A Roadmap for Design of New Therapies For Obesity, the Metabolic Syndrome and Type 2 Diabetes

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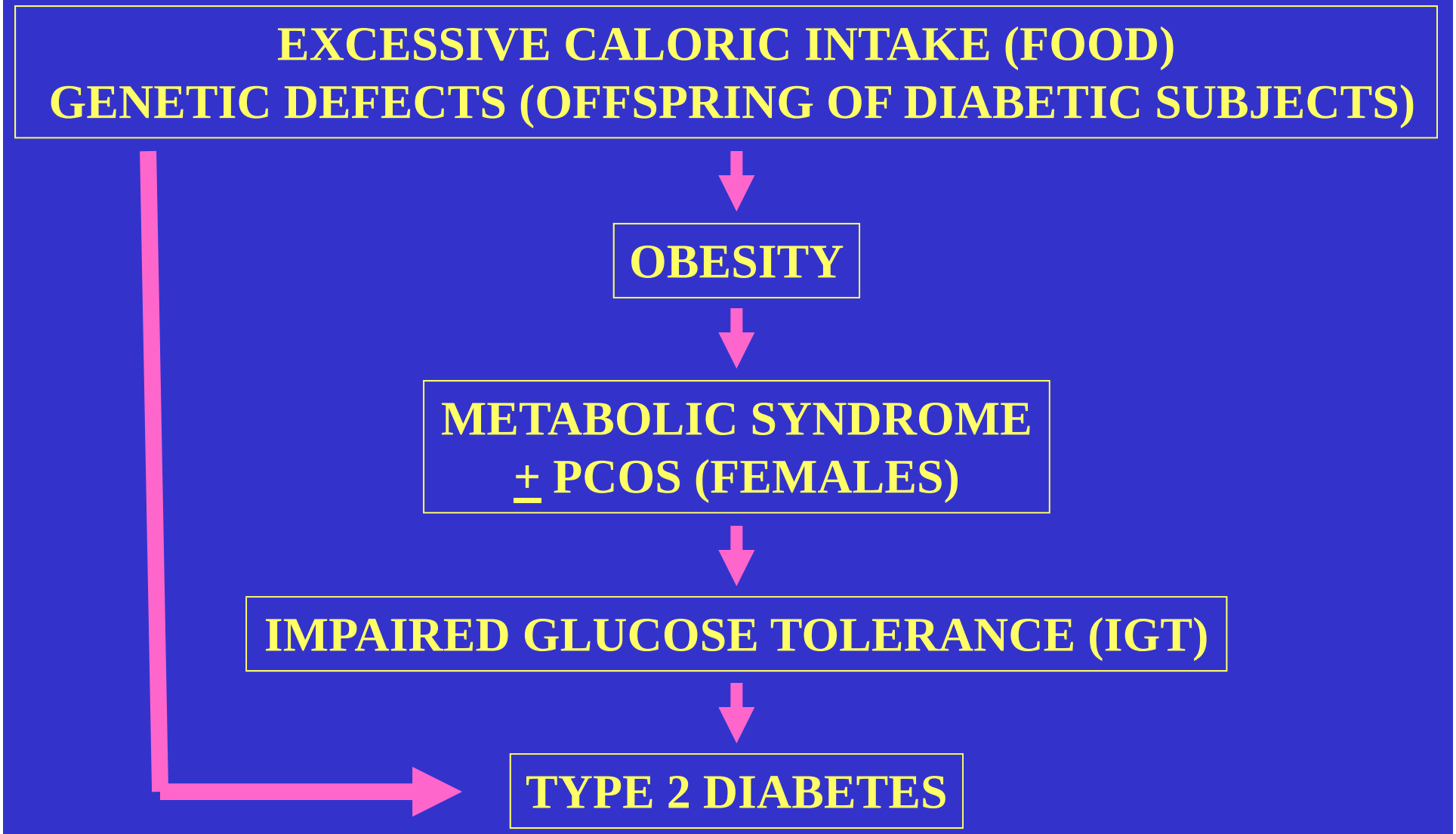
PATHOGENESIS OF TYPE 2 DIABETES



NORMAL BLOOD GLUCOSE LEVELS:

FASTING, <100 or 110 mg%

2 HOURS POST-GLUCOSE (GTT), <140 mg%

IMPAIRED FASTING GLUCOSE :

FASTING, 100 or 110-125 mg%

IMPAIRED GLUCOSE TOLERANCE:

2 HOURS POST-GLUCOSE (GTT), 140-199 mg%

DIABETES MELLITUS:

FASTING, >125 mg%

2 HOURS POST-GLUCOSE (GTT), >199 mg%

METABOLIC SYNDROME OR SYNDROME X (INSULIN RESISTANCE SYNDROME)

- **INSULIN RESISTANCE (? Sine Qua Non)**
- **HYPERINSULINEMIA**
- ***ABDOMINAL OBESITY***
- ***HYPERTENSION***
- ***VLDL-HYPERTRIGLYCERIDEMIA***
- ***LOW HDL CHOLESTEROL***
- ***GLUCOSE INTOLERANCE***
- **HYPERURICEMIA (+)**
- **ACANTHOSIS NIGRICANS**
- **POLYCYSTIC OVARY SYNDROME (+)**
- **PRECURSOR TO TYPE 2 DIABETES (+)**
- **CARDIOVASCULAR DISEASE**
- **ALZHEIMER'S DISEASE**

HYPERINSULINEMIA

IMPAIRED GLUCOSE TOLERANCE

IMPAIRED GLUCOSE TRANSPORT IN MUSCLE

CALORIC EXCESS

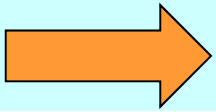
INCREASED GLUCOSE OUTPUT IN LIVER

IMPAIRED GLUCOSE TOLERANCE

HYPERINSULINEMIA

IMPAIRED GLUCOSE TRANSPORT IN MUSCLE

INSULIN RESISTANCE, HYPERINSULINEMIA



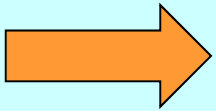
OBESITY, MS, T2DM

INCREASED GLUCOSE OUTPUT IN LIVER


CALORIC EXCESS VIA LIVER FACTORS
IMPAIRED GLUCOSE TRANSPORT
IN MUSCLE
INSULIN RESISTANCE, HYPERINSULINEMIA
OBESITY, MS, T2DM
INCREASED GLUCOSE OUTPUT
IN LIVER
CALORIC EXCESS

IMPAIRED INSULIN ACTION IN MUSCLE

INSULIN RESISTANCE, HYPERINSULINEMIA

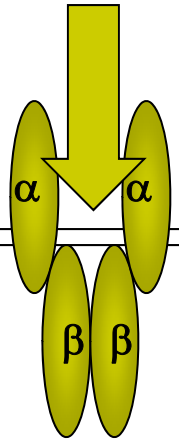


OBESITY, MS, T2DM

INCREASED HEPATIC GLUCOSE OUTPUT

INSULIN RESISTANCE in MUSCLE

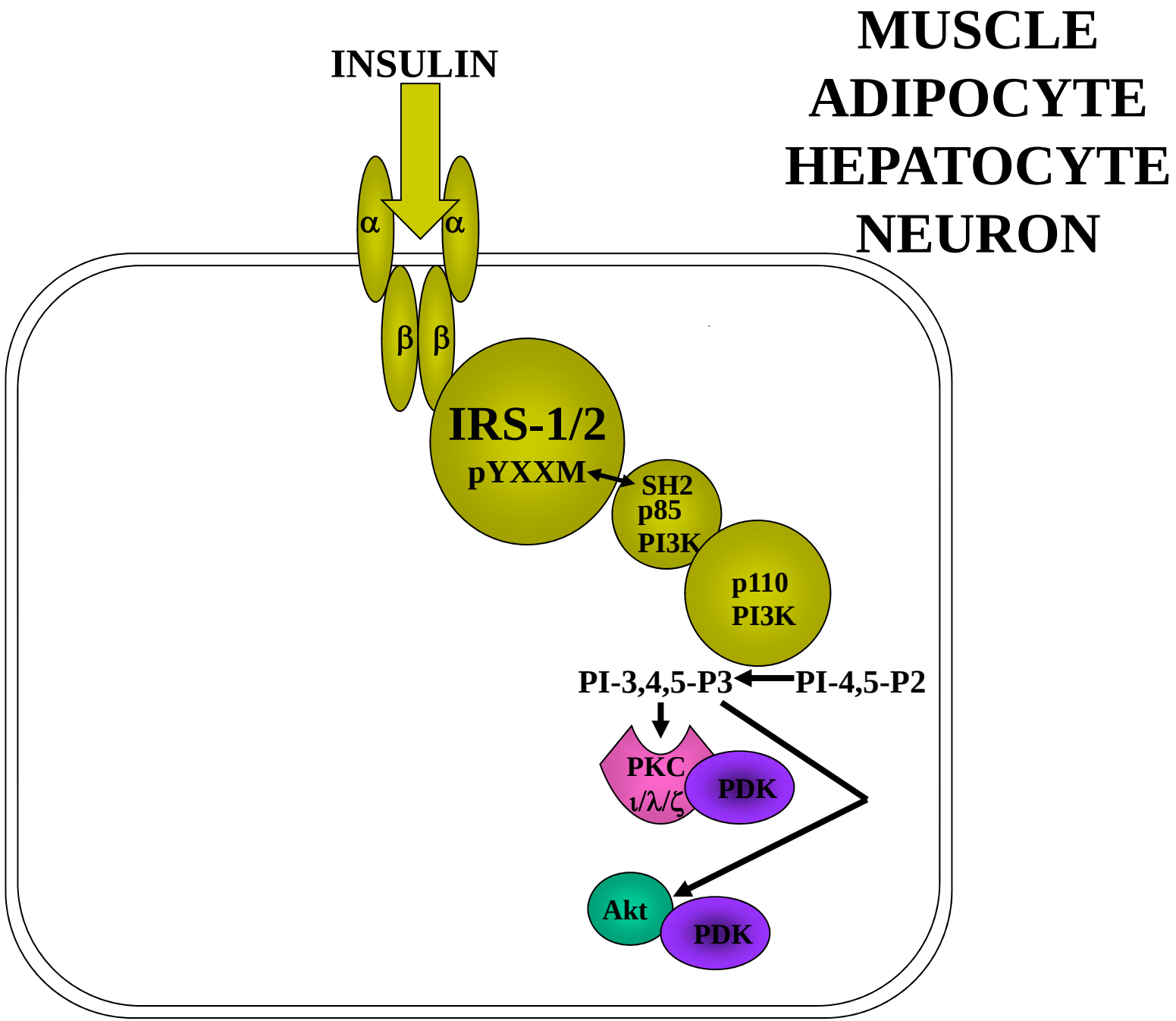
INSULIN



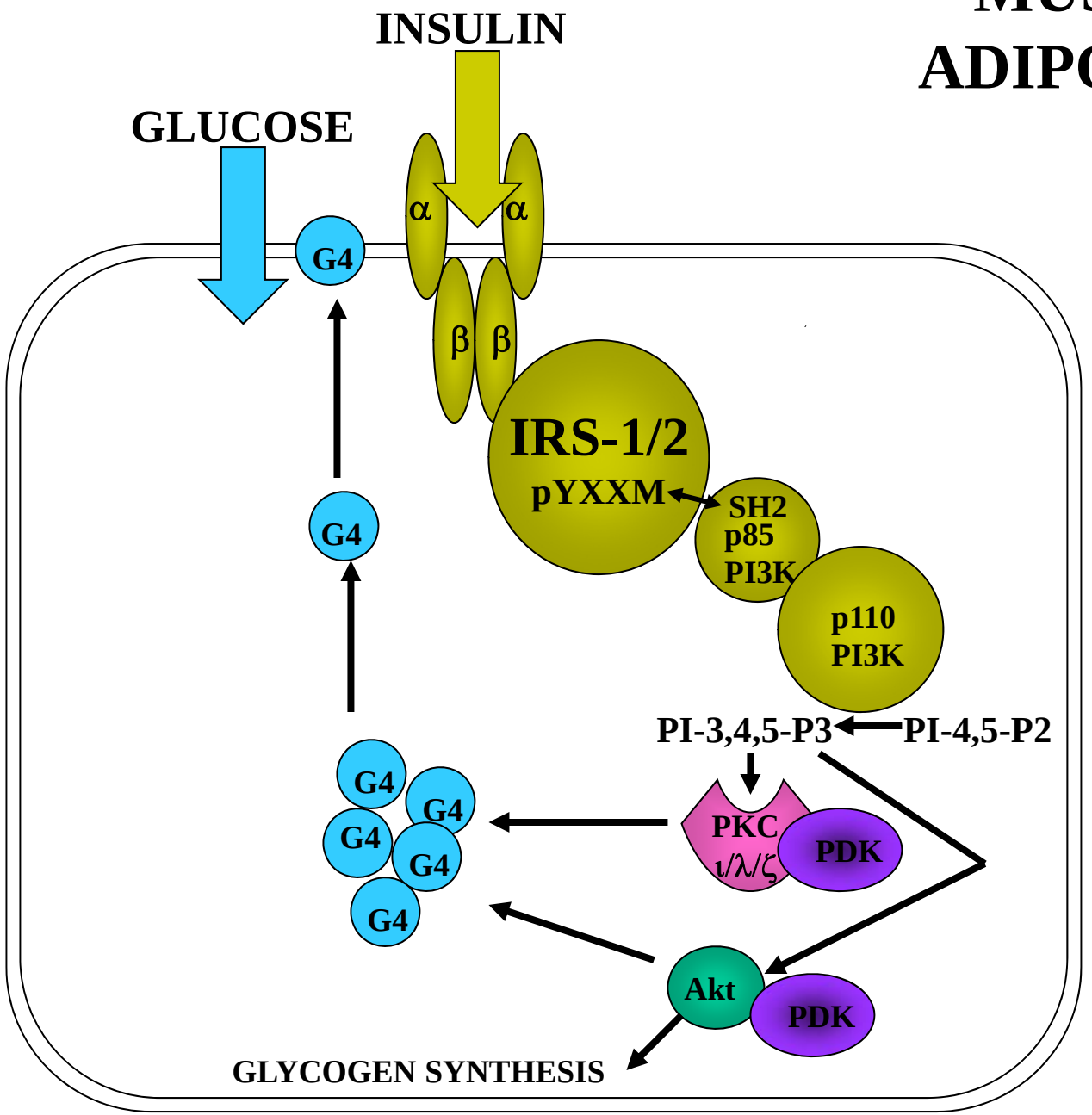
MUSCLE
ADIPOCYTE
HEPATOCYTE
NEURON

SOMETHING HAPPENS

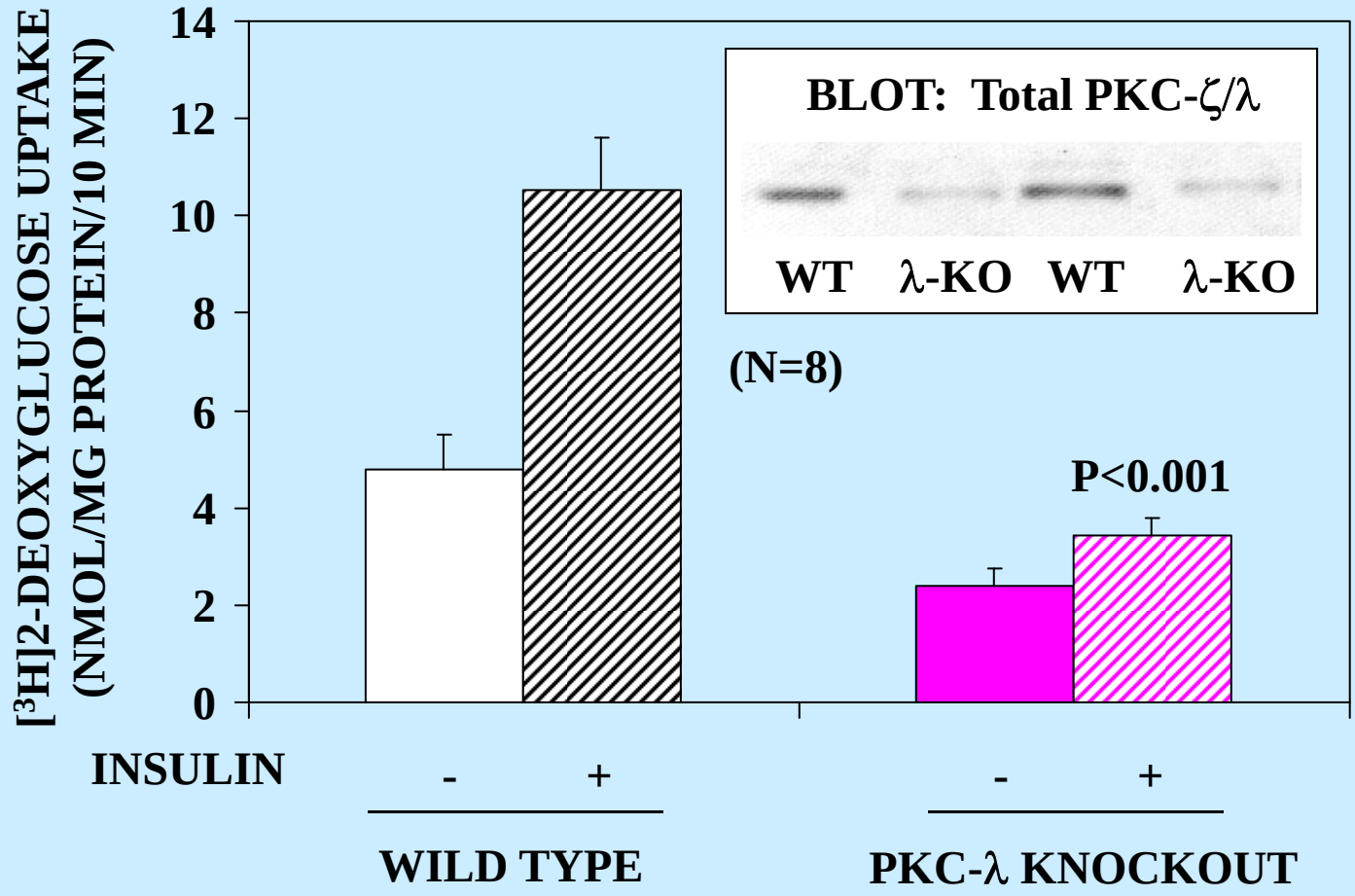
1980


MUSCLE
ADIPOCYTE
HEPATOCYTE
NEURON
INSULIN
α
α
β
β
IRS-1/2
pYXXM
SH2
p85
PI3K
p110
PI3K
PI-3,4,5-P3
PI-4,5-P2
PKC
ι/λ/ζ
PDK
Akt
PDK

