The ATP-sensitive potassium channel from the inner mitochondrial membrane (mitoKATP) is a highly selective conductor of K⁺ ions. When isolated in the presence of nonionic detergent and reconstituted in liposomes, mitoKATP is inhibited with high affinity by ATP ($K_{1/2}$ = 20–30 μM). We have suggested that holo-mitoKATP is a heteromultimer consisting of an inwardly rectifying K⁺ channel (mitoKIR) and a sulfonylurea receptor (Grover, G. J., and Garlid, K. D. (2000) J. Mol. Cell. Cardiol. 32, 677–695). Here, we show that a 55-kDa protein isolated by ethanol extraction and reconstituted in bilayer lipid membranes and liposomes is the mitoKIR. This protein, which lacks the sulfonylurea receptor subunit, is inhibited with low affinity by ATP, with $K_{1/2}$ = 55 μM. ATP inhibition of both mitoKIR and holo-mitoKATP is reversed by UDP ($K_{1/2}$ = 10–15 μM). Holo-mitoKATP is opened by cromakalim and diazoxide, and the flux through the open channel is inhibited by glibenclamide and 5-hydroxydecanoate. None of these agents has any effect upon mitoKIR. We have identified two compounds that act specifically on mitoKIR. p-diethylaminoethylbenzoate reverses inhibition of mitoKIR by ATP and ADP at micromolar concentrations and also opens mitoKATP in isolated mitochondria. Tetraphenylphosphonium inhibits K⁺ flux through both mitoKIR and mitoKATP with the same apparent affinity. These findings support the hypothesis that the 55-kDa mitoKIR is the channel component of mitoKATP.

The importance of the mitochondrial K⁺ cycle for volume regulation, reviewed by Garlid and Paucek (1) was recognized by Jolles (2). The increase in K⁺ influx occurs by diffusion and by means of ATP-sensitive potassium channel from the inner mitochondrial membrane (mitoKATP). At the high values of $\Delta V$ maintained by mitochondria, both of these processes increase exponentially with $\Delta V$ (3,4) and are consequently very sensitive to fluctuations in $\Delta V$. These fluctuations, in turn, are high in tissues such as heart, which undergo large variations in energy demand and ATP synthesis rates (5). Thus, regulation of K⁺ influx and efflux pathways can be seen as a means of regulating volume in the face of the changing energy requirements of the cell. MitoKATP plays more than a housekeeping role in cell physiology. There is now general agreement that mitoKATP plays a key role in cardioprotection against ischemia-reperfusion injury (6,7). The proposed mechanism of this protective effect of mitoKATP opening (5,8,9) are plausible; however, it is evident that more needs to be known about the functional properties of mitoKATP before its role in vivo can be ascertained.

By using a novel ethanol extraction technique, Mironova et al. (10) were the first to report reconstitution in lipid bilayer membranes of a 55-kDa K⁺ channel from mitochondria. Paucek et al. (3) used a detergent extraction technique and were the first to report reconstitution of mitoKATP in liposomes. The latter channel was associated with two proteins of molecular mass 55 and 63 kDa, and we hypothesized that mitoKATP is a heteromultimeric complex consisting of a 55-kDa inwardly rectifying K⁺ channel (mitoKIR) and a 63-kDa sulfonylurea receptor (mitoSUR), analogous to the plasma membrane ATP-sensitive K⁺ channel (cellKATP) (11,12).

In this report, we focus on three interactions that address the key question of whether the 55-kDa K⁺ channel protein observed in the ethanol purification is the same as the 55-kDa protein purified with detergents. First, we show that UDP reverses ATP-inhibition of K⁺ flux mediated by both mitoKIR and mitoKATP, reconstituted in liposomes. Moreover, UDP exerts the same action in isolated mitochondria, and the affinities for the opening effect of UDP are about the same in each preparation. Second, we show that the mitoKIR opener diethylaminoethylbenzoate (DEB) also activates K⁺ flux through mitoKATP in isolated mitochondria and this effect is inhibited by 5-HD and glibenclamide.

Third, we show that tetraphenylphosphonium ion (TPP⁺) inhibits reconstituted mitoKIR and mitoKATP with similar affinities. We conclude that the 55-kDa protein obtained by ethanol extraction is the channel component of mitoKATP.

