Different Subtypes of $\alpha_1$-Adrenoceptor Modulate Different $K^+$ Currents via Different Signaling Pathways in Canine Ventricular Myocytes

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Huizheng Wang‡‡‡, Baofeng Yang‡, Yiqiang Zhang‡, Hong Han‡***, Jingxiong Wang§, Hong Shi‡, and Zhiguo Wang§****

From the ‡Research Center, Montreal Heart Institute, Montreal, Quebec H1T 1C8, Canada, the §‡Department of Medicine, University of Montreal, Montreal, Quebec H3C 3J7, Canada, and the †Department of Pharmacology, Harbin Medical University, Harbin, Heilongjiang 150086, China

Over the past decade, evidence from pharmacological studies and molecular cloning has been accumulating indicating that $\alpha_1$-adrenoceptors ($\alpha_1$ARs)1 are actually a heterogeneous group of distinct but related protein subsets. Many cellular responses to $\alpha_1$ARs are mediated by multiple subtypes ($\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1D}$) (1–4). In the heart, whereas the $\alpha_{1A}$ and $\alpha_{1D}$ subtypes have been well characterized, the presence of $\alpha_{1B}$AR was indicated only recently (5–7). Moreover, although the pathophysiological roles of $\alpha_{1A}$ and $\alpha_{1B}$ receptors have been well appreciated, those of $\alpha_{1D}$ subtype in the heart remain to be determined.

Enhanced $\alpha_1$AR activity has been implicated in various types of arrhythmias, particularly those in the pathogenesis of myocardial ischemia, ischemia-reperfusion and preconditioning, cardiac hypertrophy, etc. (1, 3). Drug intervention with $\alpha_1$ARs has thus become an attractive issue for developing new compounds for potential therapy. A significant mechanism underlying $\alpha_1$AR-induced alteration of cardiac electrical activity is attributable to the ability of $\alpha_1$ARs to modulate ion channels. To date, no less than seven cardiac ionic currents are on the list of $\alpha_1$AR modulation, including inward rectifier $K^+$ current ($I_{\text{K1}}$), transient outward $K^+$ current ($I_{\text{to}}$), delayed rectifier $K^+$ current ($I_{\text{K1}}$), ultrarapid delayed rectifier $K^+$ current ($I_{\text{Kur}}$), acetylcholine-induced $K^+$ current ($I_{\text{Kach}}$), calcium current ($I_{\text{Ca}}$), and chloride current (1, 3, 8–11). However, it is not known whether the effects are the results from participation of all three different subtypes of $\alpha_1$ARs or of a particular individual subtype, although evidence is accumulating that different subtypes may have different roles in regulating cardiac contraction and electrical activities (12–16). Moreover, recent studies also demonstrated subtype differences in the signal transduction (17–19). In light of these studies, we speculated that different subtypes of $\alpha_1$ARs may have distinct effects on ion channels. Understanding subtype specificity of $\alpha_1$ARs in ion channel regulation is of theoretical and practical importance.

$K^+$ currents play critical roles in determining cardiac electrical activities. Besides stabilizing resting potential, $I_{\text{K1}}$ in cardiac cells also plays an important role in modulating cellular excitability and regulating membrane repolarization, therefore an important determinant of action potential initiation. Another important cardiac $K^+$ current is transient outward $K^+$ current ($I_{\text{to}}$), which is known to be critical for initiating cardiac repolarization in the early phase of action potentials. Both of these currents have been implicated in the pathology of cardiac electrophysiological disorders and heart failure (20). For these reasons, we explored the potential subtype selectivity and signal transduction mechanisms of $\alpha_1$ARs in regulating $I_{\text{to}}$ and $I_{\text{K1}}$ in isolated canine ventricular myocytes using whole cell patch clamp techniques.
a1-Adrenoceptor Modulation of Cardiac K⁺ Currents

Fig. 1. a1AR modulation of transient outward K⁺ current (Iₒ) and inward rectifier K⁺ current (Iᵣᵣ) in canine ventricular myocytes. A and B, raw traces recorded from representative cells showing the inhibition of Iₒ, and Iᵣᵣ, produced by Phen at concentrations of 10 and 100 μM, respectively. Voltage protocols for current recordings are shown in the insets. C and D, current-voltage (I-V) relationships of Iₒ (n = 19 cells) and Iᵣᵣ (n = 22 cells). When Phen concentration was 10 μM, statistically significant inhibition (p < 0.05) of Iₒ was seen at potentials positive to 0 mV, and the effect on Iᵣᵣ was not statistically significant (p > 0.05). When Phen concentration was raised to 100 μM, Iₒ blockade was statistically significant (p < 0.05) at potentials positive to −20 mV, and Iᵣᵣ blockade was statistically significant (p < 0.05) at potentials more negative than −80 mV.

