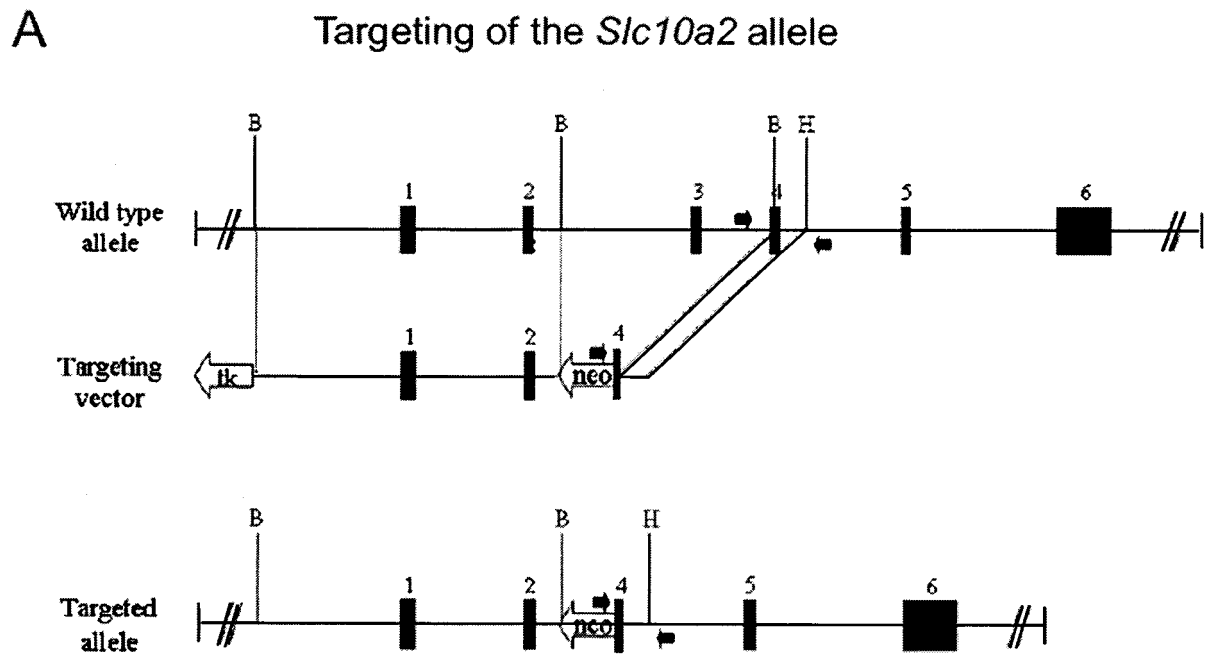
Figure 1


A
Targeting of the Slc10a2 allele
B
B
B H
1
2
3
4
5
6
Wild type allele
Targeting vector
tk
neo
Targeted allele
H

