Syntaxin-1A Inhibits Cardiac K_{ATP} Channels by Its Actions on Nucleotide Binding Folds 1 and 2 of Sulfonylurea Receptor 2A*

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ATP-sensitive potassium (K_{ATP}) channels couple the metabolic status of the cell to its membrane potential to regulate a number of cell actions, including secretion (neurons and neuroendocrine cells) and muscle contractility (skeletal, cardiac, and vascular smooth muscle). K_{ATP} channels consist of regulatory sulfonylurea receptors (SUR) and pore-forming (Kir6.X) subunits. We recently reported (Pasyk, E. A., Kang, Y., Huang, X., Cui, N., Sheu, L., and Gaisano, H. Y. (2004) J. Biol. Chem. 279, 4234–4240) that syntaxin-1A (Syn-1A), known to mediate exocytotic fusion, was capable of binding the nucleotide binding folds (NBF1 and C-terminal NBF2) of SUR1 to inhibit the K_{ATP} channels in insulin-secreting pancreatic islet beta cells. This prompted us to examine whether Syn-1A might modulate cardiac SUR2A/K_{ATP} channels. Here, we show that Syn-1A is present in the plasma membrane of rat cardiac myocytes and binds the SUR2A protein (of rat brain, heart, and human embryonic kidney 293 cells expressing SUR2A/Kir6.2) at its NBF1 and NBF2 domains to decrease K_{ATP} channel activation. Unlike islet beta cells, in which Syn-1A inhibition of the channel activity was apparently mediated only via NBF1 and not NBF2 of SUR1, both exogenous recombinant NBF1 and NBF2 of SUR2A were found to abolish the inhibitory actions of Syn-1A on K_{ATP} channels in rat cardiac myocytes and HEK293 cells expressing SUR2A/Kir6.2. Together with our recent report, this study suggests that Syn-1A binds both NBFs of SUR1 and SUR2A but appears to exhibit distinct interactions with NBF2 of these SUR proteins in modulating the K_{ATP} channels in islet beta cells and cardiac myocytes.

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1 The abbreviations used are: K_{ATP} channel, ATP-sensitive potassium channel; SUR, sulfonylurea receptor; NBF, nucleotide binding fold; Syn-1A, syntaxin-1A; GST, glutathione S-transferase; ADP, adenosine 5'-diphosphate; SNARE, soluble N-ethylmaleimide-sensitive factor attachment protein receptor; HEK, human embryonic kidney; SNAP-25, synaptic protein of 25 kDa.


glucose and supplemented with 10% fetal bovine serum (Cansaex, Rexdale, Ontario, Canada). The HEK293 cells were transiently co-transfected with green fluorescent protein, pECE-Kir6.2, and pECE-SUR2A using Lipofectamine 2000 (Invitrogen) according to the manufacturer’s instructions. One day after transfection, the cells were transfused and placed in 35-mm culture dishes overnight prior to voltage clamp experiments. Transfected cells were identified by visualization of the fluorescence of the co-expressed green fluorescent protein. For binding assay, the HEK293 cells were transfected with pcDNA3-Syn-1A or pECE-SUR2A and pECE-Kir6.2.


dicavitation and Brain Membrane—Rat cardiac membrane was prepared according to the method originally described by Mayanil et al. (18) and modified by Barry et al. (19). To prepare rat brain membranes, we followed the method reported previously by Hutter et al. (20). Finally, both membranes were solubilized in 1× radioligand binding assay buffer (50 mM Tris-HCl, pH 7.4, containing 150 mM NaCl and 1% Triton X-100, 2 μM pepstatin A, 1 μg/ml leupeptin, and 5 μg/ml aprotinin) on ice for 30 min, and then insoluble material was removed following centrifugation at 4 °C for 25 min. The supernatant was used for binding assay.

