**ONLINE SUPPLEMENT**

**Maintaining Myocardial Glucose Utilization in Diabetic Cardiomyopathy
Accelerates Mitochondrial Dysfunction**

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**Online Supplemental Figure I**

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**Time course and tissue specificity of mycGLUT4 transgene induction, related to Fig. 1*.*****A,** Western blot of heart GLUT4 protein levels in Con and mG4H mice following 2, 4, and 8 days of induction. **B,** Western blot of heart and various skeletal muscles in mG4H mice following 2 weeks of DOX treatment reveals no transgene expression in tissues other than the heart including gastrocnemius (Gastroc), vastus lateralis (Vastus), tibialis anterior (Tibialis), and soleus. **C,** Liver tissue and **D,** skeletal muscle glycogen levels in Con and mG4H mice following 2 weeks of DOX induction.Quantitative data are means ± s.e.m.

**Online Supplemental Table I.** *In vivo echocardiographic evaluation of contractile function in Veh and STZ treated Con and mG4H mice, related to Fig. 2.*

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| --- | --- | --- | --- | --- |
| **Parameter** | **Con-****Veh** | **Con-****STZ** | **mG4H-****Veh** | **mG4H-****STZ** |
| No. of mice | 6 | 6 | 6 | 6 |
| LVDd (mm) | 3.80 ± 0.04 | 3.63 ± 0.09 | 3.64 ± 0.12 | 3.63 ± 0.12 |
| LVDs (mm) | 2.45 ± 0.08 | 2.47 ± 0.07 | 2.38 ± 0.14 | 2.36 ± 0.13 |
| IVSd (mm) | 0.80 ± 0.05 | 0.81 ± 0.04 | 0.88 ± 0.04 | 0.79 ± 0.05 |
| IVSs (mm) | 1.32 ± 0.05 | 1.23 ± 0.07 | 1.42 ± 0.05 # | 1.25 ± 0.05 |
| LVPWd (mm) | 0.89 ± 0.05 | 0.75 ± 0.07 | 0.87 ± 0.07 | 0.80 ± 0.05 |
| LVPWs (mm) | 1.14 ± 0.04 | 0.96 ± 0.10 | 1.06 ± 0.08 | 1.00 ± 0.11 |
| Relative wall thickness | 0.45 ± 0.02 | 0.43 ± 0.02 | 0.49 ± 0.04 | 0.44 ± 0.04 |
| Fractional shortening (%) | 35.6 ± 2.1 | 31.8 ± 1.6 | 34.7 ± 1.9 | 34.8 ± 3.0 |
| Ejection fraction (%) | 72.9 ± 2.5 | 68.0 ± 2.2 | 71.9 ± 2.4 | 71.4 ± 3.7 |
| Stroke volume (µL) | 44.3 ± 1.7 | 35.8 ± 2.6 \* | 38.3 ± 2.2 | 39.7 ± 2.6 |
| Cardiac output (mL/min) | 18.6 ± 1.2 | 13.4 ± 1.2 \* | 14.9 ± 0.9 | 14.1 ± 1.1 \* |
| Heart rate (beats/min) | 418 ± 16 | 374 ± 19 | 391 ± 20 | 356 ± 19 \* |

LVDd, Left ventricular cavity diameter at diastole; LVDs, Left ventricular cavity diameter at systole; IVSd, Interventricular septum thickness at diastole; IVSs, Interventricular septum thickness at systole; LVPWd, Left ventricular posterior wall thickness at diastole; LVPWs, Left ventricular posterior wall thickness at systole. Quantitative data are mean ± s.e.m. \* P < 0.05 versus Con-Veh; # P < 0.05 versus Con-STZ and mG4H-STZ.

**Online Supplemental Table II.** *Hemodynamic measurements obtained following left ventricular catheterization* *in Veh and STZ treated Con and mG4H mice, related to Fig. 2.*

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| --- | --- | --- | --- | --- |
| **Parameter** | **Con-****Veh** | **Con-****STZ** | **mG4H-****Veh** | **mG4H-****STZ** |
| No. of mice | 10 | 10 | 10 | 10 |
| Pulse pressure (mmHg) | 32.8 ± 2.2 | 29.1 ± 2.1 | 36.5 ± 1.9 | 33.1 ± 1.9 |
| Arterial SP (mmHg) | 95.5 ± 3.9 | 86.3 ± 3.3 | 100.9 ± 2.5 # | 91.0 ± 3.6 |
| Arterial DP (mmHg) | 62.7 ± 3.3 | 57.1 ± 3.4 | 64.3 ± 2.8 | 57.9 ± 5.0 |
| LVSP (mmHg) | 94.4 ± 2.7 | 81.5 ± 2.5 $ | 98.1 ± 3.2 | 85.9 ± 3.2 $ |
| LVEDP (mmHg) | 13.2 ± 3.0 | 13.1 ± 2.8 | 14.3 ± 2.2 | 12.0 ± 1.9 |
| LV Dev P (mmHg) | 94.3 ± 2.9 | 81.0 ± 3.0 $ | 98.1 ± 3.4 | 84.3 ± 2.9 $ |
| +dP/dt (mmHg/sec) | 7764 ± 647 | 5306 ± 392 $ | 7736 ± 459 | 5574 ± 411 $ |
| -dP/dt (mmHg/sec) | -6560 ± 562 | -5201 ± 284 $ | -6490 ± 343 | -5042 ± 357 $ |
| Tau (ms) | 9.3 ± 1.0 | 10.2 ± 0.8 | 9.1 ± 0.7 | 10.3 ± 0.5 |
| Heart rate (beats/min) | 414 ± 19 | 352 ± 27 $ | 409 ± 12 | 334 ± 10 $ |

