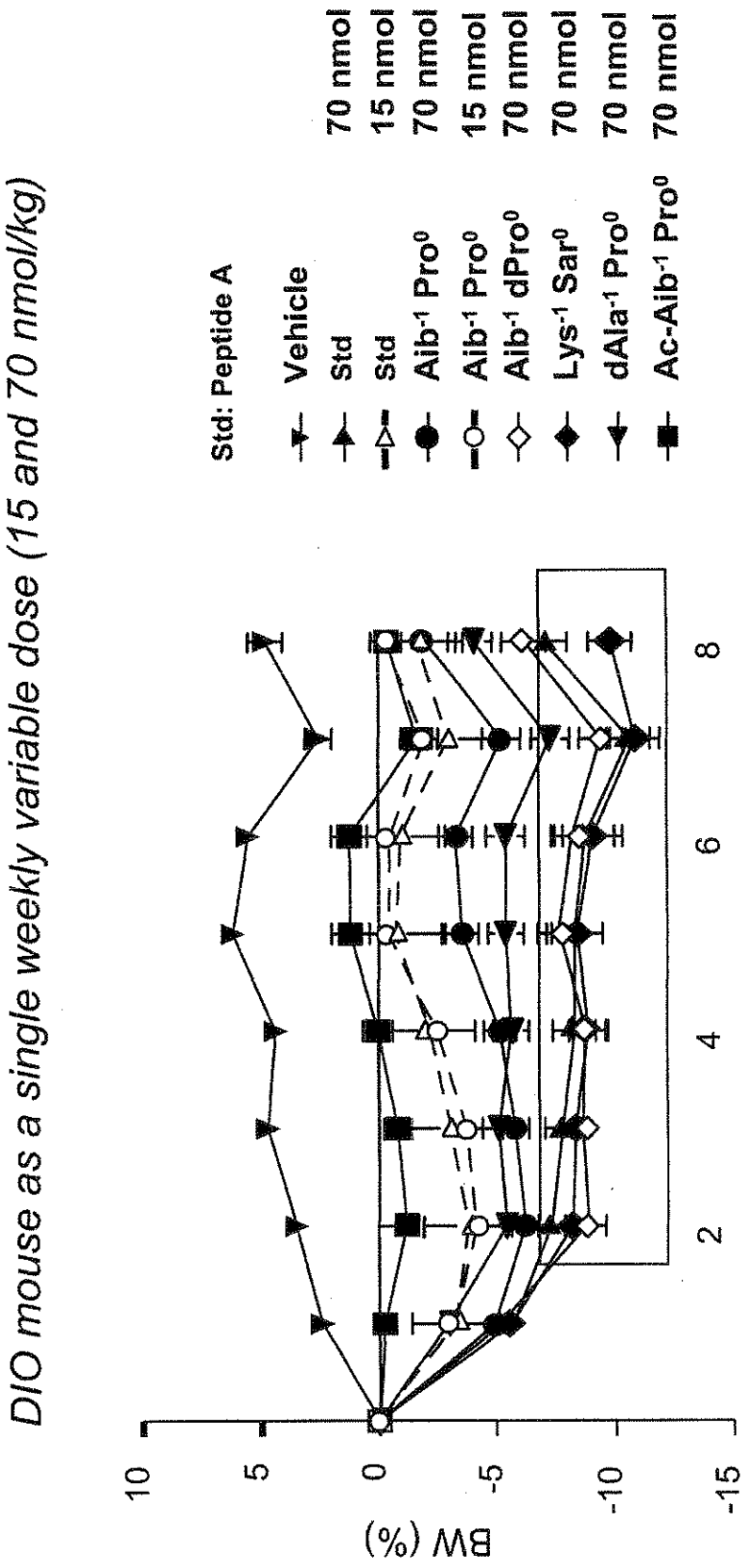

Change in Body Weight
as a Function of Prodrug
DIO mouse as a single weekly variable dose (15 and 70 nmol/kg)
Std: Peptide A
Vehicle
Std 70 nmol
Std 15 nmol
Aib-1 Pro0 70 nmol
Aib-1 Pro0 15 nmol
Aib-1 dPro0 70 nmol
Lys-1 Sar0 70 nmol
dAla-1 Pro0 70 nmol
Ac-Aib-1 Pro0 70 nmol
BW (%)
10
5
0
-5
-10
-15
2
4
6
8
Time (days)

FIG. 1

Change in Body Weight as a Function of Prodrug Concentration

DIO mouse as a single weekly variable dose (0.5, 3, 15, 70 nmol/kg)