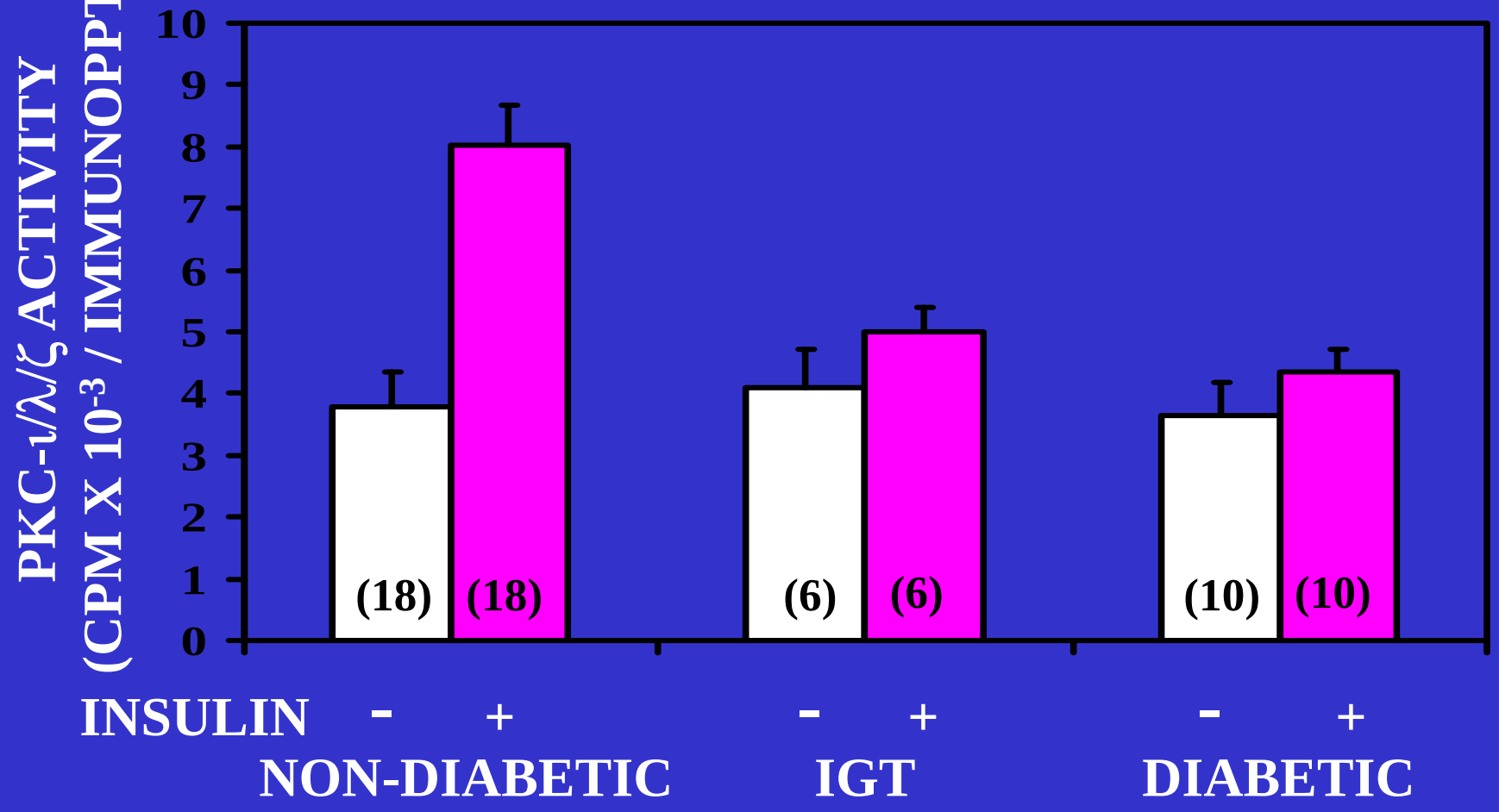
MUSCLE
ADIPOCYTE



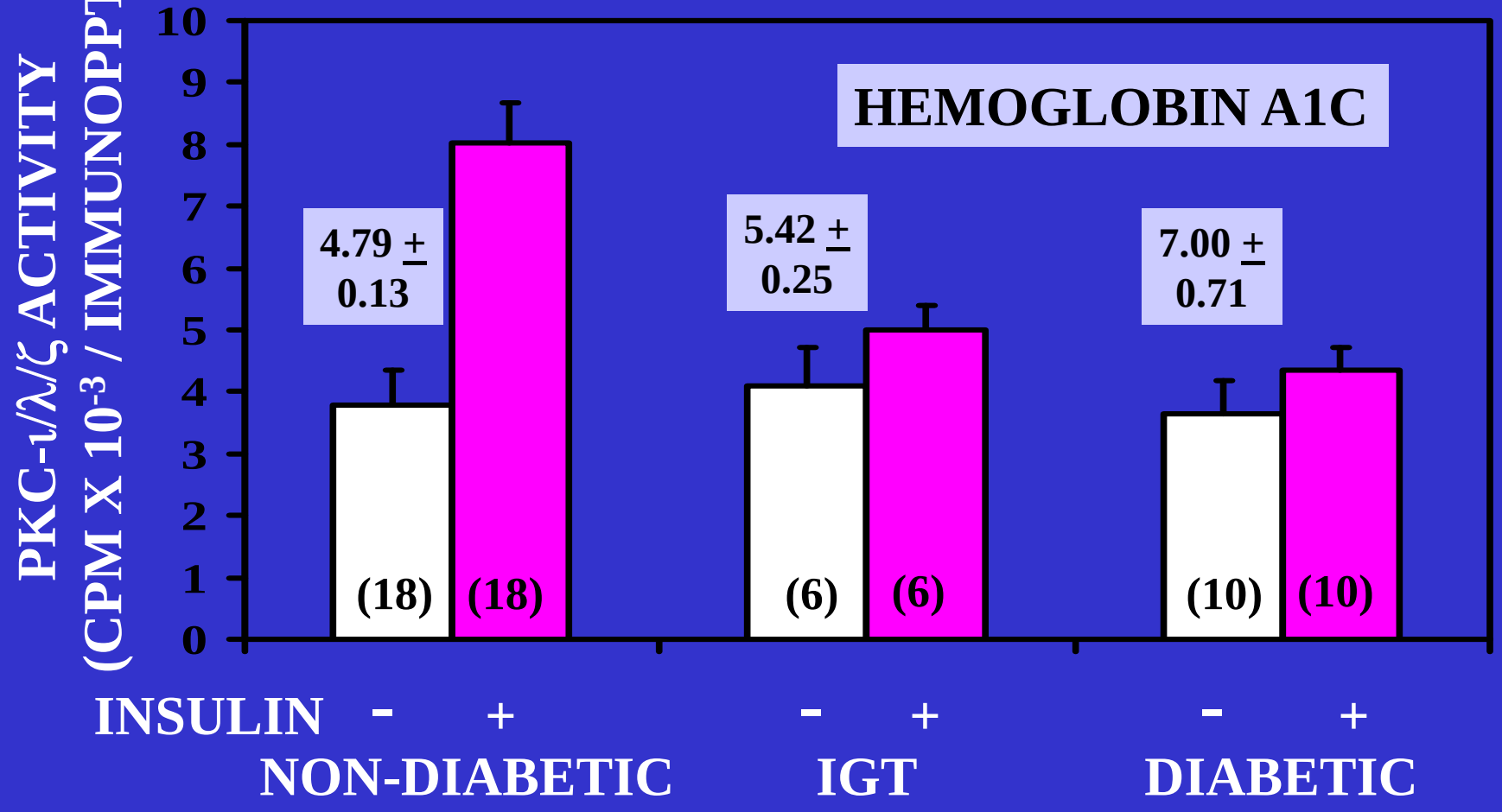
KNOCKOUT OF PKC-λ DIMINISHES INSULIN-STIMULATED GLUCOSE TRANSPORT IN MOUSE VASTUS LATERALIS MUSCLE



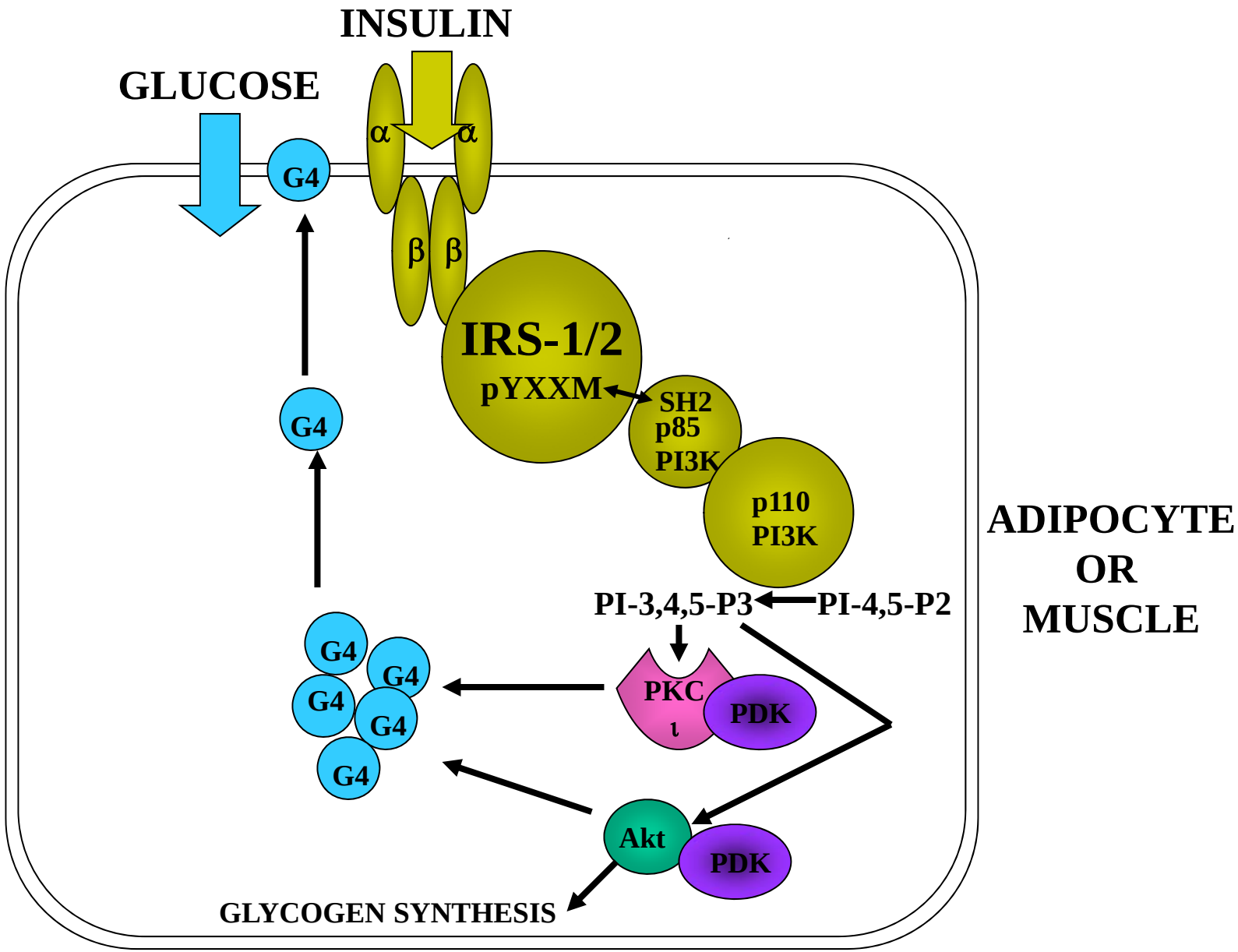
DEFECTIVE ACTIVATION OF PKC-ι/λ/ζ BY INSULIN IN MUSCLES OF HUMANS WITH IMPAIRED GLUCOSE TOLERANCE OR TYPE 2 DIABETES



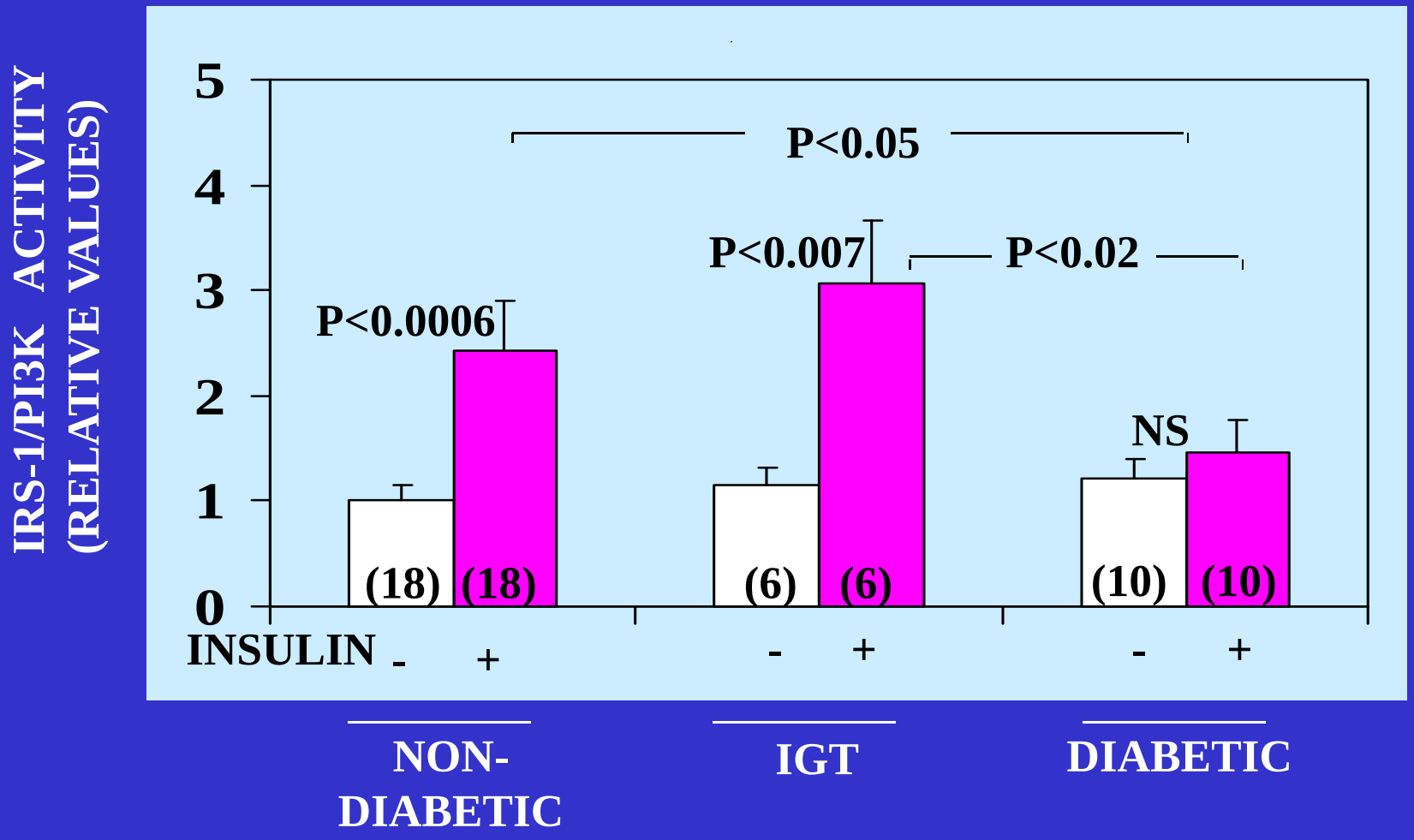
HEMOGLOBIN A1C LEVELS IN OUR PATIENT POPULATION OF SUBJECTS WITH IMPAIRED GLUCOSE TOLERANCE AND TYPE 2 DIABETES



