METABOLIC DISEASE

Systemic pan-AMPK activator MK-8722 improves glucose homeostasis but induces cardiac hypertrophy

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5′-Adenosine monophosphate–activated protein kinase (AMPK) is a master regulator of energy homeostasis in eukaryotes. Despite three decades of investigation, the biological roles of AMPK and its potential as a drug target remain incompletely understood, largely because of a lack of optimized pharmacological tools. We developed MK-8722, a potent, direct, allosteric activator of all 12 mammalian AMPK complexes. In rodents and rhesus monkeys, MK-8722–mediated AMPK activation in skeletal muscle induced robust, durable, insulin-independent glucose uptake and glycogen synthesis, with resultant improvements in glycemia and no evidence of hypoglycemia. These effects translated across species, including diabetic rhesus monkeys, but manifested with concomitant cardiac hypertrophy and increased cardiac glycogen without apparent functional sequelae.

The 5′-adenosine monophosphate–activated protein kinase (AMPK) pathway is the primary mechanism for detecting and responding to changes in cellular energy levels in eukaryotes (*1*). AMPK is a Ser/Thr protein kinase consisting of one α-catalytic subunit (two isoforms), one β-"scaffold" subunit (two isoforms), and one γ-regulatory subunit (three isoforms) (*2*). Excluding splice variants, higher mammals therefore possess 12 distinct AMPK complexes. Physiological activation of AMPK function is mediated by α-subunit Thr^{172} phosphorylation (yielding pAMPK) as well as by allosteric activation and is regulated by changes in intracellular "adenylate charge" and calcium levels (*3*).

AMPK activation has a broad impact on carbohydrate and lipid metabolism via pAMPK-mediated phosphorylation of downstream target proteins (*1*–*3*). For example, pAMPK induces insulin-independent skeletal muscle glucose uptake by increasing localization of Glut4 to the plasma membrane (*4*) and further stimulates intracellular glucose utilization by increasing glycogen synthesis (*5*) and likely glycolysis (*6*). In part because of these effects, AMPK activation represents a potential target for the treatment of type 2 diabetes mellitus (T2DM) (*7*) as well as other metabolic diseases and cancer (*8*).

Conversely, numerous dominant missense mutations have been identified in the nucleotide-binding region of the human AMPK γ2 subunit (PRKAG2 mutations) (*8*, *9*). These disinhibition/gain-of-function mutations result in hypertrophic cardiomyopathy and electrocardiogram (ECG) abnormalities as well as increased cardiac glycogen. A key question is which, if any, of these pathologies would be replicated by pharmacological activation of AMPK in mature animals.

Despite widespread interest, few direct systemic pan-AMPK activators have been described to date (*10*, *11*). The majority of reported activators are indirect and work by elevating cellular AMP and ADP (adenosine mono- and diphosphate) levels (*12*). By contrast, direct AMPK activators fall into two main classes: (i) nucleoside analogs of adenosine, such as the widely used 5-aminoimidazole-4-carboxamide ribofuranoside (AICAR), which is 5′-phosphorylated in cells to the active ribonucleotide (ZMP), and (ii) non-nucleoside activators, the most widely studied of which is A-769662, which is β1 complex–selective. Here, we report the development and biological effects of MK-8722 (Fig. 1A), a potent pan-activator of all 12 mammalian AMPK isoforms.

MK-8722 activates pAMPK complexes with increased potency and magnitude versus AMP (see e.g., Fig. 1B), with half-maximal effective concentration (EC_{50}) values of ~1 to 60 nM and increased activation by factors of ~4 to 24 (table S1). Although MK-8722 exhibits higher affinity for β1-containing (~1 to 6 nM) versus β2-containing (~15 to 63 nM) pAMPK complexes, it is the most potent activator of β2 complexes reported to date (*11*). pAMPK activation by maximal AMP plus MK-8722 is synergistic (Fig. 1C), demonstrating that the agents act at distinct sites. This is consistent with x-ray crystallography data obtained for compound 991 (a precedent structural analog of MK-8722) bound to pAMPK (*13*). Homology modeling strongly suggests that MK-8722 and 991 bind pAMPK in a similar manner (fig. S1).

