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Mini-review

Cardiovascular ATP-sensitive K^+ channel as a new molecular target for development of antihypertensive drugs[1]

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There are one hundred million hypertensive patients or more in China[1]. Most of them take medicine in their daily life. And the demands for antihypertensive drugs are great[2]. Now about two hundreds of drugs are available and can be used in antihypertensive treatments. These drugs can be classified into several types, such as blockers for central and peripheral sympathetic nervous system, inhibitors of renin-angiotensin system, diuretics, and ion channel modulators. Although some of the antihypertensive drugs including calcium channel blockers and angiotensin-converting enzyme inhibitors (ACEI) have many advantages in pharmacodynamics[3,4], they are not recommended as the first line drugs. Only β receptor blockers and diuretics have been recognized as antihypertensive drugs of first choice. These two kinds of antihypertensive drugs have some metabolic adverse effects. For example, β receptor blockers increase serum triglyceride level and reduce HDL cholesterol; and diuretics induce electrolyte and fluid derangement. Thus the interests in developing novel antihypertensive drugs especially acting in new molecular targets are increasing.

ATP-sensitive potassium channels were first discovered in 1983, and the channel nomination was established in 1988. Since then ATP-sensitive potassium channels have been recognized as a new molecular target for developing novel antihypertensive drugs[5,6]. Now 1 compound is in clinical trial of phase 3, 8 compounds are in clinical trial of phase 2, 9 compounds are in clinical trial of phase 1, 104 compounds have revealed some pharmacological advantages, and are in preclinical investigations.

In recent years, the pharmacological characteristics of cardiovascular ATP-sensitive potassium channels and the activator (KCA) pinacidil have been extensively studied, which suggests that it is a promising molecular target for developing novel KCA antihypertensive drugs[7].

Experimental therapeutic effects of pinacidil on hypertensive cardiovascular remodeling

Essential hypertension in human and spontaneously hypertensive rats (SHR) are associated with the structural and functional changes in cardiovascular system, which have been recognized as hypertensive cardiovascular remodeling. All antihypertensive drugs are capable of reducing blood pressure, but the effects on cardiovascular remodeling are different from each other. Recently, the therapeutic effects of the inhibitors for renin-angiotensin system on hypertensive cardiovascular remodeling have been identified in human and laboratory animals[8]. The experimental therapeutic effects of KCA pinacidil on hypertensive cardiovascular remodeling have been investigated in SHR.

SHR of 3-month-old, were treated with pinacidil 2 $mg \cdot kg^{-1}$ or ACEI lisinopril 12 $mg \cdot kg^{-1}$, *po*, once a day for 30 d. The blood pressure was decreased by 6 - 8 kPa to the level of normotensive rats (NTR) at the same age, the therapeutic effects of pinacidil on hypertensive cardiovascular remodeling were evaluated.

Effects of pinacidil on hypertensive vascular remodeling The structural hypertensive remodeling of SHR aorta was characterized by the increase in media thickness and the ratio between media thickness and lumen diameter, but lumen diameters remained unchanged. And that of SHR mesenteric arteries was characterized by the increase in media thickness, the decrease

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in lumen diameter, and the increase in ratio between media thickness and lumen diameter. These increases in the media thickness and in the ratio between media thickness and lumen diameter could be reversed, but the lumen diameter could not be affected by the treatment with pinacidil. The therapeutic effects of pinacidil on hypertensive structural vascular remodeling were similar to those of ACEI lisinopril[9].

In the isolated preparations of aorta derived from SHR, the constrictive responses to norepinephrine or potassium chloride were decreased, which could be reversed by the treatment with pinacidil or lisinopril[10]. The isolated aorta derived from SHR, preconstricted with norepinephrine 10 $\mu mol \cdot L^{-1}$, the decreased vasodilatory effects of pinacidil could be reversed by the treatments with pinacidil rather than lisinopril. The increased vasodilatory effects of nifedipine and the decreased vasodilatory effects of sodium nitroprusside could be reversed by the treatment with pinacidil or lisinopril[10]. It was suggested that the hypertensive vascular remodeling can be reversed by the treatment with pinacidil in SHR. The therapeutic characteristics of pinacidil are similar to those of lisinopril, excepting that the decreased sensitivity of ATP-sensitive potassium channels to the activator pinacidil-induced vasodilations can be reversed by the treatment with pinacidil rather than lisinopril.