**EXPERIMENTAL PROCEDURES**

**Mitochondrial Preparations**—The experiments in this paper utilized mitochondria isolated from rat liver (13), rat heart (14), and rat brain cortex (15). Different mitochondrial preparations were used in different protocols, largely for practical reasons. We have shown previously that the properties of liver, heart, and brain mitochondria are qualitatively and quantitatively similar (12).
Regulation of mitoKIR

Electrophysiological Measurements of mitoKIR in Lipid Bilayer Membranes—Rat liver mitochondria were diluted to 7 mg of protein/ml with 20 mM Tris-HCl (pH 7.4), stirred for 20 min at 4°C, and centrifuged at 7000 g for 15 min at 4°C. The pellet was resuspended in 10 mM Tris-HCl (pH 7.4) to 44 mg of protein/ml, and this was diluted with 10 parts of 66% ethanol in water (20°C). After stirring for 30 min at 4°C, the suspension was centrifuged at 7000 × g for 15 min, and the supernatant was dialyzed overnight against 5 mM Tris-HCl (pH 7.4), 0.5 g/liter mercaptoethanol at 4°C. The dialyzed sample was centrifuged at 100,000 g for 30 min to remove remaining particulate matter and then loaded on a 1-ml DEAE-cellulose column pre-equilibrated with column buffer containing 50 mM Tris-HCl, 0.5 g/liter mercaptoethanol, and 1 mM EDTA (pH 7.4). The bound proteins were eluted with a KCl step gradient, and the active fraction was eluted with 250 mM KCl (16). This fraction was dialyzed against column buffer for 3 h, applied to a second DEAE column (1 ml), and again eluted with a KCl step gradient, to be recovered in the 250 mM KCl fraction.

Ion conductance of the partially purified 55-kDa protein, mitoKIR, was measured in lipid bilayer membranes (17) using bovine brain lipid (20 mg/ml) plus 10% cardiolipin dissolved in decane. The solution on both sides of the bilayer contained 100 mM KCl, 20 mM Tris-HCl (pH 7.4). Potentials (10–100 mV) were applied across the membrane, and currents were registered using an operational amplifier (AD 711C, Analog Devices).

Potassium Flux Measurements of Holo-mitoKATP in Liposomes—Rat brain mitochondria were solubilized in Triton X-100 and purified on DEAE-cellulose, as described previously (12). The active fraction, eluting with 250 mM KCl, was dialyzed overnight at 4°C against column buffer and reconstituted into liposomes containing potassium-binding benzofuran isophthalate (PBFI) (12). Proteins in the fraction were visualized by Coomassie Blue R-250 staining of SDS-PAGE gels (18). The procedure described for mitoKIR studies in lipid bilayer membranes (see Materials and Methods) was followed with respect to ATP inhibition: (i) the apparent affinities for ATP differ widely, with K_{ATP} values of about 600 μM in liposomes or lipid bilayer membranes containing mitoKIR, 20–30 μM in liposomes containing holo-mitoKATP (3, 23), and 1 μM in mitochondria; (ii) ATP inhibition of holo-mitoKATP in liposomes or mitochondria exhibits an absolute requirement for Mg^{2+} (3, 23), whereas ATP inhibition of mitoKIR is indifferent to Mg^{2+}; (iii) we always observed a 10-fold higher ATP affinity in isolated mitochondria over liposomes (24), and we have no explanation for this finding at present.

The Effects of Cromakalim, Diazoxide, Glibenclamide, and 5-HD on Mitochondria—In additional experiments (data not shown), we found that the K^+ conductance catalyzed by mitoKIR in lipid bilayer membranes and in liposomes is insensitive to 5-HD (50–500 μM), glibenclamide (1–10 μM), cromakalim (10–100 μM), and diazoxide (1–30 μM). In contrast, each of these agents has been shown to be a potent modulator of holo-mitoKATP (3, 7, 22, 25).