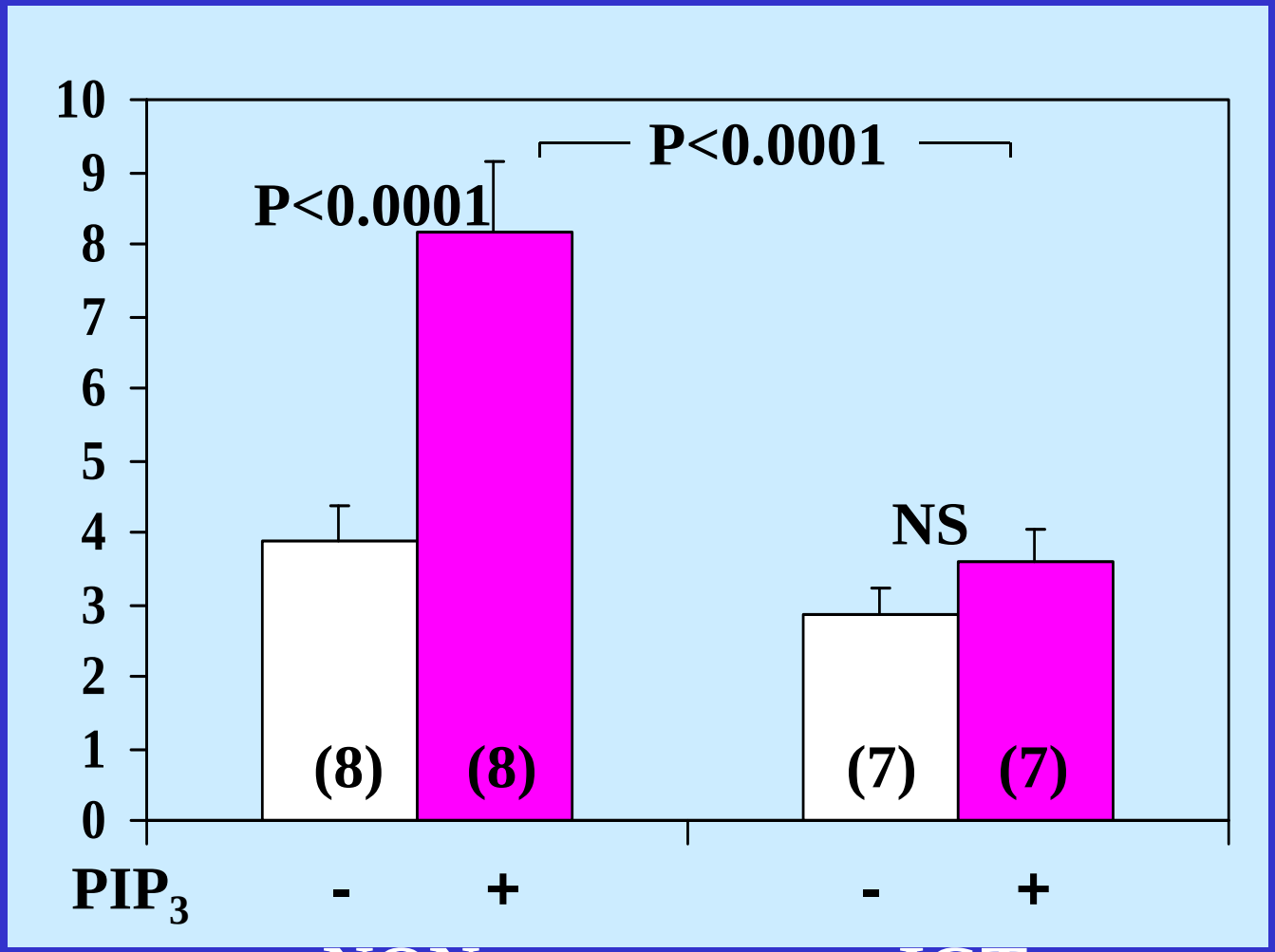
WHAT IS THE MECHANISM FOR POOR PKC-ζ ACTIVATION?



IRS-1-DEPENDENT PI 3-KINASE ACTIVATION IS DEFECTIVE IN DIABETES, BUT NOT IN IGT

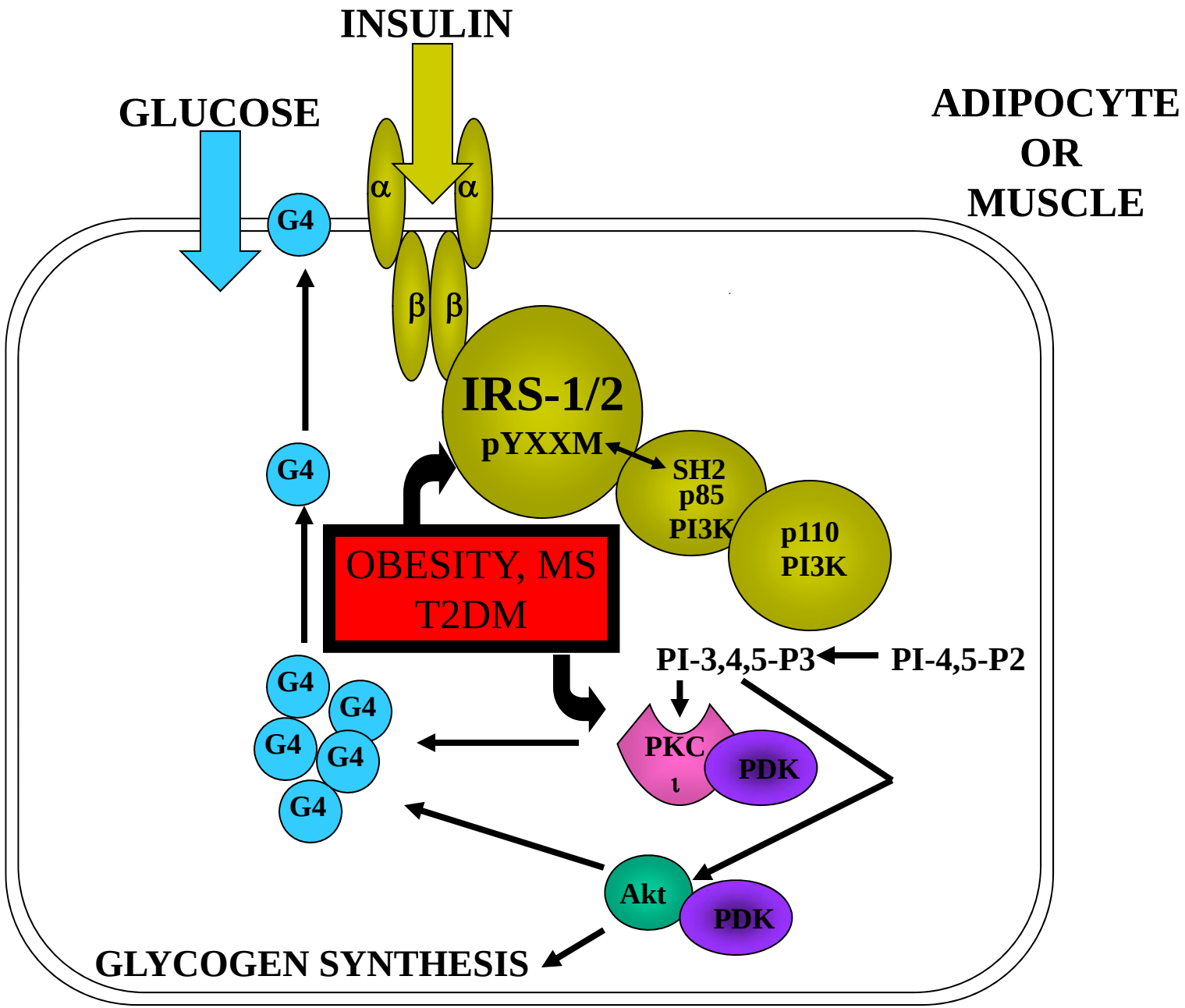


POOR ACTIVATION OF PKC-ζ BY PIP_3 IN IGT AND DIABETES

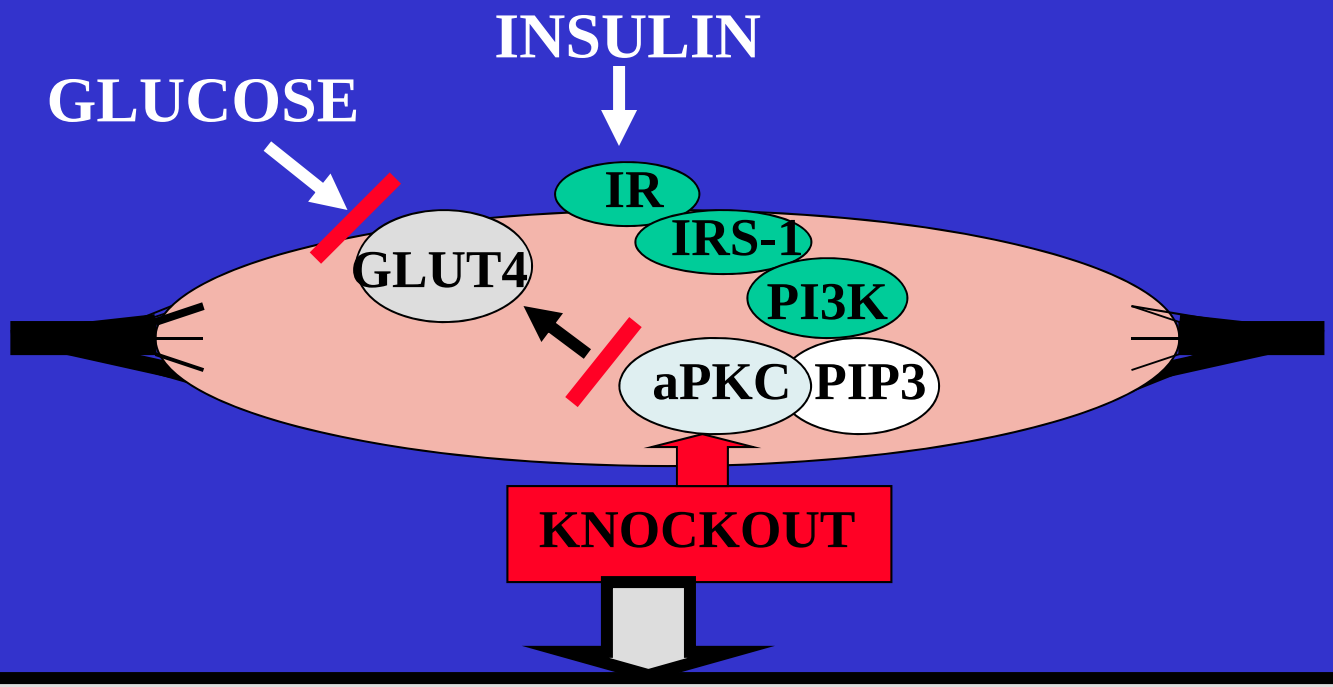


LEVELS OF PKC-ι ARE DECREASED IN MUSCLES OF HUMANS WHO HAVE IGT AND TYPE 2 DIABETES

ND = NON-DIABETIC
DM = DIABETES MELLITUS


INSULIN
GLUCOSE
ADIPOCYTE
OR
MUSCLE
α
α
β
β
G4
G4
G4
G4
G4
G4
G4
IRS-1/2
pYXXM
SH2
p85
PI3K
p110
PI3K
OBESITY, MS
T2DM
PI-3,4,5-P3
PI-4,5-P2
PKC
ι
PDK
Akt
PDK
GLYCOGEN SYNTHESIS

MUSCLE-SPECIFIC KNOCKOUT OF ATYPICAL PKC-λ/ι



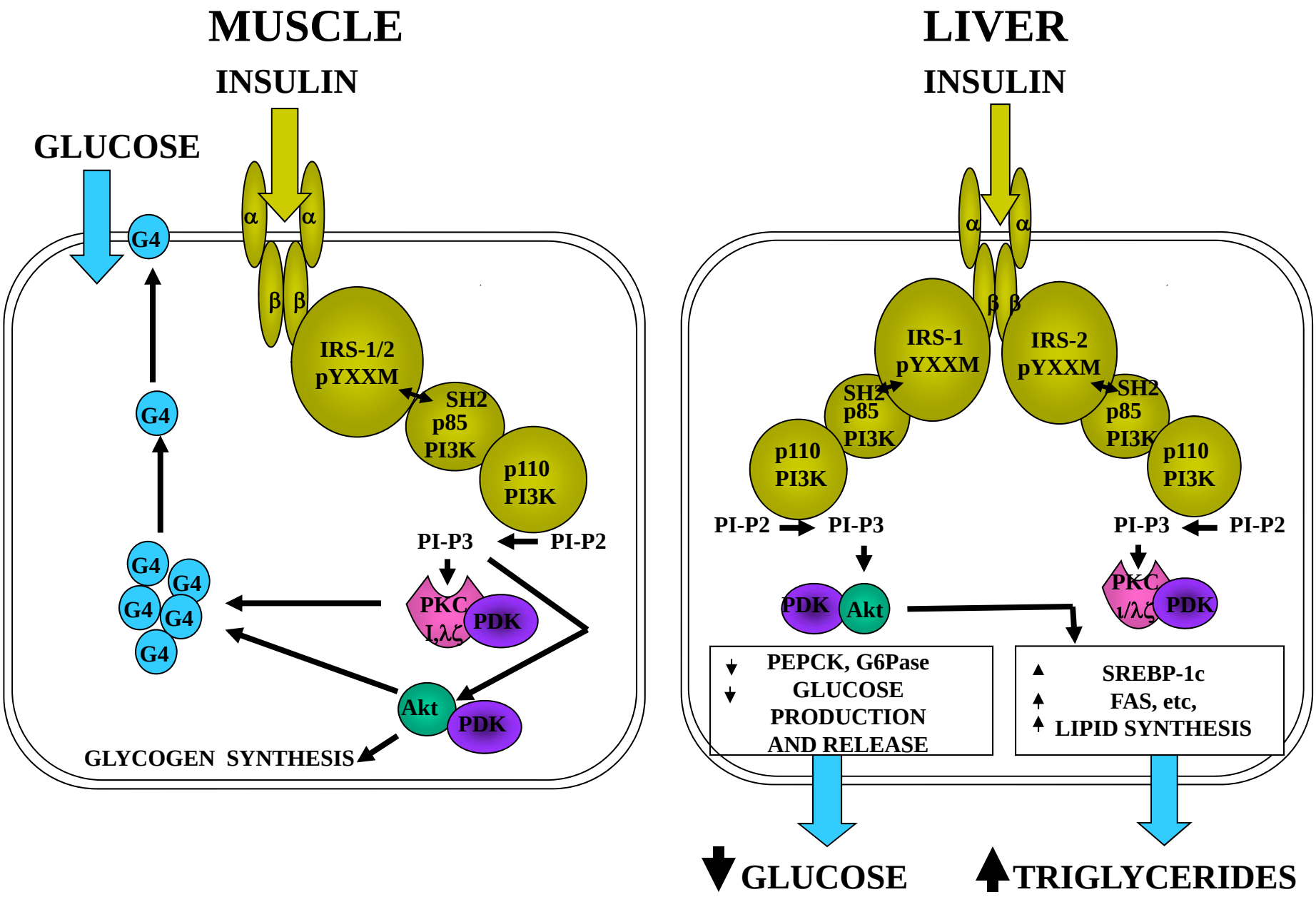
- IGT and INSULIN RESISTANCE
- HYPERINSULINEMIA
- GLUCOSE INTOLERANCE
- ABDOMINAL OBESITY
- HYPERLIPIDEMIA

(↑TG, ↑FFA, ↑LDL-CHOL, ↓HDL-CHOL)

