Abstract. G protein-coupled receptor kinase 2 (GRK2) is a key member of the G protein-coupled receptor kinase (GRK) family. GRK2 activity is regulated by the C-terminus of GRK2 which contains a plekstrin homology domain and the N-terminus of GRK2 which contains the RGS homology domain with binding sites for several proteins and lipids such as G protein-coupled receptors (GPCRs), G protein, phospholipase C, phosphatidylinositol 4,5-bisphosphate, extracellular signal-regulated kinase, protein kinase A and Gβγ. GRK2 phosphorylates the GPCR and enhances the affinity of binding to arrestins, which uncouple the receptors from G proteins, and target the receptors for desensitization and internalization. GRK2 also regulates non-GPCR desensitization and internalization by phosphorylation, and is important in maintaining the balance between the receptors and signal transduction. Previous findings have indicated that the upregulation of GRK2 in heart failure enhances dysfunctional adrenergic signaling and myocyte death. Collagen-induced arthritis induces the upregulation of GRK2 expression in fibroblast-like synoviocytes. In this review, we discussed the evidence for the association between altered GRK2 levels and various diseases, which suggests that GRK2 may be an effective drug target for preventing and treating heart failure, hypertension and inflammatory disease.

1. Introduction

G protein-coupled receptor kinase 2 (GRK2) belongs to a unique family of Ser/Thr protein kinases which are best known for their role in the rapid desensitization of G protein-coupled receptors (GPCRs) (1). The structural architecture of GRK2 comprises a central catalytic domain, an N-terminal domain which contains an RH domain (regulator of G protein signaling (RGS) homology domain) and a C-terminal domain. GRK2 activity is regulated by interactions with protein and lipid, including among others extracellular signal-regulated kinase (ERK), protein kinase A (PKA), protein kinase C (PKC) and Gβγ (2). Furthermore, GRK2 is also one of the key participants in signal transduction mediated through GPCRs as well as in the internalization and resensitization of GPCRs. GRK2 is broadly distributed and participates in the regulation of β-adrenergic receptor (β-AR), angiotensin II1A receptor (AT1A-R) and chemokine receptors amongst others, which play important roles in vascular function, immunity and inflammation.

The protein and mRNA levels of GRK2 in peripheral blood lymphocytes are increased in patients with heart failure (HF) or hypertension, and collagen-induced arthritis (CIA) induces the upregulation of GRK2 expression in fibroblast-like synoviocytes (FLSs). GRK2 is upregulated in heart failure, hypertension, CIA and cancer, and it appears to play a critical role in disease progression (38,43). Previous research has shown that the inhibition of cardiac GRK2 improves the functional and morphological parameters of the failing heart and reduces cardiotoxicity by promoting a cardiomyocyte survival program (3). Decreased GRK2 expression may promote adrenergic receptor (AR)–stimulated vasodilation and protect against angiotensin II (Ang II)–induced hypertension by increasing nitric oxide bioavailability (4). Thus, the inhibition of GRK2 may represent a viable therapeutic option for the treatment of diseases including HF, hypertension and CIA.

Regulatory effects of GRK2 on GPCRs and non-GPCRs and possible use as a drug target (Review)

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2. Structural features of GRK2

The GRK2 tertiary structure domain contains a central catalytic domain, an N-terminal domain and a carboxyl-terminal domain (Fig. 1). The N-terminus of GRK2 contains the RH domain which plays a vital role in receptor recognition and intracellular membrane anchoring. The C-terminal domain of GRK2 may promote subcellular localization and agonist-dependent translocation by combining with lipids and other membrane proteins. The N-terminus of GRK2 interacts selectively with Goqα and inhibits the Goα-mediated activation of phospholipase C (PLC) by sequestering Goα. The C-terminus plekstrin homology (PH) domain of GRK2, which interacts with phosphatidylinositol 4,5-bisphosphate (PIP2) and free Gβγ subunits, can mediate the agonist-dependent translocation of GRK2 to the plasma membrane.

3. Modulation of GRK2 activity

GRK2 exists on the cell membrane and microsome membrane. It was originally described as a soluble, cytosolic enzyme that transiently translocates to the plasma membrane upon receptor activation. However, GRK2 activity is regulated by interactions with protein and lipid. The ERK phosphorylation site at Ser670 and the S-nitrosothiols (SNOs) S-nitrosylation site at Ser340 lead to the inhibition of GRK2; the PKA phosphorylation site at Ser685. Tyr-13, 86 and 92 of GRK2 phosphorylation and Gβγ binding can promote GRK2 activation.

