

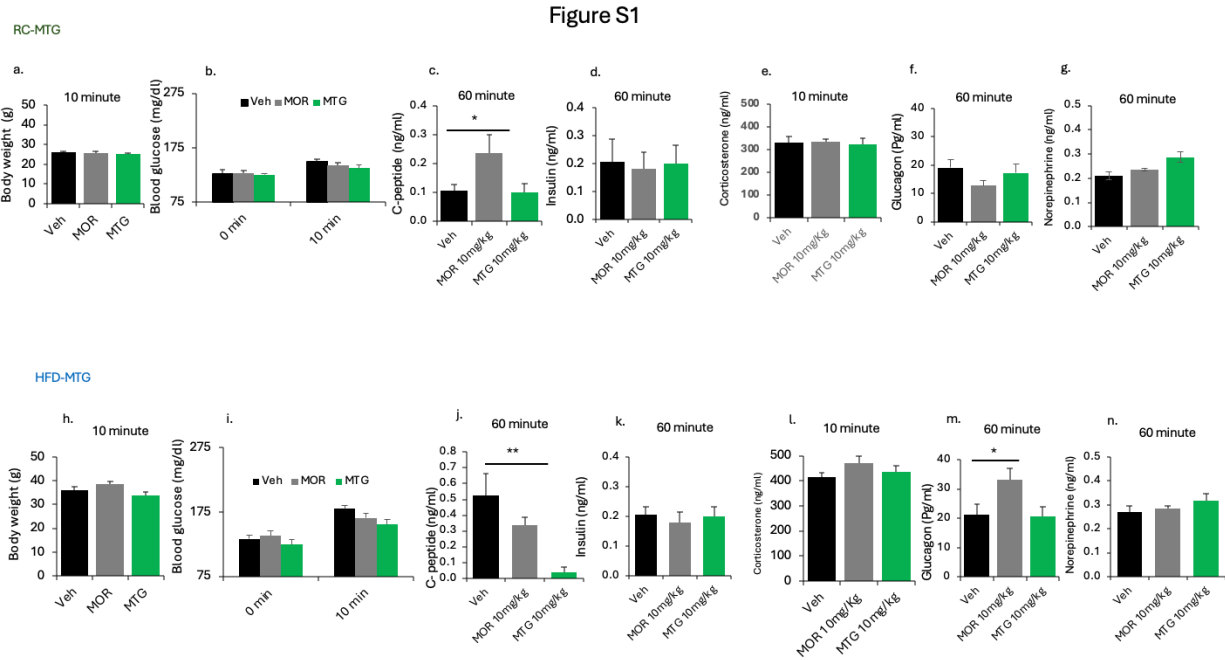


Figure 1 S. Metabolic and hormonal responses following acute morphine and mitragynine administration in RC- and HFD-fed male mice.

(a–g) Responses in RC-fed mice (RC-MTG).

(a) Initial body weight for the 10-minute group.

(b) Blood glucose at 0 and 10 min following injection.

(c) Plasma C-peptide at 60 min.

(d) Plasma insulin at 60 min.

(e) Plasma corticosterone at 10 min.

(f) Plasma glucagon at 60 min.

(g) Plasma norepinephrine at 60 min.

(h–n) Responses in HFD-fed mice (HFD-MTG).

(h) Initial body weight for the 10-minute group

(i) Blood glucose at 0- and 10-min following injection.

(j) Plasma C-peptide at 60 min.

(k) Plasma insulin at 60 min.