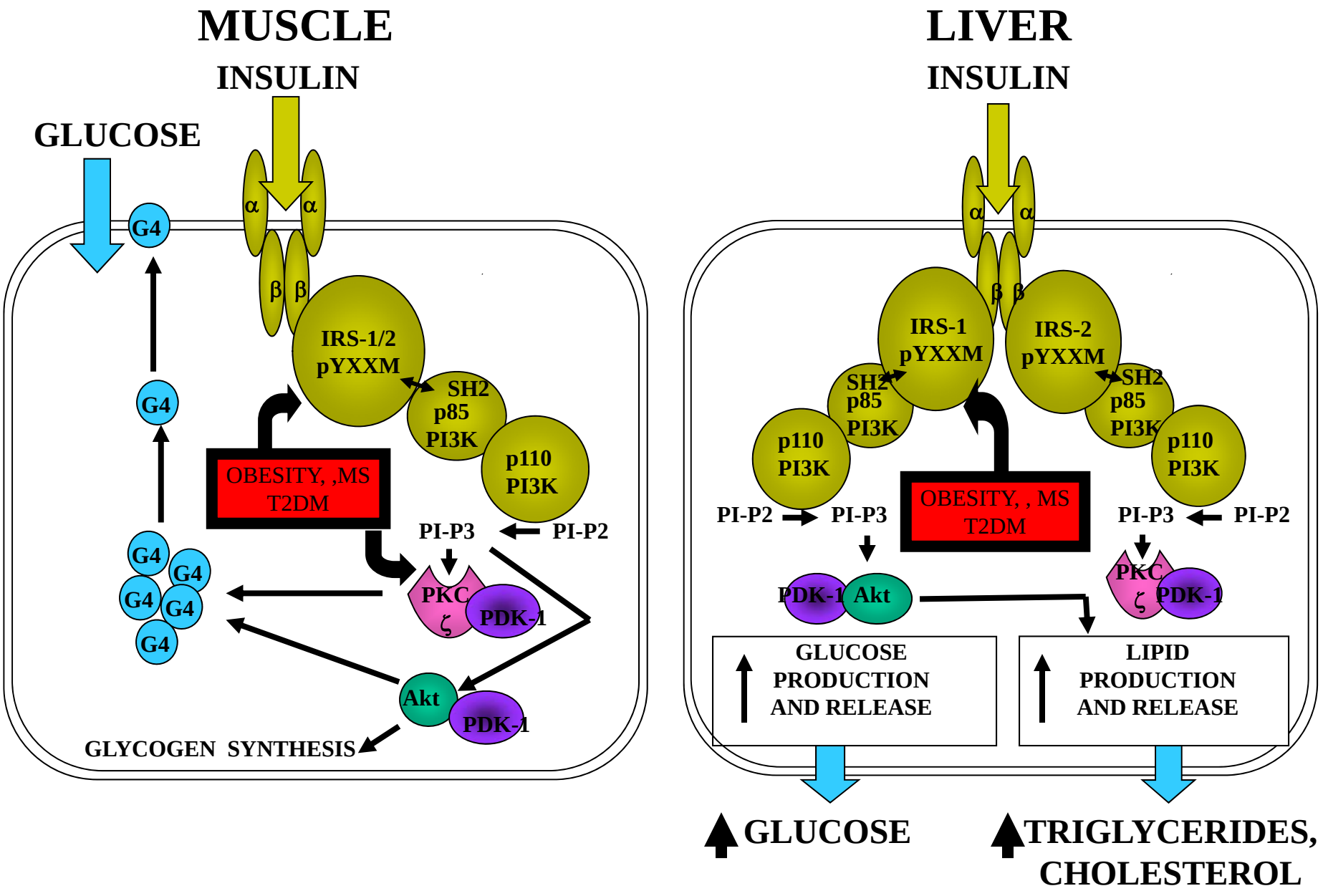
- HEPATOSTEATOSIS

INSULIN RESISTANCE in LIVER

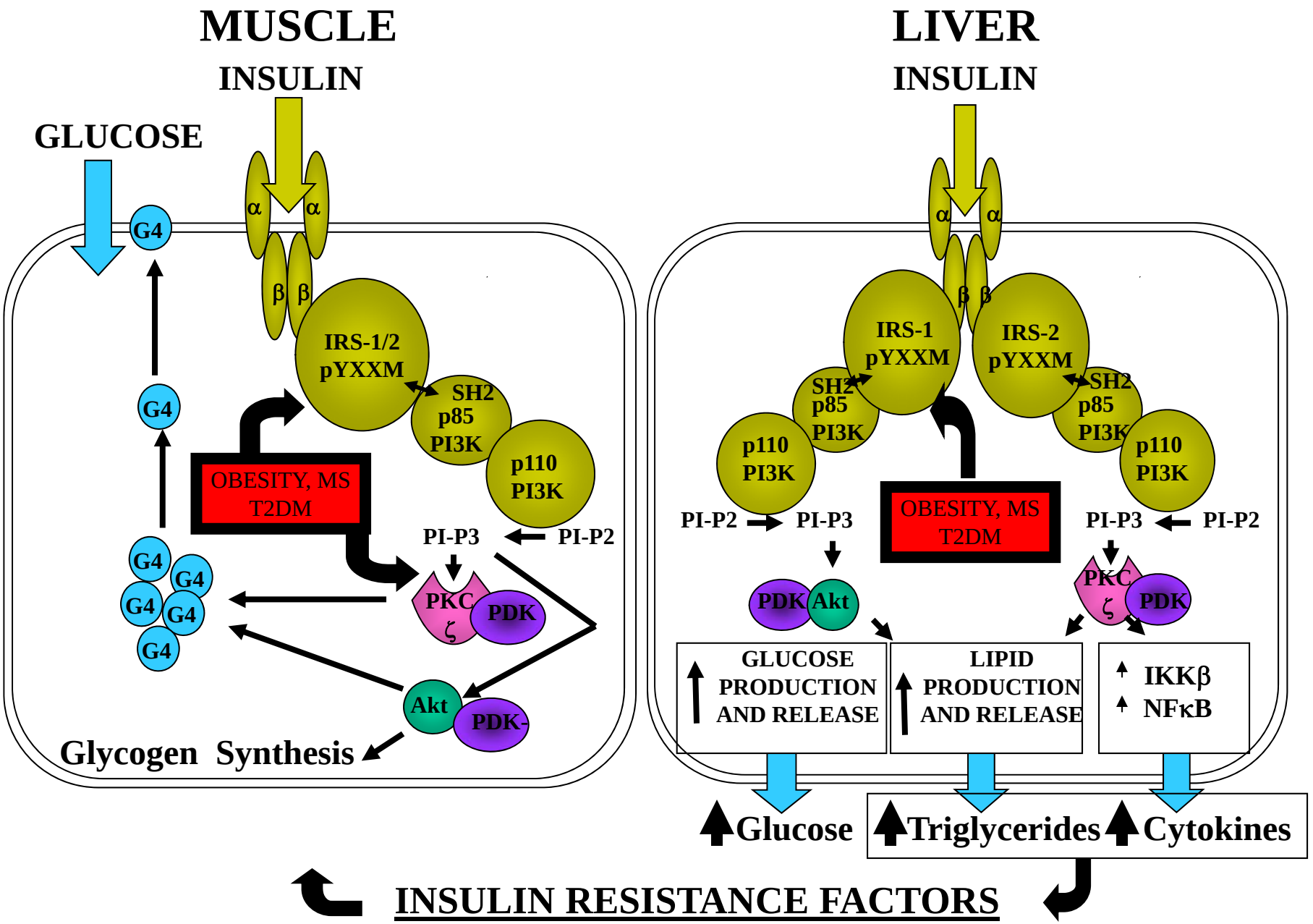
NORMAL CONDITIONS



INSULIN-RESISTANT OBESITY, MS, T2DM



INSULIN-RESISTANT OBESITY, MS, T2DM



“PREVENTION” OF DIABETES
(Diminished Onset Over 5 Yrs in Pre-Diabetics)

DIET PLUS EXERCISE 55%

METFORMIN 45%

TZD 70%

Continuation of A Roadmap for Design of New Therapies For Obesity, the Metabolic Syndrome and Type 2 Diabetes

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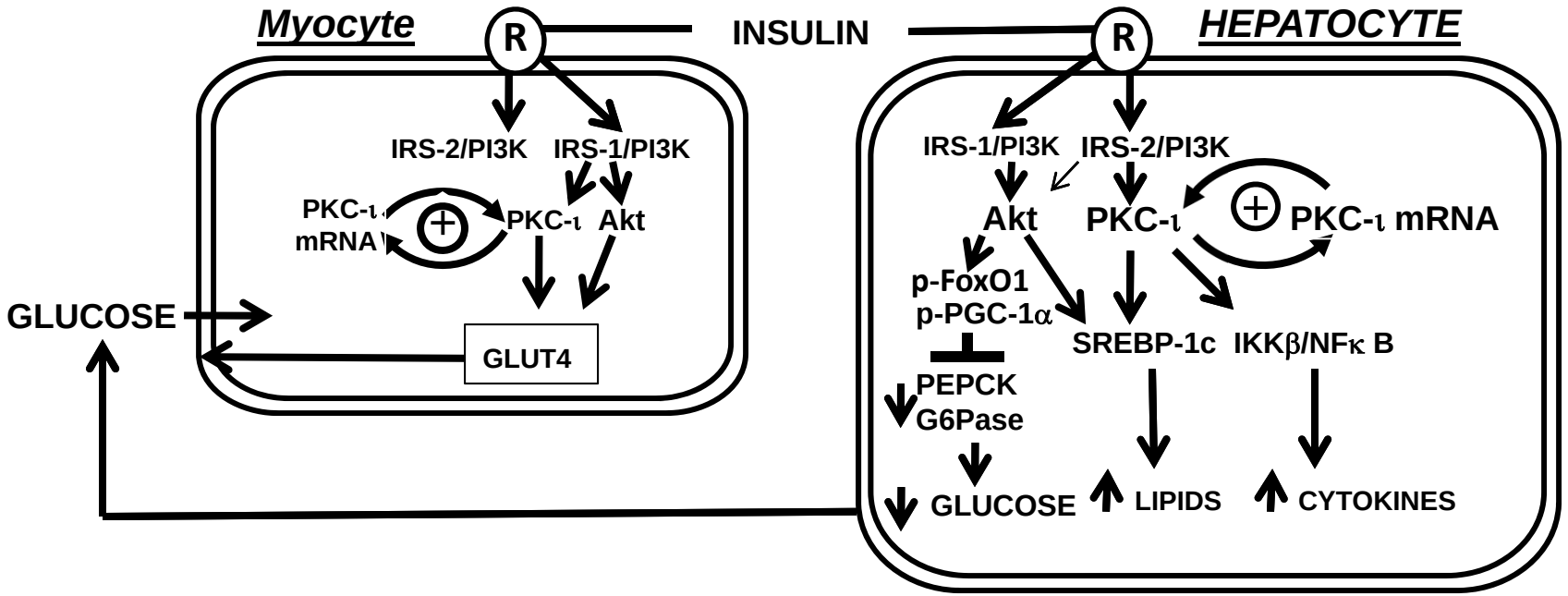
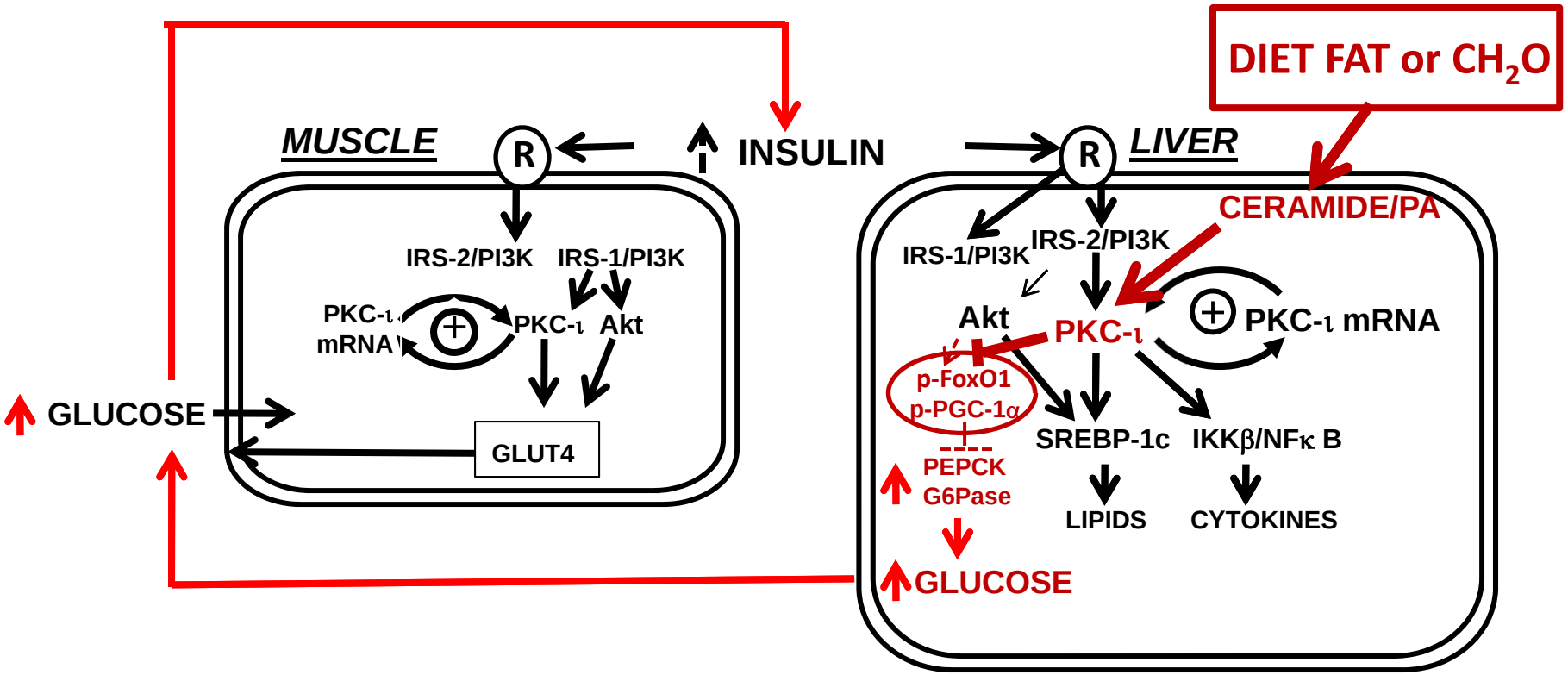
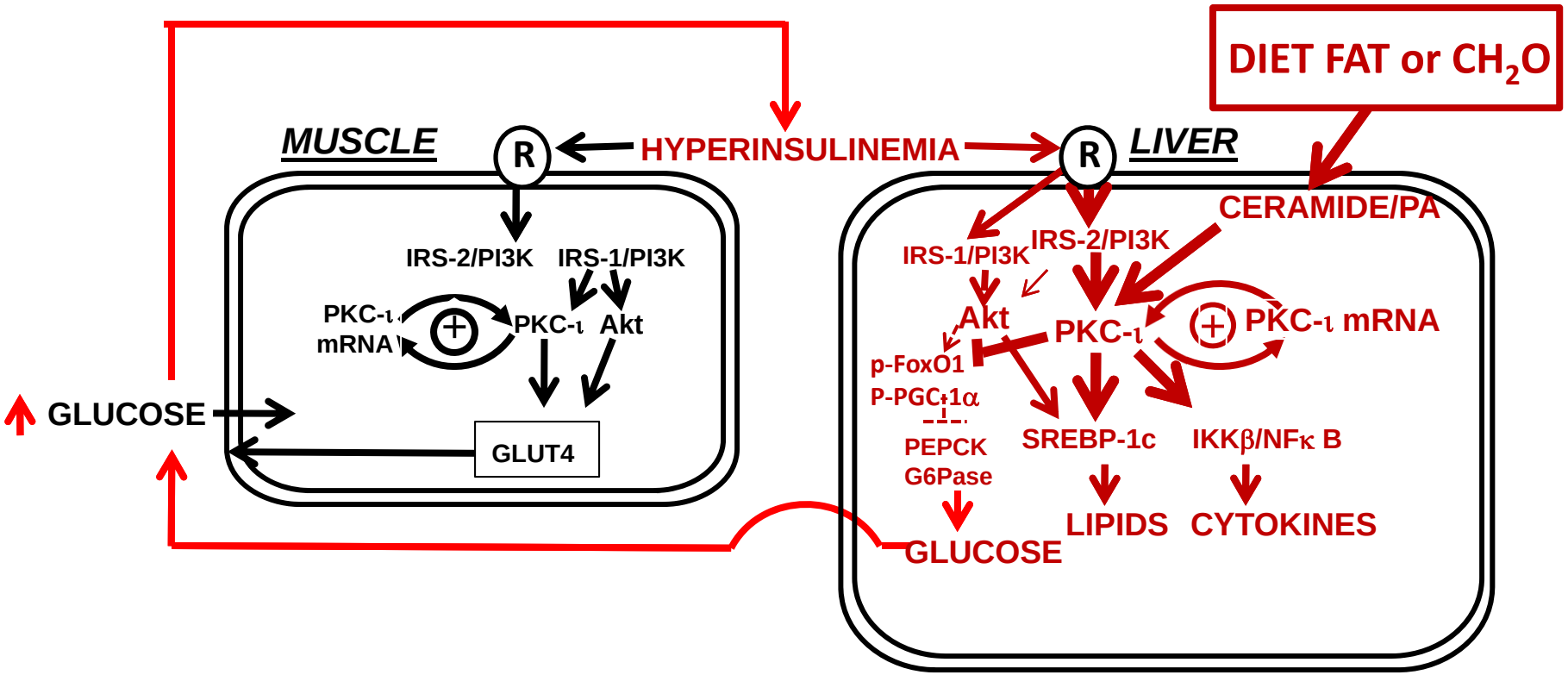
How Insulin Works in Humans (with PKC-ι)



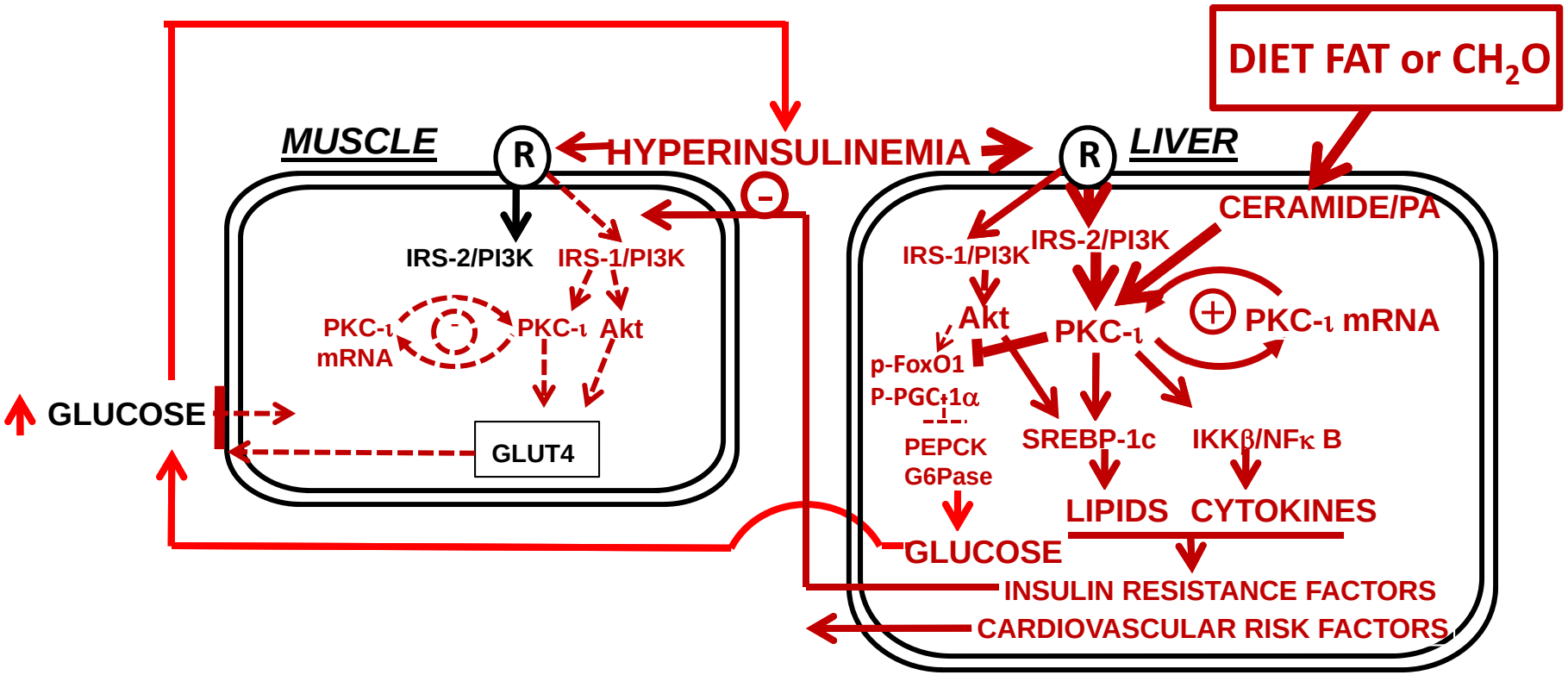
Why Insulin Doesn't Work in DIO/MS/T2DM (Phase 1)