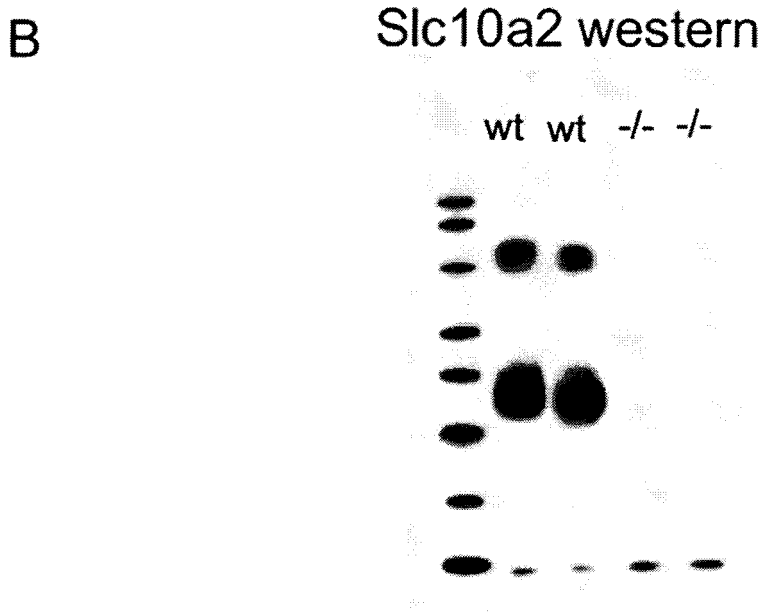

B
Slc10a2 western
wt wt -/- -/-

Figure 2

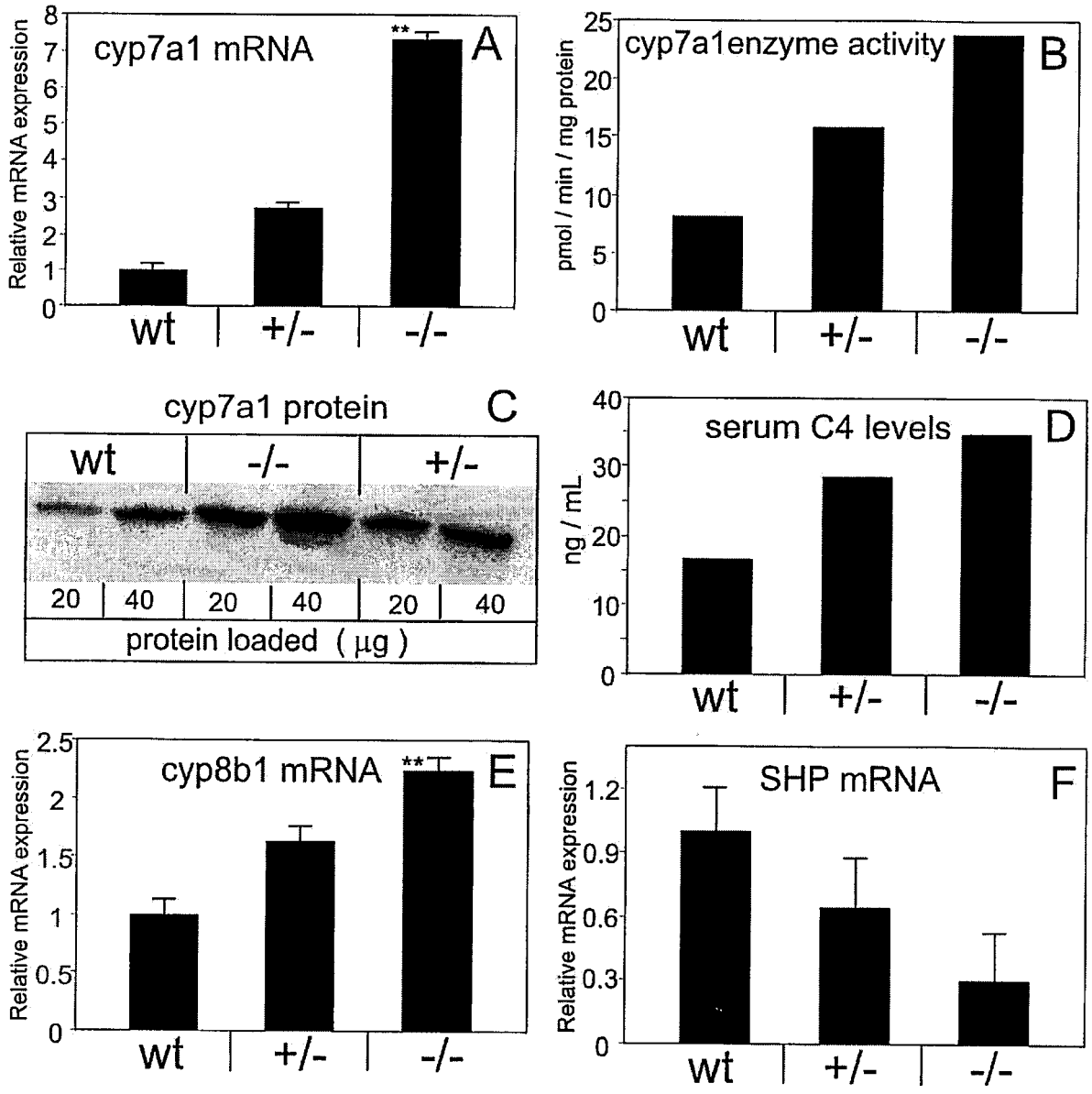

cyp7a1 mRNA
A
Relative mRNA expression
**
wt
+/-
-/-
cyp7a1enzyme activity
B
pmol / min / mg protein
cyp7a1 protein
C
20
40
protein loaded (µg)
serum C4 levels
D
ng / mL
cyp8b1 mRNA
E
SHP mRNA
F