The Effects of UTP upon Mitochondria—When reconstituted in lipid bilayer membranes, the 55-kDa protein forms potassium channels with a unitary conductance of about 10 pS (16, 26, 27). The current-voltage plot of the channel exhibits characteristic rectifying properties, as shown in Fig. 3A. We frequently observed conductances of up to 100 pS (Fig. 3B), which we have interpreted as clusters of 10 elementary channels (28). Note that in Fig. 3B, current is inhibited by 1 mM ATP, and the ATP-inhibited current is restored by 20 μM UTP. Therefore, UTP is a mitoKIR opener.
Regulation of mitoKIR

It can be seen in Fig. 3B that UDP restored K$^+$ conductance to levels higher than those in the control. We attribute this overshoot to UDP activation of channels that had lost their activity with time. Spontaneous decline in channel activity (rundown) has been described previously for both mitoKIR (29) and cellKATP (30). We discovered that the loss of channel activity because of rundown could be reversed by the addition of 100–300 μM UDP (Fig. 3C). UTP was less effective than UDP, and UMP and CDP had no effect (results not shown).

**UDP Opens MitoKIR and Holo-mitoKATP**—Fig. 4A contains representative K$^+$ flux traces from liposomes reconstituted with holo-mitoKATP. Electrophoretic K$^+$ flux (Fig. 4A, trace a) was inhibited by 200 μM ATP (Fig. 4A, trace d), and flux was partially restored by 100 μM UDP (Fig. 4A, trace b). The reactivation by UDP was largely abolished in the presence of 200 μM 5-HD, a specific inhibitor of mitoKATP (22) (Fig. 4A, trace c). Fig. 4B contains representative swelling traces from isolated mitochondria containing holo-mitoKATP. As reported previously (22), matrix swelling secondary to K$^+$ uptake (Fig. 4B, trace a) was inhibited in the presence of 100 μM ATP (Fig. 4B, trace d). Swelling was restored by the addition of 30 μM UDP (Fig. 4B, trace b) and re-inhibited by 200 μM 5-HD (Fig. 4B, trace c). In the absence of added ATP, UDP did not enhance mitochondrial K$^+$ uptake (data not shown). Each of these traces was duplicated in medium containing TEA$^+$ instead of K$^+$. As we showed previously for ATP (22, 24), none of these agents had any effect upon the light-scattering signal in TEA$^+$ medium, showing that the matrix swelling was due specifically to uptake of K$^+$ salts and water.

The data in Fig. 5 compare the UDP concentration dependences for reactivation of mitoKIR in lipid bilayer membranes (Fig. 5A) and of holo-mitoKATP in liposomes (Fig. 5B). The $K_{1/2}$ (UDP) is 10–13 μM in both preparations. In additional experiments (not shown), we found that the $K_{1/2}$ (UDP) was not affected by increasing the ATP concentration to 500 μM in liposomes and 3 mM in lipid bilayer membranes. Thus, UDP interaction with mitoKATP seems to be non-competitive with ATP.

**DEB Opens MitoKIR and Holo-mitoKATP**—DEB, functioning as an electron donor, was previously shown to reverse ATP inhibition of mitoKIR at micromolar concentrations (29). In the present study, we found that DEB also reversed ATP inhibition.
of K⁺ flux through holo-mitoK_ATP in isolated rat heart mitochondria (Fig. 6A). Opening by DEB was inhibited by 5-HD (50 μM) and glibenclamide (2 μM) (Fig. 6A). The concentration-dependence of DEB opening of mitoK_ATP in mitochondria is shown in Fig. 6B, with K_{1/2} about 10 μM.

TPP⁺ Inhibits MitoKIR and Holo-mitoK_ATP—100 nM TPP⁺ was found to inhibit the conductance of lipid bilayer membranes containing mitoKIR (Fig. 7A). TPP⁺ also inhibited mitoKIR and holo-mitoK_ATP reconstituted in liposomes, with K_{1/2} of 44–50 nM (Fig. 7B).