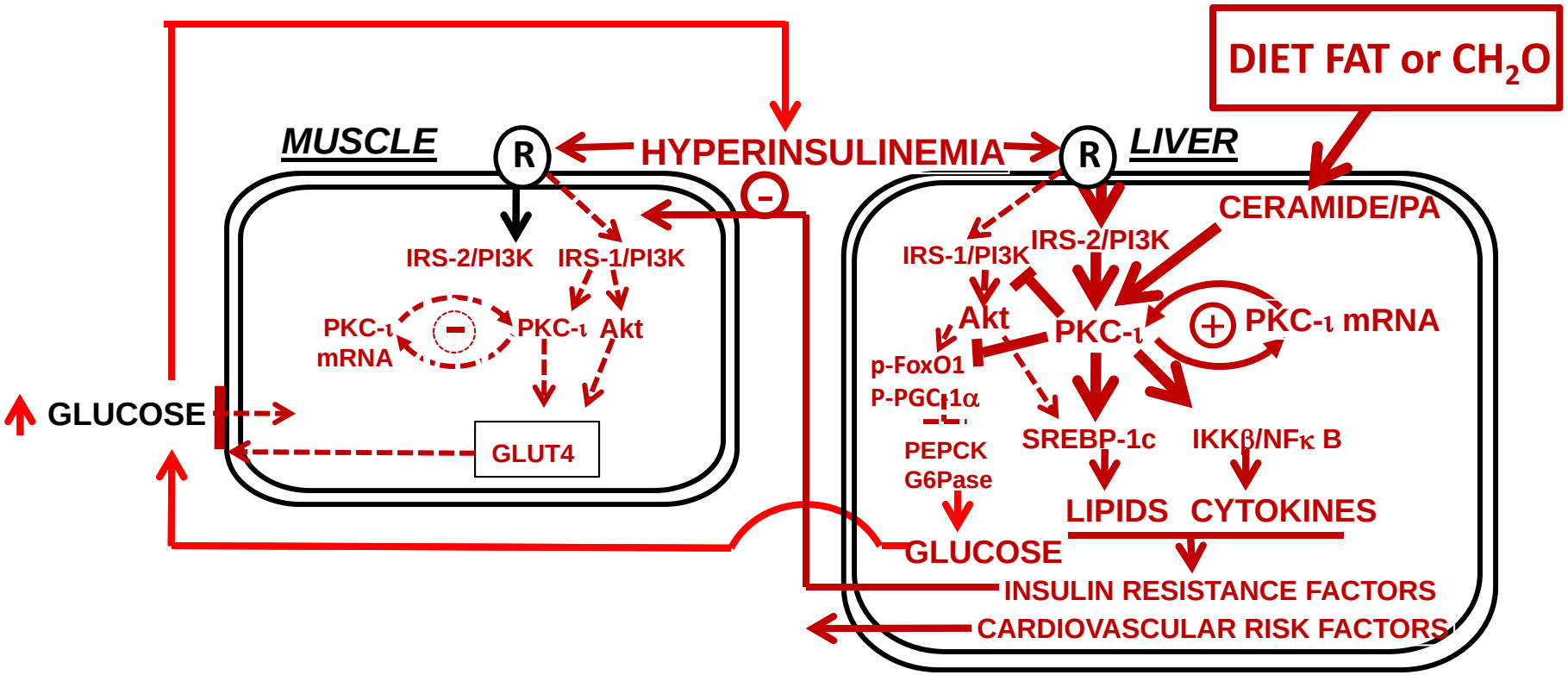
Why Insulin Doesn't Work in DIO/MS/T2DM (Phase 2)



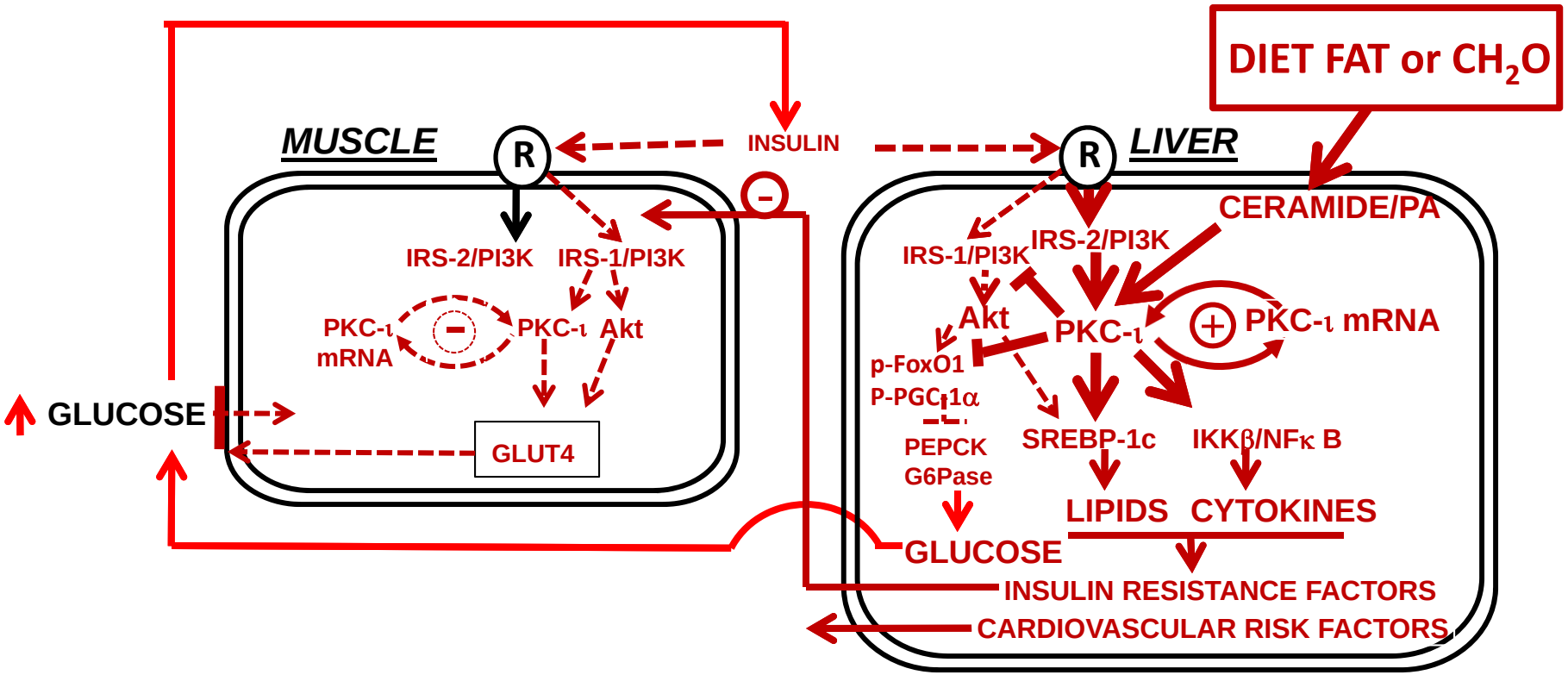
Why Insulin Doesn't Work (Phase 3)



Why Insulin Doesn't Work (Phase 4)

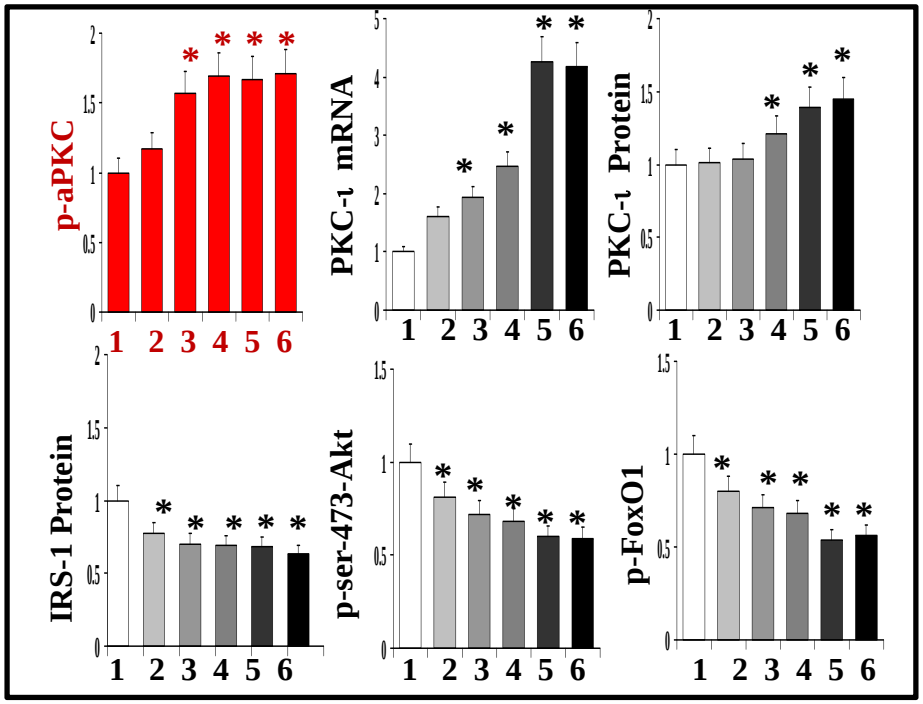


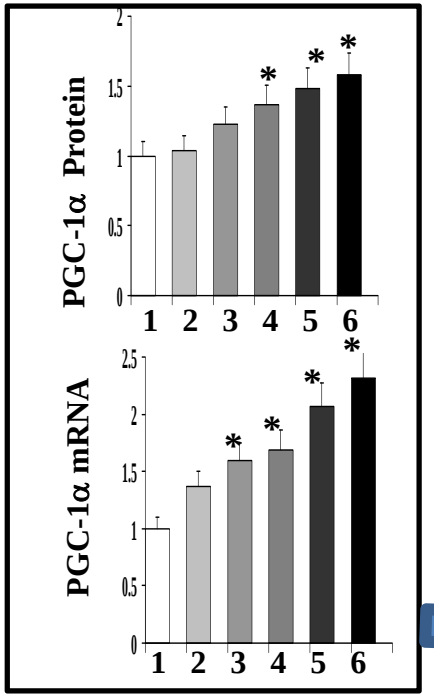
Insulin Doesn't Work *And is Diminished* (Phase 5)

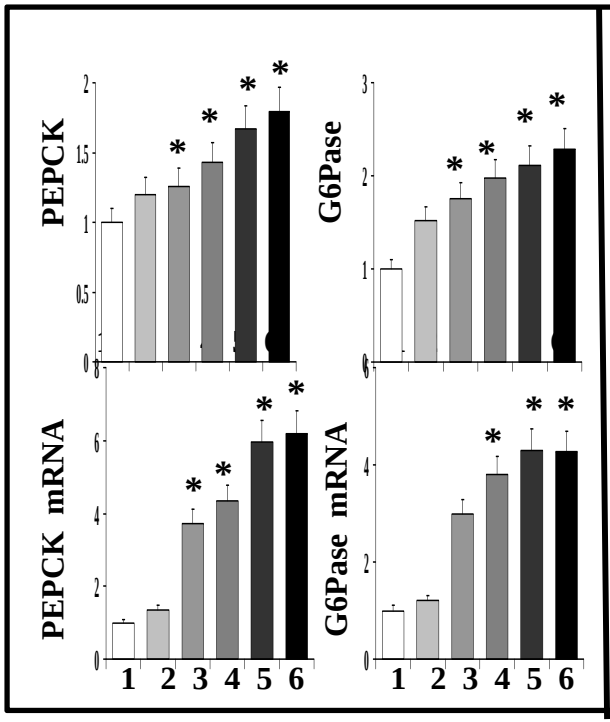


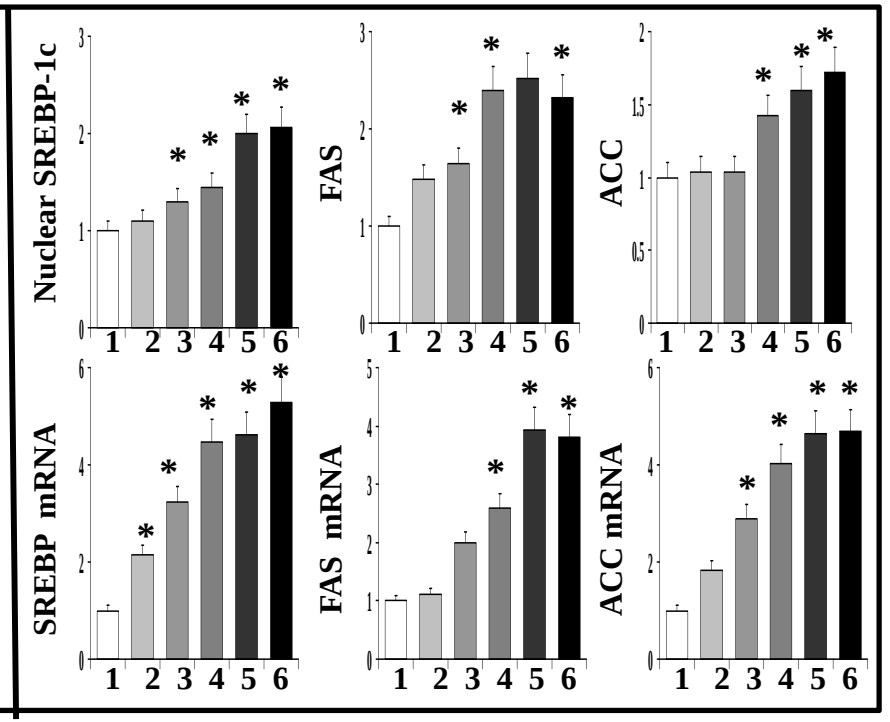
BMI GROUP

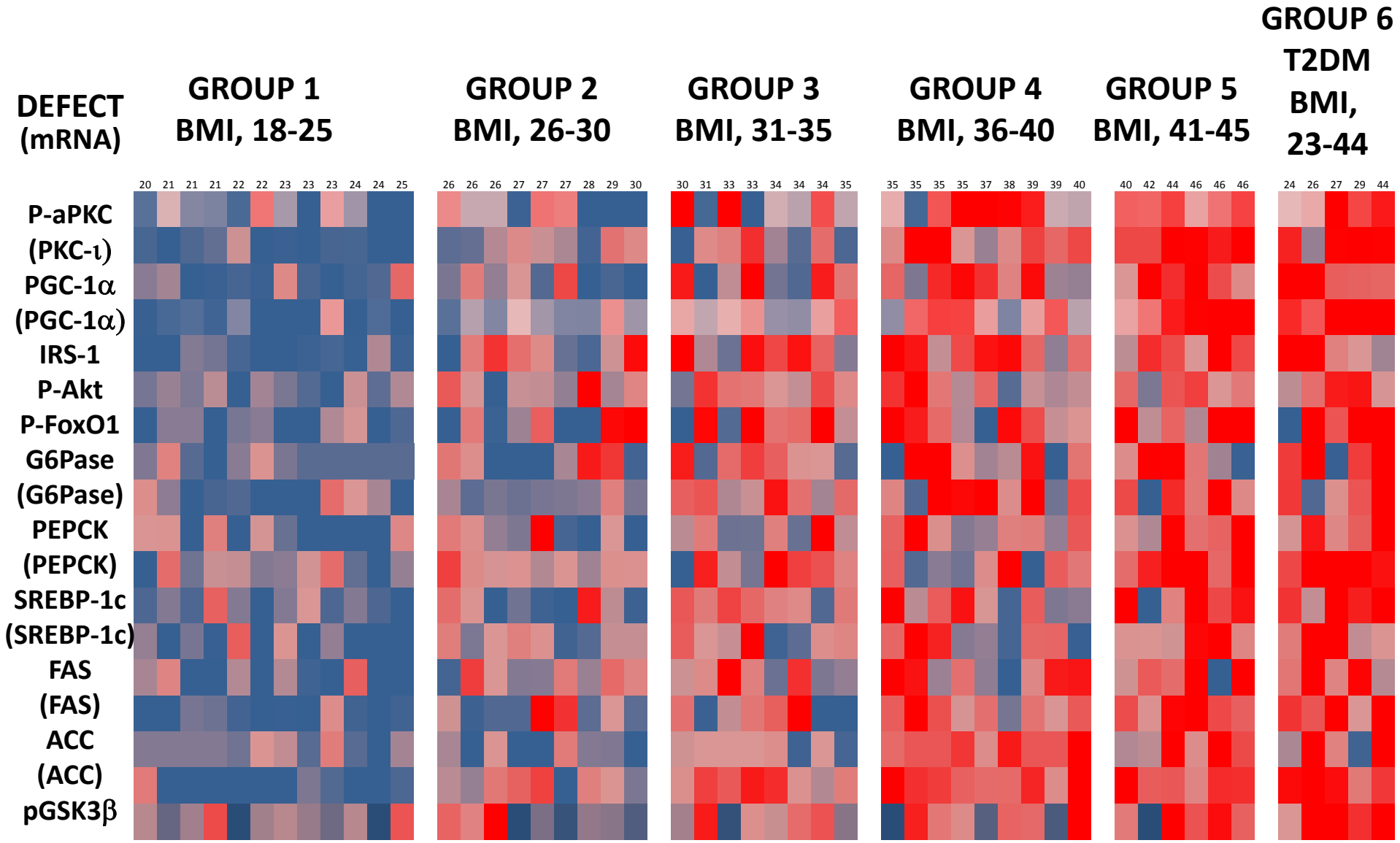
1. 26-30
3. 31-35
4. 35-40
5. 40-45
6. T2D, 23-44