In Vitro Binding Assay—Two days after transfection with pcDNA3-Syn-1A or pECE-SUR2A and pECE-Kir6.2, the HEK293 cells were washed with ice-cold saline-buffered solution (phosphate-buffered saline, pH 7.4) and then harvested in binding buffer (25 mM HEPES, pH 7.4, 100 mM KCl, 2 mM EDTA, 1% Triton X-100, 20 mM NaF, 1 mM phenylmethylsulfonyl fluoride, 2 mM EDTA, and 10 μg/ml aprotinin). The cells were lysed by sonication, and insoluble materials were removed by centrifugation at 21,000 × g at 4 °C for 30 min. For binding assay, the detergent extract (0.3 ml, 1.2–5.1 mg protein) of HEK293 cells, rat brain synaptic membranes, and rat heart membranes or thrombin-cleaved Syn-1A (650 pmol of protein in 250 μl binding buffer) was mixed with GST (as a negative control, 650 pmol of protein) or GST-SUR2A-NBF1 or GST-SUR2A-NBF2, and this measured current was examined using a laser-scanning confocal imaging system (Carl Zeiss, Oberkochen, Germany).

Recording K_{ATP} Currents from HEK293 Cells Expressing Kir6.2 and SUR2A—K_{ATP} channel current from human embryonic kidney 293 cells was recorded in the whole-cell configuration using an EPC-9 amplifier and Pulse software (HEKA Electronic, Lambrecht, Germany) as we described previously (16). Recording pipettes were pulled from 1.5-mm borosilicate glass capillary tubes (World Precision Instruments, Inc.) using a programmable micropipette puller (Sutter Instrument Co., Novato, CA). Pipettes were then heat-polished with fire, and tip resistances ranged from 1.5–3 mega-ohms when filled with intracellular solution containing 140 mM KCl, 1 mM MgCl2, 1 mM EGTA, 10 HEPES, and 0.3 mM MgATP (pH 7.25 adjusted with KOH). Fusion proteins of GST, Syn-1A, and/or SUR2A NBFs were also added to the whole-pipette solution. Bath solution contained (mM): 140 NaCl, 4 KCl, 100 glucose, 1.8 CaCl2, 10 HEPES (pH 7.3 adjusted with NaOH). After a whole-cell configuration was established, membrane potential was held at −70 mV, and a pulse of −140 mV was given every 10 s to monitor the current magnitude. When the current reached maximum amplitude, voltage pulses from −160 to 40 mV were given at 20-mV increments to yield the I-V relationship. Steady-state outward currents were determined as the mean current in the final 95–99% of the 500-ms pulse. All experiments were performed at room temperature.

Syntaxin Regulates Cardiac K_{ATP} Channels—Standard patch clamp techniques were used to record currents in the inside-out configuration so that the internal face of membrane patches could be exposed directly to test solutions using a multi-input perfusion pipette. The time required for solution change at the tip of the recording pipette was <1 s. The pipette bath solution for excised patch experiments contained 140 mM KCl, 1 mM MgCl2, 1 mM EGTA, 10 mM HEPES-KOH, pH 7.4. All currents were recorded at a holding potential of −60 mV using Axopatch 200B (Axon Instruments, Inc.), and then digitized and analyzed using Axoscope version 8.0 and pClamp version 8.0 software. Data were sampled at 2.5 kHz and filtered at 1 kHz. Excised patches were initially held in 1 mM ATP to measure base-line current. An application of 50 μM ATP then produced an increase in current to a level defined as “control” for each patch. The current level was then measured during co-application of Syn-1A with or without pre-incubation with SUR2A NBF1 or SUR2A NBF2, and this measured current was expressed as a percentage of the controlled conditions for each patch. All experiments were performed at room temperature.

RESULTS

Syntaxin-1A Is Expressed in the Plasma Membrane of Cardiac Myocytes—We examined the expression and cellular location of Syn-1A in rat cardiac myocytes. Fig. 1A is a Western blot showing that Syn-1A (top band) and Syn-1B (bottom band) were present in rat whole heart cell lysate (100 μg of protein). Both Syn-1 isoforms were recognizable by the rabbit anti-Syn-1A antibody. When the cardiac lysate was purified to a plasma membrane fraction (50 μg of protein), the Syn-1 signals increased with Syn-1A being more abundant than Syn-1B. In Fig. 1B (upper panel), we confirmed the cellular location of Syn-1A to the plasma membrane of cardiac myocyte by confocal microscopy. The bottom panel (Fig. 1B) shows a negative control, wherein the myocytes were not labeled with anti-syntaxin antibody but with fluorescein isothiocyanate-conjugated secondary antibody.