**DISCUSSION**

For insights into mitoK_ATP function, it is useful to consider the salient aspects of plasma membrane K_ATP channels (cellK_ATP). CellK_ATP consists of two subunits, an inward-rectifying potassium channel, Kir6.1 or Kir6.2, and a regulatory sulfonylurea receptor, SUR1, SUR2A, or SUR2B (see review by Ashcroft and Ashcroft, Ref. 31). The SUR are members of the
ABC-binding cassette family (32), and tetramers of KIRx and SURx peptides form functional hetero-octamers in the plasma membrane (33). An RKR domain in the C terminus of KIR6.x and in the 6th intracellular loop of SUR prevents membrane expression of either of these proteins in the absence of its partner (34). However, C-terminal truncations of KIR6.2 permit expression and measurements of channel activities (35). These studies have shown that ATP inhibits cellKATP by interacting with KIR and that SUR1 enhances the direct blockage of KIR6.2 by ATP by an unknown mechanism that involves the N terminus of KIR6.2. Sulfonylureas and KATP channel openers interact with sites on SUR (35, 36).

MitoKATP and cellKATP react with the similar ligands, including K+/H+ channel openers, sulfonylureas, nucleotides, and long-chain CoA esters. On this basis, we have proposed that they belong to the same gene family (37). Although verification of this hypothesis awaits the molecular structure of mitoKATP, the functional parallels with cellKATP lead to the working model contained in Fig. 8. Thus, the 55-kDa band seen in both preparations of Fig. 1 contains mitoKIR, and the 63-kDa band seen only in the detergent-extracted preparation contains mitoSUR (12). A key question addressed by this report is whether the channel activity of the detergent-extracted mitoKATP (3) is the same as that of the ethanol-extracted mitoKIR (10).

There is considerable evidence favoring this proposal: both fractions contain the 55-kDa band (Fig. 1), both channels are K+/H+ selective (3, 16), both manifest an ~10-pS single-channel conductance in 100 mM KCl (16, 38), and both channels are inhibited by ATP (Fig. 2). The 55-kDa protein isolated with ethanol is an inwardly rectifying K+/H+ channel, mitoKIR (Fig. 6). DEB reverses ATP inhibition of holo-mitoKATP. A, in respiring rat heart mitochondria. Shown are relative rates of K+ influx into mitochondria, from light-scattering experiments performed in K+/H+ medium (as in Fig. 4B). 100 μM ATP inhibited potassium influx in mitochondria, and this inhibition was reversed by 100 μM DEB. MitoKATP opening by DEB was prevented by 50 μM 5-HD and 2 μM glibenclamide. Three experiments were performed. B, in liposomes containing rat brain mitoKATP. K+ flux was inhibited by 200 μM ATP and reactivated by DEB. ∆J/∆Jcontrol is the normalized K+ flux, as described for Fig. 5B. K1/2 (DEB) was 10 ± 2 μM, with N = 1 (two independent experiments).
A, and the 63-kDa band is labeled with high affinity by sulfonylurea (12), consistent with identification of the 63-kDa band with mitoSUR (11).

It is also clear that the detergent-isolated fraction (holo-mitoK_ATP) differs from the ethanol-extracted fraction mitoKIR in its regulation. Thus, ATP inhibition of holo-mitoK_ATP exhibits an absolute requirement for Mg2+ ions, and the apparent affinity for ATP is an order of magnitude higher (Fig. 2). Pharmacological blockers, such as glibenclamide and 5-HD, and pharmacological openers, such as cromakalim and diazoxide (6, 7, 22), are potent regulators of holo-mitoK_ATP; however, these agents have no effect upon channel activity of the mitoKIR subunit (28, 29). CellK_ATP exhibits similar properties. Thus, co-expression of SUR1 and Kir6.2 resulted in ATP inhibition with higher affinity than expression of Kir6.2 alone (35). Moreover, holo-cellK_ATP was sensitive to sulfonylureas and diazoxide, whereas Kir6.2ΔC36 was not (35). Thus, the differences in regulation of mitoKIR and holo-mitoK_ATP can be rationalized by assuming that mitoK_ATP is a close relative of cellK_ATP.