Activation of ERK inhibits GRK2 activity. GRK2 plays an important role in the stimulation of the ERK/mitogen-activated protein kinase (MAPK) cascade to regulate the function of β2-AR. The inhibition of ERK activity potentiates GRK2 activity, and the activation of β2-AR promotes the phosphorylation of GRK2 regulated by ERK (5). COS-7 cells were transfected with GRK2, active MEK1, dominant-negative (DN) MEK and β2-AR and treated with the β-agonist isoproterenol for different periods of time. DN MEK strongly promoted a marked (2-3-fold) increase in the phosphorylation of β2-AR by GRK2, and active MEK1 weakly inhibited the phosphorylation of β2-AR by GRK2. Thus, active MEK was considered as a kinase to promote GRK2 phosphorylation; it inhibited GRK2 kinase activity leading to the increased phosphorylation of GRK2, which finally inhibited GRK2 activity and the activation of β2-AR by GRK2. Conversely, GRK2 phosphorylation by DN MEK1 results in the promotion of β2-AR phosphorylation by GRK2. The phosphorylation of GRK2 by ERK at Ser670 may inhibit GRK2 kinase activity, and this plays an important role in regulating the function of the receptor.

SNOs decrease GRK2 activity. Previous research has shown that S-nitrosylation of GRK2 at Cys340 by CysNO leads to the inhibition of GRK2 activity and the decreased phosphorylation of β2-AR (6). To identify S-nitrosylation sites in GRK2, experiments were performed by mapping the sites of S-nitrosylation among the 15 cysteines of GRK2. 293 cells were transfected with Y326A β2-AR, GRK2 wild-type (wt), GRK2 C340S and GRK2 C439S. CysNO inhibited β2-AR phosphorylation by either GRK2 wt or C439S but had no effect on receptor phosphorylation by GRK2 C340S. The results suggested that GRK2 is S-nitrosylated at the site of Cys340. S-nitrosylation inhibits exogenous GRK2 and endogenous GRK2 phosphorylation as well as S-nitrosylation. In addition, S-nitrosylation of GRK2 is associated with β2-AR internalization; S-nitrosylation of GRK2 showed a significant decrease in agonist-stimulated β2-AR internalization, whereas cells expressing GRK2 C340S actually showed a slight increase in agonist stimulated β2-AR internalization.

Binding of Gβγ promotes GRK2 activity. Free Gβγ subunits bind to GRK2 with high affinity and are involved in the association of GRK2 to lipid vesicles and GPCR phosphorylation in reconstituted systems (7). Binding of Gβγ promotes GRK2 activity upon enhancing the GPCR-mediated allosteric activation of GRK2. GRK2 has multisite contact with Gβγ involving the PH domain Arg-587 and Lys-663, 665 and 667. Notably, the Arg-587 mutant not only reduces the interaction of GRK2 with Gβγ but also impairs the allosteric activation of GRK2, which suggests that Arg-587 may be an important site for inducing the conformational switch of GRK2. In addition, Gβγ subunits aid in the targeting of GRK2 to membranes and may also assist in determining the substrate specificity of these enzymes. The N-terminus of GRK2 (1-55aa) was also a Gβγ-binding site.

PKA-mediated GRK2 phosphorylation. Agonist-stimulated PKA-mediated phosphorylation of GRK2 may represent a mechanism for enhancing receptor phosphorylation and desensitization (8). GRK2 has three potential sites of PKA phosphorylation, including S670, S676 and S685. To investigate PKA phosphorylation sites on GRK2, high pressure liquid chromatography fractionation and sequencing of radiolabeled peptides results showed that the residues 678-689 of GRK2 contain a single site of phosphorylation at serine 685. Thus, PKA directly phosphorylates GRK2 on serine 685. PKA activated by Gs-coupled receptors phosphorylates GRK2, enhances Gβγ subunit binding to membrane targeting and enhances the ability of the kinase to translocate to the membrane and phosphorylate the receptor. Mutation of S685 to alanine (S685A) greatly attenuated GRK2-mediated translocation to β2-AR and the phosphorylation of agonist-occupied β2-AR leading to a subsequent decrease in receptor internalization.