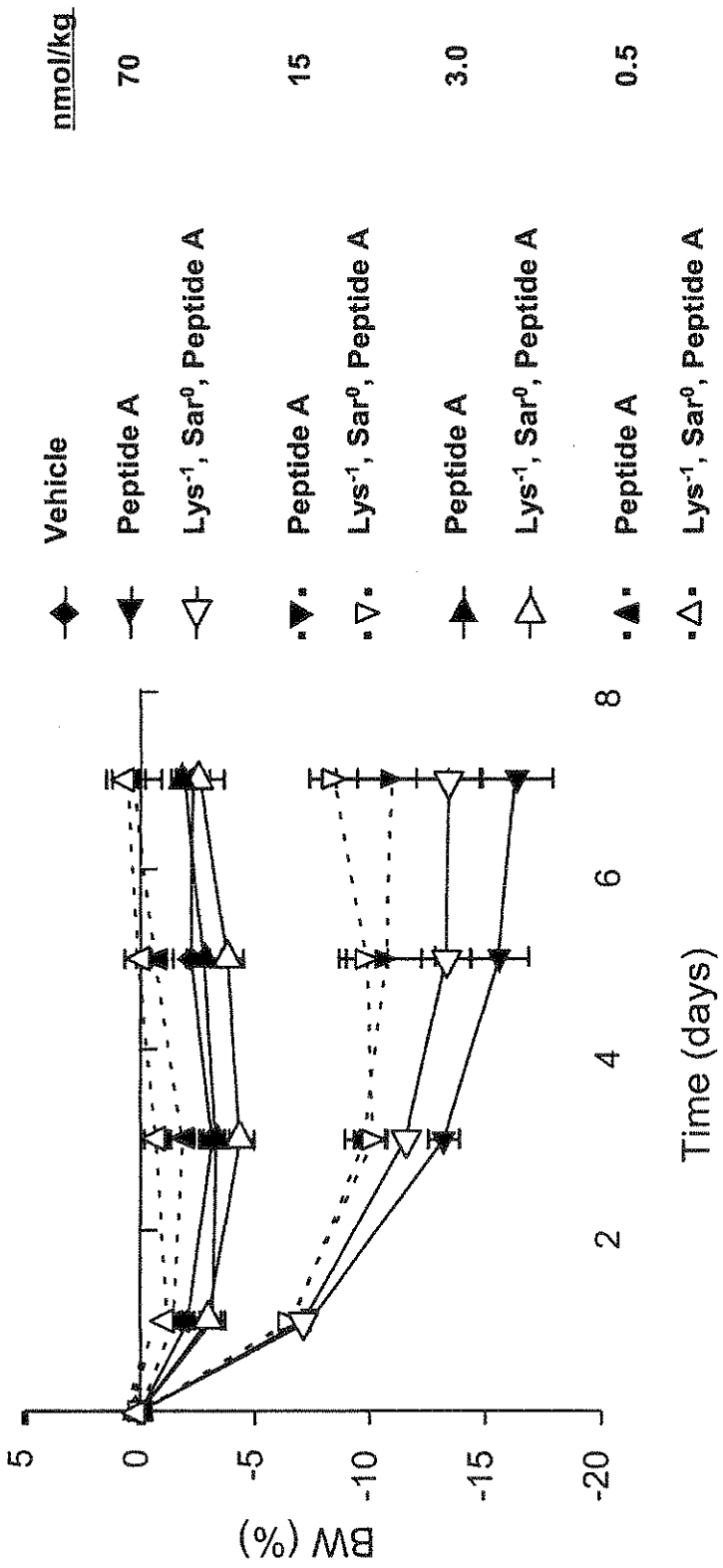


FIG. 2

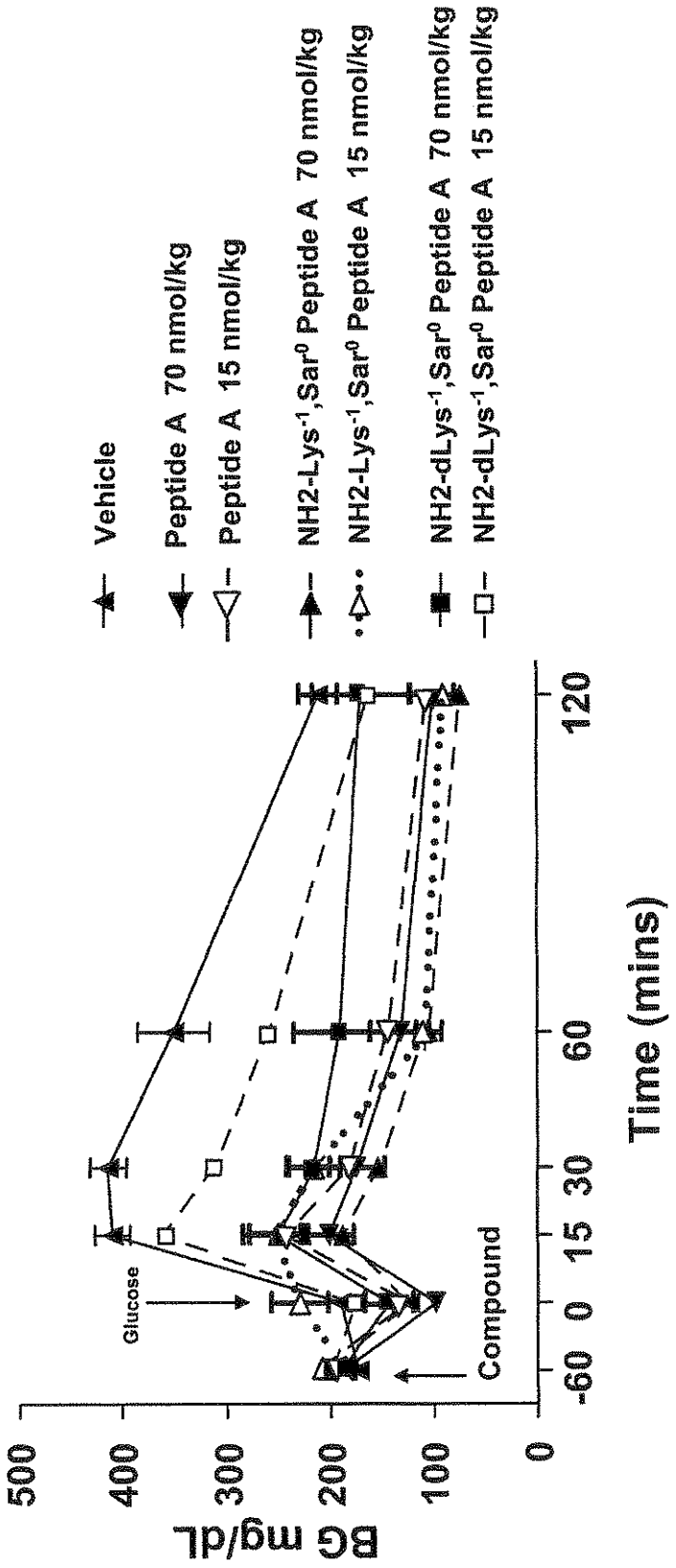

Change in Blood Glucose Levels
as a Function of Prodrug
Vehicle
Peptide A 70 nmol/kg
Peptide A 15 nmol/kg
NH2-Lys-1,Sar0 Peptide A 70 nmol/kg
NH2-Lys-1,Sar0 Peptide A 15 nmol/kg
NH2-dLys-1,Sar0 Peptide A 70 nmol/kg
NH2-dLys-1,Sar0 Peptide A 15 nmol/kg
BG mg/dL
500
400
300
200
100
0
Glucose
Compound
-60 0 15 30 60 120
Time (mins)