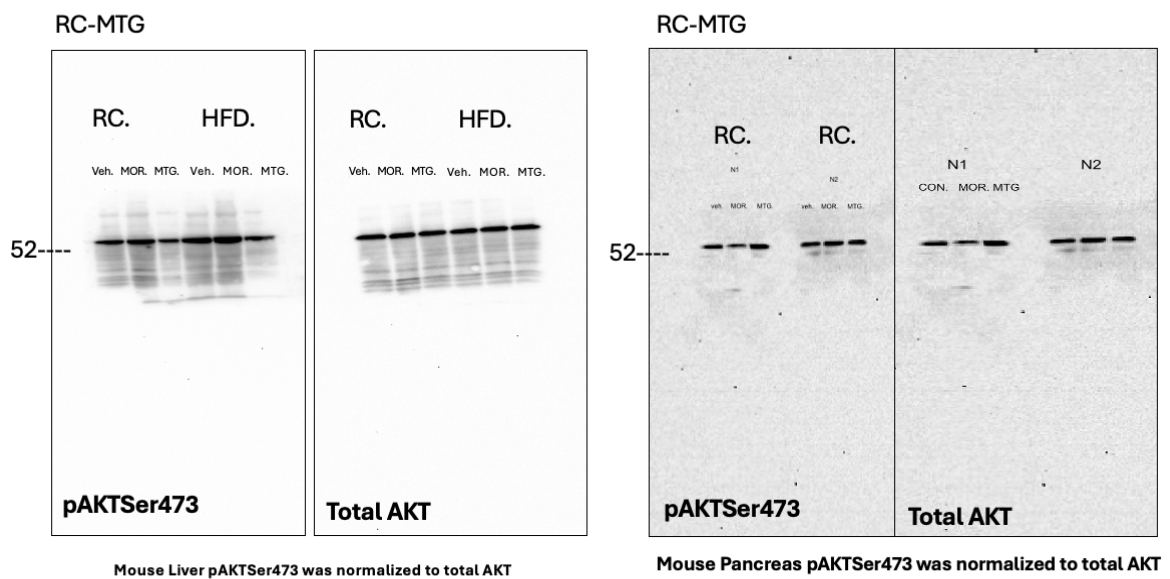
(l) Plasma corticosterone at 10 min.

(m) Plasma glucagon at 60 min.

(n) Plasma norepinephrine at 60 min.

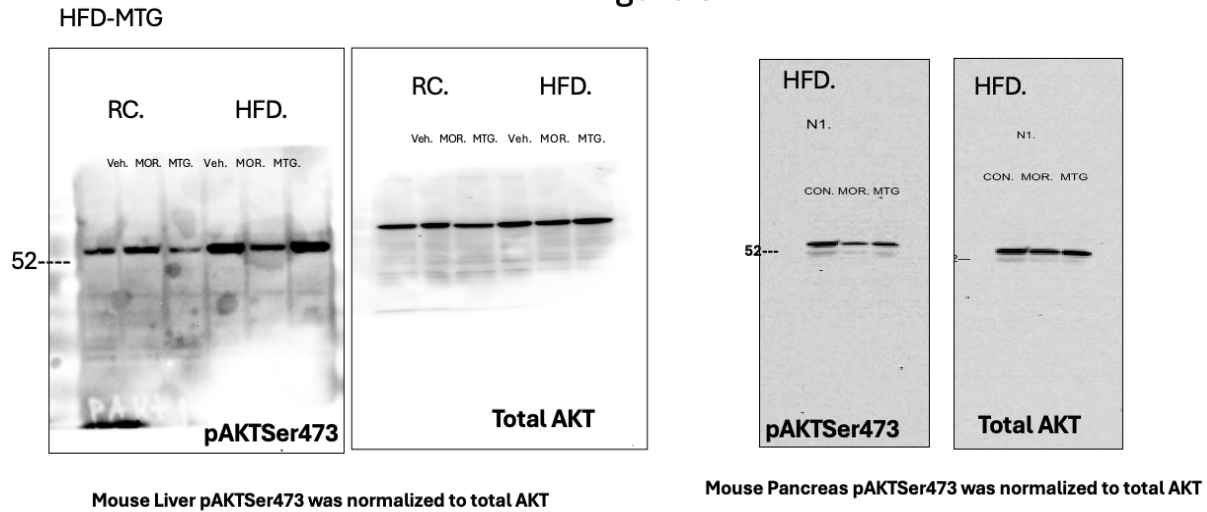
Statistical analysis was performed using one-way ANOVA, followed by Newman–Keuls post hoc tests. For RC mice: glucagon (Df = 21) showed a significant difference between vehicle and morphine ($P = 0.0307$), and C-peptide (Df = 12) showed a difference between vehicle and morphine ($P = 0.043$). For HFD mice: C-peptide (Df = 12) differed between vehicle and MTG ($P = 0.005$) and between morphine and MTG ($P = 0.035$), with no difference between vehicle and morphine ($P = 0.16$). Data are presented as mean $\pm$ SEM. * $P < 0.05$, ** $P < 0.01$ vs. vehicle.

Figure S1



Full-length Western blot images corresponding to Figure 1. I. Acute mitragynine treatment in the liver and pancreas. Western blot images display pAKTSer473 and total AKT in mouse liver and pancreas after vehicle, morphine MOR, or mitragynine MTG treatment under regular chow (RC).