Effects of pinacidil on hypertensive cardiac remodeling There were no significant differences in the structural parameters of hearts derived from SHR and NTR at the age of 4 months, including the heart weight, size, and left ventricular thickness. But the body weight of SHR were less than those of NTR. So the ratio between heart weight and body weight was increased in SHR. The structural parameters of the hearts and the increased ratio between heart weight and body weight could not be affected by the antihypertensive treatment with pinacidil or lisinopril[11].

In the isolated working hearts derived form SHR, the values of the maximal rate of the increase of left ventricular pressure ($+dp/dt_{max}$), the physiologic velocity of contractile element shorting (Vpm), coronary blood flow (CBF), and aorta blood flow (ABF) were decreased. After the SHR were treated with pinacidil or lisinopril, the decreases in $+dp/dt_{max}$ and Vpm could be reversed, the decreases in CBF remained unchanged, but the decreases in ABF were further decreased. It can be concluded that the structural parameters of the hearts derived from SHR are not affected, but some functional cardiac remodeling including the decreases in $+dp/dt_{max}$ and Vpm can be reversed by the treatment with pinacidil or lisinopril[11].

Comparison of pharmacological characteristics between ATP-sensitive potassium channels and voltage-dependent calcium channels in cardiovascular system

Activation of ATP-sensitive potassium channels can induce potassium efflux, membrane hyperpolarization, antagonizing voltage-dependent calcium channels, blocking calcium influx, and subsequently resulting in vasorelaxations[7]. KCA can block voltage-dependent calcium channels indirectly, but the calcium channel antagonists such as nifedipine can directly block voltage-dependent calcium channels. There are many similarities between pinacidil and nifedipine in antihypertensive actions in human and SHR, thus the cardiovascular pharmacological characteristics of pinacidil and nifedipine were compared in the following series of experiments.

Effects of pinacidil on intracellular calcium release-induced vasoconstriction The vasodilatory effects of pinacidil and nifedipine were compared in the isolated preparations of rat aorta. The median effective concentration (EC_{50}) values of pinacidil for dilating the arteries preconstricted with potassium chloride 20 or 80 $mmol \cdot L^{-1}$, were 9 or 81 times more than those of nifedipine, respectively. The EC_{50} value of pinacidil for dilating the arteries precontracted with norepinephrine 10 $\mu mol \cdot L^{-1}$ was 1/10 of that of nifedipine[12].

In the calcium-free solutions, pinacidil rather than nifedipine or nicardipine could dilate the arteries preconstricted with norepinephrine or endothelin-1 in a concentration-dependent manner[12-14]. It was indicated that the antagonistic effects of pinacidil on voltage-dependent calcium channels are less potent than those of nifedipine. In addition, activation of

ATP-sensitive potassium channels by pinacidil can depress vasoconstrictions evoked by intracellular calcium release. But blockage of voltage-dependent calcium channels by nifedipine, nicardipine, and its derivatives has no effects on vasoconstrictions evoked by intracellular calcium release.

Effects of pinacidil on the cardiac functions In isolated working hearts of rats, pinacidil 1 – 10 $\mu mol \cdot L^{-1}$ increased heart rates, 10 $\mu mol \cdot L^{-1}$ produced negative inotropic actions and reduced aortic output, but had no effects on the CBF. Nifedipine or nicardipine 1 $\mu mol \cdot L^{-1}$ produced a prominent negative inotropic and chronotropic actions, and decreased aortic output and CBF. It was suggested that pinacidil, nifedipine, and nicardipine had direct effects on hearts, but their characteristics were different. Pinacidil had positive chronotropic action and mild or moderate negative inotropic action, while nifedipine or nicardipine had prominent negative chronotropic and inotropic actions[13,15].

