Acyl Coenzyme A Esters Differentially Activate Cardiac and β-Cell Adenosine Triphosphate–Sensitive Potassium Channels in a Side-Chain Length-Specific Manner

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Recent evidence demonstrates that long-chain acyl coenzyme A esters (CoAs) activate cardiac and β-cell plasma-membrane (*pm*K_{ATP}) adenosine triphosphate (ATP)-sensitive potassium channels. In this study, we have investigated the differential effects of acyl CoAs of short and medium side-chain length on cardiac and β-cell *pm*K_{ATP} isoforms. At the single-channel level, the addition of acyl CoAs of differing side-chain length (2 to 16 carbons) to the inside face of membrane patches from ventricular myocytes caused varying increases in *pm*K_{ATP} channel open probability proportional to increases in acyl side-chain length (20 μmol/L acetyl CoA: 310% ± 90%, 20 μmol/L decanoyl CoA: 570% ± 150%). A similar dependence of activation on side-chain length was observed in recombinant *pm*K_{ATP} channels (SUR2A/Kir6.2) with full activation of current requiring both the acyl and CoA moieties in the esterified form. We found the recombinant β-cell K_{ATP} channel (SUR1/Kir6.2) to be much less sensitive to medium-chain acyl CoAs (decanoyl CoA: 124% ± 15% *v* 231% ± 25% in SUR2A/Kir6.2), suggesting a role for the cardiac sulfonylurea receptor, SUR2A, in the molecular mechanism of activation by these compounds. We propose that fatty acid metabolism, and the resultant generation of acyl CoAs of varying side-chain length, may be an important regulator of cellular excitability via interactions with the K_{ATP} channel.

POTASSIUM CHANNELS that are sensitive to intracellular adenosine trisphosphate (ATP), known as K_{ATP} channels, are found in many tissues and function to couple excitability to cellular metabolism.[1-3] In pancreatic β cells, glucose stimulation leads to an increase in [ATP]:[adenosine diphosphate (ADP)], inhibiting K_{ATP} channel activity. This causes a depolarization of the membrane potential, activation of voltage-gated Ca^{2+} channels, and the triggering of insulin release. In cardiac tissue, 2 distinct populations of K_{ATP} channels have been identified: one is expressed in the plasma membrane (*pm*K_{ATP}) and the second is located in the inner mitochondrial membrane (*mito*K_{ATP}). Despite the high density of *pm*K_{ATP} channels in the heart, their physiologic significance remains obscure, with data suggesting that *pm*K_{ATP} channels are maintained in a predominantly closed state by normal (millimolar) levels of ATP. However, there is good evidence to support a role for *pm*K_{ATP} channels in protection from cardiac ischemia/reperfusion injury,[4,5] and activation of *pm*K_{ATP} channels contributes to the elevation of the electrocardiographic ST segment observed during ischemia, despite the maintenance of millimolar ATP levels under these conditions.[6]

K_{ATP} channels are regulated by a variety of intracellular metabolites,[1,7] as well as by protein kinases.[8,9] Long-chain acyl coenzyme A esters (CoAs), the intracellular esters of free fatty acids, have been shown to directly activate *pm*K_{ATP} channels from ventricular myocytes[10] and also activate both recombinant[11,12] and endogenous[13] β-cell K_{ATP} channels, albeit to a lesser extent. The heart derives > 50% of its energy requirements from β-oxidation of circulating fatty acids,[14] and levels of acyl CoAs of varying side-chain length are known to increase when free fatty acids are provided and also during ischemia.[14-17] It was, therefore, the aim of this study to investigate the activation of *pm*K_{ATP} channels by a range of acyl CoA molecules with differing side-chain lengths. We demonstrate the ability of short- and medium-chain acyl CoAs to activate both native and recombinant cardiac *pm*K_{ATP} channels in a side-chain length-dependent manner. We also investigated the molecular basis of this activation, showing that both the acyl and CoA moieties are required to elicit the full effects of the acyl CoA complex. Our findings also support those of Bränström et al[13] that the β-cell K_{ATP} isoform is less sensitive to these molecules. These findings, taken together, suggest that fatty acid metabolism, and the resultant generation of acyl CoAs of varying side-chain length, is likely a novel regulator of *pm*K_{ATP} channels in the heart.