MK-8722 has high cell permeability [apparent permeability coefficient $P_{app} = 17 \times 10^{-6}$ cm/s in Lilly Laboratories porcine kidney (LLC-PK1) cells]. Activation of intracellular AMPK was assessed on the basis of ability to induce AMPK-mediated, site-specific phosphorylation of acetyl–coenzyme A carboxylase (ACC; both isoforms 1 and 2) to generate pACC (*14*) and the degree of AMPK phosphorylation. These effects were routinely quantitated using a Meso Scale Discovery (MSD) assay for pACC and an enzyme-linked immunosorbent assay (ELISA) for pAMPK (all data reported unless otherwise indicated). Similar results were generated using Western blot analysis (see e.g., fig. S2). MK-8722 induced pACC formation in all cells tested, with a factor of ~1000 potency enhancement and increased activation versus AICAR (Fig. 1D and fig. S3). Notably, pACC formation was nearly maximal at MK-8722 concentrations that did not measurably increase pAMPK; this result suggests that MK-8722 activation may not require pAMPK in cells, similar to findings for A-769662 (*15*). The effects of MK-8722 (0.5 μM), as well as those of the well-known activators ionomycin (1 μM; a calcium ionophore) and AICAR (500 μM), on pACC were largely blocked by pretreatment of cells with the nonspecific AMPK inhibitor Compound C (*16*) (40 μM) (Fig. 1E). As expected, MK-8722 treatment of primary mouse hepatocytes, HepG2 cells, or primary human myocytes resulted in the phosphorylation of a number of additional known targets of pAMPK (figs. S4 and S5).

In a broad array of pharmacologically relevant targets (120 assays, including various enzymes, receptors, ion channels, and transporters), the most potent off-target activity observed for MK-8722 was against the serotonin $5\text{-}HT_{2A}$ receptor (inhibitor dissociation constant K_I = 2.8 μM). MK-8722 treatment did not lead to decreases in cellular ATP in vitro (fig. S6), similar to our second-generation activator 991 (*17*). Furthermore, no overt toxicity has been observed in cell-based studies or upon acute or chronic dosing in vivo. These results are consistent with the selective action of MK-8722 as a direct AMPK activator. MK-8722 has biochemical (table S1) and pharmacokinetic (table S2) properties that reproducibly enable systemic and sustained AMPK activation across species

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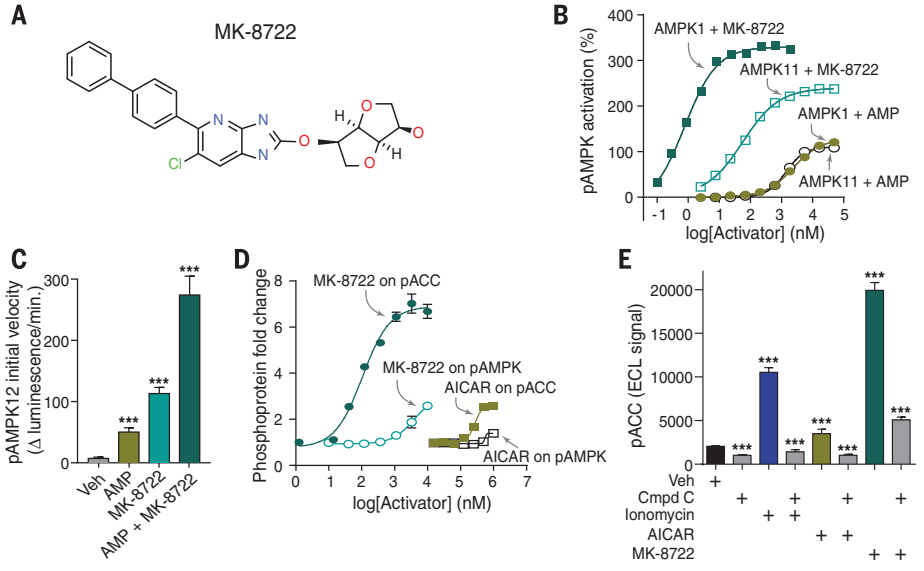

Fig. 1. In vitro properties of MK-8722. (**A**) Structure of MK-8722. (**B**) Dose-dependent activation of purified, recombinant pAMPK complexes 1 (α1β1γ1) and 11 (α2β2γ2) by MK-8722 and AMP (activity at 10 μM AMP defined as 100%). (**C**) Synergistic activation of purified, recombinant pAMPK complex 12 (α2β2γ3) by saturating AMP (25 μM), saturating MK-8722 (195 nM), and saturating levels of both activators. (**D**) Effect on pAMPK and pACC after MK-8722 and AICAR treatment in HepG2 cells. (**E**) Effect of AMPK activators ionomycin (1 μM), MK-8722 (0.5 μM), and AICAR (500 μM), with and without 1 hour of pretreatment with the AMPK inhibitor Compound C (40 μM), on pACC formation [electrochemiluminescence (ECL) units from the MSD assay] in HeLa cells. Vehicle (Veh) for all studies was dimethyl sulfoxide (DMSO). Data are means ± SEM. ***$P < 0.001$, one-way analysis of variance (ANOVA).