Syntaxin-1A Binds Cardiac SUR2A at Its NBF-1 and NBF-2—We first investigated whether the endogenous SUR2 proteins in rat cardiac muscle and brain are capable of binding the Syn-1A. Although both SUR2A proteins are only found in low abundance in the brain (1, 5, 11, 12), large amounts of purified rat brain membranes could be prepared for the protein binding studies performed in Fig. 2A. Indeed, Fig. 2, A and B, shows that Syn-1A could bind native SUR2 proteins from both rat tissues, as demonstrated by the ability of GST-Syn-1A bound to agarose beads to pull down rat brain membrane and cardiac membrane SUR2-immunoreactive proteins. Because the antibody we have used recognizes a domain (amino acids 921–1000) conserved between SUR2A and SUR2B, the SUR2-immunoreactive proteins likely include both SUR2 proteins, especially the rat brain membranes (11, 12) in Fig. 2A. Furthermore, the...
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**Fig. 1. Syntaxin-1A is expressed in the plasma membrane of cardiac myocytes.** A. Western blot analysis of Syn-1A (top band) and -1B (bottom band) in rat brain lysate (5 μg of protein), cardiac lysate (100 μg of protein), and cardiac membrane (50 μg of protein). **B.** Top panel shows Syn-1A localization in cardiac myocyte by confocal microscopy. The arrowheads point to the plasma membrane location of Syn-1A. Bottom panel shows a negative control, whereby the myocyte was not labeled with anti-syntaxin antibody but with fluorescein isothiocyanate-conjugated secondary antibody.

molecular mass of SUR2A and SUR2B differs by just 1 kDa (3, 12, 16) and therefore may not be separated on the PAGE. In fact, we observed only a single SUR2 immunoreactive band in Fig. 2, A and B. SUR2A is nonetheless the dominant SUR2 protein in cardiac muscles (1, 3, 11, 12), as shown in Fig. 2B. We have therefore focused on the cardiac SUR2A protein by overexpressing SUR2A/Kir6.2 in HEK293 (Fig. 2C). Here, GST-Syn-1A bound to agarose beads is able to pull down abundant SUR2A proteins from the HEK293 cell lysate extract. This study also demonstrated (Fig. 2C) that Syn-1A binding to SUR2A is direct and not likely via an intermadiary ternary protein contained in the brain or heart. We had previously mentioned that Syn-1A did not bind Kir6.2 cytoplasmic N- and C-terminal domains (16).

Our previous study with pancreatic islet beta cells shows that Syn-1A specifically binds to NBF1 and NBF2 domains of SUR1 (16). We therefore examined whether Syn-1A may likewise bind to the NBF1 (amino acids 684–872) and C-terminal NBF2 (amino acids 1321–1499) of SUR2A. Indeed GST-NBF1 and -NBF2 of SUR2A, bound to agarose beads, were both able to pull down overexpressed Syn-1A from HEK293 cell extract (Fig. 2D) and recombinant Syn-1A (thrombin cleaved) (Fig. 2E), but as a negative control, GST did not (Fig. 2D and E). Finally, we examined the dose dependence of SUR2A-NBF1 (Fig. 2F, i) and NBF2 (Fig. 2F, ii) binding to Syn-1A at saturating concentrations. We found that NBF1 and NBF2 bound Syn-1A with an ED\(_{50}\) of 0.52 ± 0.07 μM (n = 3) and 0.64 ± 0.13 μM (n = 3), respectively.