Whole Cell Patch Clamp Recording—Patch clamp recording techniques used have been described in detail elsewhere (22–24). Borosilicate glass electrodes (outer diameter, 1 mm) had tip resistances of 1–3 MΩ when filled with pipette solution. Junction potentials were zeroed before formation of the membrane-pipeette seal in Tyrøe’s solution. The capacitance and series resistance was electrically compensated to minimize the duration of the capacitive surge on the current recording and the voltage drop across the clamped cell membrane. Iₒ was defined as the peak current amplitude, and Iᵣᵣ was measured as the amplitude at the end of 400-ms pulses. The experiments were conducted at 36 °C.

Solutions and Drugs—The bath solution for whole cell patch clamp recording had the following composition 138 mM NaCl, 5.4 mM KCl, 1 mM MgCl₂, 0.33 mM NaH₂PO₄, 5 mM HEPES, 10 mM glucose, and 1 mM CaCl₂; pH was adjusted to 7.4 with NaOH. Unless otherwise specified, the pipette solution contained 0.1 mM GTP, 110 mM potassium aspartate, 20 mM KCl, 1 mM MgCl₂, 5 mM Mg-ATP, 10 mM HEPES, and 5 mM phosphocreatine, pH 7.3. Sodium current was prevented by holding the cells at −20 or −50 mV, and calcium current was blocked by inclusion of Cd²⁺ (200 μM) in the bathing solution. All chemicals were purchased from Sigma.

Phenylnephrine (Phen; used as a non-subtype-selective a1AR agonist), prazosin (a non-subtype-selective a1AR antagonist), (+)-migulpidine (Nig; a specific inhibitor of α₁AaARs), chloroethyclonidine (CEC; an alkylation agent for α₁BaARs), and propranolol were from Sigma (Oakville, Canada). Phen, Nig, CEC, and BMY-7378 were prepared as 100 mM, 10 μM, 10 μM, and 1 μM stock solutions in distilled water, respectively. Phen was always prepared fresh before each experiment. Control group determinations. When Phen concentration was raised to 10 or 100 μM or vehicle for 20 min before being collected for protein preparation. Similarly, isolated canine ventricular myocytes were also treated with Phen or vehicle in KB solution for 20 min. The proteins were prepared following the same procedures as described previously (25, 26). The protein content was determined with Bio-Rad protein assay kit using bovine serum albumin as a standard.

PKC activity was assayed with the PKC enzyme assay system from Amersham Pharmacia Biotech, and the assay procedures were performed according to the system instructions. The Anti-ACTIVE® CaM KII polyclonal antibody system from Promega was used to assess CaMKII activity, containing the rabbit polyclonal antibody, which recognizes autophosphorylation of Thr²⁸⁶ of all isoforms of CaMKII. Experiments were performed according to the manufacturers’ protocol. Bound antibodies were detected with Western blot Chemiluminescence Reagent Plus (PerkinElmer Life Sciences) and quantified by densitometry, as detailed previously (25–26). Coomassie staining was performed to verify the amount of protein inputs, as described previously (25–26).

Statistical Analysis—The group data are expressed as the means ± S.E. Statistical comparisons were made with Student’s nonpaired t test. All enzyme activity and Western blot determinations were performed in parallel with cells from each group for each experiment to minimize contamination by inter-day and inter-lot reagent variation, and the results for each experiment are expressed as the values normalized to control group determinations.