FIG. 3

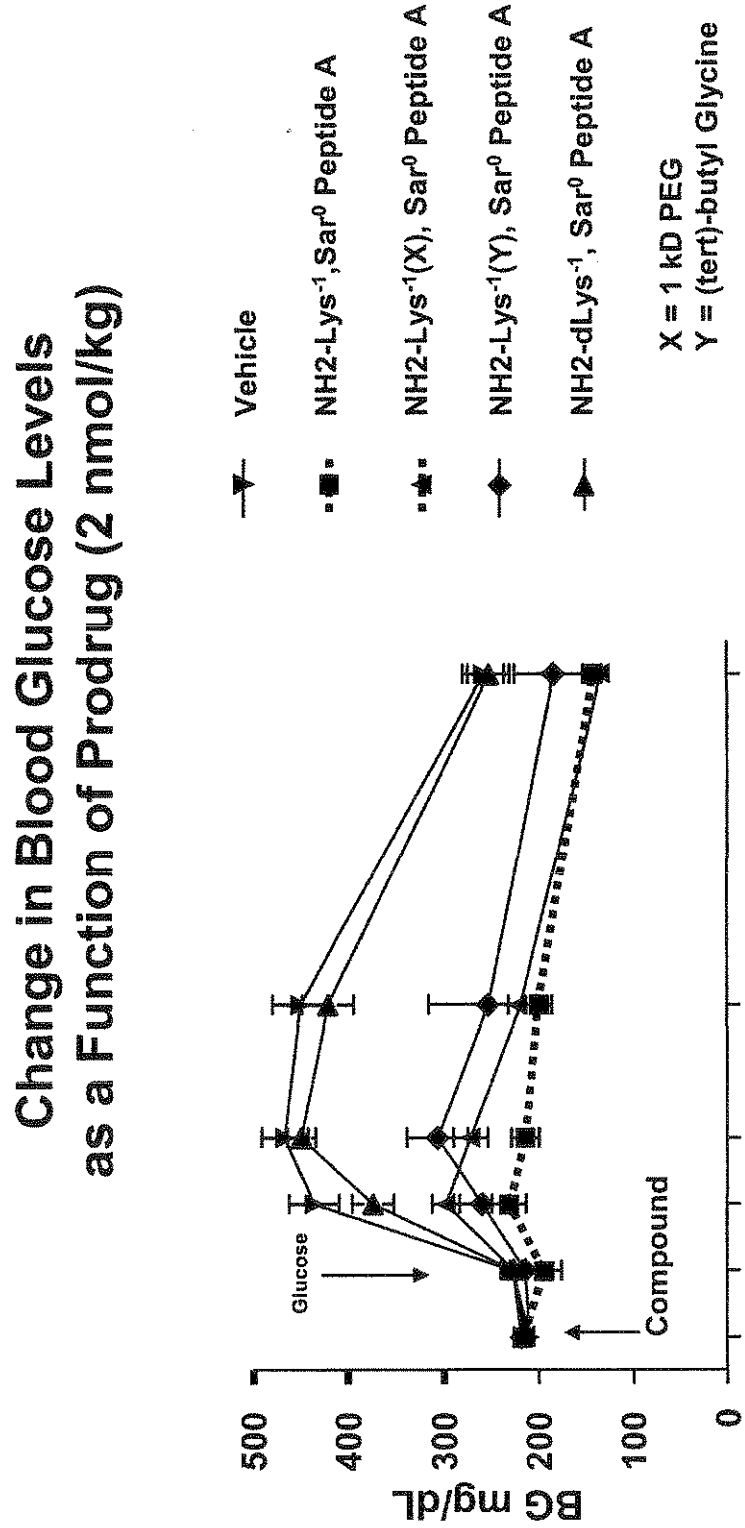

Change in Blood Glucose Levels
as a Function of Prodrug (2 nmol/kg)
Vehicle
NH2-Lys-1,Sar0 Peptide A
NH2-Lys-1(X), Sar0 Peptide A
NH2-Lys-1(Y), Sar0 Peptide A
NH2-dLys-1, Sar0 Peptide A
X = 1 kD PEG
Y = (tert)-butyl Glycine
BG mg/dL
500
400
300
200
100
0
Glucose
Compound
-15
0
15
30
60
120
Time (mins)