**Syntaxin-1A Inhibits \( K_{ATP} \) Channels in Cardiac Myocytes through Direct Interactions with NBF1 and NBF2 of SUR2A—** To show the functional significance of the interaction between Syn-1A and cardiac SUR2A-NBF-1 and -NBF-2, we examined whether recombinant Syn-1A would directly inhibit \( K_{ATP} \) currents in rat cardiac myocytes and whether such inhibition is via Syn-1A-NBF(s) interaction. We performed inside-out configuration so that the intracellular face of a cardiac membrane patch containing \( K_{ATP} \) channels could be exposed to the test solutions. As shown in Fig. 3A, the patch had minimum current activities when held in 1 mM ATP but showed bursting activities when ATP was removed, indicative of the opening of multiple \( K_{ATP} \) channels. Because sustained exposure to ATP-free solution will cause run-down of \( K_{ATP} \) channels, we applied 50 μM ATP to maintain channel activities, leading to a partial inhibition of \( K_{ATP} \) currents. The \( K_{ATP} \) current in the presence of 50 μM ATP is then defined as control for each patch. Application of Syn-1A alone markedly reduced current values to 32.2 ± 6.7% of control values (Fig. 3A, i, and B). The GST control did not affect currents (102.2 ± 20.1%, Fig. 3B). We had previously demonstrated that Syn-1A strongly inhibits pancreatic beta cell \( K_{ATP} \) currents through binding to the NBF1, but not NBF2, of SUR1 (16). We then investigated whether SUR2A NBF1 or NBF2 would mediate Syn-1A inhibition of cardiac \( K_{ATP} \) currents. Surprisingly, in contrast to pancreatic beta cells, application of both SUR2A NBF1 and NBF2 abolished Syn-1A effects to 138 ± 17.3% (n = 19) and 129.6 ± 34.5% (n = 9) of control, respectively (Fig. 3A, ii and iii, and B). This result suggests that not only NBF1 but also NBF2 of SUR2A mediates Syn-1A inhibition of cardiac \( K_{ATP} \) currents. As controls, neither SUR2A NBF1 nor SUR2A NBF2 alone produced any significant effect on current activities, which were 96.2 ± 18.0% and 110.2 ± 11.3% of control, respectively (Fig. 3B).

Both SNARE proteins Syn-1A and SNAP-25 have been shown to interact with Kv1.1 and Kv2.1 channels (15, 21–24). Because cardiac myocytes possess not only Syn-1A (Fig. 1) but also SNAP-25,\(^2\) it is possible that SNAP-25 may itself interact with cardiac \( K_{ATP} \) channel, or it may modulate Syn-1A inhibition of cardiac \( K_{ATP} \) currents. Therefore we co-expressed Kir6.2 and SUR2A in HEK293 cells (which have no detectable endogenous SNARE proteins) to examine the direct inhibition of cardiac \( K_{ATP} \) channels by Syn-1A. When Kir6.2/SUR2A-transfected cells were dialyzed with a low ATP concentration (0.3 mM) through the recording pipette, \( K_{ATP} \) currents gradually developed and reached maximum amplitude in 4–8 min. At this time, I-V relationships were obtained by a family of triggering pulses from −160 to 40 mV in 20-mV increments (Fig. 4, A and E). The I-V relationship is almost linear with the expected reversal potential of about −80 mV. When the cells were dialyzed with a high ATP concentration (5 mM), only very minute currents (0.1–0.2 nA at −140 mV) were elicited, showing the ATP sensitivity of the currents. Dialyzing Syn-1A into the cell caused significant inhibition at both hyperpolarized and depolarized potentials (Fig. 4, B and E). Consistent with the myocyte results, co-dialysis of Syn-1A with either SUR2A-NBF1 or -NBF2 prevented Syn-1A inhibition (Fig. 4, C–E). To investigate whether SUR2A NBF1 and NBF2 had any effect on the currents on their own, we dialyzed either SUR2A-NBF1 or -NBF2 into Kir6.2/SUR2A-transfected cells. Neither of these NBFs had a significant effect on \( K_{ATP} \) currents (Fig. 4F). Therefore, our results indicate that Syn-1A inhibits the cardiac \( K_{ATP} \) channel by binding to both NBFs of SUR2A.