Figure 3

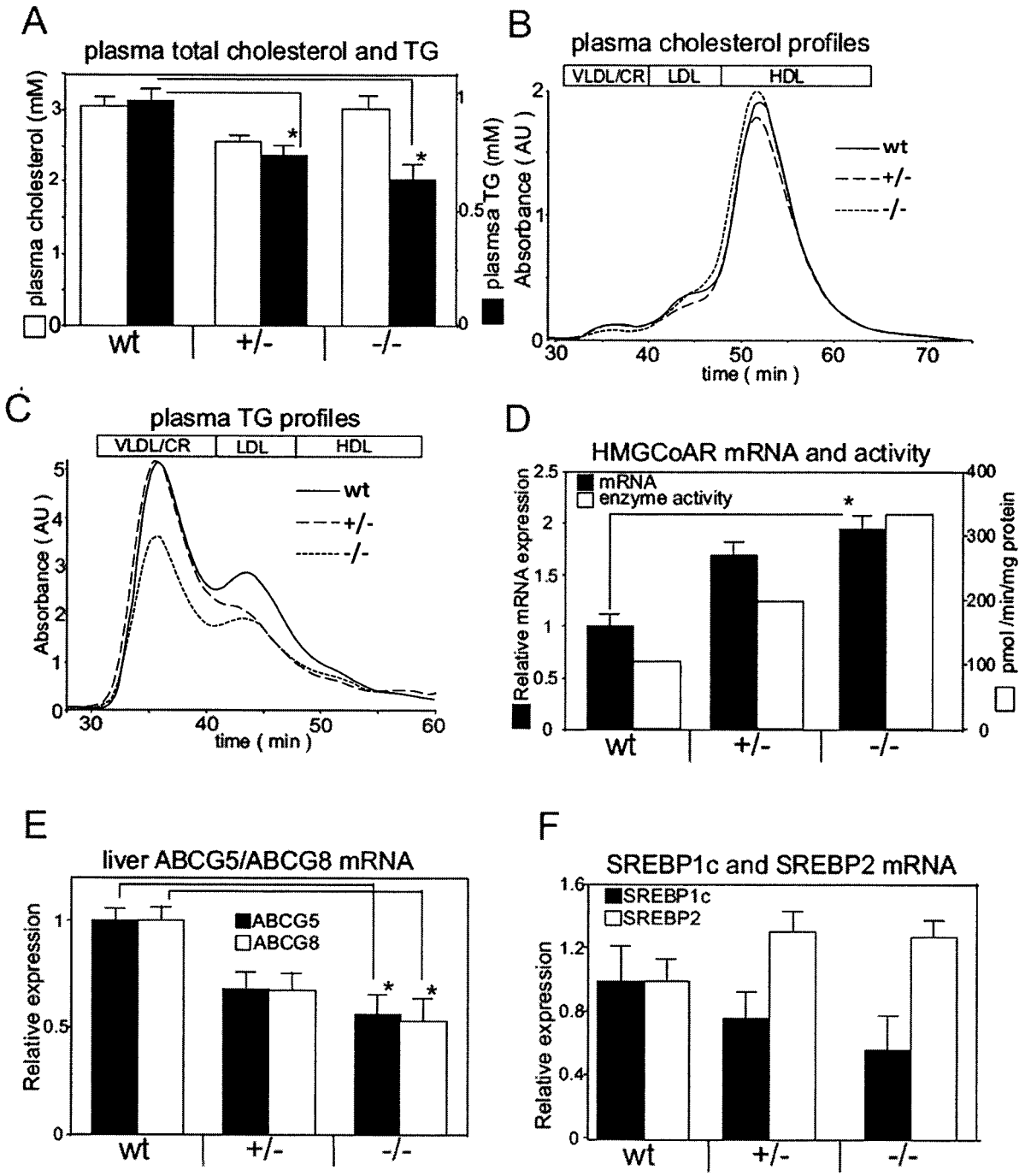

A
plasma total cholesterol and TG
plasma cholesterol (mM)
plasmsa TG (mM)
wt
+/-
-/-
B
plasma cholesterol profiles
VLDL/CR
LDL
HDL
Absorbance (AU)
time (min)
wt
+/-
-/-
C
plasma TG profiles
VLDL/CR
LDL
HDL
Absorbance (AU)
time (min)
wt
+/-
-/-
D
HMGCoAR mRNA and activity
mRNA
enzyme activity
Relative mRNA expression
pmol /min/mg protein
wt
+/-
-/-
E
liver ABCG5/ABCG8 mRNA
ABCG5
ABCG8
Relative expression
wt
+/-
-/-
F
SREBP1c and SREBP2 mRNA
SREBP1c
SREBP2
Relative expression
wt
+/-
-/-

