The mitochondrial K\textsubscript{ATP} channel (mitoK\textsubscript{ATP}) is highly sensitive to ATP, which inhibits K\textsuperscript{+} flux with \( K_{1/2} \) values of 20–40 \( \mu \)M. This raises the question, how can mitoK\textsubscript{ATP} be opened in the presence of physiological concentrations of ATP? We measured K\textsuperscript{+} flux in liposomes reconstituted with purified mitoK\textsubscript{ATP} and found that guanine nucleotides are potent activators of this channel. ATP-inhibited K\textsuperscript{+} flux was completely reactivated by both GTP (\( K_{1/2} = 7 \) \( \mu \)M) and GDP (\( K_{1/2} = 140 \) \( \mu \)M). These ligands had no effect in the absence of ATP. The \( K_{1/2} \) for ATP inhibition exhibited quadratic dependence on [GTP] and [GDP], consistent with two binding sites for guanine nucleotides. We also found that palmitoyl-CoA and oleoyl-CoA inhibited K\textsuperscript{+} flux through reconstituted mitoK\textsubscript{ATP} with \( K_{1/2} \) values of 260 nM and 80 nM, respectively. This inhibition was reversed by GTP (\( K_{1/2} = 232 \) \( \mu \)M) as well as by the K\textsuperscript{+} channel openers cromakalim (20 \( \mu \)M) and diazoxide (10 \( \mu \)M). Inhibition of mitoK\textsubscript{ATP} by long-chain acyl-CoA esters, like that of ATP, exhibited an absolute requirement for Mg\textsuperscript{2+} ions. We propose that the open-closed state of the mitochondrial K\textsubscript{ATP} channel is determined by the relative cytosolic concentrations of GTP and long-chain acyl-CoA esters.

Mitochondrial K\textsubscript{ATP} channels (mitoK\textsubscript{ATP})\textsuperscript{1} were first discovered in 1991 (1–3). Inoue et al. (1) reported electrophysiological evidence from patch clamp studies of fused mitoplasts, and we described reconstitution of a highly purified mitoK\textsubscript{ATP} (2, 3). In our protocols, which have the advantage of being free of the complexities of intact mitochondria, K\textsuperscript{+} flux is measured using steady-state spectroscopy of the fluorescent probe PBFI. These measurements have permitted initial characterization of the kinetics and regulation of mitoK\textsubscript{ATP} (4). The \( K_{1/2} \) for K\textsuperscript{+} is 32 mM, and the channel is highly selective for K\textsuperscript{+} (Na\textsuperscript{+} and TEA\textsuperscript{+} are neither transported nor do they affect K\textsuperscript{+} flux through mitoK\textsubscript{ATP}). MitoK\textsubscript{ATP} is inhibited with high affinity by ATP and ADP, and this inhibition exhibits an absolute requirement for divalent cations. We have recently shown that ATP inhibition of K\textsuperscript{+} flux through mitoK\textsubscript{ATP} is reversed by submicromolar levels of K\textsuperscript{+} channel openers (5).

We also demonstrated mitoK\textsubscript{ATP} activity in respiring rat liver mitochondria (6). The confounding and unavoidable coexistence of K\textsuperscript{+} diffusion (leak) was controlled by comparing K\textsuperscript{+} flux to TEA\textsuperscript{+} flux, for which there are no endogenous pathways other than diffusive leak. We made the simple demonstration that ATP inhibited K\textsuperscript{+} uptake to rates similar to those of TEA\textsuperscript{+} uptake and had no effect on TEA\textsuperscript{+} uptake itself.

These studies left us with a conundrum: given the high affinity for ATP, how can mitoK\textsubscript{ATP} ever be opened under normal physiological conditions? We hypothesized (4) that endogenous activators of mitoK\textsubscript{ATP} must exist to overcome the high affinity for ATP, and we now present support for this hypothesis. K\textsuperscript{+} flux through the MgATP-inhibited channel is restored to full activity by GTP and GDP, neither of which has any effect in the absence of MgATP. GTP and GDP are competitive with ATP, and their reversal of ATP inhibition exhibits hyperlinear kinetics consistent with two guanine nucleotide binding sites. We also report that palmitoyl-CoA and oleoyl-CoA inhibit mitoK\textsubscript{ATP} with high potency, and this inhibition is also reversed by GTP and by the potassium channel openers, cromakalim and diazoxide. Inhibition by long-chain acyl-CoA esters, like inhibition by ATP, exhibits an absolute requirement for Mg\textsuperscript{2+} ions and is immediately reversed upon chelation of Mg\textsuperscript{2+}. From these findings, we infer that GTP and long-chain acyl-CoA esters may be the physiological regulators of mitoK\textsubscript{ATP} and that this channel may play a role in vivo in regulating fatty acid oxidation.