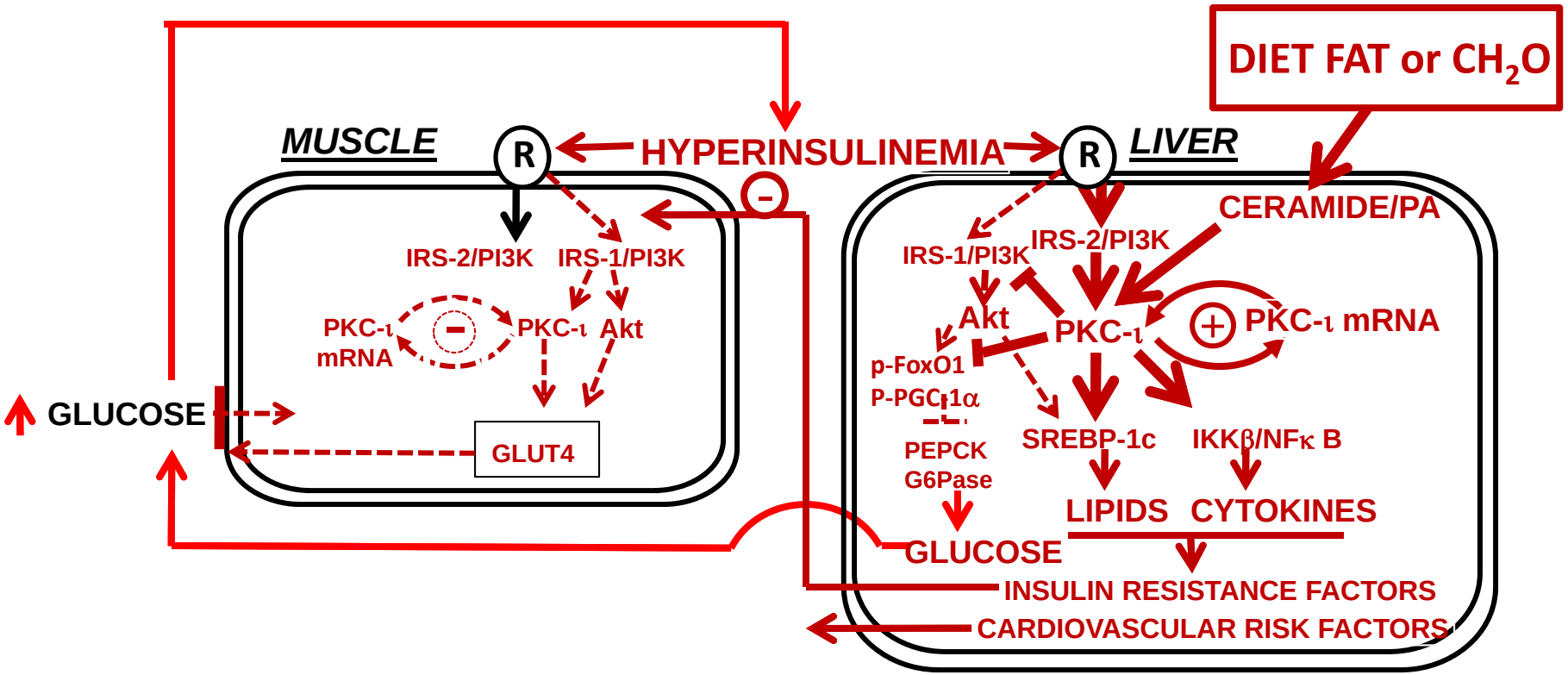




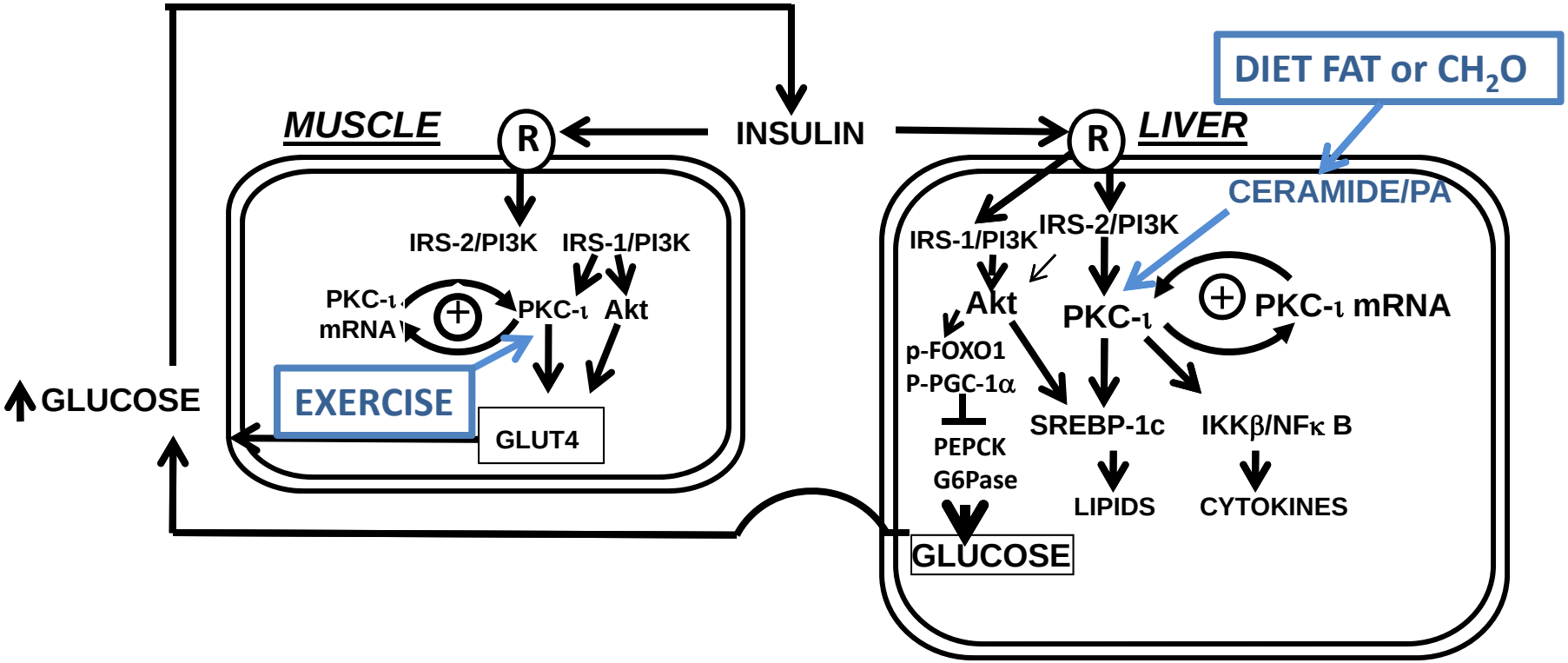



DEFECT (mRNA)
GROUP 1 BMI, 18-25
GROUP 2 BMI, 26-30
GROUP 3 BMI, 31-35
GROUP 4 BMI, 36-40
GROUP 5 BMI, 41-45
GROUP 6 T2DM BMI, 23-44
20 21 21 21 22 22 23 23 23 24 24 25
26 26 26 27 27 27 28 29 30
30 31 33 33 34 34 34 35
35 35 35 35 37 38 39 39 40
40 42 44 46 46 46
24 26 27 29 44
P-aPKC
(PKC-ι)
PGC-1α
(PGC-1α)
IRS-1
P-Akt
P-FoxO1
G6Pase
(G6Pase)
PEPCK
(PEPCK)
SREBP-1c
(SREBP-1c)
FAS
(FAS)
ACC
(ACC)
pGSK3β

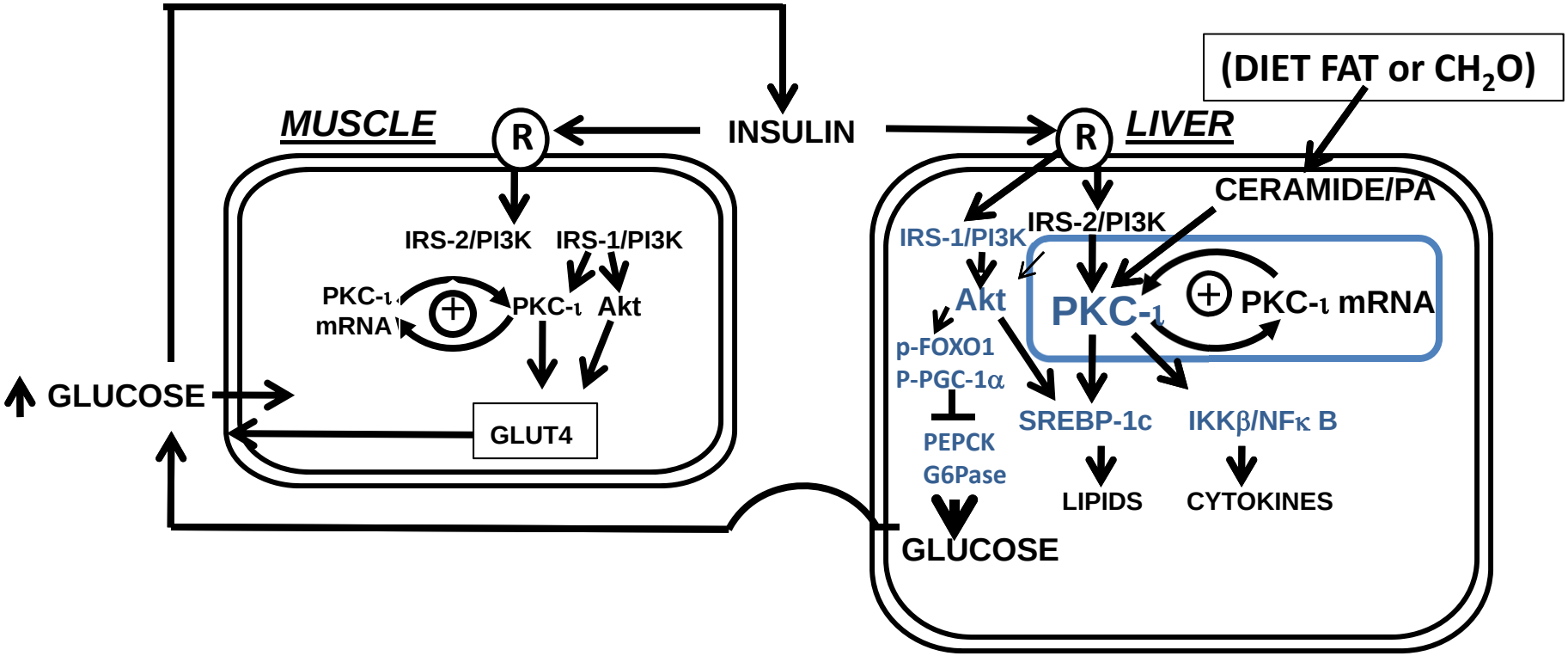
Why Insulin Doesn't Work (Phase 4)

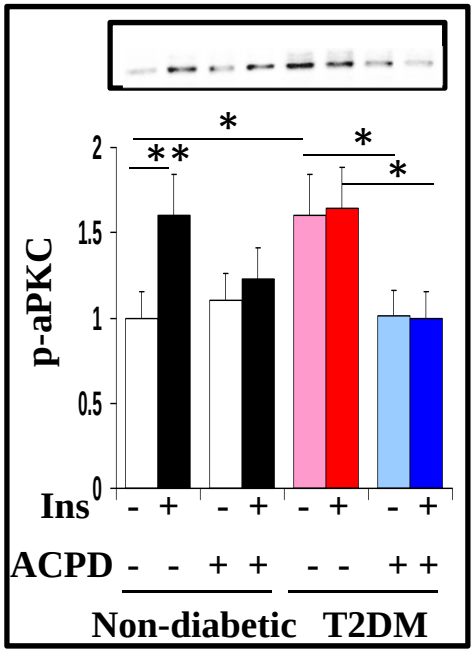


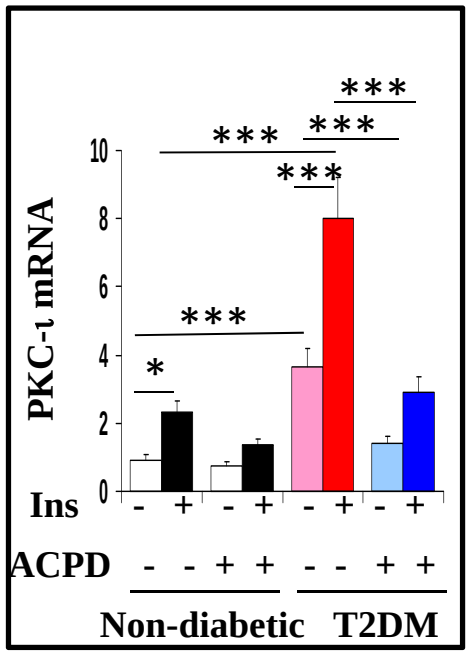
How To Get Insulin Working Again?
By Diet and Exercise