In pentobarbital-anesthetized NTR, both pinacidil and nifedipine at 1 $mg \cdot kg^{-1}$ iv decreased blood pressure and heart rates[16]. In conscious NTR, both pinacidil and nifedipine could also decrease blood pressure, but increase heart rates. The tachycardia effects of pinacidil may be attributable to its positive chronotropic action and the hypotension-induced reflex tachycardia. The cardiovascular effects of pentobarbital may be responsible for pinacidil-induced bradycardia in rats.

Hypertensive functional remodeling of ATP-sensitive potassium channels in cardiovascular system In the isolated arota derived from 4-month-old SHR, preconstricted with norepinephrine 10 $\mu mol \cdot L^{-1}$, the vasodilatory responses to pinacidil were decreased, but those to nifedipine were increased. It was suggested that the sensitivity of vascular ATP-sensitive potassium channels to the activator pinacidil was decreased, but the sensitivity of vascular calcium channels to the blocker nifedipine was increased in 4-month-old SHR[9,10].

In the isolated aorta derived from 8-month-old SHR, preconstricted with norepineprine 10 $\mu mol \cdot L^{-1}$, the vasodilatory responses to pinacidil were increased, while those to nifedipine remained unchanged[17]. It was suggested that the sensitivity of vascular ATP-sensitive potassium channels to the activator pinacidil was increased, while the sensitivity of voltage-dependent calcium channels to the antagonist nifedipine remained unchanged in 8-month-old SHR.

In the isolated aorta from SHR at the age of 15 months preconstricted with norepinephrine 10 $\mu mol \cdot L^{-1}$, pinacidil 1 – 5 $\mu mol \cdot L^{-1}$ produced vasodilations, but 10 $\mu mol \cdot L^{-1}$ produced the initial constriction and followed by dilation. On the same experimental conditions, nifedipine only produced vasodilation. When the isolated aorta preparations, derived from NTR and SHR at the age of 4 or 8 months, were preconstricted with norepinephrine or potassium chloride, pinacidil 1 – 10 $\mu mol \cdot L^{-1}$ only produced vasodilation[18].

In the isolated working hearts derived from SHR at 3 – 4 months, pinacidil 1 – 10 $\mu mol \cdot L^{-1}$ produced moderate positive chronotropic aciton and temperate negative inotropic action[15]. But in the working hearts from SHR at 8 – 15 months, pinacidil 0.1 – 10 $\mu mol \cdot L^{-1}$ had no effects on the cardiac functions[16-18]. It was suggested that the sensitivity of cardiac ATP-sensitive potassium channels to the activator pinacidil was decreased in SHR with age.

Modulations of cardiovascular ATP-sensitive potassium channels

Modulations by adenosine on cardiovascular ATP-sensitive potassium channels In pentobarbital-anesthetized rats, excitation of cardiovascular adenosine receptors by adenosine 1 – 5 $mg \cdot kg^{-1}$ iv could decrease blood pressure, Vpm, $+dp/dt_{max}$, and the maximal rate of the decrease of left ventricular pressure ($-dp/dt_{max}$), in a dose-dependent manner, which could be prevented by aminophylline 10 $mg \cdot kg^{-1}$ iv, a nonselective antagonist for adenosine receptors, and could also be prevented by glibenclamide 20 $mg \cdot kg^{-1}$ iv. Glibenclamide is a rather highly selective antagonist for ATP-sensitive potassium channels, at the dose of 20 $mg \cdot kg^{-1}$ could prevent the cardiovascular effects of pinacidil, but had no effects on cardiovascular effects of nifedipine[16]. It was suggested that the activation of ATP-sensitive potassium channels was involved in the

adenosine receptor-mediated cardiovascular actions.