Figure 4

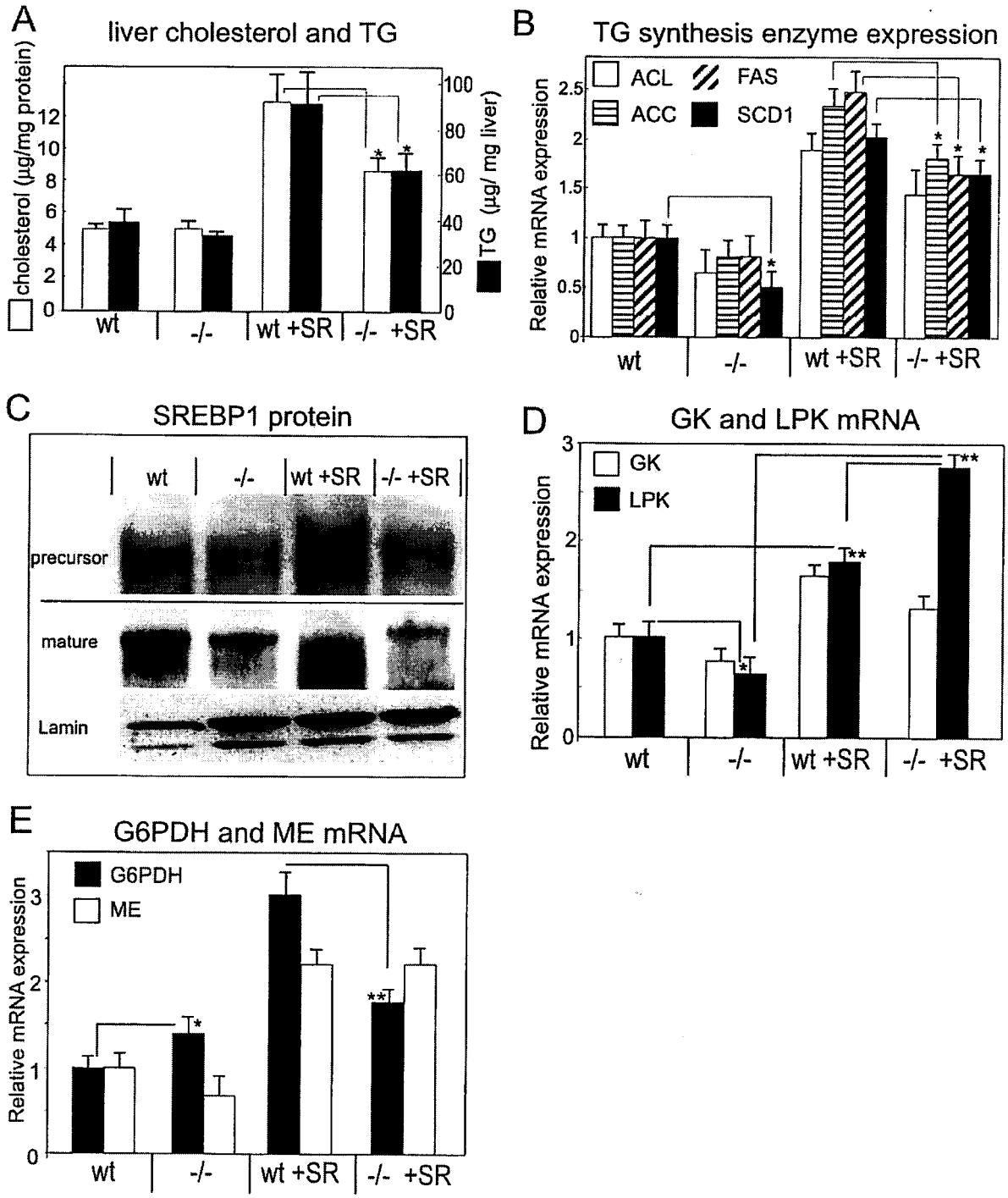

A
liver cholesterol and TG
cholesterol (µg/mg protein)
TG (µg/ mg liver)
wt
-/-
wt +SR
-/- +SR
B
TG synthesis enzyme expression
Relative mRNA expression
ACL
ACC
FAS
SCD1
C
SREBP1 protein
precursor
mature
Lamin
D
GK and LPK mRNA
GK
LPK
E
G6PDH and ME mRNA
G6PDH
ME