FIG. 4

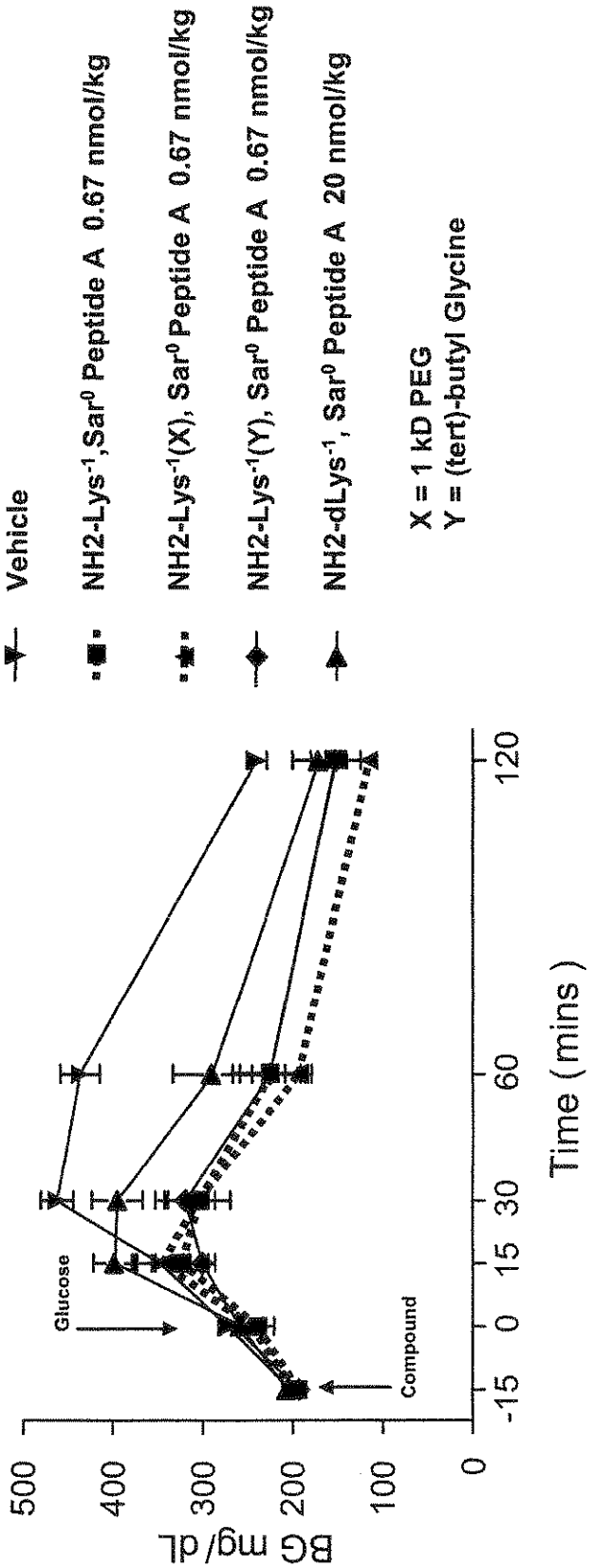

Change in Blood Glucose Levels as a Function of Prodrug (0.67 or 20 nmol/kg)
Vehicle
NH2-Lys-1,Sar0 Peptide A 0.67 nmol/kg
NH2-Lys-1(X), Sar0 Peptide A 0.67 nmol/kg
NH2-Lys-1(Y), Sar0 Peptide A 0.67 nmol/kg
NH2-dLys-1, Sar0 Peptide A 20 nmol/kg
X = 1 kD PEG
Y = (tert)-butyl Glycine
BG mg/dL
Time (mins)
Glucose
Compound
500
400
300
200
100
0
-15
0
15
30
60
120

FIG. 5

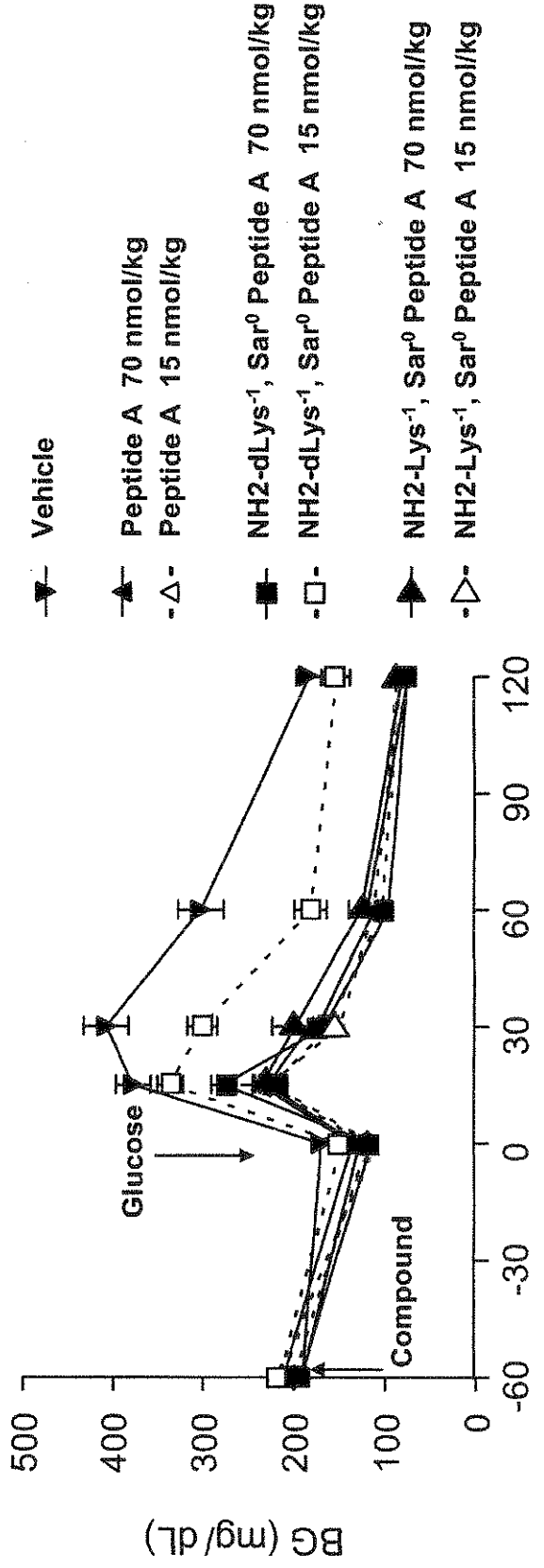

Change in Blood Glucose Levels as a Function of Prodrug (15 and 70 nmol/kg)
Vehicle
Peptide A 70 nmol/kg
Peptide A 15 nmol/kg
NH2-dLys-1, Sar0 Peptide A 70 nmol/kg
NH2-dLys-1, Sar0 Peptide A 15 nmol/kg
NH2-Lys-1, Sar0 Peptide A 70 nmol/kg
NH2-Lys-1, Sar0 Peptide A 15 nmol/kg
Glucose
Compound
BG (mg/dL)
Time (Mins)
500
400
300
200
100
0
-60
-30
0
30
60
90
120