**EXPERIMENTAL PROCEDURES**

**Extraction, Purification, and Reconstitution of MitoK\textsubscript{ATP} from Rat Liver Mitochondria—**Purification and reconstitution generally followed protocols previously described (4, 7). Rat liver mitochondria were purified on a linear sucrose density gradient and used to prepare inner membrane vesicles according to the procedure of McEnergy et al. (8). Mitochondria were suspended in 220 mM D-mannitol, 70 mM sucrose, 0.5 mM bovine serum albumin, 2 mM HEPES (K\textsuperscript{+}), pH 7.4, sonicated on ice, and centrifuged for 10 min at 10,000 \( \times g \). The supernatant was recentrifuged at 210,000 \( \times g \) for 30 min, and the resulting membrane pellet was washed three times in PA buffer (0.15 mM potassium phosphate, 1 mM ATP, 25 mM EDTA, 0.5 mM dithiothreitol, 5% ethylene glycol, pH 7.9). The final membrane pellet was suspended to 15 mg/ml bovine serum albumin, 20 mM HEPES (K\textsuperscript{+}), pH 7.4, sonicated on ice, and centrifuged for 30 min at 10,000 \( \times g \). The supernatant was recentrifuged at 210,000 \( \times g \) for 30 min, and the resulting membrane pellet was washed three times in PA buffer (30 min at 138,000 \( \times g \)) and finally solubilized (2 mg of protein/ml) in 3% Triton X-100, 20% glycerol, 0.1% β-mercaptoethanol, 0.2 mM EGTA, 1 mM MgCl\textsubscript{2}, and 50 mM Tris-HCl, pH 7.2.

After incubation on ice for 20 min, the mixture was centrifuged at 120,000 \( \times g \) for 35 min. Ten ml of the supernatant, typically containing 50–80 mg of extracted proteins, were loaded onto a DEAE-cellulose column (10-ml bed volume) that had been equilibrated with a buffer containing 1% Triton X-100, 0.1% β-mercaptoethanol, 1 mM EDTA, and 50 mM Tris-HCl, pH 7.2. The active fraction, eluting at 250 mM KCl, was

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1 The abbreviations used are: mitoK\textsubscript{ATP}, mitochondrial K\textsubscript{ATP} channel; FCCP, carbonyl cyanide-p-trifluoromethoxyphenoxyhydrox; PBFI, potassium-binding benzofuran isophthalate; TEA\textsuperscript{+}, tetraethylammonium cation.

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desalted and concentrated by filtration.

The purified mitoK<sub>ATP</sub> fraction was added to a 1:1 mixture of l-ascorbic acid and glutathione in 10% octylpolyoxethylene. The buffer composition at this stage defines the internal medium, which contained 300 μM PBFI, 100 mM TEA-SO<sub>4</sub>, 0.14 mM KCl, 1 mM TEA-EDTA, and 25 mM TEA-HEPES, pH 6.8. This mixture was loaded onto a 2-ml Bio-Beads SM-2 column (Bio-Rad) to remove detergent and form proteoliposomes. After incubation for 90 min at 0–4°C, the column was centrifuged at 40,000 × g for 2 min to collect the proteoliposomes. To remove extravesicular PBFI, 200-μl aliquots of the proteoliposome suspension were passed twice through 4-ml Sephadex G-25–300 columns. The final stock vesicle suspension (nominally 50 mg of lipid/ml) was stored on ice during the experiment. Protein content, measured by the amido black method (9), was normally 10 ng of protein per mg of lipid. Intravesicular volume of each preparation was estimated from the volume of distribution of PBFI and was normally found to be 1 μl per mg of starting lipid.

Assay of K<sup>+</sup> Flux through Reconstituted MitoK<sub>ATP</sub>—15 μl of stock vesicles were added to 2 ml of external medium containing 150 mM KCl, 1 mM TEA-EDTA, and 25 mM TEA-HEPES, pH 7.4. Electrophoretic K<sup>+</sup> flux was initiated by 1 μM FCCP to provide charge compensation via H<sup>+</sup> flux. K<sup>+</sup> flux was quantitated from the fluorescence of intraliposomal PBFI, which increases with increasing [K<sup>+</sup>]<sub>i</sub>. Fluorescence was followed with an SLM/Aminco 8000C spectrofluorometer. The K<sup>+</sup> response of intravesicular PBFI was calibrated by stepwise additions of KCl toproteoliposomes in internal medium in the presence of nigericin (7).