MATERIALS AND METHODS

Cell Isolation and Culture

Right ventricular myocytes from rat were enzymatically isolated using standard protocols described previously.[18] TsA201 and COS-1 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 2 mmol/L L-glutamine, 10% fetal calf serum, and 0.1% penicillin/streptomycin at 37°C (10% CO_2). Cells were plated at 50% to 70% confluency on 35-mm culture dishes 4 hours before transfection. The K_{ATP} channel Kir6.2 subunit from mouse was generously provided by Dr S. Seino[19,20] and hamster SUR1 by Drs L. Aguilar-Bryan and J. Bryan.[21] The SUR2A from rabbit heart was cloned in our laboratory (GENBANK accession # AF087468). Clones were inserted into the mammalian expression vector pCDNA3.1 and cotransfected with a vector encoding the green fluorescent protein (pGL, Life Technologies, Burlington, Canada) into COS-1 cells using Lipofectamine reagent as per manufacturer's instructions (Life Technologies) or

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tsA201 cells using the calcium phosphate precipitation method. Recordings were made from cells 48 to 72 hours after transfection.

Electrophysiology

Standard patch-clamp techniques were used to record single-channel 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 approximately 2 seconds. Single-channel currents were recorded at a holding potential of −60 mV, amplified (Axopatch 200B, Axon Instruments, Foster City, CA), and then digitized and analyzed using Axoscope v8.0 and pClamp 8.0 software (Axon Instruments). Data were sampled at 2.5 kHz and filtered at 1 kHz.

The pipette solution used for most excised patch recordings contained the following (in millimolars): potassium chloride (KCl) 140; HEPES 10; $MgCl_2$ 1.4; EGTA 1; glucose 10. The pH of the solution was adjusted to 7.4 with potassium hydroxide (KOH). This solution was also used in the perfusion pipette to superfuse the patches for experiments under symmetrical K^+ conditions. Experiments involving palmitoyl CoA required the use of the following pipette/perfusion solution to solublize the long-chain acyl CoA (in millimolars): KCl 110; KOH 30; EGTA 10; HEPES 5; $MgCl_2$ 1. The pH of this solution was also adjusted to 7.4 using hydrochloric acid (HCl).

Experimental Compounds

ATP (as MgATP, Sigma, St Louis, MO) was added as required from a 10-mmol/L stock, which was prepared immediately before use. Fatty acids and fatty acyl CoAs were obtained from Sigma.

Statistics

Statistical significance was evaluated using Student's paired *t* test. Differences with values of probability $P < .05$ were considered to be significant. All values in the text are mean ± SEM.

RESULTS

Direct Effects of Acyl CoAs on Single pmK_{ATP} Channels From Cardiac Myocytes

To study the mechanism by which fatty acids can directly activate *pm*K_{ATP} channels, the corresponding single-channel transitions recorded using excised inside-out ventricular myocyte membrane patches were analyzed. Recent findings from Liu et al[10] have demonstrated that palmitoyl CoA, a commonly occurring long-chain fatty acid ester, can potently activate cardiac *pm*K_{ATP} channels. We investigated the effects of acyl CoAs with differing side-chain length, as fatty acids are also found in the heart with shorter side-chain length as a result of fat metabolism. Direct application of the water-soluble fatty acid octanoyl CoA (20 μmol/L, carbon chain length C = 8) to the internal face of membrane patches of ventricular sarcolemma caused a marked enhancement of K_{ATP} channel activity (410% ± 60% increase in NPo [a function of current], $P < .01$, see Fig 1Ai,ii). This effect of octanoyl CoA was studied in detail in the presence of different internal ATP levels, and the results were compared with the inhibitory effect of ATP in the absence of octanoyl CoA. These findings, expressed as ATP-inhibition curves, show that octanoyl CoA modulates *pm*K_{ATP} channel activity by shifting the ATP levels needed for inhibition to higher values (IC_{50} = 321 μmol/L *v* 42 μmol/L for control, see Fig 1Aiii). The Hill coefficient remained unchanged (1.85 and 1.90 for control and octanoyl CoA, respectively). A similar pattern of activation of *pm*K_{ATP} channels was also observed after addition of 20 μmol/L acetyl CoA (C = 2) or 20μmol/L decanoyl CoA (C = 10). The extent of activation of K_{ATP} channels was enhanced as side-chain length increased (310% ± 90% and 570% ± 150% for acetyl CoA and decanoyl CoA, respectively, see Fig 1Aii, B, and C).

