulmonary hypertension. Ann Thorac Surg 84: 544-552, 2007.
58. Keith IM, Tjen-A-Looi S, Kraiczi H and Ekman R: Three-week neonatal hypoxia reduces blood CGRP and causes persistent pulmonary hypertension in rats. Am J Physiol Heart Circ Physiol 279: H1571-H1578, 2000.
59. Qing X and Keith IM: Targeted blocking of gene expression for CGRP receptors elevates pulmonary artery pressure in hypoxic rats. Am J Physiol Lung Cell Mol Physiol 285: L86-L96, 2003.
60. Qin XP, Ye F, Hu CP, Liao DF, Deng HW and Li YJ: Effect of calcitonin gene-related peptide on angiotensin II-induced proliferation of rat vascular smooth muscle cells. Eur J Pharmacol 488: 45-49, 2004.
61. Gao YX, Jiang LL, Zhang Q, Zuo DZ and Li XW: Rutaecarpine protects against bleomycin-induced pulmonary fibrosis through inhibiting Notch1/eIF3a signaling pathway in rats. Zhongguo Zhong Yao Za Zhi 43: 3530-3538, 2018 (In Chinese).
62. Li JZ, Peng J, Xiao L, Zhang YS, Liao MC, Li XH, Hu CP, Deng HW and Li YJ: Reversal of isoprenaline-induced cardiac remodeling by rutaecarpine via stimulation of calcitonin gene-related peptide production. Can J Physiol Pharmacol 88: 949-959, 2010.
63. Ma ZG, Yuan YP, Wu HM, Zhang X and Tang QZ: Cardiac fibrosis: New insights into the pathogenesis. Int J Biol Sci 14: 1645-1657, 2018.
64. Li WQ, Tan SL, Li XH, Sun TL, Li D, Du J, Wei SS, Li YJ and Zhang BK: Calcitonin gene-related peptide inhibits the cardiac fibroblasts senescence in cardiac fibrosis via up-regulating klotho expression. Eur J Pharmacol 843: 96-103, 2019.

65. Li J, Carnevale KA, Dipette DJ and Supowit SC: Renal protective effects of α-calcitonin gene-related peptide in deoxycorticosterone-salt hypertension. Am J Physiol Renal Physiol 304: F1000-F1008, 2013.
66. Huang W, Rubinstein J, Prieto AR, Thang LV and Wang DH: Transient receptor potential vanilloid gene deletion exacerbates inflammation and atypical cardiac remodeling after myocardial infarction. Hypertension 53: 243-250, 2009.
67. Warzecha Z, Dembinski A, Ceranowicz P, Dembinski M, Cieszkowski J, Kownacki P and Konturek PC: Role of sensory nerves in gastroprotective effect of anandamide in rats. J Physiol Pharmacol 62: 207-217, 2011.
68. Young RL, Cooper NJ and Blackshaw LA: Chemical coding and central projections of gastric vagal afferent neurons. Neurogastroenterol Motil 20: 708-718, 2008.
69. Tache Y, Pappas T, Lauffenburger M, Goto Y, Walsh JH and Debas H: Calcitonin gene-related peptide: Potent peripheral inhibitor of gastric acid secretion in rats and dogs. Gastroenterology 87: 344-349, 1984.
70. Holzer P and Guth PH: Neuropeptide control of rat gastric mucosal blood flow. Increase by calcitonin gene-related peptide and vasoactive intestinal polypeptide, but not substance P and neurokinin A. Circ Res 68: 100-105, 1991.
71. Peskar BM, Ehrlich K and Peskar BA: Role of ATP-sensitive potassium channels in prostaglandin-mediated gastroprotection in the rat. J Pharmacol Exp Ther 301: 969-974, 2002.
72. Kinoshita Y, Inui T and Chiba T: Calcitonin gene-related peptide: A neurotransmitter involved in capsaicin-sensitive afferent nerve-mediated gastric mucosal protection. J Clin Gastroenterol 17 (Suppl 1): S27-S32, 1993.
73. Hayashi H, Ohno T, Nishiyama K, Boku K, Katori M and Majima M: Transient prevention of ethanol-induced gastric lesion by capsaicin due to release of endogenous calcitonin gene-related peptide in rats. Jpn J Pharmacol 86: 351-354, 2001.
74. Ohno T, Hattori Y, Komine R, Ae T, Mizuguchi S, Arai K, Saeki T, Suzuki T, Hosono K, Hayashi I, *et al*: Roles of calcitonin gene-related peptide in maintenance of gastric mucosal integrity and in enhancement of ulcer healing and angiogenesis. Gastroenterology 134: 215-225, 2008.