**DISCUSSION**

Recently, we demonstrated that wild-type Syn-1A acted on the SUR1 subunit to close the \( K_{ATP} \) channel in cultured insulinoma cells and freshly isolated rat islet beta cells (16). Here, we show that Syn-1A can also act on cardiac myocyte SUR2A protein to close the \( K_{ATP} \) channel, even under low cytosolic ATP concentrations, indicating that Syn-1A could close the cardiac \( K_{ATP} \) channel independently of ATP. This suggests that Syn-1A

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\(^2\) R. G. Tsushima and H. Y. Gaisano, unpublished observation.
may provide an inhibitory “braking” mechanism on the cardiac $K_{\text{ATP}}$ channel isoform (SUR2A/Kir6.2). These findings therefore describe a novel regulatory pathway of $K_{\text{ATP}}$ channel function, which has important implications in both physiological and pathophysiological conditions and which could be influenced by the dynamic changes of ATP and ADP concentrations occurring under these conditions. In support, our previous report showed that ADP could reduce the efficacy of Syn-1A inhibition of islet beta cell SUR1/$K_{\text{ATP}}$ channels (16). In contrast, additional cellular factors, including phosphatidylinositol 4,5-bisphosphate (PIP$_2$) (25) and acyl-CoA (26), act directly on the Kir6.2 subunit to activate $K_{\text{ATP}}$ channels, providing a further level of fidelity to fine-tune channel activity and hence cardiac electrical excitability.

FIG. 2. Syntaxin-1A binds cardiac SUR2A at its NBF1 and NBF2. GST-Syn-1A, bound to glutathione beads, was able to pull down SUR2 proteins from detergent solubilized rat brain membrane (A) and rat cardiac membrane (B), as well as overexpressed SUR2A in HEK293 cells (C). GST-NBF1 and -NBF2, bound to beads, were capable of pulling down overexpressed Syn-1A from HEK293 cell extract (D) and thrombin-cleaved Syn-1A (E). A–E are representative blots of two or three similar experiments. F shows the dose dependence of GST-NBF1 (i) and -NBF2 (ii) binding to Syn-1A. The upper panel shows a representative blot. The bottom panel shows a summary of quantitative densitometry scanning of the specific bands from three separate experiments. The values are expressed as mean ± S.E. In A–F, molecular mass markers (kDa) are indicated on the left.
These actions of Syn-1A on the cardiac $K_{ATP}$ channels were directly on the plasma membrane SUR2A protein because Syn-1A was able to bind the full-length SUR2A protein in SUR2A/Kir6.2-expressing HEK293 cells, which resulted in inhibition of $K_{ATP}$ currents. Also, SUR2A is the dominant SUR2 protein in the heart plasma membrane (1, 3, 11, 12, 17) where we found Syn-1A to be also most abundant. We had previously shown that the Kir6.2 cytoplasmic N or C terminus did not bind Syn-1A or modify Syn-1A inhibition of $K_{ATP}$ currents (16). In our previous report (16), we found that only recombinant NBF1 blocks the inhibitory action of Syn-1A on pancreatic beta cell $K_{ATP}$ channels, whereas NBF2 does not, even though NBF2 binds with similar affinity to Syn-1A as NBF1. In contrast, in the present study, we used inside-out cardiac patches and found that both NBF1 and NBF2 of SUR2A were similarly effective in completely blocking Syn-1A inhibition of the plasma membrane cardiac $K_{ATP}$ channels. These results are surprising because NBF2 is highly conserved between the SUR isoforms, whereas more heterogeneity exists at the NBF1 domains, N-terminal transmembrane, and distal C-terminal domain (3, 12). In fact, the distal 42-amino acid C-terminal portion of the SUR1 is distinct and has been shown to confer higher ATP sensitivity of SUR1 (4-fold higher) than SUR2A and SUR2B (27); it also conferred the distinct MgADP actions (28). It therefore seems that the Syn-1A binding domain of NBF2 of SUR2A and SUR1 is likely at the N-terminal portion of both NBFs and transduces the Syn-1A binding into channel modulation, whereas the distinct 42-amino acid C-terminal domain in SUR1-NBF2 seems to reduce the ability of Syn-1A in transducing this inhibitory action on $K_{ATP}$ opening. Consistent with this thinking, the structural determinants within the NBF2s which confer adenine nucleotide binding were found to be distinct from those which transduce nucleotide binding into $K_{ATP}$ channel activation (29). Previous studies have shown that NBF1 and NBF2 exist as heterodimers in the intact cells (30). Our findings demonstrate that Syn-1A binds both NBF1s and NBF2s of SUR2A and SUR1 (16) with similar affinity, therefore suggesting that an important action of Syn-1A might be to stabilize this NBF1/NBF2 complex and finely modulate its interactions. It should be noted that NBF2 is functionally distinct between the SUR1 and SUR2A isoforms (1, 2, 3, 12). Although NBF1 has a similar role in regulating gating kinetics of the channel complex, NBF2 in SUR1 renders the channel susceptible to the antagonistic stimulatory action of ADP. The
ADP sensitivity in the SUR2A/Kir6.2 channel is markedly lower. The differing sensitivities between SUR1- and SUR2A-NBF2 to Syn-1A may contribute to these differences in nucleotide sensitivity.