FIG. 6

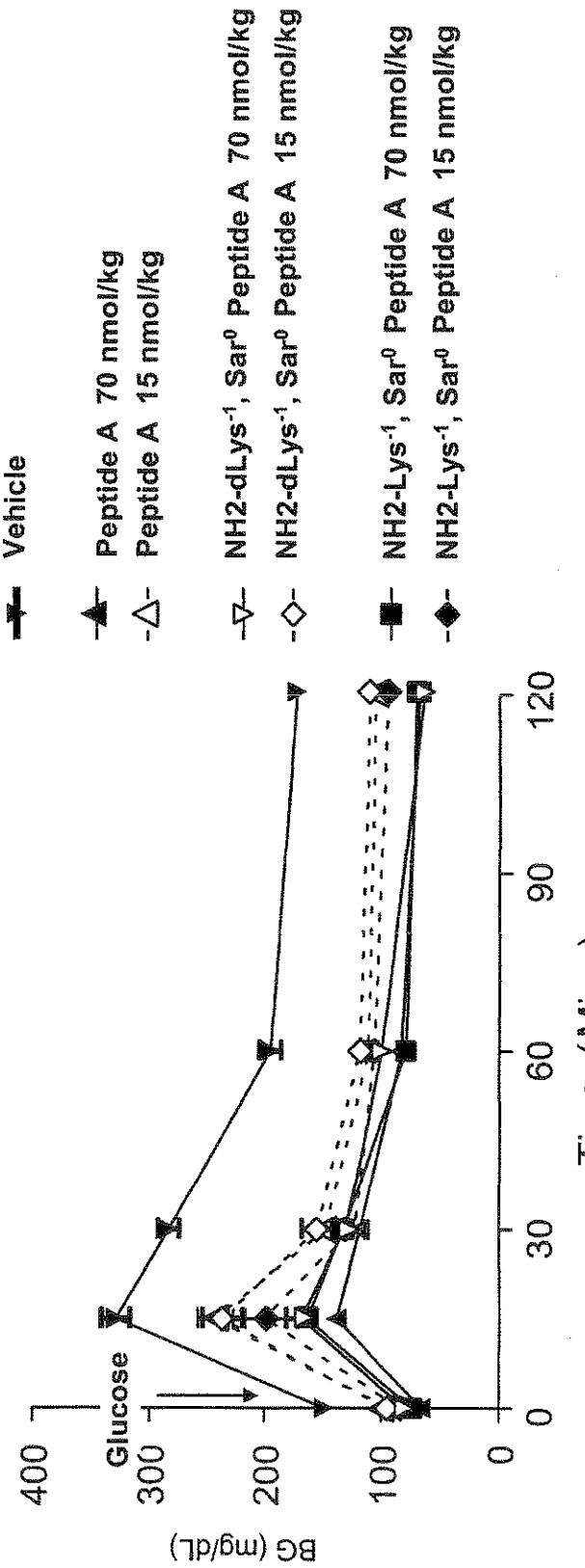

Change in Blood Glucose Levels as a Function of Prodrug (15 and 70 nmol/kg)
Vehicle
Peptide A 70 nmol/kg
Peptide A 15 nmol/kg
NH2-dLys-1, Sar0 Peptide A 70 nmol/kg
NH2-dLys-1, Sar0 Peptide A 15 nmol/kg
NH2-Lys-1, Sar0 Peptide A 70 nmol/kg
NH2-Lys-1, Sar0 Peptide A 15 nmol/kg
Glucose
BG (mg/dL)
400
300
200
100
0
0
30
60
90
120
Time (Mins)