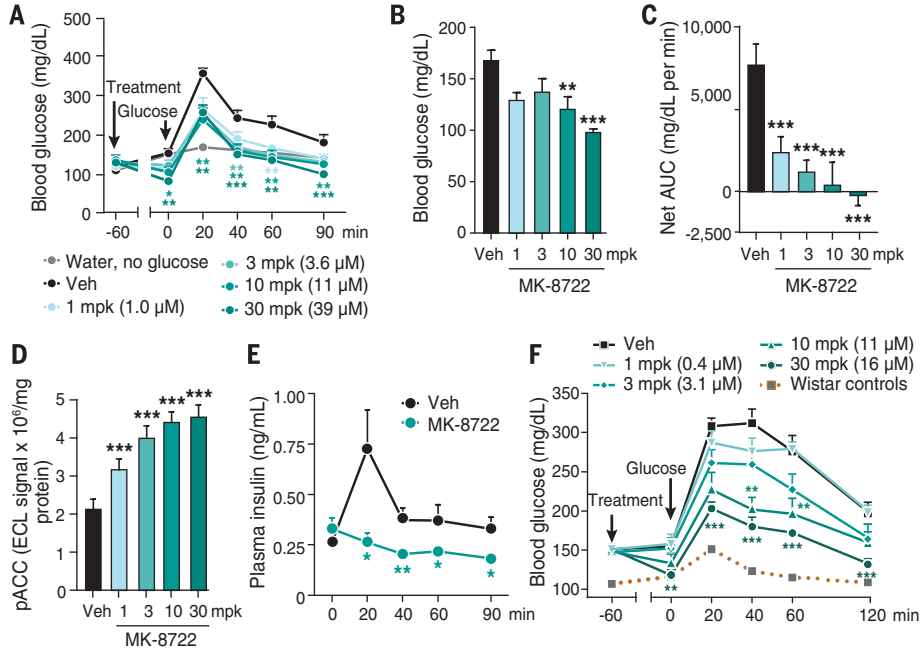

Fig. 2. Acute glucose-lowering efficacy of MK-8722 in rodents. (**A** to **E**) Effect of acute MK-8722 administration (1 to 30 mpk, p.o.) in an ipGTT in lean C57BL/6 mice (8- to 10-week-old male, $n = 8$ per group; data are representative of three independent experiments, unblinded). (A) Blood glucose versus time. (B) Fasting blood glucose 1 hour after dose, prior to the glucose challenge. (C) Net AUC of the data in (A). (D) Skeletal muscle pACC levels 2.5 hours after dose. (E) Plasma insulin versus time after glucose challenge in mice pretreated with vehicle or MK-8722 (30 mpk). (**F**) Effect on blood glucose versus time after MK-8722 administration (1 to 30 mpk, p.o.) in an oGTT in diabetic GK rats (14-week-old male, $n = 7$ or 8 per group; data are representative of three independent experiments, unblinded). Data are means ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, one-way ANOVA.

after once-daily oral dosing. The unbound fraction of MK-8722 in mammalian plasma is ~0.1%.

On the basis of these properties, we next examined the acute effects of MK-8722 on glucose homeostasis in rodents. Remarkably, MK-8722 administration to lean, normoglycemic C57BL/6 mice reduced fasting blood glucose levels 1 hour after dose [immediately prior to the glucose challenge of an intraperitoneal glucose tolerance test (ipGTT)] (Fig. 2, A and B). MK-8722 also improved glucose tolerance during the glucose challenge (Fig. 2, A and C). Elevation of skeletal muscle pACC (*14*) established systemic AMPK activation by MK-8722 treatment (Fig. 2D). The effects of MK-8722 were dose-dependent. Notably, improved glucose homeostasis using MK-8722 [30 mg/kg (mpk)] was achieved at significantly reduced plasma insulin levels during the ipGTT (Fig. 2E). Similar improvements in glucose homeostasis were observed after acute MK-8722 treatment in every dysmetabolic and diabetic rodent model examined (fig. S7), including the diabetic Goto-Kakizaki (GK) rat (Fig. 2F and fig. S8). Efficacious MK-8722 plasma concentrations were similar across all models, requiring minimal levels of ~3 μM (~3 nM unbound).