RESULTS

a1AR Modulation of Iₒ and Iᵣᵣ—Application of depolarizing or hyperpolarizing voltage steps (voltage protocols shown in the non-graphical parts of Fig. 1) elicited outward Iₒ with transient properties (rapid activation and inactivation) or Iᵣᵣ with strongly inward rectification. Bath application of Phen at 10 μM produced marked reduction of Iₒ amplitude without apparent alterations in its activation and inactivation kinetics but did not affect Iᵣᵣ (Fig. 1). When Phen concentration was elevated to 100 μM, Iᵣᵣ was significantly decreased, Iₒ was further reduced, and the inactivation kinetics was slightly decelerated. Co-application with prazosin (1 μM) completely converted the depressed Iₒ and Iᵣᵣ caused by Phen back to predrug base-line values, indicating the role of α₁ARs in mediating the effects of Phen.
Subtype Specificity of α1AR Modulation of İ<sub>to</sub> and İ<sub>K1</sub>-To determine which receptor subtypes, α<sub>1A</sub>, α<sub>1B</sub>, or α<sub>1D</sub>, mediate the effect of α<sub>1</sub>AR modulation of İ<sub>to</sub> and İ<sub>K1</sub>, we performed experiments using subtype-selective antagonists. Current recordings made under control conditions were repeated 10 min after exposure of the cells to Phen (10 μM). Subsequently, Nig (10 nM) was concurrently applied with Phen to the bathing solution. As illustrated in Fig. 2, Nig reversed Phen-induced İ<sub>to</sub> depression. Nig also reduced the further reduction of İ<sub>to</sub> caused by raising Phen concentration to 100 μM. On the other hand, Nig failed to change the depressed İ<sub>K1</sub> caused by Phen (100 μM).

We then turned to study the effects of CEC (10 μM), an alkylating agent selective toward α<sub>1B</sub>Rs over other subtypes. Following a 30-min incubation with CEC to inactivate the α<sub>1B</sub>Rs, the cells were superfused with drug-free Tyrode’s solution for 20 min, and then measurements of İ<sub>to</sub> and İ<sub>K1</sub> were made as baseline values. Then Phen was added to the superfusate. The same degrees of İ<sub>to</sub> and İ<sub>K1</sub> diminishment as in cells without pretreatment with CEC were consistently seen in a total of six cells (Fig. 2).

CEC (10 nM), a specific antagonist of α<sub>1B</sub>Rs (3, 4, 27), when co-applied with Phen, nearly fully reversed the inhibitory effects of Phen (100 μM) on İ<sub>K1</sub> but not İ<sub>to</sub> (Fig. 3). CEC-7378 alone did not exert any detectable effects on İ<sub>K1</sub> (n = 5).

Signal Transduction Mechanisms of α1AR Modulation of İ<sub>to</sub> and İ<sub>K1</sub>-α<sub>1</sub>Rs are known to stimulate activation of PKC (17, 19, 28), which in turn can phosphorylate the channel proteins. To investigate whether PKC can account for the α<sub>1</sub>AR modulation of İ<sub>to</sub> and İ<sub>K1</sub>, the effects of PKC inhibitor Bis and activator PDD were assessed (10, 11). 10 min after superfusion with Phen (10 μM) to verify the effect on İ<sub>K1</sub>-PDD (100 nM) experiments, the data were acquired in control conditions, 10 min after bath application with Phen (10 μM for İ<sub>to</sub> and 100 μM for İ<sub>K1</sub>), 15 min after wash-out of Phen (After Phen), and 10 min after superfusion with PDD (100 nM, or 4α-PDD 100 nM). Only current traces recorded in control and after PDD were shown for the sake of clarity. For Bis experiments, current recordings made in control conditions and 10 min after Phen were repeated 15 min after co-application of Phen and Bis (50 nM) and 10 min after Bis and PDD. The averaged values were the data obtained at a potential of +30 mV for İ<sub>to</sub> and −120 mV for İ<sub>K1</sub>. The values in parentheses indicate the number of cells studied. *p < 0.05, Student t test, comparison versus control; +, p < 0.05, comparison versus Phen or After Phen. The order of the bar data follows the same order of experimental procedures.
aged values were the data obtained at a potential of 120 mV. The values in parentheses indicate the number of cells studied. *, p < 0.05, Student t test, comparison versus control. The order of the bar data follows the same order of experimental procedures.

suppression of $I_{\text{wo}}$ amplitude. Moreover, no significant effect of 4α-PDD (100 nM, the inactive stereoisomer of PDD) on $I_{\text{wo}}$ was seen, and when in the presence of Bis, PDD had little effect on $I_{\text{wo}}$. Slight reduction of canine $I_{K1}$ (about 7%) was observed when treated with PDD (100 nM).