Figure 5

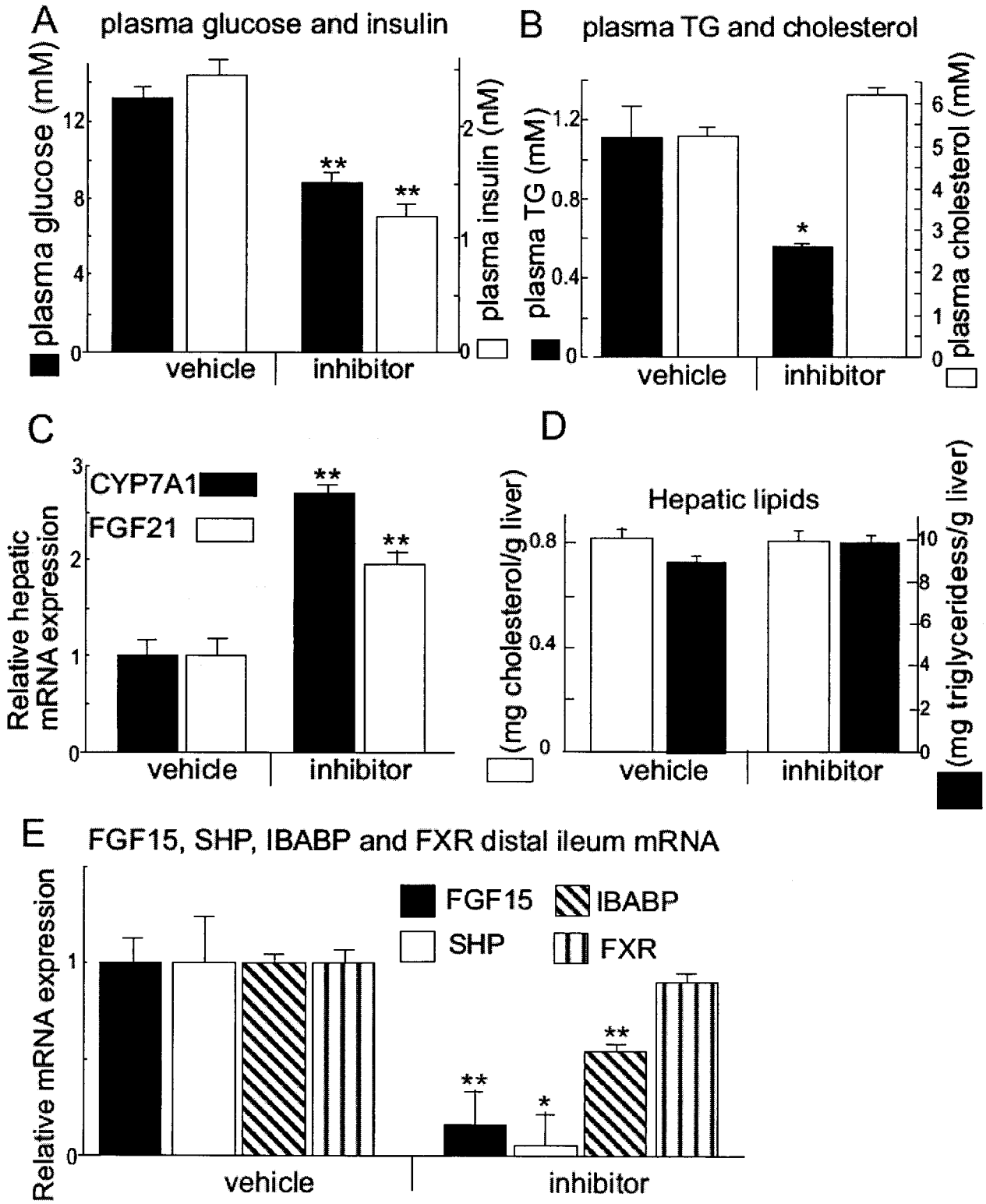

A
plasma glucose and insulin
plasma glucose (mM)
plasma insulin (nM)
vehicle
inhibitor
B
plasma TG and cholesterol
plasma TG (mM)
plasma cholesterol (mM)
vehicle
inhibitor
C
CYP7A1
FGF21
Relative hepatic mRNA expression
vehicle
inhibitor
D
Hepatic lipids
(mg cholesterol/g liver)
(mg triglyceriess/g liver)
vehicle
inhibitor
E
FGF15, SHP, IBABP and FXR distal ileum mRNA
FGF15
IBABP
SHP
FXR
Relative mRNA expression
vehicle
inhibitor