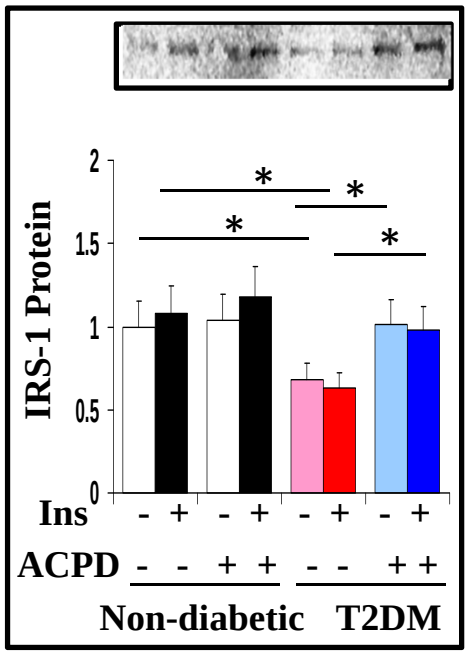


How To Get Insulin Working Again?
By Inhibiting Liver aPKC with ACPD

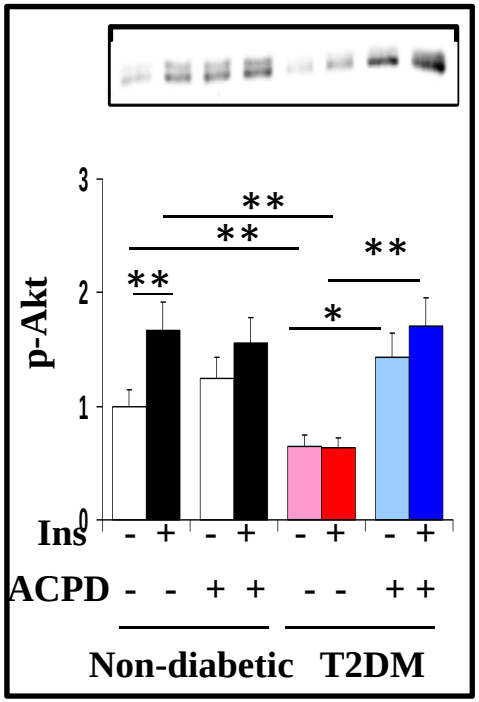


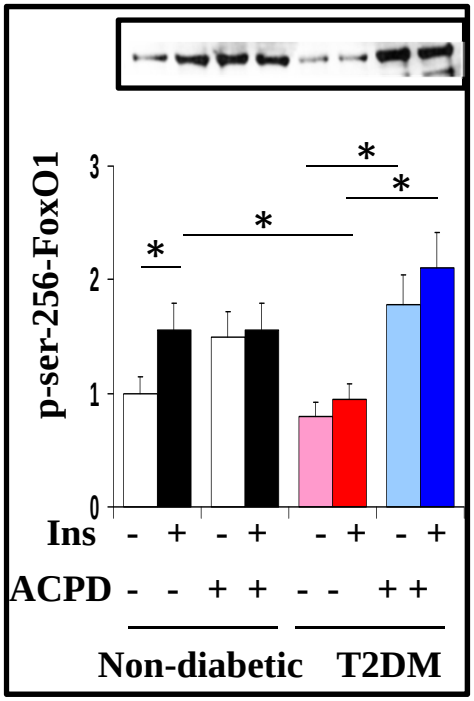


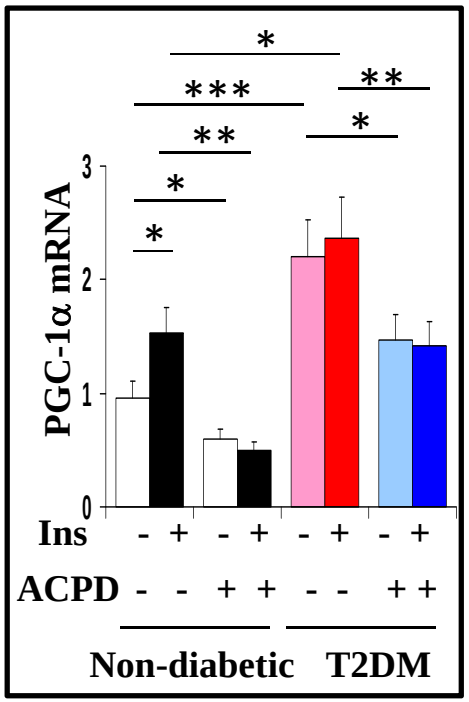


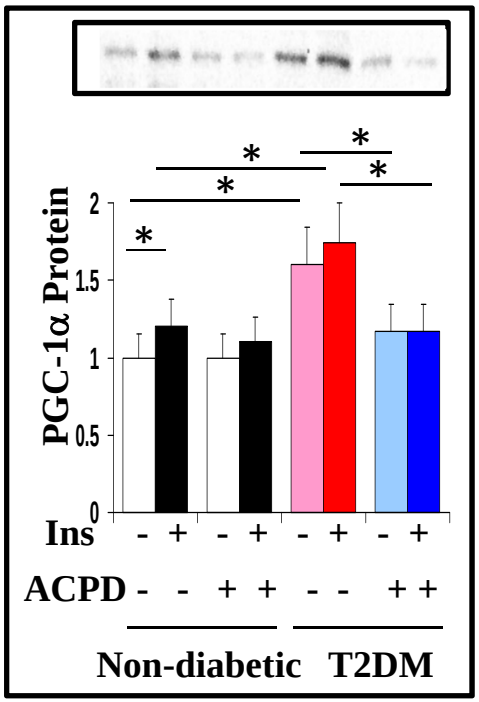


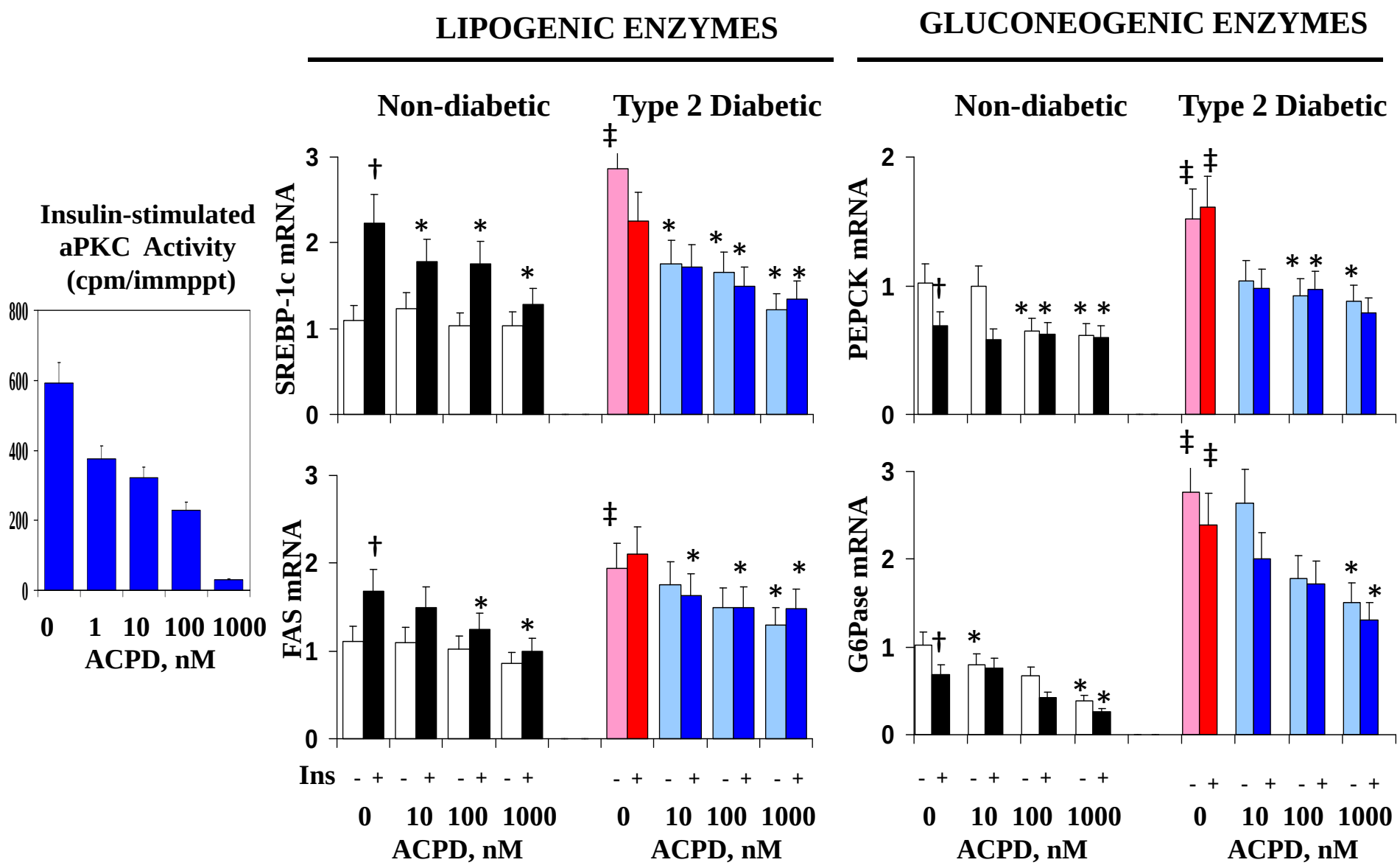
HUMAN HEPATOCYTES INCUBATED 24 HRS ± Insulin ± ACPD





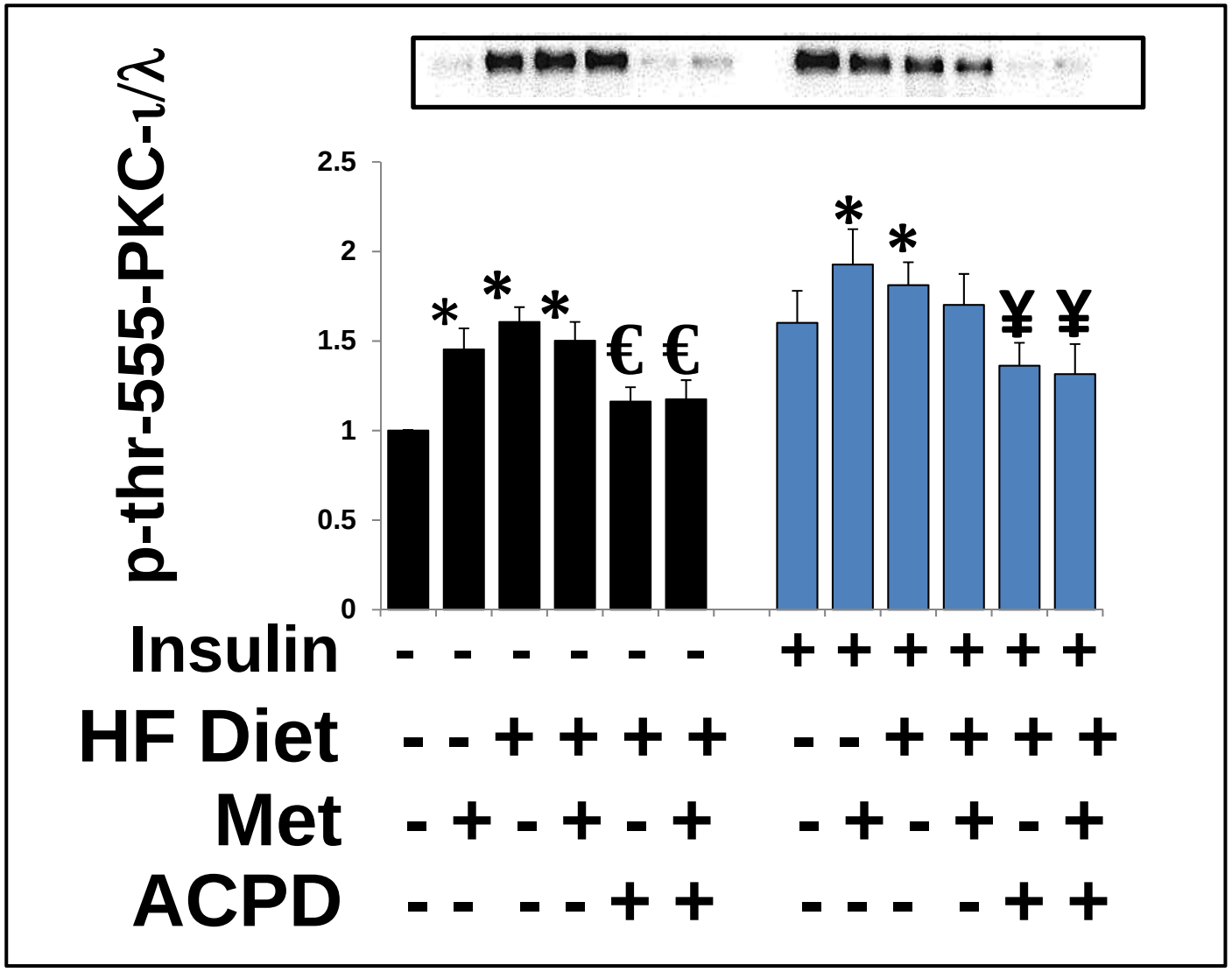




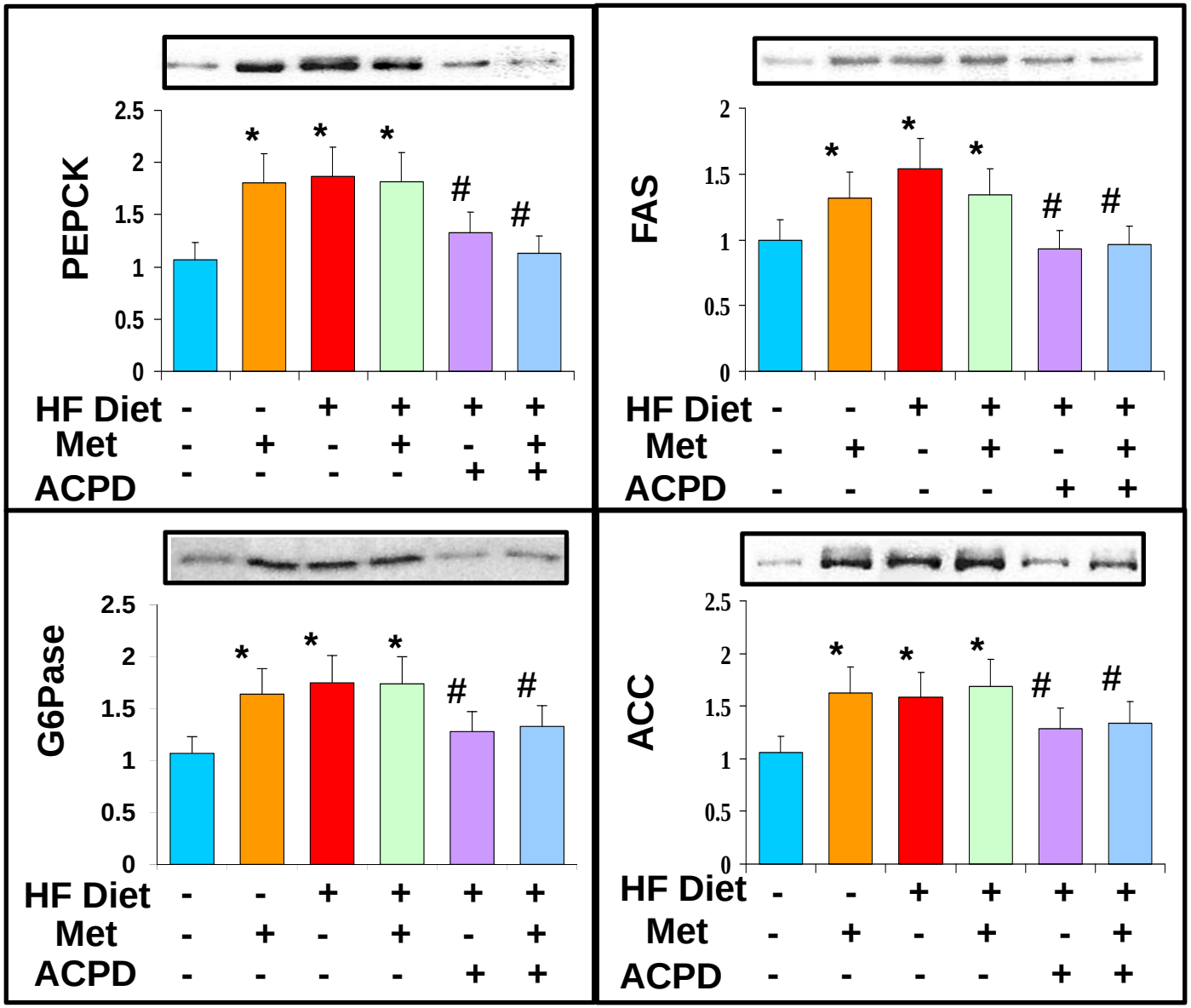

LIPOGENIC ENZYMES
GLUCONEOGENIC ENZYMES
Non-diabetic
Type 2 Diabetic
Non-diabetic
Type 2 Diabetic
Insulin-stimulated
aPKC Activity
(cpm/immppt)
800
600
400
200
0
0 1 10 100 1000
ACPD, nM
SREBP-1c mRNA
FAS mRNA
PEPCK mRNA
G6Pase mRNA
Ins
- + - + - + - + - + - + - + - +
0 10 100 1000 0 10 100 1000
ACPD, nM
ACPD, nM
0 10 100 1000 0 10 100 1000
ACPD, nM
ACPD, nM

How To Get Insulin Working Again
In HFF and Other Insulin-Resistant Mice?
By Inhibiting Liver aPKC with ACPD

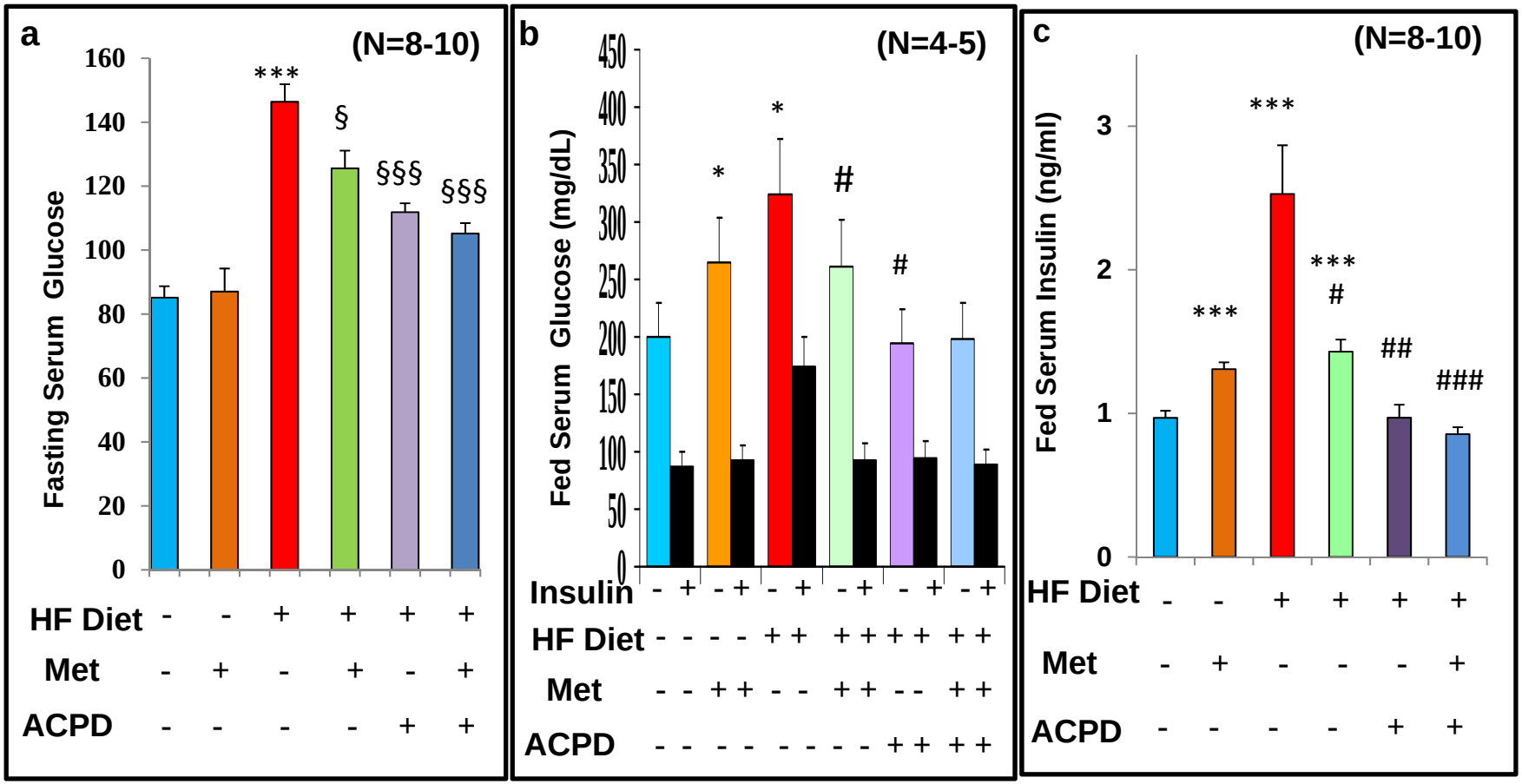
Mouse Liver PKC-ι/λ is Activated by High Fat Diet and Metformin and Reverted to Normal by ACPD Treatment