CaMKII has recently been reported to be involved in regulating ion currents (29–31). Accordingly, we also studied the potential participation of CaMKII in α1ARs or Phen modulation of $I_{\text{wo}}$ and $I_{K1}$. As illustrated in Fig. 4, Phen at 10 μM produced the similar effects on $I_{\text{wo}}$ with and without KN-93 (3 μM, a potent CaMKII inhibitor) present in the bath solution. However, with 100 μM Phen, $I_{\text{wo}}$ reduction was slightly smaller in the presence of KN-93 than in the absence of the compound (Fig. 4B). The CaMKII inhibitor peptides P281–309 or ACP dialyzed into the cells did not affect $I_{\text{wo}}$ neither the ability of Phen to inhibit $I_{\text{wo}}$ (Fig. 4, A and C). By comparison, the reduction of $I_{K1}$ caused by Phen (100 μM) alone was completely prevented by KN-93 (Fig. 5). We then examined whether the effects of KN-93 on $I_{K1}$ were related to the inhibition of CaMKII activity or to a direct effect on K⁺ channels. KN-92 (10 μM), the inactive analog of KN-93, failed to affect $I_{K1}$ reduction caused by Phen (Fig. 5B). Further evidence that $I_{K1}$ is regulated by CaMKII was obtained by dialyzing cells with the inhibitor peptides P281–309 or ACP. The cells were bathed in the solution containing either 100 μM or for at least 10 min before the formation of whole cell configuration. The currents recorded immediately after membrane rupture with minimal dialysis were considered the base-line data, and the data acquired 15 min after membrane rupture with complete dialysis were taken as the effects of CaMKII inhibition by ACP or P281–309 (Fig. 5). In addition, addition of EGTA (10 mM) to the pipette solution also substantially weakened the ability of Phen to suppress $I_{K1}$ (data not shown). The effects of KN-93 on Phen-induced depression in $I_{K1}$ were also assessed in myocytes pretreated with the calmodulin inhibitor calmidazolium. Similar to KN-93, calmidazolium converted the depressed $I_{K1}$ to the base-line amplitude (Fig. 5B). External application of KN-93 (3 μM) when the steady-state effect of calmidazolium had been achieved failed to cause further changes on $I_{K1}$ (data not shown).

PKC Activity Assay and Immunoblotting Analysis of CaMKII Activity—Based on the results from the above functional studies, we believed that suppression of $I_{\text{wo}}$ by Phen at 10 μM is primarily mediated by PKC activation as a result of α1AR activation, whereas an increase in CaMKII activity caused by α1DARs stimulation by 100 μM Phen leads to $I_{K1}$ inhibition. To test this point, we performed analyses for PKC and CaMKII activities. Fig. 6 shows the results from PKC activity assay. A pronounced increase in PKC activity was seen in HEK293 cells stably transfected with α1aARs and pretreated with Phen, relative to nontransfected and untreated cells. Only a minor increase in PKC activation was observed in α1DAR-transfected cells, even with elevated Phen concentration to 100 μM. Coincidentally, canine ventricular myocytes pretreated with 10 μM (or higher) Phen also resulted in a significant increase in PKC activity relative to untreated cells.