Effects of Acyl CoAs on Recombinant pmK_{ATP} Channels

It has previously been reported that only long-chain acyl CoAs (C > 12) can activate the native and recombinant pancreatic β-cell K_{ATP} channel (SUR1/Kir6.2).[11-13] Previous studies on native cardiac *pm*K_{ATP} channels have also only investigated long-chain (C > 16) acyl CoAs.[10] However, our data demonstrate that short- and medium-chain acyl CoAs can also significantly increase the open probability of native cardiac *pm*K_{ATP} channels (Fig 1). Experiments were performed to determine if recombinant cardiac *pm*K_{ATP} channels (SUR2A/Kir6.2) are similarly activated by medium-chain acyl CoAs. Using excised inside-out membrane patches from COS-1 cells expressing the SUR2A and Kir6.2 subunits, the addition of 50 μmol/L octanoyl CoA resulted in an increase in current to 256% ± 18% of that seen in the absence of octanoyl CoA (control) (n = 6 patches, Fig 2A and C).

Acyl CoAs consist of a hydrophilic coenzyme A moiety disulphide-bonded to a saturated fatty acid side-chain of varying length to form the acyl ester. Using recombinant cardiac *pm*K_{ATP} channels, the relative contributions of the CoA and fatty acid components of acyl CoA were assessed separately. At a concentration of 50 μmol/L, addition of CoA alone caused an increase to 157% ± 11% of SUR2A/Kir6.2 control current (n = 7, $P < .01$). Conversely, 50 μmol/L free octanoate alone had no effect on channel activity when compared with control. The effect of decanoyl CoA (C = 10) was similar to that of octanoyl CoA. A total of 50 μmol/L decanoyl CoA increased SUR2A/Kir6.2 current to 231% ± 25% of control ($P < .01$ see Fig 2C).

The addition of lower concentrations of the long-chain acyl CoA palmitoyl CoA (C = 16) produced a much more potent activation of recombinant K_{ATP} (SUR2A/Kir6.2) current. At 2 μmol/L, palmitoyl CoA enhanced the SUR2A/Kir6.2 current to 420% ± 82% of control (Fig 2B and C).

Differential Effects of Decanoyl CoA on Recombinant β-Cell and Cardiac pmK_{ATP} Channels

Previous studies have shown β-cell K_{ATP} channels to be insensitive to short- and medium-chain acyl CoAs (C < 12)[13] and less sensitive than cardiac *pm*K_{ATP} channels to long-chain acyl CoAs.[10,12] We made a direct comparison of the effects of the 10 carbon acyl ester, decanoyl CoA, on the recombinant channels SUR1/Kir6.2 and SUR2A/Kir6.2. A total of 50 μmol/L decanoyl CoA was found to activate the β-cell isoform to a lesser extent than the cardiac *pm*K_{ATP} isoform (124% ± 15% *v* 231% ± 25% of control current, respectively, Fig 3Ai and B). Interestingly, inhibition of the 2 isoforms by the free fatty acid derivative of this molecule, decanoate (100 μmol/L), was identical (39% ± 5% *v* 39% ± 5% for SUR1/6.2 and SUR2A/6.2, respectively, Fig 3Aii and C).