Figure S1



Full-length Western blot images corresponding to Figure 1. R. Acute mitragynine treatment in liver and pancreas. Western blot images display pAKTSer473 and total AKT in mouse liver and pancreas after vehicle, morphine MOR, or mitragynine MTG treatment under R high-fat diet (HFD) conditions. Samples were run on different gels. Blots for each antibody were imaged using the same exposure settings.

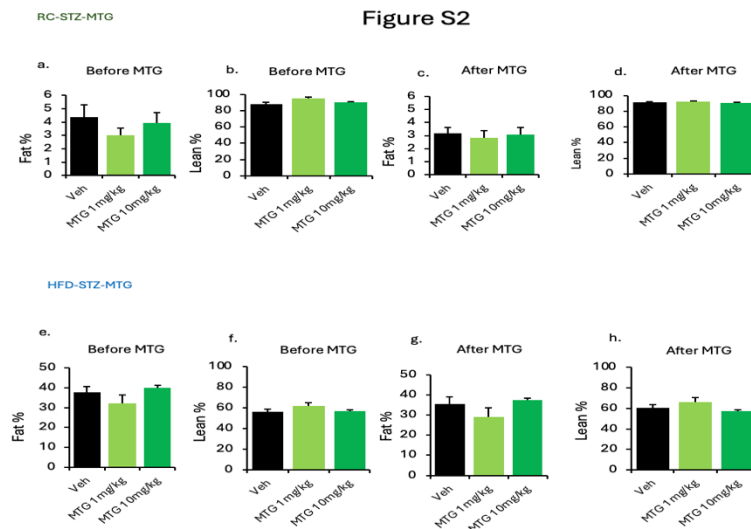


Figure S2. Effects of mitragynine on body composition in STZ-induced diabetic RC- and HFD-fed male mice before and after treatment.

(a–d) Body composition in RC-STZ-MTG mice.

(a) Fat mass (%) before MTG treatment.

(b) Lean mass (%) before MTG treatment.

(c) Fat mass (%) after MTG treatment.

(d) Lean mass (%) after MTG treatment.

(e–h) Body composition in HFD-STZ-MTG mice.

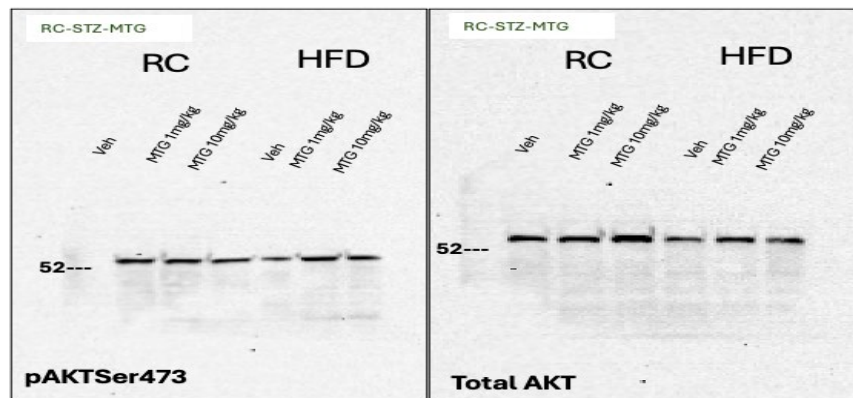
(e) Fat mass (%) before MTG treatment.

(f) Lean mass (%) before MTG treatment.

(g) Fat mass (%) after MTG treatment.

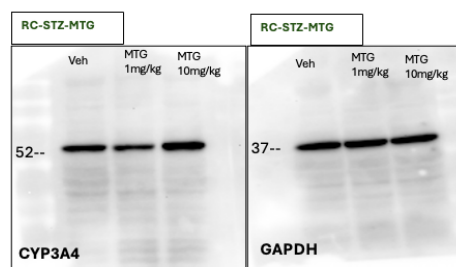
(h) Lean mass (%) after MTG treatment.

Data are presented as mean $\pm$ SEM (n = 3–10 per group). Comparisons between groups were analyzed using one-way ANOVA followed by Newman–Keuls post hoc test. *P < 0.05, **P < 0.01 vs. vehicle.