Syn-1A is known to regulate exocytosis and several membrane ion channels involved in secretion. Less work has been done in examining the role of SNARE proteins in non-secretory cells. Here, we show that Syn-1A plays an important role in modulating membrane excitability of a muscle cell, the cardiac myocyte, through its action on the \( K_{\text{ATP}} \) channel. Consistently,
we had previously shown that SNAP-25, another SNARE protein, could modulate voltage-gated K⁺ channels in gastrointestinal smooth muscles (23). Because NBF-1 and NBF-2 domains are highly homologous between SUR2A and SUR2B (1, 3, 12, 16), Syn-1A would be expected to interact similarly with the NBF-1 and NBF-2 of SUR2B, which regulate vascular smooth muscle KＡТＰ channels. In fact, the SUR2 immunoreactive proteins in the brain (this study) pulled down by Syn-1A are likely to contain more SUR2B than SUR2A, which in part are contributed by the vascular beds in the brain (11, 12). More work will have to be done to examine the specific actions of Syn-1A on vascular KＡТＰ (SUR2B) channel activity. Nonetheless, Syn-1A binding to both SUR1 (16) and SUR2 (this study) proteins indicate the importance of Syn-1A regulation of these KＡТΡ channels. Taken together, these studies also indicate that SNARE proteins, particularly Syn-1A, play an important role in coordinating the ion channel events in both secretory and non-secretory cells.

Syn-1A interactions with KＡТΡ channels are potentially important in the health and disease of the heart, pancreatic islet beta cell, vascular smooth muscle, and neurons (1). In insulin-secreting beta cells, we recently demonstrated that Syn-1A and other SNARE proteins are sequestered within plasma membrane lipid raft domains along with Ca²⁺ and Kv2.1 channel proteins, whereas SUR1/Kir6.2 KＡТＰ channel proteins are in non-lipid raft domains (31). Interestingly, cholesterol depletion shifted Syn-1A out of the lipid rafts into non-lipid raft domains, which had a profound effect on channel regulation and insulin exocytosis. It therefore appears that membrane compartmentalization of ion channels and SNARE proteins is critical for the temporal and spatial coordination of insulin release and also presumably for cardiac membrane excitability and contractility, which could be profoundly altered by lipid metabolism occurring in health and diabetes.

KＡТΡ channel regulation plays a central role in protecting the heart from ischemia/reperfusion injury (32) and calcium homeostasis during exercise (33). ATP levels decrease during exercise and ischemia, leading to opening of KＡТΡ channels, thereby shortening the action potential duration to reduce Ca²⁺ influx and myocardial contraction. This leads to energy conservation and an optimization of the contractile response (33). Increased local concentrations of Syn-1A may inhibit cardiac KАТΡ channels and potentially offset pro-arrhythmic activity via excessive action potential shortening. Syn-1A-mediated inhibition may therefore act as a brake to oppose the potentially deleterious effects of sustained KＡТΡ channel activity during periods of metabolic compromise. However, this remains to be tested experimentally.

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