**Chemicals and Reagents**—Tris salts of adenine and guanine nucleotides were titrated to pH 7.2 with Tris base. PBFI was from Molecular Probes Inc. (Eugene, OR). All other chemicals were obtained from Sigma unless otherwise indicated.

**RESULTS**

**Activation of the ATP-inhibited K<sub>ATP</sub> Channel by GTP and GDP**—The results in Fig. 1 demonstrate activation of ATP- and ADP-sensitive K<sup>+</sup> flux by GTP and GDP. The following observations can be made from these data: (i) K<sup>+</sup> flux was completely restored by both GTP and GDP, and (ii) GTP was 20–30 times more potent than GDP, irrespective of whether ATP or ADP was used to inhibit K<sup>+</sup> flux. In 0.5 mM ATP, the K<sub>1/2</sub> values for GTP and GDP activation were 6.9 μM and 143 μM, respectively. In 0.5 mM ADP, the K<sub>1/2</sub> values for GTP and GDP activation were 0.12 μM and 3.4 μM, respectively.

Additional experiments (not shown) further characterize guanine nucleotide reversal of ATP inhibition of K<sup>+</sup> flux through mitoK<sub>ATP</sub>. (i) Guanine nucleotides had no effect on K<sup>+</sup> flux through the open channel, measured in the absence of MgATP. (ii) Activation required that guanine nucleotides be added to the same side as MgATP. Thus, external GTP had no effect on K<sup>+</sup> flux when it was inhibited by internal MgATP. (iii) GTP or GDP activated K<sup>+</sup> flux when added 30 s after inhibition by MgATP had already been established.

**Kinetics of Guanine Nucleotide Activation of the K<sub>ATP</sub> Channel**—To examine the kinetics of activation, we measured ATP inhibition of K<sup>+</sup> flux in the presence of 3 mM Mg<sup>2+</sup> and different concentrations of GTP or GDP. Fig. 2 contains representative dose-response curves.

In the absence of GTP, ATP inhibited K<sup>+</sup> flux through reconstituted mitoK<sub>ATP</sub> with a K<sub>1/2</sub> of 21 μM in this experiment (solid circles, Fig. 2). We observed K<sub>1/2</sub> values for ATP ranging between 20 and 30 μM in 4 independent experiments, and the Hill coefficient was always 1.0 ± 0.1. These K<sub>1/2</sub> values are lower than our previously reported value of 39 μM (4) because they are calculated from ATP-sensitive, rather than total, K<sup>+</sup> flux. We have recently established that 10–15% of channels are transfected with their regulatory sites facing inward and are, therefore, inaccessible to external ATP (10, 11).

In the presence of increasing doses of GTP, the K<sub>1/2</sub> value for ATP inhibition was shifted sharply higher (Fig. 2). It is striking that 20 μM GTP increased the K<sub>1/2</sub> for ATP inhibition from 21 μM to 6 mM. ATP was ineffective in the presence of 3 mM GTP (not shown).

**Activation of ATP- and ADP-inhibited mitoK<sub>ATP</sub> by GTP and GDP**. The relative ATP-sensitive K<sup>+</sup> uptake into liposomes reconstituted with mitoK<sub>ATP</sub> was illustrated versus concentration of GTP or GDP. All assay media contained 3 mM Mg<sup>2+</sup>, and K<sup>+</sup> influx was initiated by adding 1 μM FCCP to assay medium at 10 s. Nucleotides were added to assay medium. A, activation of ADP-inhibited K<sup>+</sup> flux. GTP or GDP was added to assay medium containing 0.5 mM ADP. The ΔJ<sub>max</sub> is the difference between control fluxes in the absence or presence of ATP, which inhibited total K<sup>+</sup> flux by 65% (4). ΔJ<sub>max</sub> is the difference between fluxes in the presence or absence of guanine nucleotide measured in the presence of 0.5 mM ATP. The K<sub>1/2</sub> values and Hill slopes (in parentheses) for activation were 0.12 μM (1.0) for GTP and 3.4 μM (1.6) for GDP. B, activation of ATP-inhibited K<sup>+</sup> flux. GTP or GDP was added to assay medium containing 0.5 mM ATP. ΔJ<sub>max</sub> is the difference between fluxes in the absence or presence of 0.5 mM ATP, which inhibited total K<sup>+</sup> flux by 85% to 90% (4). ΔJ<sub>max</sub> is the difference between fluxes in the presence or absence of guanine nucleotide with both fluxes measured in the presence of 0.5 mM ATP. The K<sub>1/2</sub> values and Hill slopes (in parentheses) for activation were 6.9 μM (1.2) for GDP and 140 μM (1.2) for GDP.