75. Shimozawa N, Okajima K, Harada N, Arai M, Ishida Y, Shimada S, Kurihara H and Nakagata N: Contribution of sensory neurons to sex difference in the development of stress-induced gastric mucosal injury in mice. Gastroenterology 131: 1826-1834, 2006.
76. Zhao Z, Gong S, Wang S and Ma C: Effect and mechanism of evodiamine against ethanol-induced gastric ulcer in mice by suppressing Rho/NF-κB pathway. Int Immunopharmacol 28: 588-595, 2015.
77. Li NS, Luo XJ, Dai Z, Liu B, Zhang YS, Yang ZC and Peng J: Beneficial effects of capsiate on ethanol-induced mucosal injury in rats are related to stimulation of calcitonin gene-related Peptide release. Planta Med 78: 24-30, 2012.
78. Luo XJ, Li NS, Zhang YS, Liu B, Yang ZC, Li YJ, Dong XR and Peng J: Vanillyl nonanoate protects rat gastric mucosa from ethanol-induced injury through a mechanism involving calcitonin gene-related peptide. Eur J Pharmacol 666: 211-217, 2011.
79. Liu YZ, Zhou Y, Li D, Wang L, Hu GY, Peng J and Li YJ: Reduction of asymmetric dimethylarginine in the protective effects of rutaecarpine on gastric mucosal injury. Can J Physiol Pharmacol 86: 675-681, 2008.
80. Luo XJ, Peng J and Li YJ: Recent advances in the study on capsaicinoids and capsinoids. Eur J Pharmacol 650: 1-7, 2011.
81. Czekaj R, Majka J, Ptak-Belowska A, Szlachcic A, Targosz A, Magierowska K, Strzalka M, Magierowski M and Brzozowski T: Role of curcumin in protection of gastric mucosa against stress-induced gastric mucosal damage. Involvement of hypoacidity, vasoactive mediators and sensory neuropeptides. J Physiol Pharmacol 67: 261-275, 2016.
82. Czekaj R, Majka J, Magierowska K, Sliwowski Z, Magierowski M, Pajdo R, Ptak-Belowska A, Surmiak M, Kwiecien S and Brzozowski T: Mechanisms of curcumin-induced gastroprotection against ethanol-induced gastric mucosal lesions. J Gastroenterol 53: 618-630, 2018.
83. Luo DN, Li FJ and Zou YY: Therapeutic effects of rutaecarpine on dextran sodium sulfate-induced experimental colitis in mice. Zhonghua Yi Xue Za Zhi 98: 533-538, 2018 (In Chinese).
84. Satyanarayana MN: Capsaicin and gastric ulcers. Crit Rev Food Sci Nutr 46: 275-328, 2006.
85. Yan L, Li QF, Rong YT, Chen YH, Huang ZH, Wang ZZ and Peng J: The protective effects of rutaecarpine on acute pancreatitis. Oncol Lett 15: 3121-3126, 2018.
86. Hu R, Li YJ and Li XH: An overview of non-neural sources of calcitonin gene-related peptide. Curr Med Chem 23: 763-773, 2016.
87. Luo D, Zhang YW, Peng WJ, Peng J, Chen QQ, Li D, Deng HW and Li YJ: Transient receptor potential vanilloid 1-mediated expression and secretion of endothelial cell-derived calcitonin gene-related peptide. Regul Pept 150: 66-72, 2008.
88. Li W, Zhang Z, Li X, Cai J, Li D, Du J, Zhang B, Xiang D, Li N and Li Y: CGRP derived from cardiac fibroblasts is an endogenous suppressor of cardiac fibrosis. Cardiovasc Res 116: 1335-1348, 2020.
89. Zhang YM, Peng J, Hu CP, Jiang QT, Jiang GL and Li YJ: Clonidine induces calcitonin gene-related peptide expression via nitric oxide pathway in endothelial cells. Peptides 30: 1746-1752, 2009.
90. Zhou Z, Peng J, Wang CJ, Li D, Li TT, Hu CP, Chen XP and Li YJ: Accelerated senescence of endothelial progenitor cells in hypertension is related to the reduction of calcitonin gene-related peptide. J Hypertens 28: 931-939, 2010.
91. Randhawa PK and Jaggi AS: TRPV1 channels in cardiovascular system: A double edged sword? Int J Cardiol 228: 103-113, 2017.
92. Eberhardt M, Dux M, Namer B, Miljkovic J, Cordasic N, Will C, Kichko TI, de la Roche J, Fischer M, Suárez SA, *et al*: H2S and NO cooperatively regulate vascular tone by activating a neuroendocrine HNO-TRPA1-CGRP signalling pathway. Nat Commun 5: 4381, 2014.