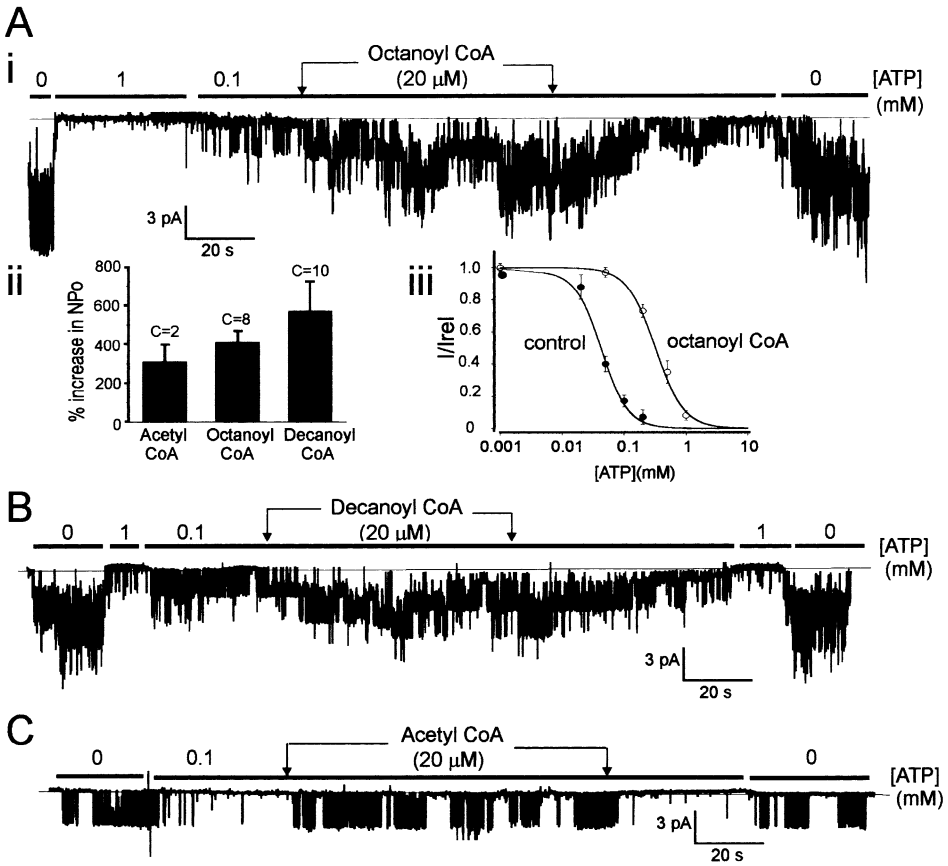

Fig 1. (Ai), (B), and (C) show representative excised inside-out myocyte membrane patch recordings of *pm*K_{ATP} channels. Note the significant enhancement of *pm*K_{ATP} channel activity in response to (Ai) octanoyl CoA, (B) decanoyl CoA, and (C) acetyl CoA. (Aii) Grouped data from patch recordings demonstrating the stimulatory effects of acetyl, octanoyl, and decanoyl CoA on *pm*K_{ATP} channel activity. (Aiii) ATP inhibition of *pm*K_{ATP} channel activity in the absence and presence of octanoyl CoA (20 μmol/L). In all experiments selected water-soluble fatty acyl CoAs were applied during the time period between the arrows. Mean data was obtained from 4 to 9 patches for each group.

Interaction of Acyl CoAs With ADP

It has previously been reported that coapplication of oleoyl CoA and ADP to β-cell K_{ATP} channels produces an activation of current that is supra-additive than the individual effects of the 2 compounds.[13] We investigated whether such an interaction occurs between ADP and palmitoyl CoA when applied to the recombinant cardiac *pm*K_{ATP} channel. The activation of current produced by 0.2 mmol/L ADP was expressed as a percentage of that produced by 0 mmol/L ATP alone and found to be no different in the presence of 1 μmol/L palmitoyl CoA than in the absence of palmitoyl CoA (23% ± 2% n = 6 *v* 28% ± 7%, n = 7, Fig 4).

DISCUSSION

Our results suggest that acyl CoAs function as physiologic activators of *pm*K_{ATP} channels in the heart. These findings, and the recent report of Liu et al,[10] show that fat metabolism is likely a key regulatory pathway of *pm*K_{ATP} channels, the importance of which is likely even greater during metabolic insult when cellular acyl CoA levels increase.[16] The large rightward shift in the ATP-inhibition curve (Fig 1Aiii) provides a mechanism for enhanced *pm*K_{ATP} channel opening under conditions that reduce the ATP content of the cell, such as hypoxia. This "priming effect" of fatty acyl CoAs on *pm*K_{ATP} channels would be expected to amplify the effects of other second messenger systems, which regulate *pm*K_{ATP} channel activation, such as the receptor-coupled regulation by protein kinase C.[22,23]

Previous failure to define a functional role for *pm*K_{ATP} channels in the heart may be explained by the almost exclusive provision of carbohydrates, such as glucose, as the sole energy source in the majority of in vitro studies. Indeed, it is known that intracellular levels of acyl CoAs increase significantly when fatty acids are provided in addition to glucose[14,17] and also increase during the first 5 minutes of low-flow ischemia.[14,16,17] Recent evidence suggests that the enzyme responsible for conversion of free fatty acids to acyl CoAs, fatty acyl CoA synthetase isoform 1 (ACS1), may be located in the plasma membrane,[24] and cytosolic acyl CoA levels are likely to increase in response to both elevated free fatty acids and ischemia.