To determine whether enhanced skeletal muscle glucose uptake underlies the acute glucose-lowering effects of MK-8722, we quantitated the formation of nonmetabolizable 2-deoxy-D-glucose-6-phosphate (2DG6P), a product of cellular transport and intracellular phosphorylation, after exposure of cells or tissues to 2-deoxy-D-glucose (2DG) with or without MK-8722. Similar to insulin, MK-8722 treatment of primary human skeletal myocytes, in the absence of insulin, produced a dose-dependent increase in 2DG uptake by as much as a factor of 3 (Fig. 3A). Unlike insulin, MK-8722 treatment significantly increased intracellular pACC, reflective of AMPK activation (Fig. 3A). Only the MK-8722 effects on 2DG uptake were suppressed by preincubation with the nonspecific AMPK inhibitor Compound C (Fig. 3C). We also used a rat hindlimb in situ perfusion system in which 2DG and various concentrations of either insulin or MK-8722 were added to the perfusion buffer. MK-8722, in the absence of insulin, stimulated 2DG uptake and phosphorylation in a dose-dependent manner, with an EC_{50} of ~2 to 4 μM (Fig. 3B), identical to the minimal plasma levels required for glucose-lowering efficacy in vivo. Treatment with MK-8722 increased the amount of phosphorylated TBC1D1, an integral component of the Glut4 translocation pathway (*4*, *18*), in muscle cells (fig. S5).

To confirm these effects in vivo, we challenged lean C57BL/6 mice with [^{3}H]2DG plus glucose. Acute treatment with MK-8722 (30 mpk) significantly suppressed blood glucose and insulin levels secondary to the challenge (fig. S9), and this was accompanied by a significant increase in skeletal muscle [^{3}H]2DG6P formation (Fig. 3D). To investigate the fate of the MK-8722–mediated glucose transported into muscle, we treated diabetic GK rats with vehicle or MK-8722 (10 mpk) followed by an oral GTT (oGTT) using [1-^{13}C]D-glucose (Fig. 3E). MK-8722 treatment led to significant increases

in skeletal muscle [1-^{13}C]glucose-6-phosphate (Glc6P), [1-^{13}C]glycogen, and [3-^{13}C]lactate, consistent with an increase in glycogen synthesis (*5*) and glycolysis (*6*).

Chronic antihyperglycemic efficacy of MK-8722 was evaluated in *db/db* mice, a leptin receptor–deficient T2DM model (*19*). Once-daily administration of MK-8722 resulted in dose-dependent lowering of ambient blood glucose (Fig. 4A). On treatment day 12, glucose reductions after MK-8722 treatment (30 mpk/day) were comparable to those observed with the PPARγ agonist rosiglitazone (3 mpk/day) (Fig. 4A and fig. S10). Unlike rosiglitazone, the glucose-lowering action of MK-8722 manifested without significant effects on body weight (fig. S10), which was a consistent finding. Dose-dependent increases in tissue pACC were maintained throughout the dosing period (fig. S10). Chronic efficacy, without tachyphylaxis, was also observed in additional dysmetabolic and diabetic rodent models (figs. S11 and S12). In all cases, efficacy was associated with trough MK-8722 plasma levels comparable to the concentrations required to acutely stimulate skeletal muscle glucose uptake (Fig. 3). Notably, chronic MK-8722 dosing in mice also increased muscle Glut4 protein levels, possibly contributing to efficacy (fig. S13) (*20*).

Efficacy was also assessed in a cohort of type 2 diabetic rhesus macaque nonhuman primates (T2DM NHPs) (*21*). For these studies, we developed a less-invasive measure of AMPK activation that monitored pACC in peripheral blood mononuclear cells (PBMCs). The correlation between pACC formation in PBMCs versus muscle using both MSD and Western blot analysis is shown in fig. S14. After administration of MK-8722 (5 mpk), pACC in PBMCs remained elevated for at least 10 hours (fig. S15); these effects were sustained during 7 weeks of dosing in T2DM NHPs (fig. S16), demonstrating that AMPK activation by MK-8722 is not subject to tachyphylaxis.

The effect of both 5- and 10-mpk doses of MK-8722 in a mixed meal tolerance test (MMTT) was studied both acutely and after 7 weeks of continuous administration of MK-8722 [5 mpk/day orally (p.o.)]. A significant improvement in glucose excursion in the MMTT was observed only in the NHPs treated with MK-8722 (10 mpk) after both acute and chronic treatment (Fig. 4, B and C, and fig. S17). A significant decrease in plasma insulin AUC (area under the curve) was observed at both doses and both time points (fig. S17).