Data shown are from studies in which aortic valve function returned to baseline at the end of the recording. If aortic regurgitation was present, then data were excluded from analysis. MP, mean pressure; SP, systolic pressure; DP, diastolic pressure; LV, left ventricular; EDP, end-diastolic pressure; Dev P, developed pressure, +dP/dt, peak rate of LV pressure rise; -dP/dt, peak rate of LV pressure decline. Quantitative data are mean ± s.e.m. \* P < 0.05 vs. Con-Veh, # P < 0.05 vs. Con-STZ and mG4H-STZ, $ P < 0.05 vs. Con-Veh and mG4H-Veh.

**Online Supplemental Table III.** *Cardiac contractile function in isolated perfused working hearts (IWH)**in Veh and STZ treated Con and mG4H mice, related to Fig. 3.*

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| --- | --- | --- | --- | --- |
| **Parameter** | **Con-****Veh** | **Con-****STZ** | **mG4H-****Veh** | **mG4H-****STZ** |
| HR (beats/min) | 193 ± 8 | 166 ± 8 \* | 181 ± 7 | 157 ± 7 $ |
| SP (mmHg) | 73.0 ± 1.0 | 71.6 ± 1.4 | 80.0 ± 1.3 \*,# | 71.9 ± 1.3 |
| DP (mmHg) | 36.0 ± 0.8 | 32.8 ± 0.9 \*,# | 38.2 ± 1.1 | 36.6 ± 1.0 |
| DevP (mmHg) | 37.0 ± 0.7 | 38.8 ± 1.7 | 41.8 ± 1.3 \*,# | 35.3 ± 1.0 |
| Coronary Flow (mL/min) | 2.9 ± 0.1 | 3.2 ± 0.1 | 3.1 ± 0.1 | 2.6 ± 0.1 $ |
| Aortic Flow (mL/min) | 6.9 ± 0.1 | 6.2 ± 0.2 \* | 7.6 ± 0.2 | 6.1 ± 0.3 $ |
| CP (mW/g) | 18.5 ± 0.7 | 19.9 ± 1.5 | 25.1 ± 1.3 \*,# | 18.0 ± 0.8 |
| CO (mL/min) | 9.8 ± 0.2 | 9.4 ± 0.3 | 10.7 ± 0.3 \*,# | 8.7 ± 0.4 $ |

HR, heart rate; SP, systolic pressure; DP, diastolic pressure; CP, cardiac power; CO, cardiac output. Quantitative data are mean ± s.e.m. \* P < 0.05 vs. Con-Veh, # P < 0.05 vs. Con-STZ and mG4H-STZ, $ P < 0.05 vs. Con-Veh and mG4H-Veh.

**Online Supplemental Table IV.** *Genes from Venn diagram, Related to Fig. 7E.*

Owing to page number listed at end.

**Online Supplemental Table V.** *Pathway analysis for genes co-regulated in all three experimental groups being upregulated (yellow) or downregulated (blue), related to Fig. 7G.*

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| --- | --- | --- | --- | --- | --- |
| **Term** | **Overlap** | ***P*-value** | **Z-score** | **Combined Score** | **Genes** |
| Unsaturated fatty acid biosynthesis | 3/23 | 0.001 | -1.669 | 11.9 | *Acot2; Acot1; Acot4* |
| Fatty acid elongation | 3/25 | 0.001 | -1.483 | 10.2 | *Acot2; Acot1; Acot4* |
| Melanoma | 3/71 | 0.020 | -1.890 | 7.4 | *Cdkn1a; Fgf1; Fgf21* |
| Peroxisome | 3/83 | 0.029 | -1.629 | 5.7 | *Nudt7; Pex11a; Ephx2* |
| Bladder cancer | 2/41 | 0.043 | -1.714 | 5.4 | *Cdkn1a; Thbs1* |
| Ketone body metabolism | 2/5 | 0.002 | -1.887 | 11.4 | *Bdh1; Oxct1* |
| Amino acid metabolism | 6/92 | 0.003 | -1.980 | 11.2 | *Mpst; Glud1; Hibadh; Cth; Mccc1; Mut* |
| Tryptophan metabolism | 3/43 | 0.031 | -1.926 | 6.7 | *Gcdh; Echs1; Hsd17b10* |
| Trans-sulfuration | 2/11 | 0.013 | -1.505 | 6.6 | *Mpst; Cth* |
| Fatty acid oxidation | 2/10 | 0.010 | -1.323 | 6.0 | *Slc25a29; Echs1* |
| Glycolysis | 3/48 | 0.041 | -1.635 | 5.2 | *Pgam2; Slc2a4; Hk2* |