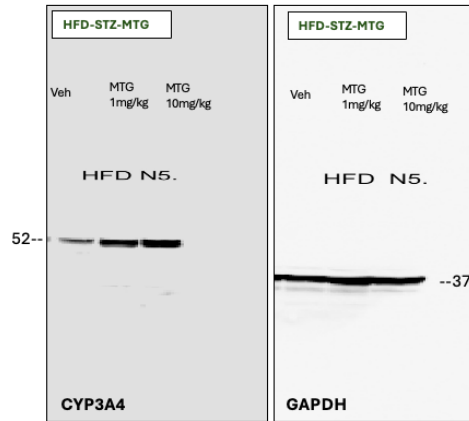
Mouse Liver pAKTSer473 was normalized to total AKT

Full-length Western blot images corresponding to Figure 2. M & V chronic STZ-mitragynine treatment in the liver. Western blot images display pAKTSer473 and total AKT in mouse liver following vehicle, 1 mg/kg mitragynine MTG, or 10 mg/kg MTG treatment in RC-STZ-MTG and HFD-STZ-MTG groups. Samples were run on different gels. Blots for each antibody were imaged using the same exposure settings.



Mouse Liver CYP3A4 was normalized to GAPDH

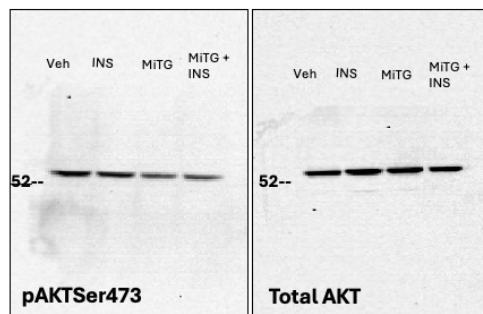
Full-length Western blot images corresponding to Figure 2. N. chronic STZ-mitragynine treatment in the liver. Western blot images display CYP3A4 and GAPDH in mouse liver following vehicle, 1 mg/kg mitragynine MTG, or 10 mg/kg MTG treatment in RC-STZ-MTG groups. Samples were run on different gels. Blots for each antibody were imaged using the same exposure settings.



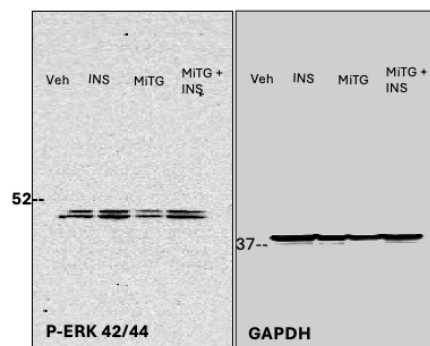
Mouse Liver CYP3A4 was normalized to GAPDH

Full-length Western blot images corresponding to Figure 2. W. chronic STZ-mitragynine treatment in the liver. Western blot images display CYP3A4 and GAPDH in mouse liver following vehicle, 1 mg/kg mitragynine MTG, or 10 mg/kg MTG treatment in HFD-STZ-MTG groups.

Figure S3

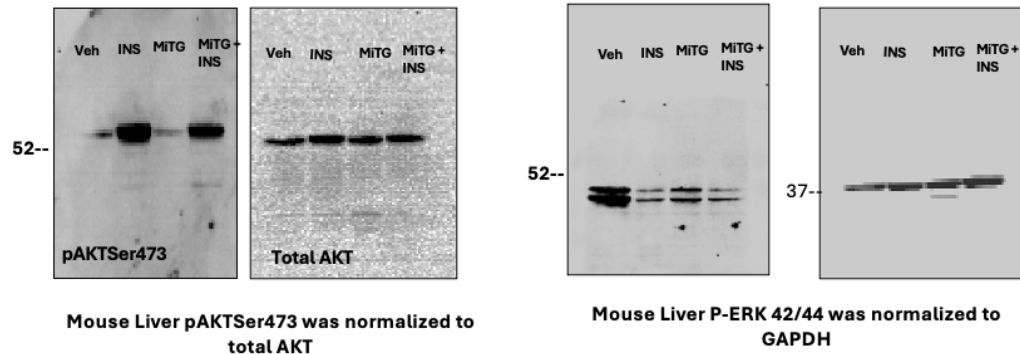


Mouse NTS pAKTSer473 was normalized to total AKT



Mouse NTS P-ERK 42/44 was normalized to GAPDH

Full-length Western blot images corresponding to Figure 3. E.F.G. shown for pAKT Ser473, total AKT, p-ERK42/44, and GAPDH in mouse NTS following vehicle, mitragynine MTG, insulin INS, or mitragynine plus insulin MTG+INS treatment.



Full-length Western blot images corresponding to Figure 3. H.I.J. shown for pAKT Ser473, total AKT, p-ERK42/44, and GAPDH in mouse liver following vehicle, mitragynine MTG 10 mg/kg, insulin INS 5U/kg, or mitragynine plus insulin (MTG+INS 10 mg/kg+5U/kg) treatment.