HbA1c, a glycosylated form of hemoglobin, provides an integrated measure of blood glucose over ~2 to 3 months in humans (*22*). The relatively short duration of our T2DM NHP study suggested that HbA1c measurements might underestimate the "true" improvement in glucose control. Nonetheless, we observed an average 0.4% decrease in HbA1c in the 14 T2DM NHPs (Fig. 4D). Ten NHPs exhibited a substantial 0.9% (±0.1% SEM) reduction in HbA1c. One NHP started the study with a nondiabetic HbA1c of 4.3%, which was not lowered further. Three severely diabetic NHPs did not respond to treatment; their HbA1c increased over the study period. 1,5-Anhydroglucitol

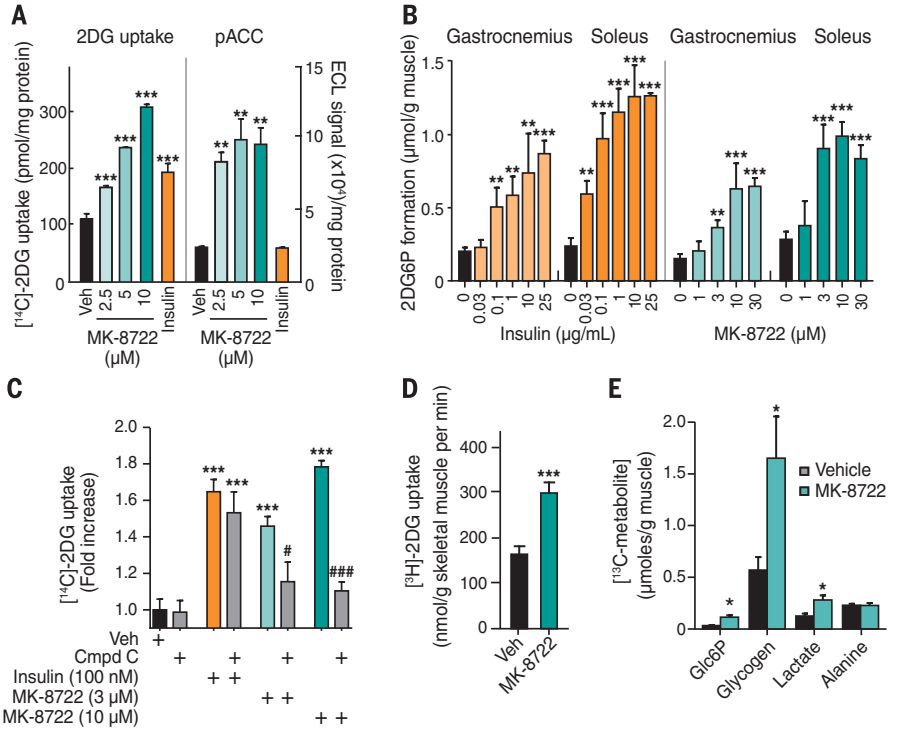

Fig. 3. MK-8722 increases glucose uptake into skeletal muscle in vitro and in vivo. (**A**) Effect on [^{14}C]2DG uptake and intracellular pACC after treatment with MK-8722 and insulin (100 nM) in human skeletal myocytes. (**B**) Effect of MK-8722 and insulin treatment on 2DG6P formation in perfused, lean rat hindlimb skeletal muscles. (**C**) Effect on [^{14}C]2DG uptake after treatment with MK-8722 (3 and 10 μM) and insulin (100 nM) in primary human myocytes, with and without pretreatment with Compound C (30 μM). #P < 0.05, ###P < 0.001 versus corresponding no–Compound C treatment group. (**D**) Effect on [^{3}H]2DG6P production in gastrocnemius muscle 90 min after MK-8722 administration (30 mpk, p.o.) to lean C57BL/6 mice (10-week-old male, n = 8 per group; single experiment, unblinded). (**E**) Effect on [1-^{13}C]D-glucose metabolite production in gastrocnemius muscle 2 hours after MK-8722 administration (10 mpk, p.o.) to GK rats (14-week-old male, n = 8 per group; data are representative of three independent experiments, unblinded). Data are means ± SEM. *P < 0.05, **P < 0.01, ***P < 0.001, one-way ANOVA.

and fructosamine, biomarkers of integrated glycemic control over shorter time frames [2 to 14 days and 2 to 3 weeks, respectively (*22*)], responded appropriately to MK-8722 treatment (Fig. 4, E and F). There were no significant effects of MK-8722 treatment on food intake (fig. S18). Blood chemistry was analyzed weekly. No reduction in fasted glucose levels before dosing (when MK-8722 concentrations were low) was observed (fig. S19). However, significant and comparable reductions in blood glucose were observed at both the beginning and end of the study 2 hours after dose using MK-8722 (10 mpk) (fig. S19). Taken together, the results suggest that the observed antihyperglycemic effects were driven by acute, daily reductions in glucose that remained constant throughout the study. After the treatment period, the NHPs underwent a washout period. Although the time course for each NHP varied, all parameters returned to baseline, confirming that the changes were MK-8722–mediated and reversible (Fig. 4, E and F, unshaded portion of the curves).