Figure 6

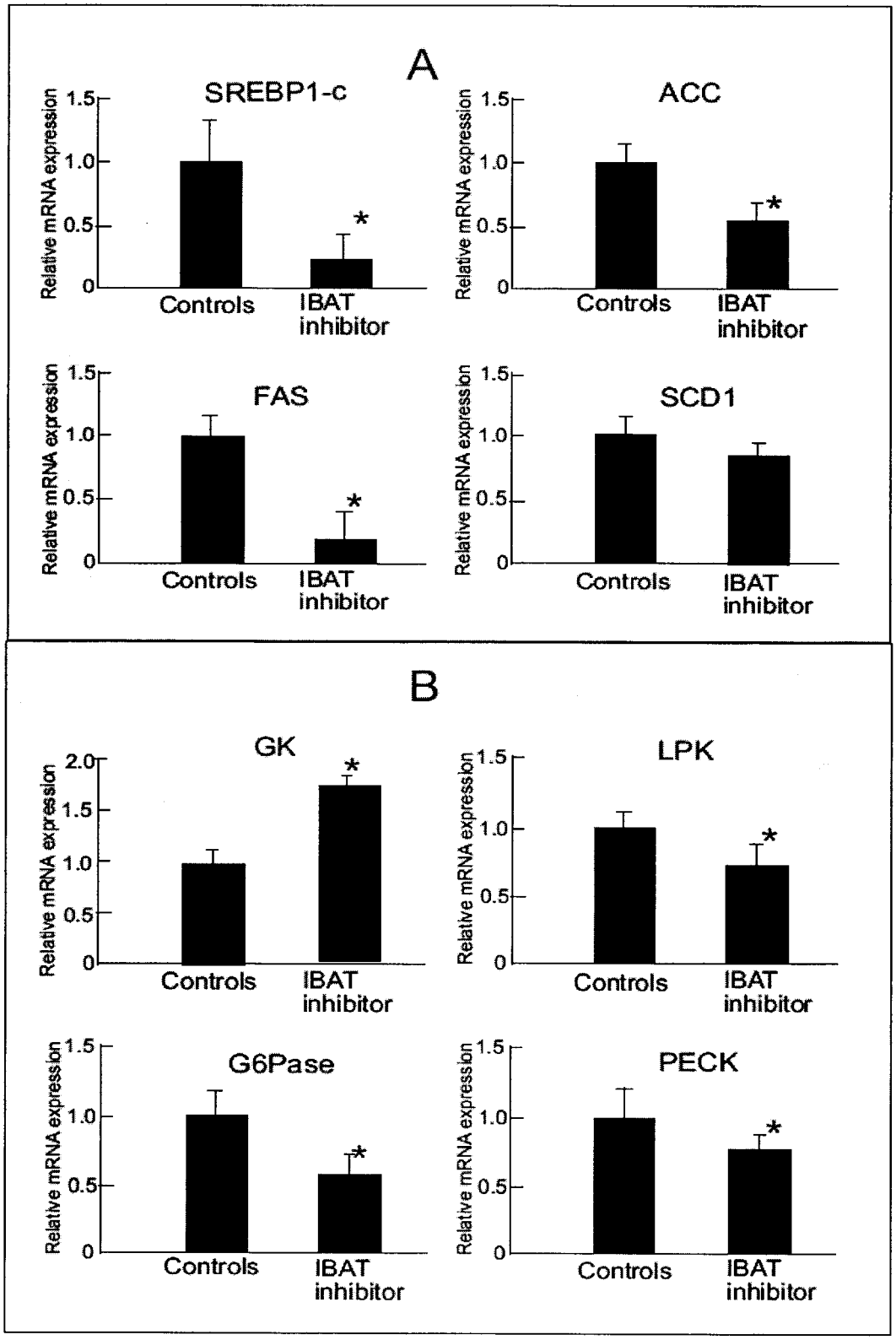

A
SREBP1-c
ACC
FAS
SCD1
Relative mRNA expression
1.5
1.0
0.5
0
*
Controls
IBAT inhibitor
B
GK
LPK
G6Pase
PECK
2.0
1.5
1.0
0.5
0
*
Controls
IBAT inhibitor