It is interesting to note that 5-hydroxydecanoate, thought to specifically inhibit the putative *mito*K_{ATP} channel, has recently been shown to be a substrate for acyl CoA synthase.[25,26] It is possible that some of the observed effects of this inhibitor may be mediated through the product, 5-hydroxydecanoyl CoA, and might include its binding to the *mito*K_{ATP} channel. However, testing of such hypotheses must wait until the molecular identification of the *mito*K_{ATP} channel.

The molecular mechanism of the effects of fatty acids is of considerable importance. Our data show that while micromolar CoA alone can activate the recombinant SUR2A/Kir6.2

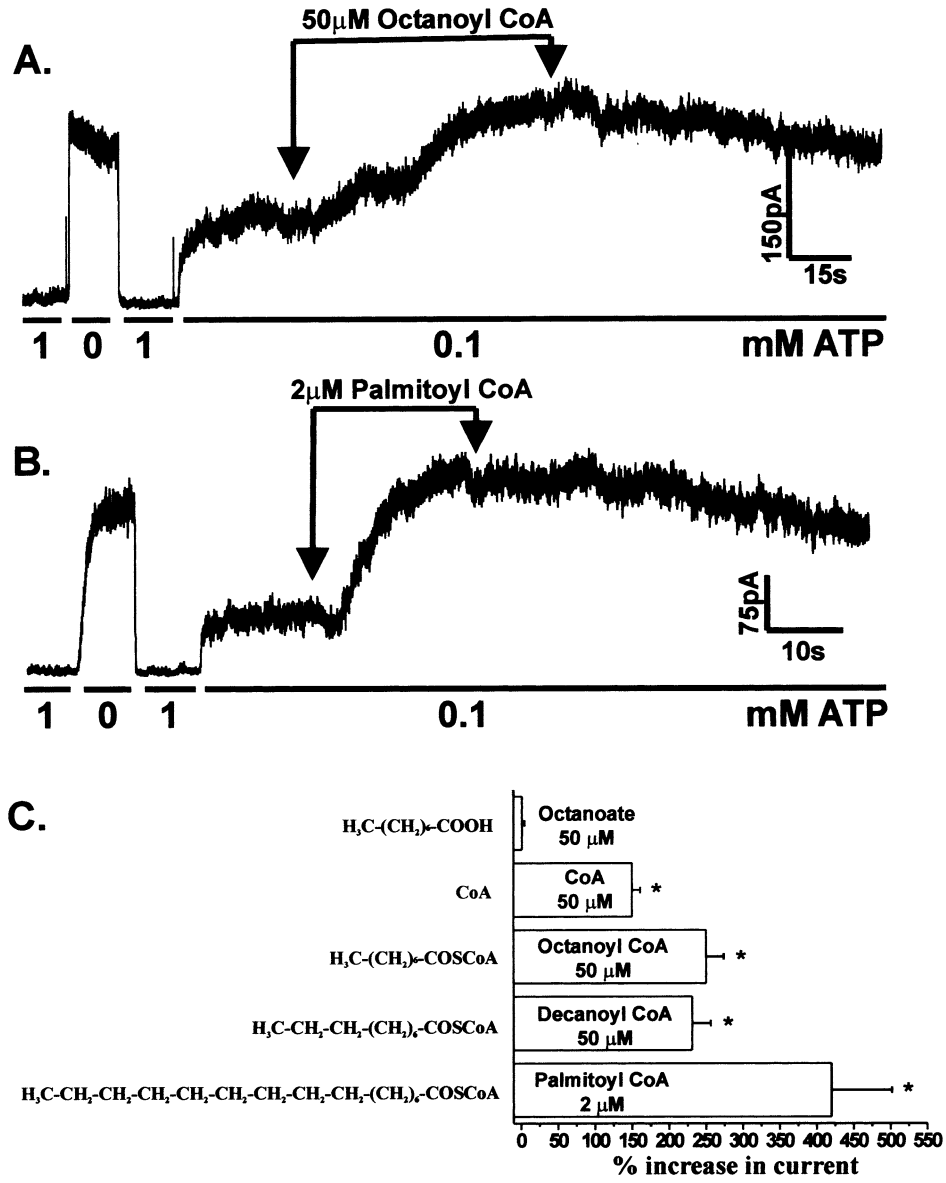

Fig 2. Macroscopic pmK_{ATP} channel activity recorded in the inside-out patch configuration from COS-1 cells expressing the SUR2A/Kir6.2 subunits. (A) Representative trace of the stimulatory actions of 50 μmol/L octanoyl CoA (C = 8) on SUR2A/Kir6.2 current. (B) Representative trace of the stimulatory action of 2 μmol/L almitoyl CoA (C = 16) on SUR2A/Kir6.2 current. (C) Grouped data of the effects of palmitoyl CoA, decanoyl CoA, octanoyl CoA, CoA, and octanoate on activation of SUR2A/Kir6.2 current (5 to 9 patches in each group). All groups were significantly different from the control current ($P < .01$) except octanoate at 50 μmol/L.

pmK_{ATP} channel, the acyl CoA thio-ester moiety is a much more effective stimulator of pmK_{ATP} channel activity. These results suggest a complex mechanism of action requiring both the hydrophilic CoA and hydrophobic acyl side-chain to elicit the full stimulatory