To confirm the mechanism of glucose lowering in NHP and examine a potentially useful clinical biomarker, we used [^{18}F]fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) to monitor MK-8722–mediated increases in glucose uptake in various tissues in vivo. Three male lean rhesus NHPs were imaged by [^{18}F]FDG PET/CT starting 30 min after intravenous (iv) infusion acute dosing with either vehicle or MK-8722 (0.3 to 5 mpk). We detected a doubling of the Patlak rate constant in [^{18}F]FDG uptake into the biceps muscle after the 5-mpk dose of MK-8722 (P = 0.01; see Fig. 4G and fig. S20). MK-8722 did not stimulate [^{18}F]FDG uptake into liver (hepatocytes lack Glut4). The effect of MK-8722 on cardiac [^{18}F]FDG uptake was too variable to draw conclusions.

We also investigated the potential cardiac safety concerns associated with chronic systemic AMPK activation. Cardiac safety was evaluated preclinically in Wistar Han rats and rhesus monkeys in studies lasting up to 8 months. Increased heart weight (normalized relative to brain weight, as compared with vehicle control) was observed in both male and female rats dosed with MK-8722 for 1 month at 10 and 30 mpk/day (Fig. 5A). The increase in heart size was associated with increases in both cardiac and skeletal muscle

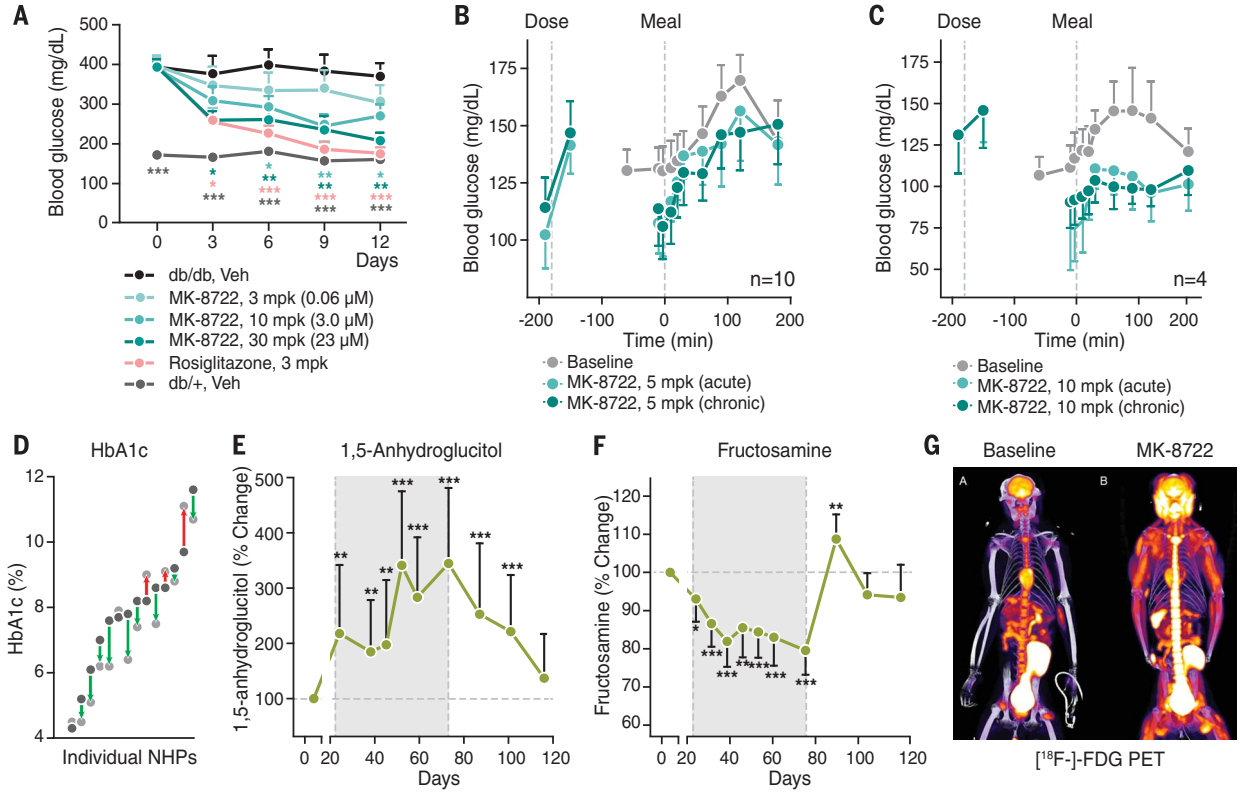

Fig. 4. Effects of MK-8722 in the *db/db* T2DM mouse model and on glucose homeostasis in diabetic and lean rhesus macaque monkeys. (**A**) Effect on trough ambient blood glucose during 12 days of administration of MK-8722 (3 to 30 mpk/day, p.o.) or rosiglitazone (3 mpk/day, p.o.) in *db/db* mice (8-week-old male, $n = 8$ to 10 per group; data are representative of three independent experiments, unblinded). (**B** to **F**) Effect of MK-8722 in diabetic rhesus monkeys (mixed ages and sexes, single unblinded experiment). [(B) and (C)] Effect of MK-8722 treatment (5 and 10 mpk p.o.) on blood glucose during an MMTT performed acutely and after chronic treatment with MK-8722 (5 mpk/day p.o.) ($n = 10$ and 4 for 5- and 10-mpk groups, respectively). [(D) to (F)] Effect of chronic treatment with MK-8722 (5 mpk/day p.o.) on integrated blood glucose measurements. (D) Effect on HbA1c after 7 weeks of MK-8722 administration. (E) Effect on 1,5-anhydroglucitol throughout the study. (F) Effect on fructosamine throughout the study. Shaded portions of graphs in (E) and (F) represent the MK-8722 administration period. (**G**) Effects on [^{18}F]FDG PET maximum intensity projection at baseline and after acute MK-8722 administration (5 mpk, iv), 90 min after injection of [^{18}F]FDG in the same lean rhesus monkey (6-year-old male, $n = 1$; data are representative of three independent experiments, unblinded). Data are means ± SEM. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, one-way ANOVA.