Figure 7

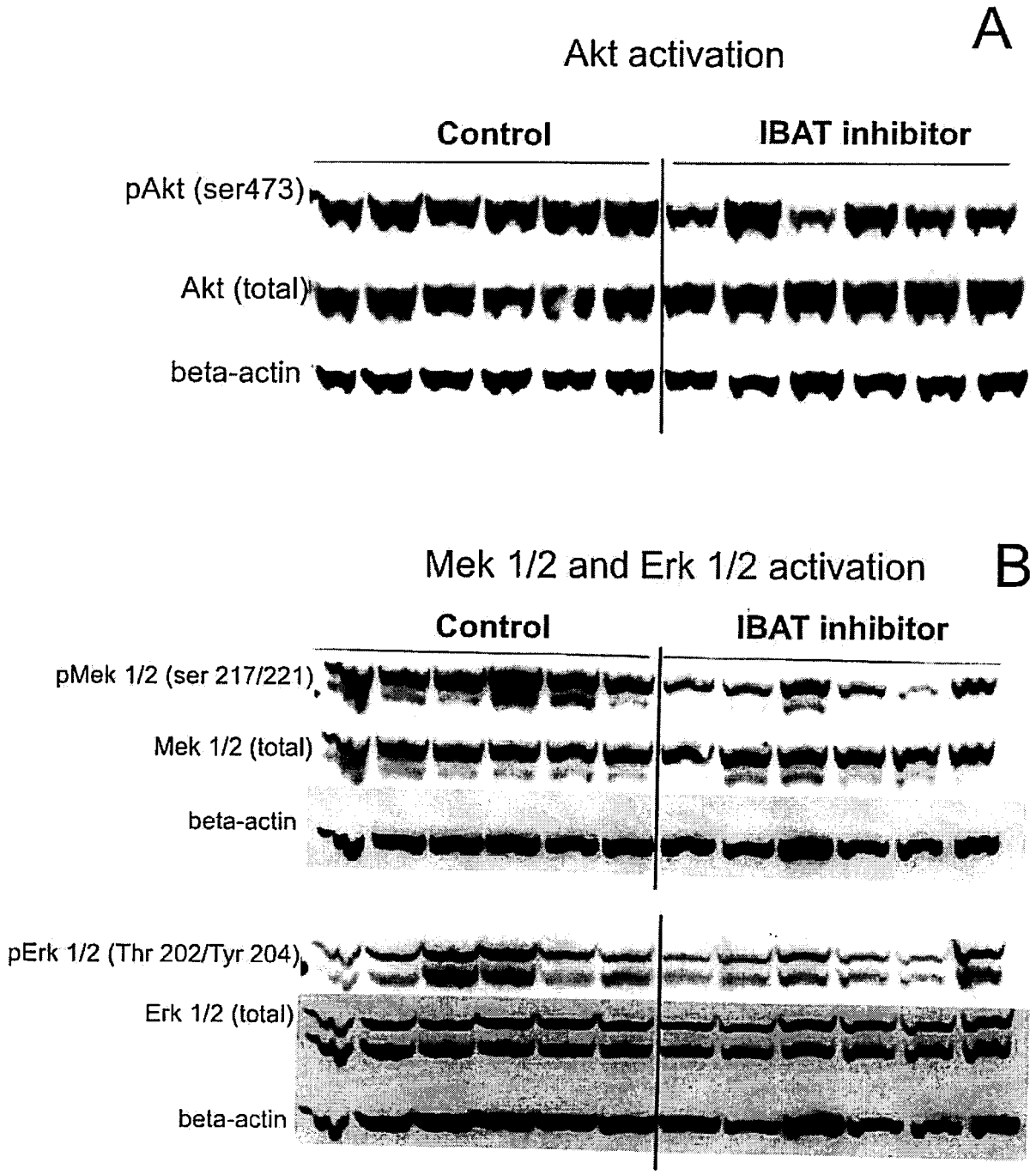

A
Akt activation
Control
IBAT inhibitor
pAkt (ser473)
Akt (total)
beta-actin
B
Mek 1/2 and Erk 1/2 activation
Control
IBAT inhibitor
pMek 1/2 (ser 217/221)
Mek 1/2 (total)
beta-actin
pErk 1/2 (Thr 202/Tyr 204)
Erk 1/2 (total)
beta-actin