FIG. 7

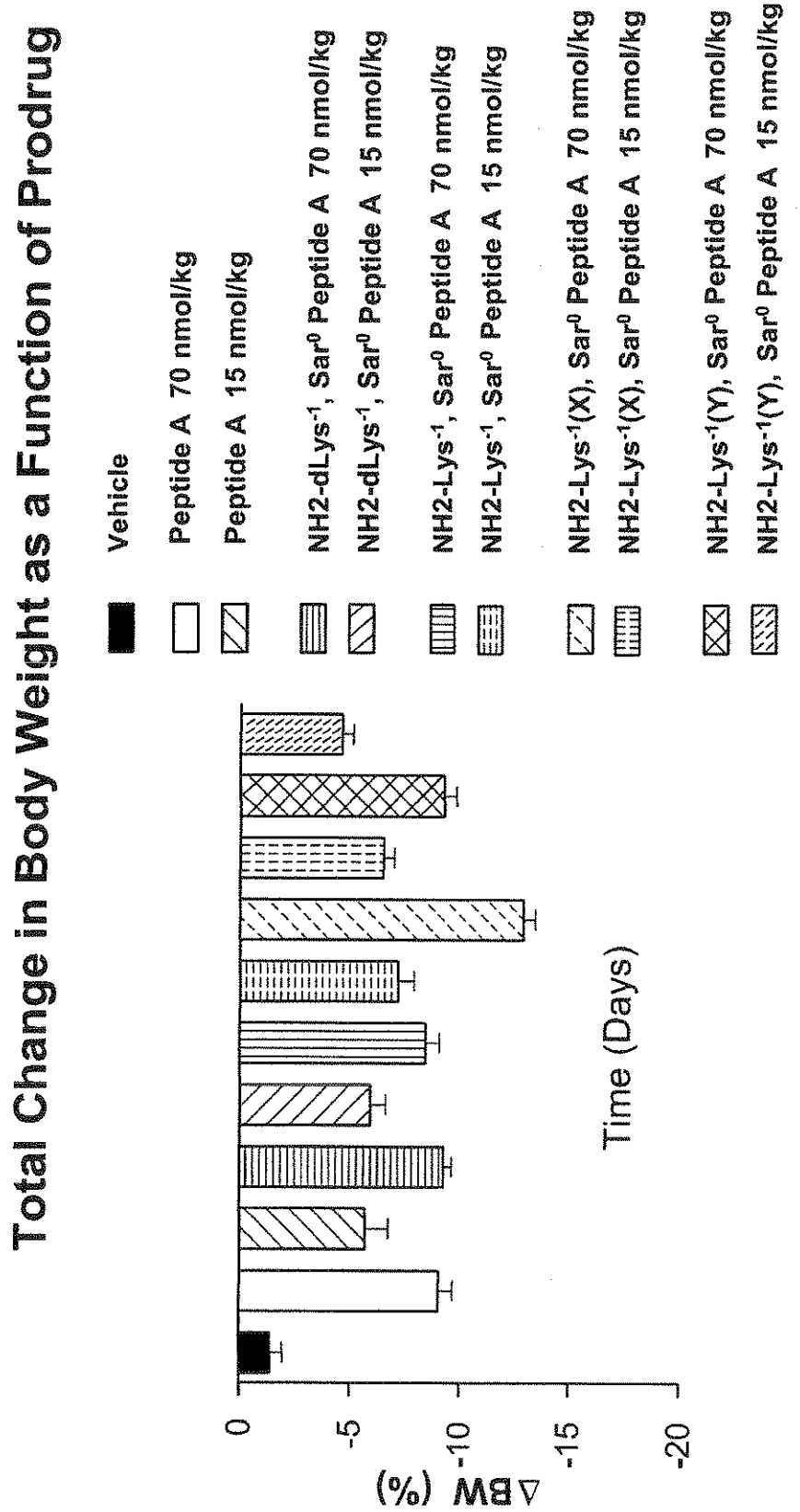

Total Change in Body Weight as a Function of Prodrug
Vehicle
Peptide A 70 nmol/kg
Peptide A 15 nmol/kg
NH2-dLys-1, Sar0 Peptide A 70 nmol/kg
NH2-dLys-1, Sar0 Peptide A 15 nmol/kg
NH2-Lys-1, Sar0 Peptide A 70 nmol/kg
NH2-Lys-1, Sar0 Peptide A 15 nmol/kg
NH2-Lys-1(X), Sar0 Peptide A 70 nmol/kg
NH2-Lys-1(X), Sar0 Peptide A 15 nmol/kg
NH2-Lys-1(Y), Sar0 Peptide A 70 nmol/kg
NH2-Lys-1(Y), Sar0 Peptide A 15 nmol/kg
X = 1 kD PEG
Y = (tert)-butyl Glycine
0
-5
-10
-15
-20
ΔBW (%)
Time (Days)