glycogen (fig. S21). Increased glycogen content was also evident upon histological assessment of cardiac samples from the study (fig. S22). After a 2-month drug-free recovery period, both heart weight (Fig. 5A) and muscle glycogen (fig. S21) returned to near control levels, demonstrating that the effects were both MK-8722–mediated and reversible.

The observed increases in cardiac glycogen after MK-8722 administration are much lower than those observed in the transgenic mouse models (*23*) and are dose-dependent, in contrast to heart weight increases (Fig. 5B). Thus, the observed cardiac hypertrophy is not proportional to, nor solely a result of, glycogen accumulation. Cardiac hypertrophy in the absence of significant glycogen accumulation has been demonstrated in a human N488I PRKAG2 transgenic mouse model that coexpresses a mutant glycogen synthase incapable of Glc6P stimulation, but it is unclear whether the hypertrophy observed in this model is developmental in origin (*23*).

Similarly, cardiac hypertrophy associated with increased cardiac and skeletal muscle glycogen was observed in rhesus monkeys dosed with MK-8722 for 1 month (Fig. 5C and fig. S23). Morphometric evaluation of the heart wall area confirmed an increase in one or both ventricles (table S3). In rats, heart weight increases were greater after 6 months of dosing than after 1 month of dosing, demonstrating progression of the cardiac hypertrophy with increased duration of drug administration (table S4).

ECG tracings obtained over an 8-month rhesus monkey study showed an increase in the amplitude of QRS at all doses, likely an effect secondary to the observed cardiac hypertrophy (fig. S24). However, ECG changes similar to those associated with PRKAG2 mutation Wolff-Parkinson-White (WPW) syndrome (PR interval shortening, QRS prolongation) were not observed (*9*, *23*, *24*). These results are consistent with data generated in transgenic PRKAG2 mouse models, which suggested that such conductance abnormalities (in particular, ventricular preexcitation) are due to structural defects created during cardiac development, possibly as a result of abnormal glycogen deposition secondary to AMPK disinhibition/activation caused by the PRKAG2 mutations (*23*, *24*). Normal cardiac function (ejection fraction and stroke volume) was demonstrated in rats that exhibited a 13% increase in heart weight after 1 month of MK-8722 administration (fig. S25). Similar hypertrophic effects after chronic treatment were observed in all species and models examined, including both insulin-resistant mice dosed orally (fig. S26) and diabetic *db/db* mice dosed in feed (Fig. 5D).