4. Effects of GRK2 on receptor function

As the most widely expressed member of GRK family, GRK2 plays an important role in the regulation of GPCRs and non-GPCRs (Table I). GRK2 phosphorylates GPCRs and enhances the affinity of binding to arrestins, which uncouple the receptors from G proteins, and target the receptors for desensitization and internalization (Fig. 2A). G protein is not involved in the phosphorylation of GRK2 on non-GPCRs, and the association of β-arrestin1 (β-arrestin1) and insulin-like growth factor-1 receptor (IGF-1R) is one of transient binding (Fig. 2B).

Regulatory effects of GRK2 on β2-AR. β2-AR is a GPCR with a common structural signature of seven membrane-spanning helices (3). β2-AR which is activated by epinephrine plays a key role in physiologic cardiovascular processes. The β2-AR contains relatively unstructured regions that are involved in functionally important protein-protein interactions. The C-terminus and...
the third intracellular loop of β2-AR are the most unstructured regions (9). The N- and C-terminal ends of the third intracellular loop of β2-AR are associated with G protein activation and the selectivity of the interaction of GPCR and G protein. The C-terminus of β2-AR interacts with GRK2, arrestins and other signaling molecules (10). In 293 cells, the phosphorylation of β2-AR is regulated by GRK2, which promotes β2-AR desensitization and internalization. To identify the phosphorylation sites on the β2-AR for which GRK2 is responsible, experiments were performed involving the silencing of these kinases separately from cells and subsequently using stable isotope labeling with amino acids in cell culture (SILAC) to quantitatively measure the extent of phosphorylation at each site in cells stimulated with isoproterenol. The following GRK2 phosphorylation sites of β2-AR were examined: Thr360, Ser364, Ser396, Ser401, Ser407, and Ser411 (11).

Regulatory effects of GRK2 on angiotensin II receptor. The AT1A-R is well known to mediate multifarious angiotensin-dependent physiological responses such as vasoconstriction, smooth muscle cell motility and growth, and secretion (12). Furthermore, Ang II type-1 (AT1) receptors exert complex and diverse physiological actions which are associated with a number of diseases or disorders such as hypertension, hypertrophy, fibrosis, thrombosis and atherosclerosis. It demonstrates that overexpression of GRK2 significantly promotes agonist-induced phosphorylation of AT1A-R in 293 cells. Knockdown of GRK2 leads to a significant decrease in the internalization of the AT1A-R, and it mainly slows down the speed of AT1A-R internalization (13). It has been suggested that GRK2 may promote AT1A-R overexpression in the myocardium, which attenuated contractility and heart rate in response to Ang II (14). GRK2 as a major kinase may promote the phosphorylation of AT1A-R, and it can regulate β-arrestin-mediated internalization and endocytosis of AT1A-R.

Regulatory effects of GRK2 on chemokine receptor. Chemotactic chemokine, relative molecular mass of 7-10 kDa of proinflammatory cytokines, can be produced by a variety of cells. Chemokine receptors are widely expressed in various cells of the immune system and regulate the immune cells during the inflammatory response. The activation of white blood cells and the chemotaxis function of chemokines play an important role in a number of physiological and pathological processes such as embryonic development, angiogenesis and tumor development. The activation of T cells produces different chemokines and their receptors; these substances are capable of inducing a target cell to migrate to the inflammatory site.

Many studies have shown the involvement of GRK2 in the desensitization and internalization of chemokine receptors such as CCR5, CCR2, CXCR4, CXCR2 as well as chemotactic receptors for substance P. GRK2 expression and kinase activity are associated with ERK1/2 and MEK1/2 of chemokine receptor signaling in astrocytes (15). A decreased GRK2 level significantly promoted the CCL2-induced phosphorylation of ERK1/2. Overexpression of GRK2 inhibited CCL2-induced Akt phosphorylation without altering CCL2-induced ERK1/2 phosphorylation. Simultaneously, chemokine-induced Akt phosphorylation required the kinase activity of GRK2, but the change in the activation of GRK2 was not sufficient to alter CCL2-induced ERK1/2 phosphorylation (15). In astrocytes, GRK2 controls the internalization of CXCR7 and regulates SDF-1/CXCL12 signaling (16). Chemokine receptor and the related substances regulated by GRK2 are associated with the migration of white blood cells to the inflammatory lesion as well as the activation and proliferation of white blood cells.