effects on pmK_{ATP} channel activity. In addition, the acyl side-chain seems to be an important determinant of acyl CoA efficacy in activating pmK_{ATP} channels, with increasing side-chain length producing more potent activation of pmK_{ATP} channels.

The precise binding region for fatty acyl CoAs has not been established, although recent evidence on the pancreatic pmK_{ATP} channel (SUR1/Kir6.2) suggests that acyl CoAs act upon the pore-forming Kir6.2 subunit of the K_{ATP} channel complex.[12] However, it should be noted that medium-chain acyl CoAs, such as octanoyl CoA, had no effect on either the SUR1/Kir6.2 subunit complex or Kir6.2ΔC26 channel,[12] but we observed an increase in current to 256% of control when using the cardiac subunit complex of SUR2A/Kir6.2 (see Fig 2A and C). In addition, it has previously been reported that oleoyl CoA produced a much larger increase in SUR2A/Kir6.2 channel activity compared with the effects seen on the SUR1/Kir6.2 channel.[10] In our study, direct comparison of the effects of decanoyl CoA on these 2 channel isoforms also reveals a difference in their sensitivity to acyl CoAs. These findings indicate that the SUR2A subunit also has a role to play in mediating the stimulatory effects of the acyl CoA esters of medium- and long-chain fatty acids.

In contrast to findings previously reported for the β-cell K_{ATP} channel,[13] we see no interaction between acyl CoA and ADP activation of the recombinant cardiac pmK_{ATP} channel. It is possible that the effect is due to an interaction at a specific site on the SUR1 subunit, which the SUR2A subunit does not