Our results show that systemic, pharmacological pan-AMPK activation by MK-8722 leads to chronically sustainable improvements in glucose homeostasis, including the amelioration of insulin resistance and hyperglycemia (*7*, *8*, *25*). No evidence of hypoglycemia was found in any study using MK-8722, including high-dose 6- to 8-month studies in normoglycemic rats and rhesus monkeys. These effects appear to be mediated predominantly by insulin-independent skeletal muscle glucose uptake. Glucose lowering without a requirement for increased insulin levels should

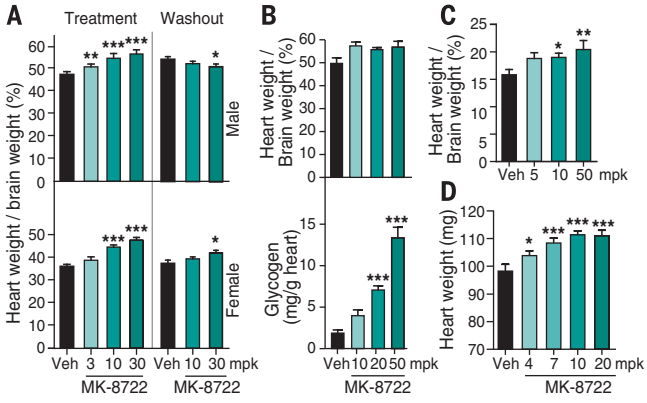

Fig. 5. Effect of chronic MK-8722 administration on cardiac parameters in rodents and rhesus monkeys. (**A**) Effect on heart weight/brain weight ratio after 1 month of MK-8722 administration (3 to 30 mpk/day, p.o.), followed by 2 months of drug withdrawal (washout) in Wistar Han rats (5-week-old male and female, $n = 10$ each; single unblinded study). (**B**) Effect on heart weight/brain weight ratio and cardiac glycogen after 2 weeks of MK-8722 administration (10 to 50 mpk/day, p.o.) in Wistar Han rats (6-week-old male, $n = 5$, single unblinded study). (**C**) Effect on heart weight/brain weight ratio of 1 month of MK-8722 administration (5 to 50 mpk/day, p.o.) in rhesus monkeys (sexes combined, $n = 6$ total; single unblinded study). (**D**) Effect on heart weight of 14-day MK-8722 administration (4 to 20 mpk/day in feed) in *db/db* mice (8-week-old male, $n = 8$; single unblinded study). Data are means ± SEM. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, trend analysis (C), one-way ANOVA (other panels).

reduce the demand on the pancreatic β cell for insulin and, as a consequence, may increase the durability of antihyperglycemic action. This profile is both unique and highly desirable for patients with T2DM, differing from all currently available therapeutic agents (*26*, *27*).

On the other hand, MK-8722 treatment induced reversible cardiac hypertrophy that was not associated with notable functional sequelae or ECG abnormalities in the time frames studied. Our data suggest that this hypertrophy is not due to the observed cardiac glycogen accumulation. Rather, the effect is reminiscent of the physiological cardiac hypertrophy observed in elite athletes (*28*). It is well established that exercise can activate cardiac AMPK (*29*). Whether this effect is tolerable in humans having the pathophysiology of metabolic syndrome, obesity, and overt diabetes remains to be determined.

While this manuscript was in the final stages of review, Cokorinos *et al.* reported that a close analog of MK-8722 (PF-739) was able to activate skeletal muscle AMPK and lower glucose in preclinical species independent of hepatic AMPK activation (*30*).

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SUPPLEMENTARY MATERIALS

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Science

Systemic pan-AMPK activator MK-8722 improves glucose homeostasis but induces cardiac hypertrophy

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Hitting a dozen enzymes with one drug

The adenosine monophosphate-activated protein kinase (AMPK) controls cellular energy status. AMPK is activated when energy levels fall. This stimulates adenosine triphosphate (ATP)-generating pathways that promote glucose uptake and inhibits ATP-consuming pathways associated with glucose synthesis. In principle, these effects would be beneficial in metabolic diseases, including diabetes. Pharmacological activation of AMPK has been challenging, however, because in mammals, the enzyme exists as 12 distinct complexes. Myers *et al.* describe an orally available compound (MK-8722) that activates all 12 complexes (see the Perspective by Hardie). In animal models, MK-8722 ameliorated diabetes, but it also caused enlargement of the heart. MK-8722 may be a useful tool compound for laboratory research on AMPK function.

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