Regulatory effects of GRK2 on IGF-1R. IGF-1R is a transmembrane receptor tyrosine kinase (RTK), and it regulates cellular proliferation, survival and metastasis, making this receptor an attractive target for cancer treatment (28). A previous study showed that GRK2 as serine kinases for IGF-1R, DN GRK2 mutant resulted in reduced cellular proliferation by regulating the IGF-1R (29). The GRK2-dependent phosphorylation of IGF-1R serine residues is the underlying mechanism responsible for β-arrestin binding to these residues, and serines 1248 and 1291 are the major phosphorylation sites of the IGF-1R. In 293T cells, GRK2 overexpression enhanced the association of GRK2 with the IGF-1R, augmented IGF-1-induced ubiquitination, and increased basal levels of β-arr1/IGF-1R association.
Table I. GRK2 regulates GPCRs and non-GPCRs.

<table>
<thead>
<tr>
<th>Type of receptor</th>
<th>Function</th>
<th>Refs.</th>
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<tbody>
<tr>
<td><strong>GPCRs</strong></td>
<td></td>
<td></td>
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<tr>
<td>β₂-adrenergic receptor (β₂-AR)</td>
<td>GRK2-mediated phosphorylation promotes desensitization and internalization of β₂-AR</td>
<td>(3,11)</td>
</tr>
<tr>
<td>Angiotensin II receptor (ATⅡ-R)</td>
<td>GRK2 promotes phosphorylation of AT₁A-R, and participates in β-arrestin-mediated internalization and endocytosis of AT₁A</td>
<td>(13,14)</td>
</tr>
<tr>
<td>Chemokine receptor</td>
<td>GRK2 involved in the desensitization and internalization of chemokine receptors</td>
<td>(15)</td>
</tr>
<tr>
<td>Adenosine receptors</td>
<td>GRK2-mediated desensitization of adiponectin receptor</td>
<td>(18)</td>
</tr>
<tr>
<td>TPβ isofrom of human</td>
<td>Effect of overexpressing a dominant-negative form</td>
<td>(19)</td>
</tr>
<tr>
<td>thromboxane A₂ receptor (TP)</td>
<td>of GRK2 on agonist-induced desensitization of TPβ</td>
<td></td>
</tr>
<tr>
<td>GABAB receptors (GABABR)</td>
<td>Co-expression of GRK2 had no effect on GABA(B) receptor-mediated desensitization processes</td>
<td>(20,21)</td>
</tr>
<tr>
<td>Lysophosphatidic acid receptor (LPAr)</td>
<td>GRK2 and β-arrestin1 desensitized LPAr-mediated signaling and regulated LPA-stimulated functional effects in FRTL-5 cells</td>
<td>(22)</td>
</tr>
<tr>
<td>Dopamine receptor</td>
<td>GRK2 was capable of regulating D2DAR activity in the absence of receptor phosphorylation</td>
<td>(23,24)</td>
</tr>
<tr>
<td>Smo</td>
<td>GRK2-mediated phosphorylation of Smo signaling cascade</td>
<td>(25,26)</td>
</tr>
<tr>
<td><strong>Non-GPCRs</strong></td>
<td></td>
<td></td>
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<tr>
<td>Platelet-derived growth factor receptor-β (PDGFR)</td>
<td>GRK2-mediated phosphorylation induced desensitization of PDGFRβ</td>
<td>(27)</td>
</tr>
<tr>
<td>Insulin-like growth factor-1 receptor (IGF-1R)</td>
<td>GRK2 negatively regulated IGF-1R signaling pathway</td>
<td>(28)</td>
</tr>
<tr>
<td>Epidermal growth factor receptor (EGFR)</td>
<td>GRK2 promoted serine phosphorylation of EGFR</td>
<td>(30)</td>
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</tbody>
</table>

GRK2 interacts with GPCRs and non-GPCRs, and participates in the regulation of GPCR and non-GPCR signaling pathways. GRK2, G protein-coupled receptor kinase 2; GPCRs, G protein-coupled receptors.