For a more direct test of the hypothesis that the 55-kDa protein is the channel component of mitoK_ATP, we focused on three new regulatory interactions with mitoKIR and holo-mitoK_ATP. We found that 20 μM UDP reversed ATP inhibition of mitoKIR in lipid bilayer membranes (Fig. 3B), and 100–300 μM UDP rescued mitoKIR from channel rundown (Fig. 3C). UDP also reversed ATP inhibition of holo-mitoK_ATP in liposomes (Fig. 4A) and in intact mitochondria (Fig. 4B). MitoKIR and holo-mitoK_ATP were opened by UDP with similar affinities of 10–13 μM (Fig. 5). UDP seems to be non-competitive with ATP. UDP is the first nucleotide shown to open mitoK_ATP via the mitoKIR subunit, but there is precedent for this action from studies on cellK_ATP: oleoyl CoA opens cellK_ATP (39), and this effect has been shown to be mediated by means of the KIR 6.2 subunit (40, 41).
TPP$^\text{+}$ is commonly used to estimate mitochondrial membrane potential. It is also a potent inhibitor of holo-mitoKATP and mitoKIR (Fig. 7). Indeed, the apparent affinities of mitoKATP and holo-mitoKATP for TPP$^\text{+}$ are identical: $-60 \text{ nM}$.

We suggested previously (29) that some agents may regulate the activity of mitoKATP via intraprotein electron transport, and we showed that micromolar concentrations of the electroneutral reducing agent, DEB, opens the ATP-inhibited channel in lipid bilayer membranes. The DEB-activated mitoKATP can be re-activated by a petalagonidine, an electron acceptor. Here we show that DEB also opens holo-mitoKATP in isolated mitochondria (Fig. 6A) and in liposomes reconstituted with mitoKATP (Fig. 6B). Whereas DEB-activated mitoKATP is inhibited by 5-1H or glibenclamide, DEB-activated mitoKATP is inhibited by both agents, consistent with their presumed action upon mitoSUR.

Our strategy in these studies was to identify agents that act directly on mitoKIR and then to determine whether they have similar actions upon holo-mitoKATP. This was found to be the case for UDP, DEB, and TPP$^\text{+}$ (summarized in Fig. 8). On the basis of these results, we conclude that the ethanol-extracted mitoKIR is the channel responsible for the channel activity of mitoKATP.