**Fig. 3** contains a summary of the results of five experiments in which the K<sub>1/2</sub> for ATP inhibition of mitoK<sub>ATP</sub> was measured at various concentrations of GTP (●) or GDP (○). These data show that the apparent affinity of mitoK<sub>ATP</sub> for ATP decreases (K<sub>1/2</sub> increases) in a quadratic manner with guanine nucleotides. In order to extract parameters from the data in Fig. 3, we constructed a simple model for nucleotide interaction with the mitoK<sub>ATP</sub> receptor, R:

\[
K_i \frac{k_1}{K_R \cdot [G]} + \frac{k_2}{[G]_R^2} = K_{1/2} (\text{Eq. 1})
\]

This model is consistent with available data. For example, if ATP binds to a second binding site, its affinity is too low to be detected. Solving the kinetic equations for K<sub>1/2</sub> (ATP),

\[
K_{i/2} = K_i + [G]_R k_1 + [G]_R^2 k_2 (\text{Eq. 2})
\]
and K metabolism sites appear to have similar affinities for ATP, GTP, and GDP. The low-affinity site for ATP is that GTP reacts at a high-affinity and a low-affinity site, indicating two nucleotide binding sites. The effects on the ATP inhibition of KATP channel openers—physiological ligands. MitoKATP is inhibited by ATP, ADP (4), and Mg2+ chelators. It is noteworthy that ADP and acyl-CoA esters, which are chemical analogues, exert opposite effects on KATP channels from mitochondria and plasma membranes. They inhibit mitoKATP (4), (this paper), but they activate the plasma membrane KATP channels of pancreatic β cells (14).

Inhibition by adenine nucleotides or acyl-CoA esters can be fully overcome by GTP and GDP, and by the pharmacological agents known as K+ channel openers (5, this paper). Guanine nucleotide activation is competitive with ATP, with kinetics indicating two nucleotide binding sites. The effects on the K1/2 moved the K1/2 for GTP activation toward the physiological range of GTP concentration and that ATP had no effect on the K1/2 for GTP in the presence of palmitoyl-CoA.

**DISCUSSION**

**Regulation of the Mitochondrial KATP Channel**—The purpose of these experiments was to explore regulation of mitoKATP by physiological ligands. MitoKATP is inhibited by ATP, ADP (4), and long-chain acyl-CoA esters. Inhibition of mitoKATP by long-chain acyl-CoA esters with high affinity is consistent with a proposed signaling role of this channel in regulating β-oxidation of fatty acids (13). Inhibition by these ligands exhibits an absolute requirement for Mg2+ ions, and Mg2+ reduces the apparent affinity for glibenclamide in inhibiting K+ flux through mitoKATP (4). These findings suggest that Mg2+ interacts separately with the mitoKATP complex, because acyl-CoA esters and glibenclamide are not Mg2+ chelators. It is noteworthy that ADP and acyl-CoA esters, which are chemical analogues, exert opposite effects on KATP channels from mitochondria and plasma membranes. They inhibit mitoKATP (4), (this paper), but they activate the plasma membrane KATP channels of pancreatic β cells (14).

**Fig. 2. Effect of GTP on the kinetics of ATP inhibition of mitoKATP.** Figure contains dose-response curves for ATP inhibition of K+ flux through reconstituted mitoKATP. ATP titrations were done in the presence of GTP added to assay medium in concentrations of 0 μM (●), 2 μM (○), 4 μM (●), 8 μM (■), and 20 μM (▲). ∆Jmax is the difference between control fluxes in the absence or presence of 0.5 mM ATP measured in the presence of GTP. ∆J is the difference between fluxes in the presence or absence of GTP measured in the presence of 0.5 mM ATP (90% inhibition of total K+ flux). In four separate experiments carried out in the absence of GTP, K1/2 values for ATP inhibition ranged between 20 μM and 30 μM, and the Hill slope was 1.0 ± 0.1.

**Fig. 3. Quadratic competitive opening of the ATP-inhibited mitoKATP by GTP and GDP.** Observed K1/2 values for ATP inhibition of K+ flux through the reconstituted mitoKATP channel are plotted versus [GTP] (●) and [GDP] (○). The K1/2 values were obtained from nonlinear regression of dose-response curves (∆J/∆Jmax versus log[ATP]) for ATP inhibition in the presence of indicated concentrations of GTP or GDP. The data plotted were from three separate experiments, each with GTP and GDP. The solid lines were fitted to the second-order polynomial, K1/2 = 1 + [G]/k1 + [G]/k2, as described under "Results."
for ATP inhibition (Fig. 3) suggest both high-affinity and low-affinity GTP sites.