In isolated rat aorta preconstricted with norepinephrine 10 $\mu mol \cdot L^{-1}$, adenosine 1 – 300 $\mu mol \cdot L^{-1}$ produced initial constriction and subsequent dilation in a concentration-dependent manner. When the functions of ATP-sensitive K^+ channels were blocked by glibenclamide 1 – 100 $\mu mol \cdot L^{-1}$, only vasoconstrictions could be induced by adenosine. When ATP-sensitive potassium channels were activated by pinacidil at the EC_{60}, adenosine could not produce further vasodilations[19]. The association and dissociation kinetics of [^{3}H]glibenclamide binding with ATP-sensitive potassium channels in blood vessels could be delayed and accelerated respectively in the presence of adenosine (unpublished data). Excitation of adenosine A_1 or A_2 receptors by selective agonist N^6-cyclopentyladenosine or 5′-(*N*-cyclopropyl) carbox-amido adenosine respectively mediated vasorelaxations, which could not be prevented by glibenclamide (unpublished data). It was suggested that the activation of ATP-sensitive potassium channels was involved in adenosine receptor-mediated vasodilations rather than vasoconstrictions. And only a part of vascular adenosine receptors may be coupled with ATP-sensitive potassium channels, but the pharmacological characteristics of these adenosine receptor subtypes remains to be further investigated.

Modulation of vascular [^{3}H]glibenclamide binding sites ATP-sensitive potassium channels are composed of the inward rectifier potassium channels (Kir 6.2) and sulfonylurea receptors. Glibenclamide is a highly selective ligand for sulfonylurea receptors, and can block the functions of ATP-sensitive potassium channels. The molecular pharmacological characteristics of [^{3}H]glibenclamide binding sites were studied in blood vessels.

The KCA pinacidil could not displace the specific binding of [^{3}H]glibenclamide. But the association and dissociation kinetics of [^{3}H]glibenclamide binding with sulfonylurea receptors were delayed and accelerated respectively by pinacidil. Thus the binding sites of ATP-sensitive potassium channel activators and blockers were different, and there was allosteric modulation between them. ATP at the concentration of 1 $mmol \cdot L^{-1}$ could accelerate the association kinetics but could delay the dissociation kinetics of [^{3}H] glibenclamide (unpublished data). It was suggested that ATP was an allosteric factor of [^{3}H] glibenclamide binding sites, and the antagonistic effects of glibenclamide on ATP-sensitive potassium channels were more potent in the presence of ATP.

Modulation of vascular KCA binding sites The specific binding of the KCA [^{3}H]P1075{*N*-cyano-*N*′[1,1-dimethyl(2,2,3,3[^{3}H])propyl]-*N*″-3-pyridinylguanidine} could not be displaced by glibenclamide. But the dissociation kinetic of [^{3}H]P1075 binding with ATP-sensitive potassium channels could allosterically be accelerated by glibenclamide[20]. Since both dissociation and association kinetics of [^{3}H]glibenclamide binding could also allosterically be modulated by KCA pinacidil, it is reasonable to suggest that the interactions between glibenclamide and KCA are uncompetitive and with allosteric characteristics.

Differences of ATP-sensitive potassium channels in cardiovascular system and in other tissues

Molecular structure of ATP-sensitive potassium channels ATP-sensitive potassium channel is a complex of Kir 6.2, a member of the inwardly rectifying potassium channel superfamily, and the sulfonylurea receptor, a member of the ATP-binding cassette superfamily. Sulfonylurea receptor sensitive changes in ATP and ADP concentration, affect Kir 6.2 activities, and thereby reveals the diverse functions of ATP-sensitive potassium channels.

Sulfonylurea receptor has been divided into the pancreatic sulfonylurea-binding protein (SUR) and extrapancreatic sulfonylurea-binding protein (SUR2). Human SUR and SUR2 was localized to chromosome 12 P12.1 and 11 P15.1 respectively. SUR2 is expressed in the parenchyma of the heart, skeletal muscle, vessel and other tissues, with two isoforms, SUR 2A and SUR 2B. SUR 2A is expressed exclusively in heart, while SUR 2B is ubiquitously expressed in skeletal and smooth muscles. The differences in sequence between SUR and SUR2 isoforms

may underlie the tissue-specific pharmacology of ATP-sensitive potassium channels[21,22].