5. Possible effects of GRK2 in some diseases

GPCRs are involved in regulating the actions of messengers such as catecholamines, endothelins, angiotensins and chemokines. Such substances are important regulators of cardiovascular functions, which participate in cardiovascular development, and in controlling the growth and remodeling of myocardial cells. Simultaneously, the desensitization of GPCR contributes to the regulation of cardiovascular disease. The β-adrenergic receptor, Ang II AT1R and chemokine receptor are regulated by GRK2; these receptors are known to play a central role and represent an important target for the treatment of chronic HF, angina pectoris and hypertension, rheumatoid arthritis and malignant tumors. GRK2 inhibition may prove to be positive and valuable as a therapy for these diseases.

**Potential role of GRK2 in HF.** HF is a chronic clinical syndrome, which is characterized by reduced left ventricular function. The prominent physical characteristic is the desensitization and downregulation of β-adrenergic receptors modulated by GRK2 (31). The β-adrenergic receptor regulates the normal function of the heart and the activation of myocardial β-adrenergic receptors leads to the activation of cAMP signaling pathways and increased ventricular ejection, heart rate and cardiac output. Overexpression of cardiac GRK2 leads to sympathetic hyperactivity and the attenuation of β-adrenergic receptor activity, which promotes the development of HF. To elucidate the role of GRK2 in the development of HF, lymphocyte GRK2 may be a surrogate for myocardial GRK2 in human heart disease (32). Evidence suggests that myocardial GRK2 activity is increased almost three fold in the ventricles of patients with congestive HF and the protein and mRNA levels of GRK2 are also increased (33). With the exacerbation of hemodynamic dysfunction and HF, the expression of lymphocyte GRK2 is also upregulated in HF (34). Thus, adrenal GRK2 appears to be a major regulator of the sympathetic stimulation of the heart. Recently, the selective serotonin reuptake inhibitor antidepressant paroxetine
was shown to play a role as a selective inhibitor of GRK2 activity both in vitro and in living cells (35). It specifically bound to the catalytic domain of GRK2 as an off-target and inhibited kinase activity in the micromolar range of affinity and inhibited the phosphorylation of the thyrotropin-releasing hormone receptor by GRK2 (36). In a mouse model of HF, paroxetine-mediated inhibition of GRK2 may have improved cardiovascular signaling and function (37). Chronic paroxetine treatment improves cardiac function, reverses sympathetic nervous system overdrive and normalizes the myocardial β-adrenergic system after myocardial infarction.

Potential role of GRK2 in hypertension. The exploration of GRK2 functions provided a novel research area for developing treatments for hypertension. Essential hypertension is the most dangerous factor in the development of myocardial infarction, HF and cerebrovascular disease. GRK2 plays an important role in the development of hypertension (25).

Moreover, GRK2 is also involved in the cell cycle as well as the migration and differentiation of vascular smooth muscle. GRK2 protein levels and activity in peripheral blood lymphocytes are also increased in hypertensive patients (38). With the increased GRK2-mediated phosphorylation of β-adrenergic receptor, the diastolic function of blood vessels weakens and blood pressure increases. GRK2 overexpression in vascular smooth muscle cells in mice decreased the β-adrenergic receptor signal transduction and led to myocardial hypertrophy and hemal wall thickening (39). Based on previous research, the increased GRK2 expression in the arterial smooth muscle may enhance the proliferation and migration of vascular smooth muscle cells leading to atherosclerosis (40).

Potential role of GRK2 in inflammatory and immune diseases. Rheumatoid arthritis (RA) is a chronic, destructive autoimmune and inflammatory disease characterized by chronic synovial...
inflammation and progressive articular damage to multiple joints (41). FLSs, the key effector cells in the inflamed joint, release many proinflammatory and matrix-degrading effector molecules (42). Alterations in GRK2 levels in immune cells play an important role in the development of inflammation. A previous study indicated that a chronic inflammatory process in CIA induces the upregulation of GRK2 expression in FLSs (43). Paeoniflorin is a monoterpenic glucoside and the main component of the total glucosides of paeony (TGP) extracted from the roots of *Paeonia lactiflora* (*Paeoniaceae*), which has been reported to be therapeutically effective in the treatment of RA, to decrease GRK2 expression in FLSs in vitro and to suppress the proliferation of FLSs in CIA. Downregulation of GRK2 may be one of the most important mechanisms through which Pae suppresses the proliferation of FLSs in CIA.