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REFERENCES
1. Garlid, K. D., and Paucek, P. (2001) *IUBMB Life* 52, 151–158
2. Mitchell, P. (1966) *Biol. Rev. Camb. Philos. Soc.* 153, 157–159
3. Paucek, P., Mironova, G., Mahdi, F., Beavis, A. D., Woldegiorgis, G., and Garlid, K. D. (1992) *J. Biol. Chem.* 267, 26062–26069
4. Garlid, K. D., Beavis, A. D., and Ratcliffe, S. K. (1989) *Biochim. Biophys. Acta* 976, 109–120
5. Kowalski, A. J., Seetharaman, S., Paucek, P., and Garlid, K. D. (2001) *Am. J. Physiol.* 280, H649–H657
6. Garlid, K. D., Paucek, P., Yarov-Yarovoy, V., Sun, X., and Schindler, P. A. (1996) *J. Biol. Chem.* 271, 8796–8799
7. Garlid, K. D., Paucek, P., Yarov-Yarovoy, V., Murray, H. N., Darbenzio, R. B., D’Alonso, A. J., Lodge, N. J., Smith, M. A., and Grover, G. J. (1997) *Circ. Res.* 81, 1072–1082
8. Garlid, K. D. (2000) *Basic Res. Cardiol.* 95, 275–279
9. Dos Santos, P., Kowalski, A. J., Laclau, M. N., Seetharaman, S., Paucek, P., Boudina, S., Thambo, J. B., Tariasso, L., and Garlid, K. D. (2002) *Am. J. Physiol.* 283, H262–H265
10. Mironova, G. D., Frolocheva, N. I., Makarov, P. R., Prunevich, L. A., and Mironov, G. P. (1981) *Biophysical (USSR)* 26, 458–465
11. Grever, J. J., and Garlid, K. D. (2000) *J. Mol. Cell. Cardiol.* 32, 677–695
12. Baijaj, R., Seetharaman, S., Kowaltowski, A. J., Garlid, K. D., and Paucek, P. (2001) *J. Biol. Chem.* 276, 33369–33374
13. Pedersen, P. L., Greenawalt, J. W., Reynalbarje, B., Hullihen, J., Decker, G. L., Sepper, J. W., and Bustamante, B. (1978) *Methods Cell Biol.* 20, 411–481
14. Matlib, M. A., Rouslin, W., Vaghy, P. L., and Schwartz, A. (1984) *Methods Enzymol.* 5, 25–37
15. Roktanek, R. E., Hamud, F., Fiskum, G., Varghese, J. P., and Sharpe, S. (1987) *J. Cereb. Blood Flow Metab.* 7, 752–758
16. Mironova, G. D., Skarga, Y. Y., Grigoriev, S. M., Yarov-Yarovoy, V. M., Alexandrow, A. V., and Kolomytkin, O. V. (1996) *Membr. Cell. Biol.* 16, 429–437
17. Mio, D., Rudin, D. O., Tien, H., and Weszott, W. (1982) *Nature* 194, 797–981
18. Lasemml, U. K. (1970) *Nature* 227, 680–685
19. Garlid, K. D., Sun, X., Paucek, P., and Woldegiorgis, G. (1995) *Methods Enzymol.* 260, 331–348
20. Beavis, A. D., Brannan, R. D., and Garlid, K. D. (1985) *J. Biol. Chem.* 260, 13424–13431
21. Fabre, M., Yarov-Yarovoy, V., Paucek, P., and Garlid, K. D. (1998) *J. Biol. Chem.* 273, 13578–13582
22. Paucek, P., Yarov-Yarovoy, V., Sun, X., and Garlid, K. D. (1996) *J. Biol. Chem.* 271, 32084–32088
23. Beavis, A. D., Lu, Y., and Garlid, K. D. (1993) *J. Biol. Chem.* 268, 997–1004
24. Garlid, K. D., Orosz, D. E., Medriansky, M., Vassanelli, S., and Jezeck, P. (1996) *J. Biol. Chem.* 271, 2615–2620
25. Inoue, I., Nagase, H., Kishi, K., and Higuti, T. (1991) *Nature* 352, 244–247
26. Mironova, G. D., Skarga, Y. Y., Grigoriev, S. M., Negoda, A. E., Kolomytkin, O. V., and Marinov, B. S. (1999) *J. Bioenerg. Biomembr.* 31, 159–163
27. Mironova, G. D., Grigoriev, S. M., Skarga, Y., Negoda, A. E., and Kolomytkin, O. V. (1997) *Membr. Cell. Biol.* 10, 583–591
28. Garlid, K. D. (1992) *J. Biol. Chem.* 267, 1082–1090
29. Mueller, P., Rudin, D. O., Tien, H., and Wescott, W. (1962) *J. Biol. Chem.* 237, 8799–8799
30. Garlid, K. D. (1996) *Biochim. Biophys. Acta* 1410, 91–96
31. Findlay, I., and Dunne, M. J. (1996) *Pfluegers Arch.* 407, 238–240
32. Ashcroft, S. J., and Ashcroft, P. F. (1990) *Cell Signal.* 2, 197–214
33. Higgins, C. F. (1995) *Cell* 82, 693–696
34. Clement, J. P. T., Kunjilwar, K., Gonzalez, G., Schwantecher, M., Panten, U., Aguilar-Bryan, L., and Bryan, J. (1997) *Neuron* 18, 627–638
35. Zerangue, N., Schwappach, B., Jan, Y. N., and Jan, L. Y. (1999) *Neuron* 22, 537–548
36. Tucker, S. J., Gribble, F. M., Zhao, C., Trapp, S., and Ashcroft, P. F. (1997) *Nature* 387, 179–183
37. Babenko, A. P., Aguilar-Bryan, L., and Bryan, J. (1998) *Ann. Rev. Physiol.* 59, 849–867
38. Yarov-Yarovoy, V., Paucek, P., Jaburek, M., and Garlid, K. D. (1996) *Biochim. Biophys. Acta* 1275, 123–126
39. Yarov-Yarovoy, V., Paucek, P., Jaburek, M., and Garlid, K. D. (1997) *Biochim. Biophys. Acta* 1321, 128–136
40. Braestrup, R., Corkey, B. E., Berggren, P. O., and Larsson, O. (1997) *J. Biol. Chem.* 272, 17390–17394
Functional Distinctions between the Mitochondrial ATP-dependent K⁺ Channel (mitoK ATP) and Its Inward Rectifier Subunit (mitoKIR)
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