The antibody to the autophosphorylation site Thr²⁸⁶ of CaMKII recognized a band of 51 kDa in both HEK and a band of 48 kDa in canine ventricular cells, which is in agreement with the size of CaMKII reported by other laboratories (29–31). As shown in Fig. 7, a more prominent band was seen only in α1aAR-transfected cells pretreated with 100 μM Phen. There are slight increases in the phosphorylated CaMKII in α1aAR-transfected cells or in α1aAR-transfected cells treated with 10 μM Phen. For canine ventricular myocytes, only samples from cells pretreated with 100 μM Phen showed an enhanced phosphorylation of CaMKII, and the immunoreactive band was nearly invisible in control and 10 μM Phen-treated cells.
We have shown in this study that $\alpha_{1}$AR stimulation by phenylephrine produces important suppression of $I_{\text{to}}$ and $I_{K1}$ in dog ventricular myocytes. The effects on $I_{\text{to}}$ and $I_{K1}$ can be separated by the strength of $\alpha_{1}$AR stimulation (Phen concentrations), and the use of subtype-selective antagonists suggests a possibility of differential modulation of $I_{\text{to}}$ and $I_{K1}$ by activation of different subtypes of $\alpha_{1}$ARs: $\alpha_{1\text{A}}$AR for $I_{\text{to}}$, and $\alpha_{1\text{D}}$AR for $I_{K1}$. Moreover, our data also suggest that the differential modulation of $I_{\text{to}}$ and $I_{K1}$ by $\alpha_{1}$ARs is mediated by different signaling systems: $I_{\text{to}}$ primarily by PKC and $I_{K1}$ mainly by CaMKII. Our data therefore provide evidence that different subtypes of $\alpha_{1}$ARs modulate different cardiac K$^+$ currents via different signal transduction mechanisms. Our results also represent, to our knowledge, the first to define the functional role of $\alpha_{1\text{D}}$ARs in modulating cardiac ion channels and the role of CaMKII in modulating inward rectifier K$^+$ current.

With the development of pharmacological tools and molecular cloning, it is now possible to study $\alpha_{1}$AR subtypes separately. The $\alpha_{1\text{A}}$ARs show a high affinity to (+)-niguldipine that has been demonstrated to be $100-4000$-fold more selective toward $\alpha_{1\text{A}}$AR over the other two subtypes (4, 32). The $\alpha_{1\text{D}}$ARs are readily and irreversibly inactivated by the alkylation agent CEC (4, 33). BMY-7378 distinguishes $\alpha_{1}$AR from the other two subtypes ($\alpha_{1\text{A}}$ and $\alpha_{1\text{D}}$) with a binding affinity at least $2$ orders of magnitude higher for the former over the latter (4, 7, 27). We show here that neither Nig nor CEC produced any appreciable influences on the inhibitory effects of Phen on $I_{K1}$. In sharp contrast, BMY-7378, at a concentration of as low as $1$ nM, readily reversed Phen actions on $I_{K1}$. These data strongly suggest that $\alpha_{1\text{D}}$ARs mediate $\alpha_{1}$AR/Phen modulation of $I_{K1}$ in canine ventricular myocytes. $\alpha_{1}$AR modulation of $I_{K1}$ in rabbit (34) and human (9) atria has also been previously studied, and consistent with the present study $\alpha_{1}$AR stimulation was found to decrease atrial $I_{K1}$. However, the involvement of particular subtypes of $\alpha_{1}$ARs was not investigated in these studies. Although our study probably is the first to establish the functions of $\alpha_{1\text{D}}$ARs in the heart, its roles may not be restricted to the modulation of $I_{K1}$.

The present study appears to favor the notion that modulation of $I_{\text{to}}$ in canine ventricular cells by $\alpha_{1}$AR stimulation is primarily mediated by a subclass of $\alpha_{1}$ARs, that is, $\alpha_{1\text{A}}$ARs. A similar decrease in $I_{\text{to}}$ upon $\alpha_{1}$AR stimulation was also previously documented in other species such as rabbits (36) and rats (37, 38), but no information regarding involvement of particular subtypes of $\alpha_{1}$ARs was provided. In another study reported by Wang et al. (39) in rat ventricular cells, phenylephrine at $30$ $\mu$M was shown to reduce peak $I_{\text{to}}$ and both of the $\alpha_{1\text{A}}$AR-selective antagonists 5-methylurapidil and (+)-niguldipine ($0.1$ $\mu$M each) and the irreversible $\alpha_{1\text{D}}$AR-subtype antagonist CEC ($100$ $\mu$M) blocked the phenylephrine effect on $I_{\text{to}}$. They concluded that stimulation of both $\alpha_{1}$AR subtypes contributes to the phenylephrine-induced reduction in $I_{\text{to}}$ of rat myocytes. However, it should be noted that CEC concentration used in this study was $100$ $\mu$M, high enough to inactivate subtypes (e.g. $\alpha_{1\text{A}}$ and $\alpha_{1\text{D}}$) other than $\alpha_{1\text{D}}$ARs.