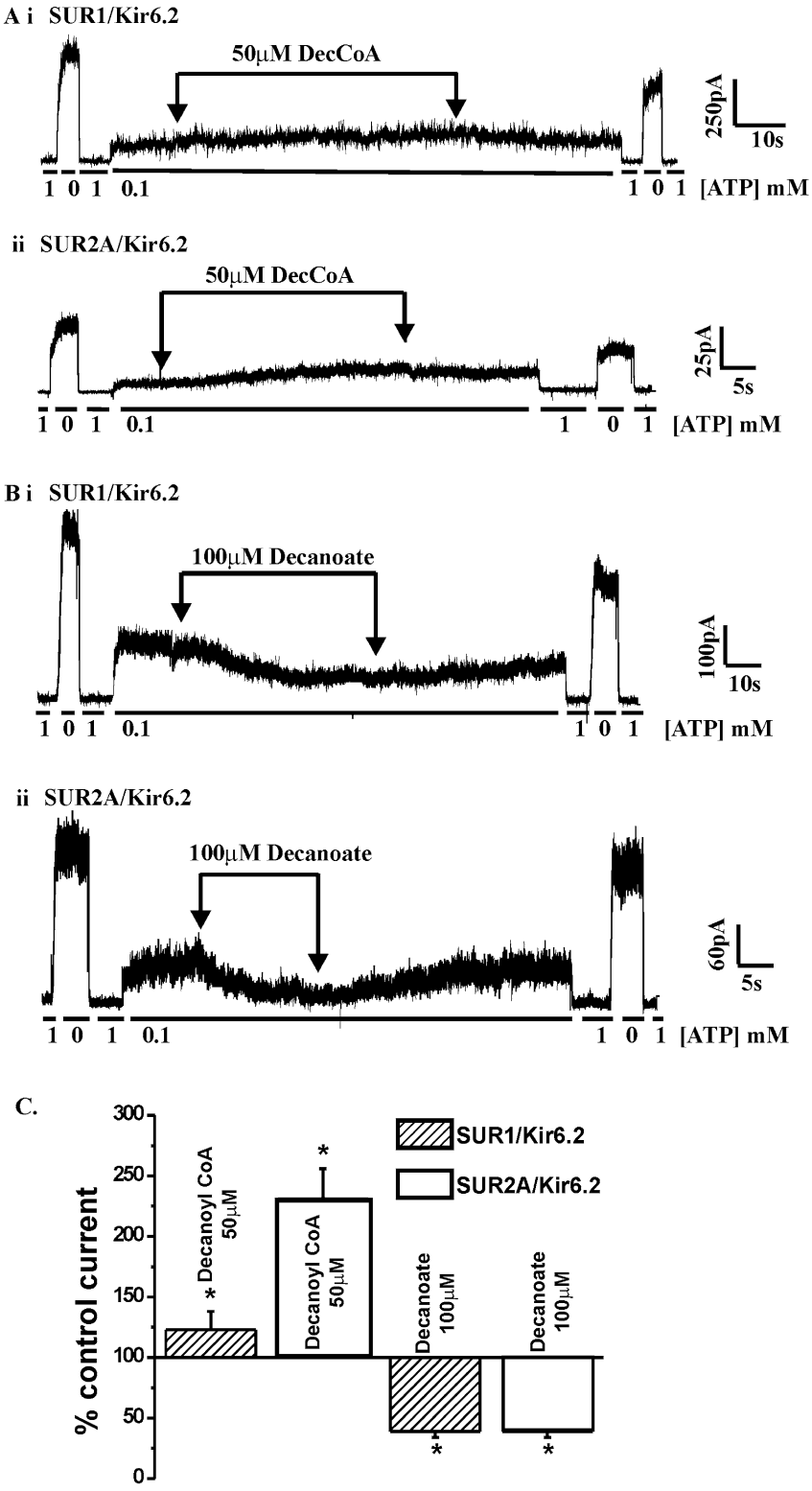

Fig 3. SUR1/6.2 and SUR2A/6.2 have different sensitivities to decanoyl CoA. Macroscopic K_{ATP} channel activity recorded in the inside-out patch configuration from COS-1 cells expressing SUR1/6.2 or SUR2A/6.2 subunits. Representative traces of the action of (A) 50 μmol/L decanoyl CoA and (B) 100 μmol/L decanoate on (i) SUR1/6.2 and (ii) SUR2A/6.2 current. (C) Grouped data of the effects of 50 μmol/L decanoyl CoA and 100 μmol/L decanoate on SUR1/6.2 and SUR2A/6.2 current. All groups were significantly different from control ($P < .05$).