FIG. 8

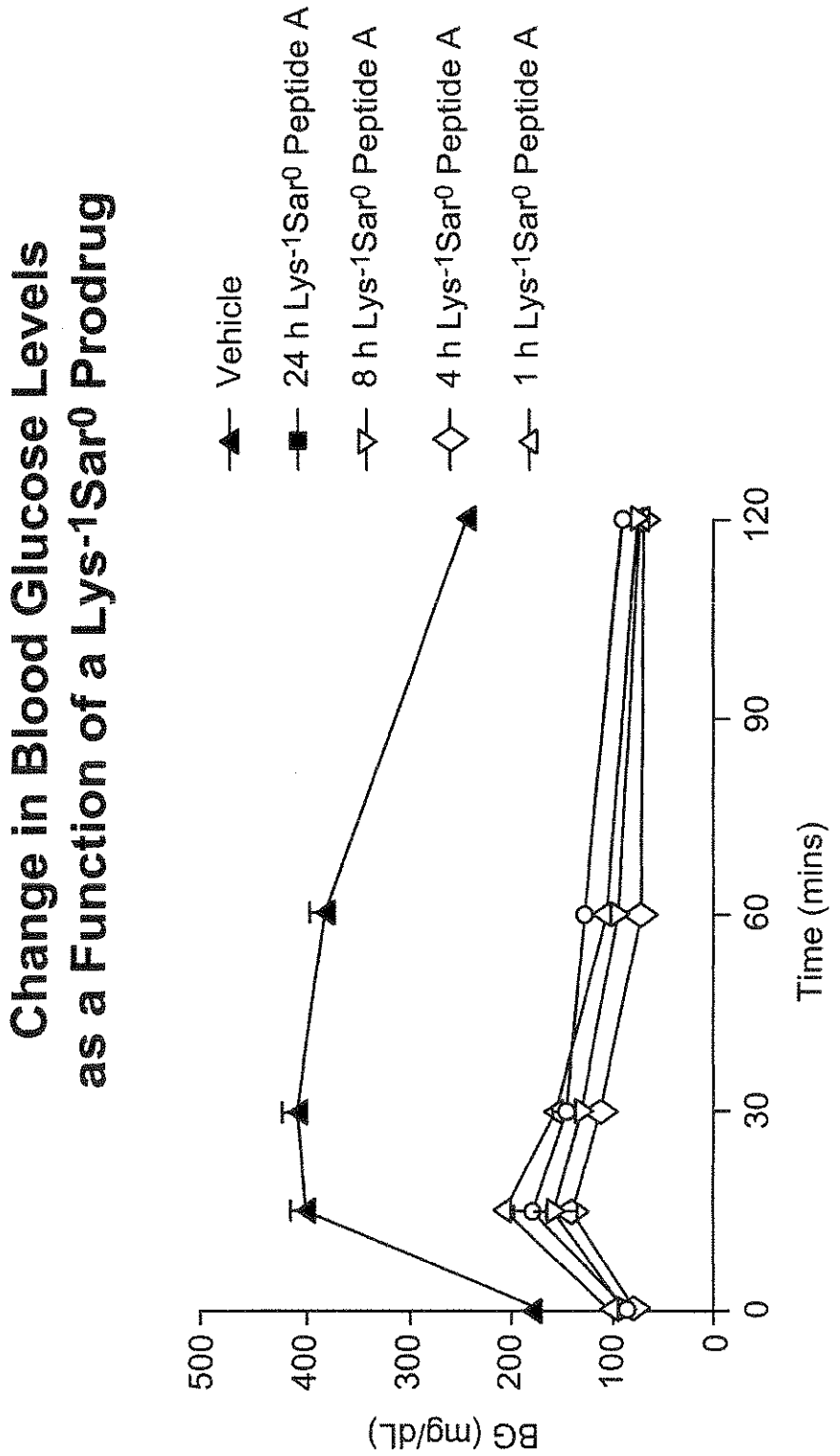

Change in Blood Glucose Levels
as a Function of a Lys-1Sar0 Prodrug
Vehicle
24 h Lys-1Sar0 Peptide A
8 h Lys-1Sar0 Peptide A
4 h Lys-1Sar0 Peptide A
1 h Lys-1Sar0 Peptide A
BG (mg/dL)
500
400
300
200
100
0
0
30
60
90
120
Time (mins)

FIG. 9A

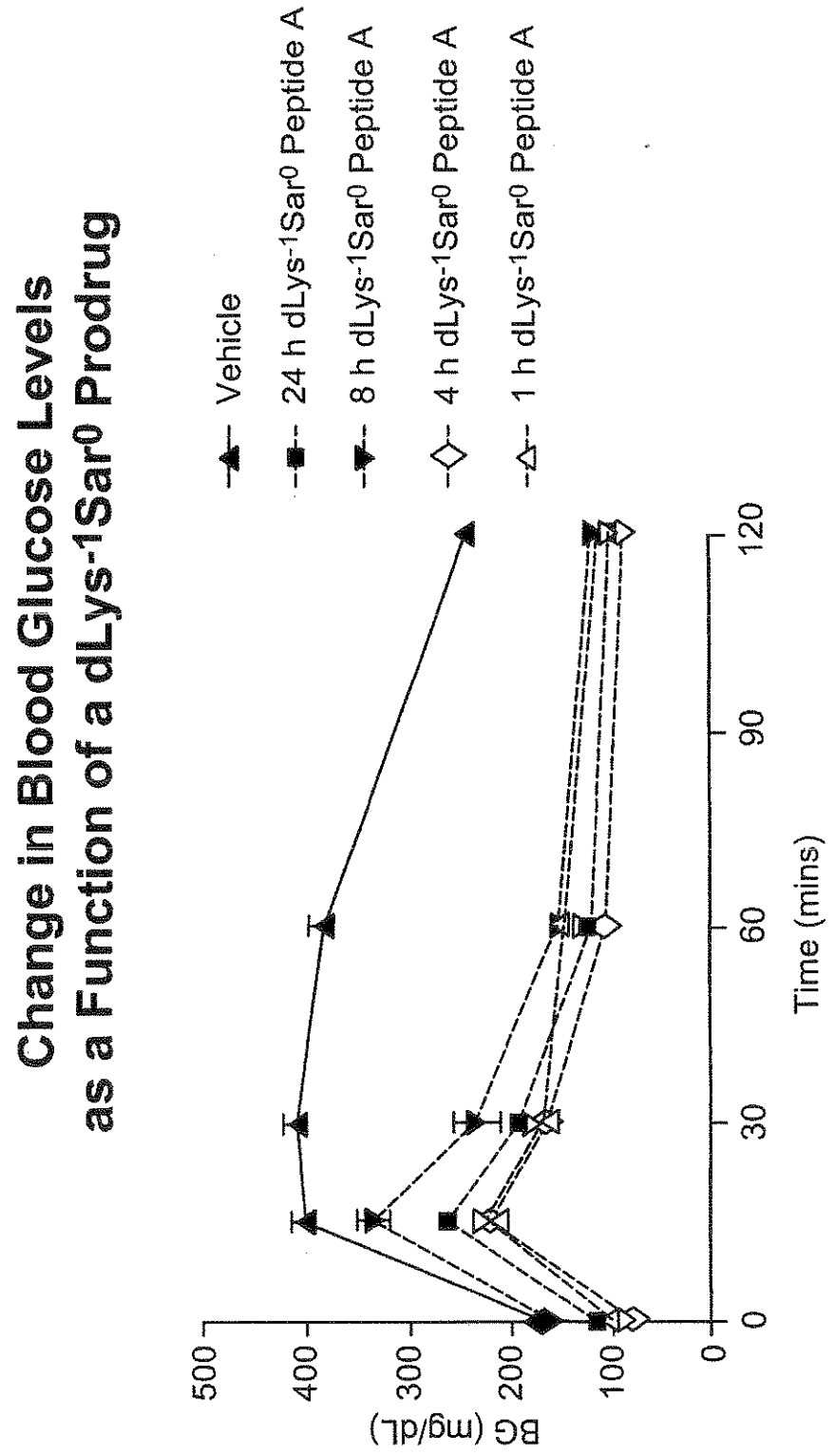

Change in Blood Glucose Levels
as a Function of a dLys-1Sar0 Prodrug
Vehicle
24 h dLys-1Sar0 Peptide A
8 h dLys-1Sar0 Peptide A
4 h dLys-1Sar0 Peptide A
1 h dLys-1Sar0 Peptide A
BG (mg/dL)
500
400
300
200
100
0
0
30
60
90
120
Time (mins)