Figure 8

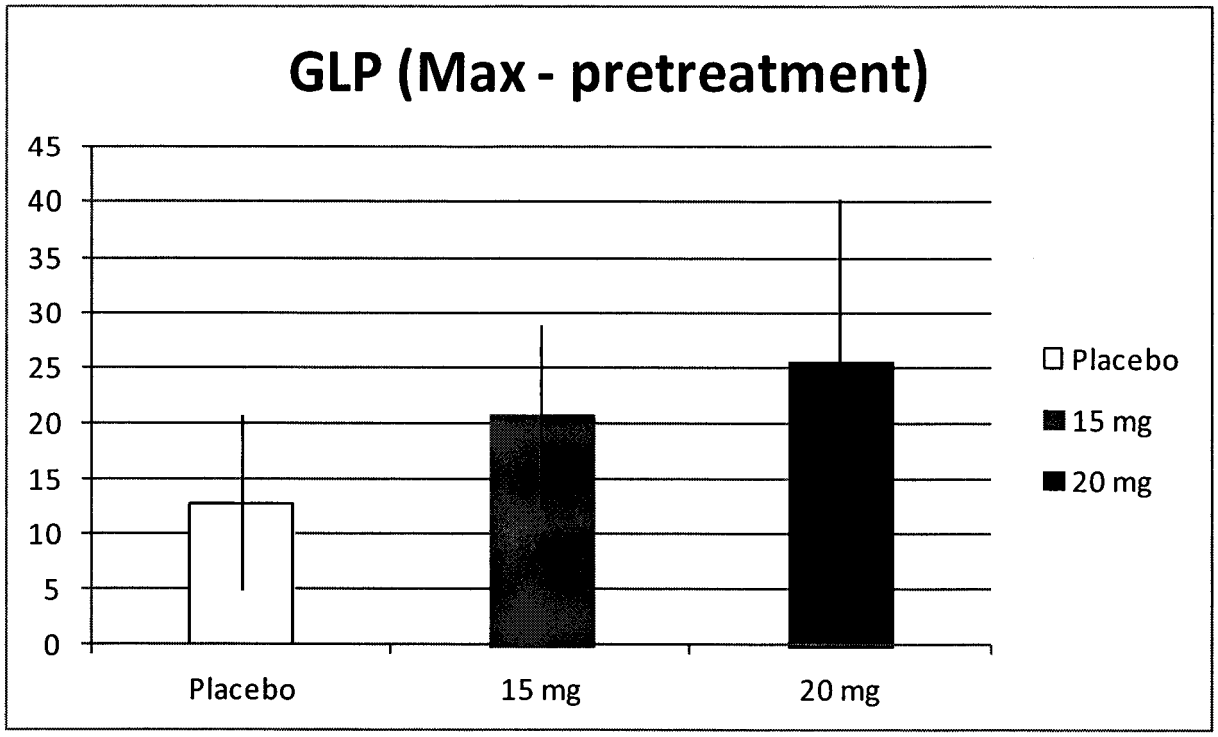
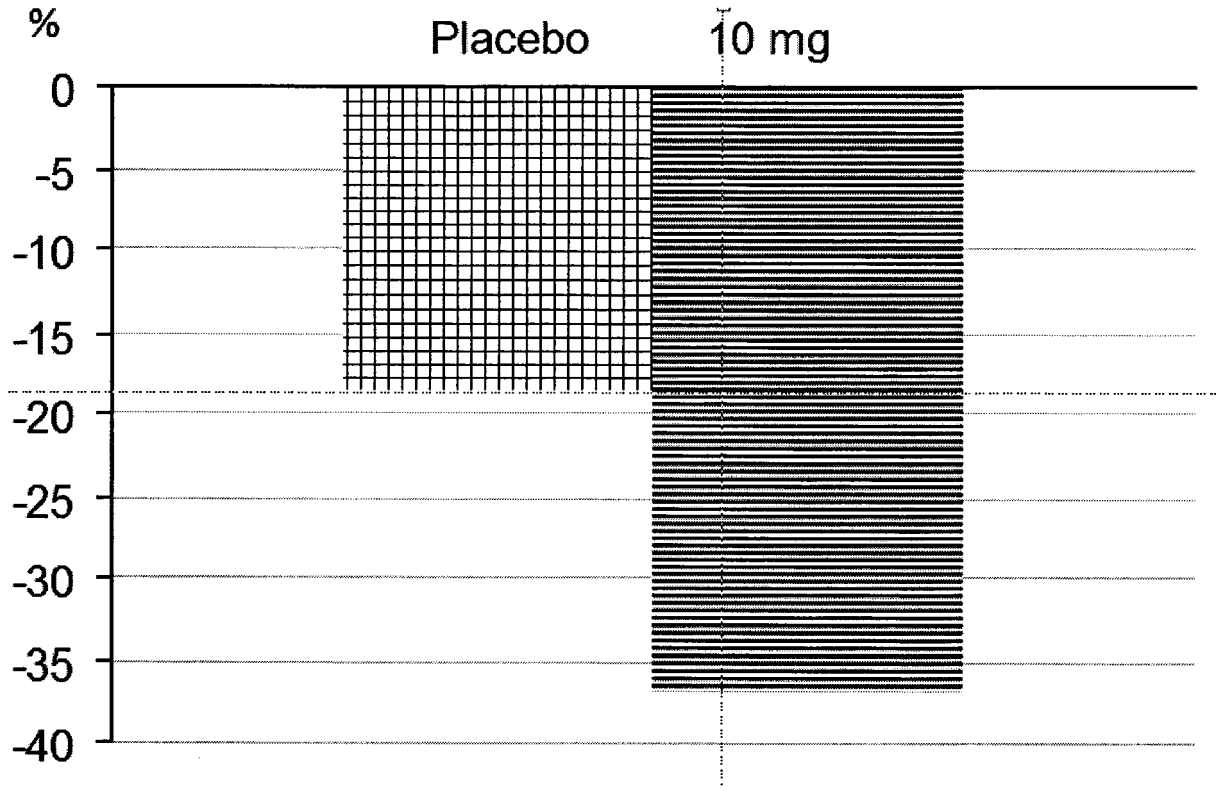

GLP (Max - pretreatment)
45
40
35
30
25
20
15
10
5
0
Placebo
15 mg
20 mg
Placebo
15 mg
20 mg

Figure 9



[All]