It is characteristic of all K_{ATP} channels that the K_{1/2} values for ATP inhibition are roughly 2 orders of magnitude lower than normal cytosolic [ATP]. We now show that the K_{1/2} values for GTP inhibition of mitoK_{ATP} are 2 orders of magnitude less than normal cytosolic [GTP]. These results can, however, be rationalized by the simple consideration that the nucleotide binding sites will be occupied in situ by high-affinity ligands other than ATP. The data suggest that ATP cannot inhibit mitoK_{ATP} in the presence of physiological [GTP], raising the possibility that ATP is not a physiological regulator of mitoK_{ATP}. On the other hand, when long-chain acyl-CoA esters and GTP are present together, as in the experiments of Fig. 6, their K_{1/2} values fall within their respective physiological ranges. We infer from our results that the nucleotide binding sites on mitoK_{ATP} are fully occupied by GTP or long-chain acyl-CoA esters under physiological conditions, and that the fraction of open channels is determined by the balance between these regulators.

Mitochondrial Volume Is Controlled by the Potassium Cycle—The mitochondrial K^+ cycle consists of electrophoretic K^+ uptake and electroneutral K^+ efflux across the inner membrane. Any net K^+ flux will be accompanied by electroneutral flux of anions and osmotically obligated water (15). Because matrix [K^+] is about 180 mM, net K^+ transport will have little effect on the matrix concentration of K^+, but it will have a profound effect on matrix volume. Thus, the redox energy consumed by the K^+ cycle is the cost of regulating matrix volume (15). The K^+ cycle is mediated by two highly regulated processes. Efflux is mediated by the K^+/H^+ antiporter, whose existence was predicted by Mitchell (16) and first demonstrated by Garlid (17) nearly 20 years later. Influx is mediated by the mitochondrial K_{ATP} channel (mitoK_{ATP}), which was described by Inoue et al. (1) and Paucek et al. (4).

A primary role of regulated K^+/H^+ antiport is to compensate for unregulated K^+ leak into the matrix, driven by the high voltages required for oxidative phosphorylation. Uncompensated K^+ uptake amounting to as little as 10% of proton pumping would double matrix volume within 1–2 min (18). The K^+/H^+ antipporter is inhibited by matrix Mg^{2+} (K_i ∼ 300 μM) as well as by matrix protons, and the concentrations of these inhibitors decrease with uptake of K^+ salts, causing compensatory activation of K^+ efflux (15). Thus, the K^+/H^+ antipporter is responsible for volume homeostasis and is essential for maintaining vesicular integrity in the face of high ionic traffic across the inner membrane.

The discovery of mitoK_{ATP} has profound new implications for mitochondrial physiology, because the existence of a regulated
K+ influx pathway permits volume regulation. For example, opening mitoKATP will transiently shift the balance between K+ uniport and K+/H+ antiport until the antiport catches up with the higher rate of K+ influx. This will cause transient swelling to a higher steady-state volume that will persist for as long as mitoKATP remains open. Such a “regulated interplay” between K+ uniport and K+/H+ antiport was correctly postulated many years ago by Brierley (19).

Matrix Volume Regulates Electron Transport—Fatty acids are the fuel for thermogenesis by brown adipose tissue mitochondria, and their rate of oxidation is strictly controlled by matrix volume (20). A thorough characterization of this phenomenon by Halestrap (21) has demonstrated that increasing matrix volume, over the narrow range thought to obtain in vivo, greatly stimulates activity of the respiratory chain in both heart and liver mitochondria. β-oxidation of fatty acids is particularly sensitive to matrix volume. The site of activation has been suggested by Halestrap (23), Szewczyk et al. (24), and Garlid (13), and the exquisite sensitivity of mitoKATP to long-chain acyl-CoA esters dovetails nicely with this hypothesis. A plausible scenario is that mitoKATP will open in the glucose-depleted state, where long-chain acyl-CoA esters are low. The resulting matrix expansion will activate β-oxidation and direct energy to support gluconeogenesis in liver, increased mechanical work in heart and skeletal muscle, and thermogenesis in brown adipose tissue. Conversely, elevated long-chain acyl-CoA esters in the fed state may inhibit mitoKATP, and, together with inhibition of carnitine palmitoyltransferase I (25), promote diversion of energy to fatty acid esterification in hepatocytes, adipocytes, and pancreatic β-cells, and to glycolysis in heart and skeletal muscle.

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