For the signal transduction mechanisms underlying $\alpha_{1}$AR modulation of $I_{\text{to}}$, studies on cloned channels that generate $I_{\text{to}}$-like K$^+$ currents in heterologous expression systems demonstrated that activation of PKC reduces $Kv4.2$ and $Kv4.3$ (40).
This result is in good agreement with ours, which points to an important role of PKC activation mediated by α1AR stimulation in regulating I_{op} particularly when considering that Kv4.3 is the major molecular component of native I_{op} in dogs (41). The results from previous studies on PKC modulation of inward rectifier K^+ channels (Kir) have been controversial. For the cloned Kirs, the study from Henry et al. (42) convincingly demonstrated that PKC activation by phorbol 12-myristate 13-acetate or phorbol 12,13-dibutyrate significantly inhibited Kir2.3 but did not alter Kir1.1 and Kir2.1. In light of our previous finding that Kir2.1 is the most abundantly expressed Kir subunit in human hearts (22), our present data are in line with the results from the study by Henry et al. Yet Fakler et al. (43) reported that stimulation of PKC by 12-O-tetradecanoylphorbol 13-acetate suppressed Kir2.1. It is unclear whether this is due to the use of different PKC activators by the two laboratories. Similarly, in native cells no consistent data have been reported. In the study performed by Braun et al. (34) it was shown that α1AR inhibition of I_{K1} in rabbit atrial cells did not depend on PKC activation, and direct PKC activation or inhibition did not affect I_{K1} either. In contrast, one study conducted in human atrial myocytes suggested that α1AR inhibition of I_{K1} is mediated by PKC activation (9). One possible explanation for the discrepancy is that different species might have distinct molecular compositions of I_{K1} because to date no less than 10 different Kir cDNAs have been cloned (44).

Several lines of evidence from the present study suggest that suppression of I_{K1} by α1AR stimulation in canine ventricular myocytes is mediated by CaMKII activation. To date, no other studies have published regarding CaMKII modulation of I_{K1}. However, CaMKII modulation of I_{op} or the cloned channels expressing I_{op}-like currents has been documented in several studies. Consistent in all these studies is the reduction of current amplitude. In the present study, we show that Phen at a concentration of 10 µM mainly activates PKC pathway, as indicated by inhibitor experiments, PKC assay, and CaMKII immunoblotting analysis. We therefore speculate that I_{op} modulation by 10 µM Phen is mainly mediated by PKC phosphorylation, whereas I_{op} reduction by 100 µM Phen might be the consequence of combined PKC and CaMKII activation. This is supported by our data showing that inhibition of CaMKII partially reversed I_{op} reduction caused by Phen at 100 µM but not at 10 µM. In addition, 100 µM Phen slightly slowed the inactivation kinetics of canine I_{op} (Fig. 1A), which was not seen with 10 µM Phen.

The α1AAR is generally far more efficient in stimulating PKC activation than the α1DAR (19). For example, Taguchi et al. (17) showed that Phen significantly stimulates PKC in rat-1 fibroblasts stably expressing α1AARs and α1BARs but not α1DARs. Our data are consistent with this notion. Intriguingly, a study performed in a vascular smooth muscle cell line (AC01) (18) demonstrated that the α1AARs, although representing the minor population compared with the α1BARs in this cell, are the main mediators of phosphoinositide/Ca^{2+} signaling. Moreover, based on their experimental data from isolated hepatocytes, Butta et al. (45) concluded that there are at least two major α1AR signaling pathways; one is PKC-dependent and independent of variations in free cytosolic Ca^{2+}, and the other is Ca^{2+}-dependent. Actually, the ability of α1AR to activate CaMK has been previously realized. The study reported by Guo et al. (46) found that CaMK contributed to the α1AR-mediated decrease in Kv1.5 K^+ channel expression in cultured newborn rat ventricular cells. However, it was not characterized which subtype of α1ARs is responsible for the effect in these studies. Our data suggest that α1AARs are mainly associated with PKC activation, whereas α1DARs are primarily coupled to CaMKII activation. Yet it should be noted that our data do not allow us to reach a conclusion on how α1AARs are coupled to PKC and how α1DARs are coupled to CaMKII. More detailed studies are necessary for verifying this notion and for delineating the subtype-specific signaling coupling mechanisms.

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