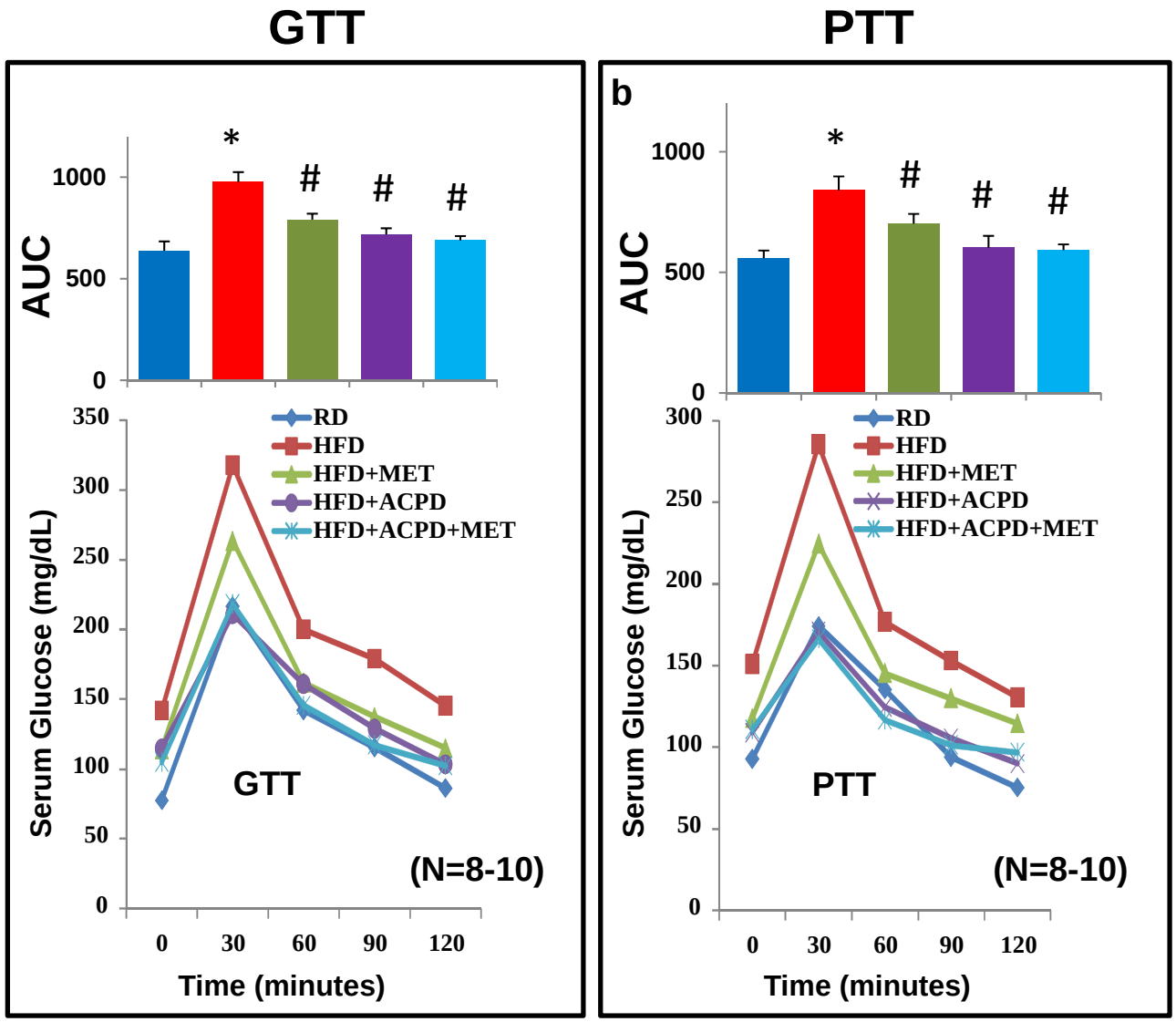
Mouse Liver Gluconeogenic (Left) and Lipogenic (Right) Enzymes are Increased by High Fat Diet and Metformin and Revert to Normal by ACPD Treatment



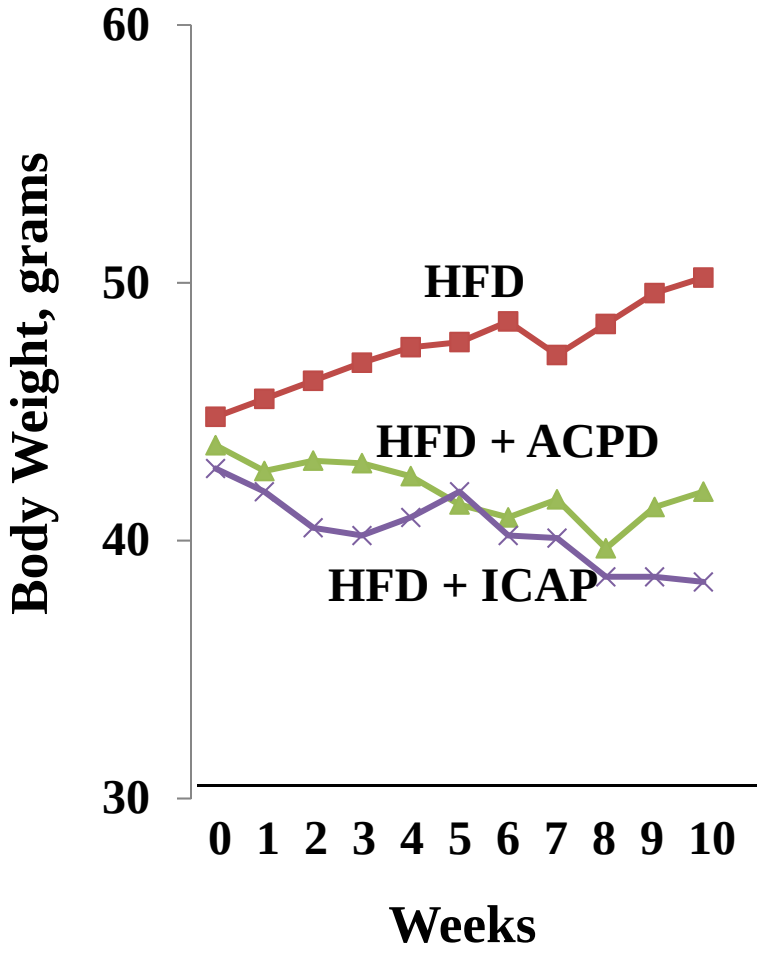
Mouse Serum Glucose and Insulin Levels are Increased by High Fat Diet and Metformin and Reverted To or Toward Normal by ACPD Treatment

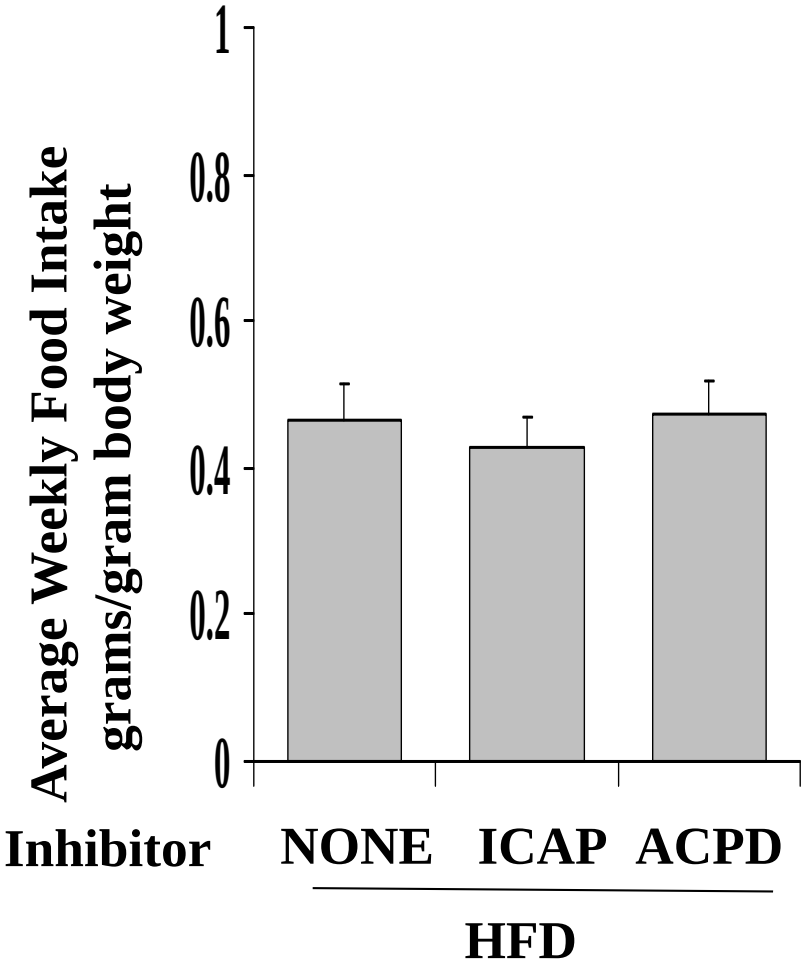


Glucose (Left) and (Pyruvate (Right) Tolerance are Impaired by High Fat Diet and Corrected Partially by Metformin and More Fully by ACPD Treatment

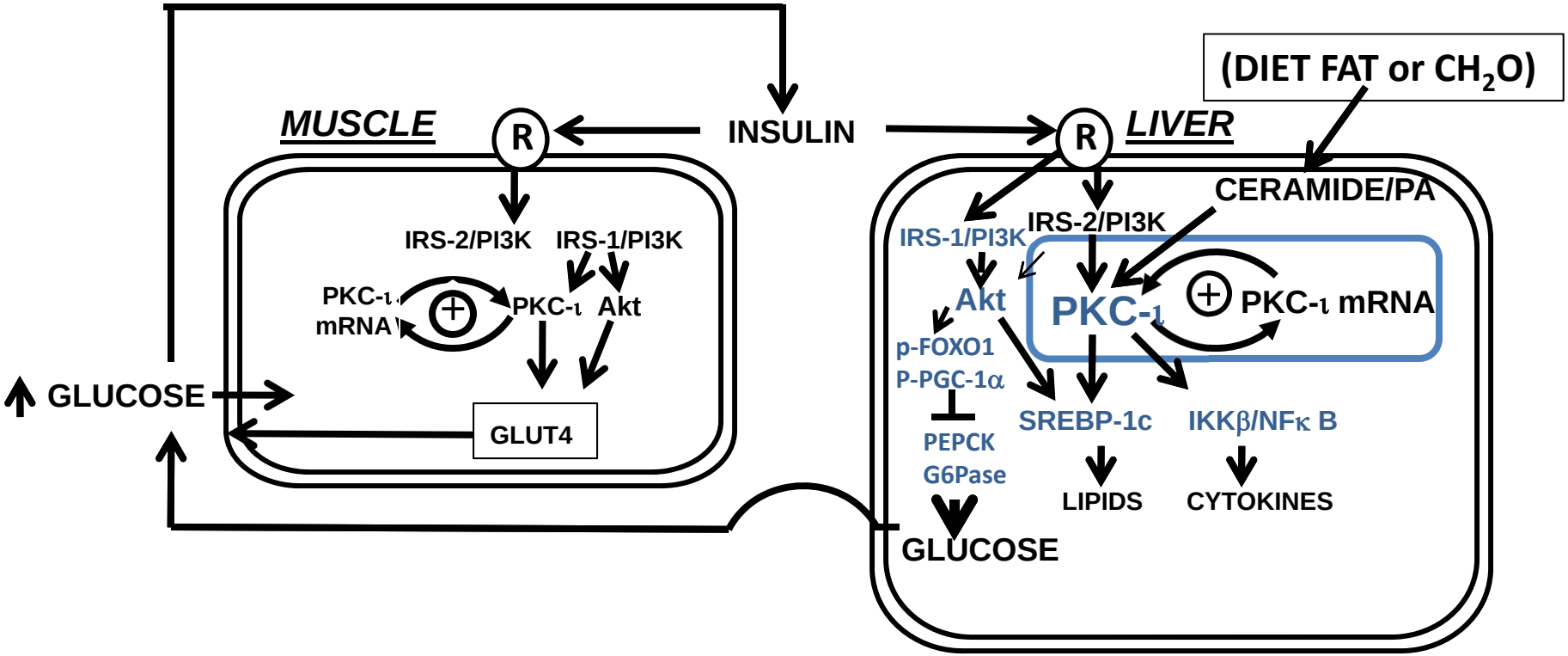


aPKC Inhibitors ACPD and ICAP Prevent Weight Gain in High-Fat-Fed (Hi) vs Low-Fat-Fed Mice



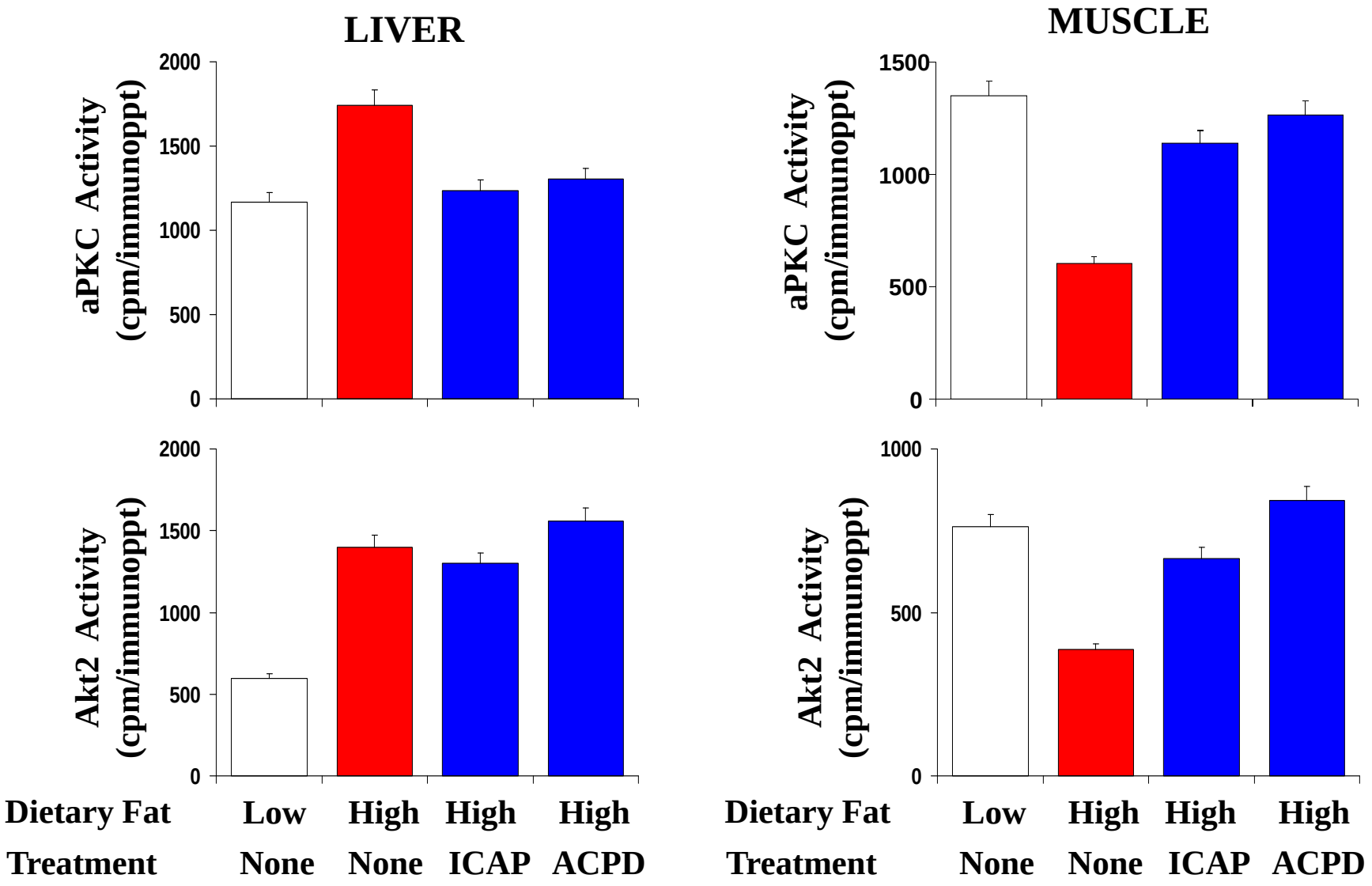


How To Get Insulin Working Again?
By Inhibiting Liver aPKC with ACPD



Note that by Inhibiting Liver aPKC with ACPD
Insulin Signaling in Skeletal Muscle is Also Corrected

LIVER-SELECTIVE PKC-ι/λ /ζ INHIBITORS ICAP and ACPD IMPROVE ACTIVITIES OF aPKC AND Akt2 in LIVER and MUSCLE IN HIGH-FAT-FED OBESE/MS/T2D MICE



50% of People Over Age 50 have O, MS or T2DM

50% of People Over Age 85 have Alzheimer's Disease

Mayo Series: 80% of Alzheimer's Patient have O,MS or T2DM

Two-fold Increase in Prevalence of AD in T2D and Vice Versa

Alzheimer's Disease = "Type 3 Diabetes"

Alzheimer's Disease = "Type 3 Diabetes"

Initial Idea: Brain is Insulin Resistant

However, in Insulin-Resistant Mice and Monkeys, Brain Akt and aPKC are Maximally Activated and this was Corrected by Lowering Serum Insulin. Thus, Hyperinsulinemia was Implicated.

Moreover, We Found That Insulin Increases Abeta and Phospho-Tau Levels, i.e., the Precursors to Plaques and Tangles of AD

Postulated Pathogenesis of Diabetes-Related and Non-Diabetes-Related Alzheimer's Disease