Selectivity of ATP-sensitive KCA The first generation of KCA diazoxide has lower tissue selectivity, can activate ATP-sensitive potassium channels in cardiovascular smooth muscles and pancreatic β cells. It has been used in the clinical antihypertensive treatments, but can produce the adverse reaction hyperglycemia. In addition, minoxidil at the hypertensive doses can also activate the cardiac ATP-sensitive potassium channels, and produces electrocardiographic changes such as T-wave abnormalities.

Pinacidil has been approved to treat hypertension. It can also activate ATP-sensitive potassium channels in parasympathetic postganglionic neurons, intestinal smooth muscles, and renal tissues[23,24], resulting in some side effects which may affect the life quality of the patients. The new generation of KCA with higher tissue selectivity, and more effective vasodilation is developed. However, some drugs produce some adverse effects related to potent vasodilation, especially edema, tachycardia, palpitations, and headache. The new compound Y-27152 [(+)-(3S, 4R)-4-(*N*-acetyl-*N*-benzyloxyamino)-6-cyano-3, 4-dihydro-2, 2-dimethyl-2H-1-benzopyran-3-ol] revealed long-lasting antihypertensive actions with less tachycardia, and had less reflex effects on plasma renin activity and sodium/water retention. The compound Y-27152 itself is pharmacologically inert and is converted to its active form Y-26763 (active desbenzyl form of Y27152) after oral administration[25]. And the compounds with higher selectivity on cardiac smooth muscle have also been evaluated. For example, bimakalim is approximately 100 times as effective at inhibiting vascular smooth muscle as it is at effecting cardiac myocyte performance. The myocardial protective activities of these compounds can be used in the treatment of cardiac ischemia[26]. Now the 5 different subtypes of ATP-sensitive potassium channels have been proposed as a consequence of selectivity to potassium and sensitivity to calcium, intracellular ATP concentration and pharmacological modulation. Furthermore, the differences already observed in the pharmacology of KCA will be important factors in the development of the second generation compounds, as novel antihypertensive drugs, which have highly selective effects on cardiovascular system. Of course, some KCA with highly selective effects on central nervous system, digestive or respiratory smooth muscles will be developed into the novel drugs, which can be used to treat mental disorders, digestive or respiratory smooth muscle spasm.[27]

Summary and perspective

As for a kind of antihypertensive drugs, KCA have many pharmacological and therapeutic advantages. In addition to the reported advantages (potent and selective antihypertensive actions, highly selective for blood vessels, without effects on glucose tolerance, beneficial effects on lipoprotein metabolism), the activator pinacidil can reverse the hypertensive vascular remodeling. From this point, KCA have the advantage over diuretics and β receptor blockers, the first line antihypertensive drugs.

There exist big differences between KCA and voltage-dependent calcium channel blockers dihydropyridines. The KCA pinacidil has antagonistic effects against intracellular calcium mobilization in blood vessels.

Although the physiologic functions of cardiovascular ATP-sensitive potassium channels remain to be further investigated, the functional hypertensive remodeling of cardiovascular ATP-sensitive potassium channels which can only be reversed by the treatment with KCA, has been identified. Thus cardiovascular ATP-sensitive potassium channels may play an important role in hypertension.

The activators and blockers act at different sites of cardiovascular ATP-sensitive potassium channels. ATP is an allosteric factor for the blocker glibenclamide binding sites, and glibenclamide is an allosteric factor for the activator P1075 binding sites. It is very important to understand the pharmacological selectivity of the activators and blockers on cardiovascular system.

ATP-sensitive potassium channels in cardiovascular system differ in pharmacological and therapeutic characteristics from those in pancreatic, renal, intestinal, or neuronal tissues. The first generation of KCA pinacidil, minoxidil, or diazoxide used in antihypertensive treatments, are unsatisfactory in the tissue

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selectivities. In the near future, the new generation of KCA will be approved as novel antihypertensive drugs, which have highly selective characteristics on cardiovascular system with milder side effects.

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抗高血压药研究的新靶点：心血管 ATP 敏感性钾通道[1]

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关键词 钾通道；硫脲受体；抗高血压药；吡那地尔；格列本脲