**Potential role of GRK2 in Alzheimer’s disease (AD).** AD is a neurodegenerative disorder, which leads to the loss of memory and other cognitive functions (44). GRK2 is an important protein in a unifying theory of AD pathogenesis, and the change in GRK2 expression is an early contributor to the development of AD pathology. The mRNA and protein expression of GRK2 was upregulated in the lymphocytes of AD patients compared with the controls (45) as well as in post-mortem hippocampal tissues in AD patients and in rats with chronic brain hyperperfusion (46). Mounting evidence points to the possible involvement of GRK2 in the early pathogenesis of AD. Overexpression of GRK2 is a primary hallmark of mitochondrial lesions during early AD, and subcellular localization of GRK2 immunoreactivity demonstrated that GRK2 immunoreactivity was associated with damaged cellular compartments, particularly mitochondria and/or mitochondria-derived lysosomes or granular/vacuolar degenerative structures (47). Therefore, the downregulated expression of GRK2 may become a novel therapeutic strategy for AD.

**Potential role of GRK2 in cancer.** The finding that GRK2 regulates chemokine receptors, thyroid stimulating hormone receptor and other members of the GPCR family, has opened new fields of research into the mechanism of tumor development and into the exploitation of targeted drugs. It has been demonstrated that overexpression of GRK2 inhibits the growth of human hepatocellular carcinoma cells (48). Compared with the transfection of GRK2 kinase-defective mutant K220R in liver cancer cells, the transfection of GRK2 wt markedly decreased the proliferation of liver cancer cells. Further research showed that GRK2 overexpression induces the phosphorylation of p53 in liver cancer cells, which inhibits liver cancer cell growth. Thus, GRK2 overexpression may provide a novel perspective for the treatment of liver cancer.

6. Conclusion

GRK2, a typical GPCR kinase, promotes the phosphorylation and internalization ofGPCRs and some non-GPCRs. The study of the structure and function of GRK2 indicated that GRK2 is composed of 689 amino acid residues and three important domain structures: an N-terminal domain, catalytic domains and a C-terminal domain (49). Each domain structure has a unique function. The composition of the N-terminal domain of approximately 185 amino acids allows it to combine with Go/11, G**β**γ, α-actin, caveolin and calmodulin for example, and contains PKC and c-Src phosphorylation sites. The catalytic domain is composed of approximately 270 amino acids and includes an S-nitrosylation site (Cys340), and an important locus for determining GRK2 catalytic activity (Lys220). The composition of the C-terminal domain of approximately 230 amino acids allows it to combine with PI3K, Akt, PIP2, clathrin, G**β**γ, caveolin and calmodulin, and includes PKA and ERK phosphorylation sites.

GRK2 is highly expressed in the brain, leukocytes, heart and spleen, and this expression pattern suggests that GRK2 plays an important role in neurotransmission, cardiovascular function and immune and inflammatory responses. Previous studies showed that the expression of GRK2 in peripheral blood lymphocytes was increased in HF. GRK2 levels may reflect haemodynamic impairment and may be of prognostic value following myocardial infarction. GRK2 protein levels and activity in peripheral blood lymphocytes are increased in hypertensive patients, which suggest that upregulated GRK2 levels may induce metabolic alterations and lead to insulin resistance, a common feature observed in hypertensive patients. A chronic inflammatory process in CIA induces the upregulation of GRK2 expression in FLSs, which may be one of the important mechanisms responsible for the change in the expression of GRK2 and in the proliferation of FLSs.

The antidepressant paroxetine and the stabilization of off-pathway conformational states unique to GRK2 offer a direction for the development of GRK2 inhibitors and even more selective inhibitors. Previous findings showed that paroxetine as an inhibitor of GRK2 exhibits 50-fold selectivity over other GRKs; the binding of paroxetine to the active site of the GRK2 kinase domain is very high, and the benzodioxole ring of paroxetine interacts with the hinge of GRK2. Paroxetine, a selective GRK2 inhibitor, has applications in the reversal of cardiac dysfunction and remodeling after myocardial infarction. The vast amount of research regarding GRK2 inhibitors suggest that the potential therapeutic effects of GRK2 inhibition may lead to novel candidates for the prevention and treatment of HF, hypertension and inflammatory diseases. The application of emerging technologies as well as gene knockout studies, gene cloning and the progress of research into functional genomics and proteomics will enable studies of GRK2 to achieve breakthroughs.

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