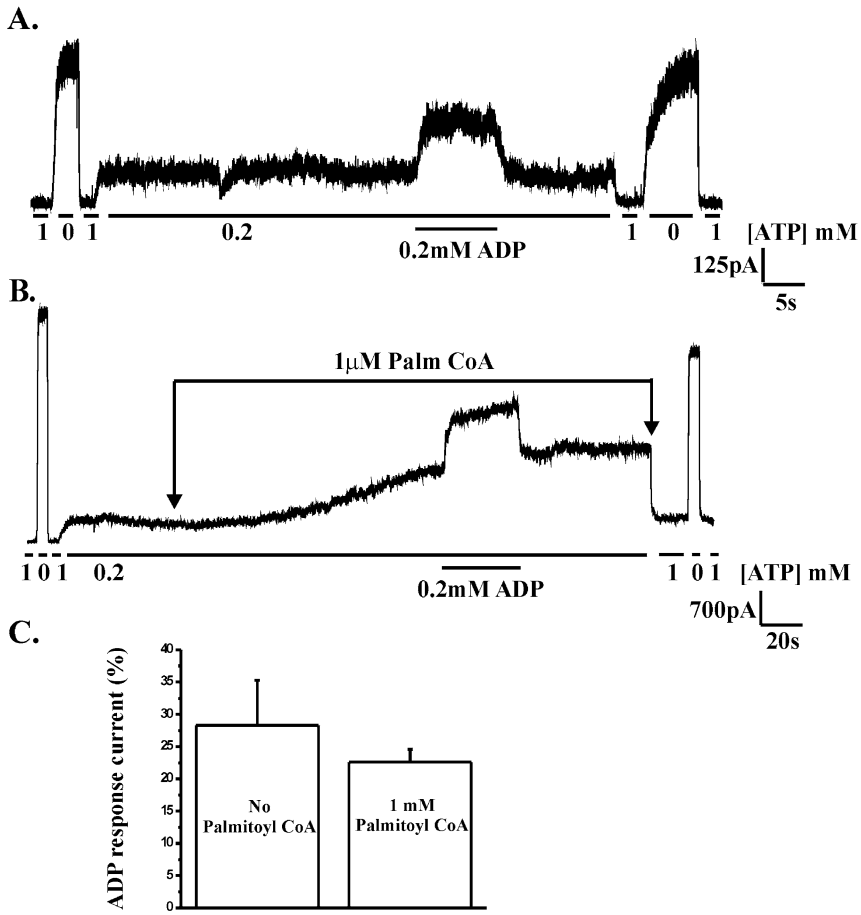

Fig 4. The effect of palmitoyl CoA on ADP sensitivity in tsA201 cells expressing SUR2A/6.2 subunits. Representitive traces of the stimulatory effect of 0.2 mmol/L ADP assessed in the (A) absence or (B) presence of 1 μmol/L palmitoyl CoA. (C) Grouped data indicates no difference in the activation produced by ADP in the absence (28% ± 7%, n = 6) or presence (23% ± 2%, n = 7) of palmitoyl CoA.

possess. Indeed, SUR1 confers a greater sensitivity to ADP than does SUR2A.[27]

The possible physiologic reasons for the apparent difference in acyl CoA sensitivity of recombinant cardiac *pm*K_{ATP} channels compared with that of recombinant β-cell channels are unclear. Although fatty acids are a major metabolic fuel for both the heart and the pancreatic β cell, the high metabolic demand of the heart means that there is a much greater turnover of fat metabolism, and acyl CoA levels are likely higher in this tissue (although definitive measurements in each have not been reported). Using a mouse Kir6.2 knockout model, Suzuki et al[4] have demonstrated that lack of cardiac *pm*K_{ATP} channels leads to greater susceptibility of the heart to ischemia and abolition of the cardioprotective effects of ischemic preconditioning. Conversely, activation of native cardiac *pm*K_{ATP} channels by low levels of acyl CoAs, as indicated in this study, may enhance the cardioprotective effects of ischemic preconditioning and protect cardiac function during metabolic insults.

Extrapolation of the apparent lower acyl CoA sensitivity of the recombinant β-cell K_{ATP} channel to the physiologic situation suggests a possible role in limiting susceptibility to metabolic dysfunction, such as diabetes. An increased sensitivity to low levels of acyl CoAs, leading to enhanced open probability, would be expected to impair insulin secretion in response to glucose. A similar scenario may occur in obese diabetic patients, in whom β-cellular acyl CoA levels are raised,[28] possibly impairing their insulin secretion.

In conclusion, our data demonstrate that acyl CoAs of varying side-chain length activate cardiac *pm*K_{ATP} channels in a side-chain length-dependent manner, whereas pancreatic β-cell K_{ATP} channels are less sensitive to medium-chain acyl CoAs. We also report differences between the 2 channel isoforms in their interaction between acyl CoA and ADP. It seems probable that this novel regulatory pathway may also be functional in other tissues where *pm*K_{ATP} channels are expressed.

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