FIG. 9B

Alignment of Amino Acid Sequences and Glucagon Superfamily Peptides

```
GHRH            YADAIFTNSYRKVLGQLSARKLLQDIMSR---------- 29
PHI             HADGVFTSDFSKLLGQLSAKKYLESLM---------- 27
VIP             HSDAVFTDNYTRLRKQMAVKKYLNSILN---------- 28
PACAP-38        HSDGIFTDSYSRYRKQMAVKKYLAAVL---------- 27
Exendin-4       HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS--- 39
GLP-1           HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG---------- 31
Glucagon        HSQGTFTSDYSKYLDSRRAQDFVQWLMNT---------- 29
Oxyntomodulin   HSQGTFTSDYSKYLDSRRAQDFVQWLMNTKRNRNNIA----- 37
GIP             YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ 42
GLP-2           HADGSFSDEMNTIIDNLAARDFINWLIQTKITD--------- 33
Secretin        HSDGTFTSELSRLREGARLQRLLQGLV---------- 27
```

FIG. 10

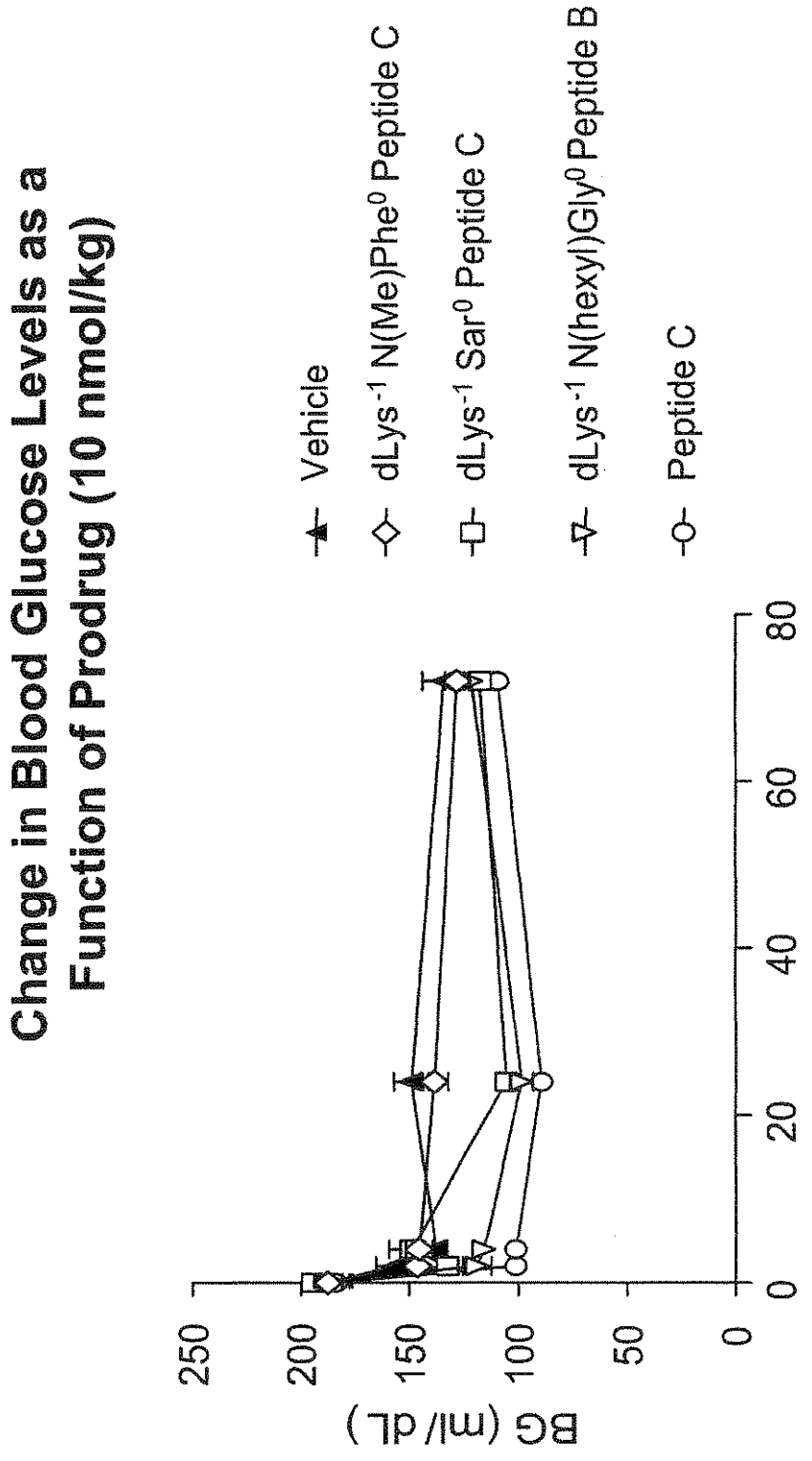

Change in Blood Glucose Levels as a Function of Prodrug (10 nmol/kg)
Vehicle
dLys-1 N(Me)Phe0 Peptide C
dLys-1 Sar0 Peptide C
dLys-1 N(hexyl)Gly0 Peptide B
Peptide C
BG (ml/dL)
250
200
150
100
50
0
0
20
40
60
80
Time (hours)

FIG. 11

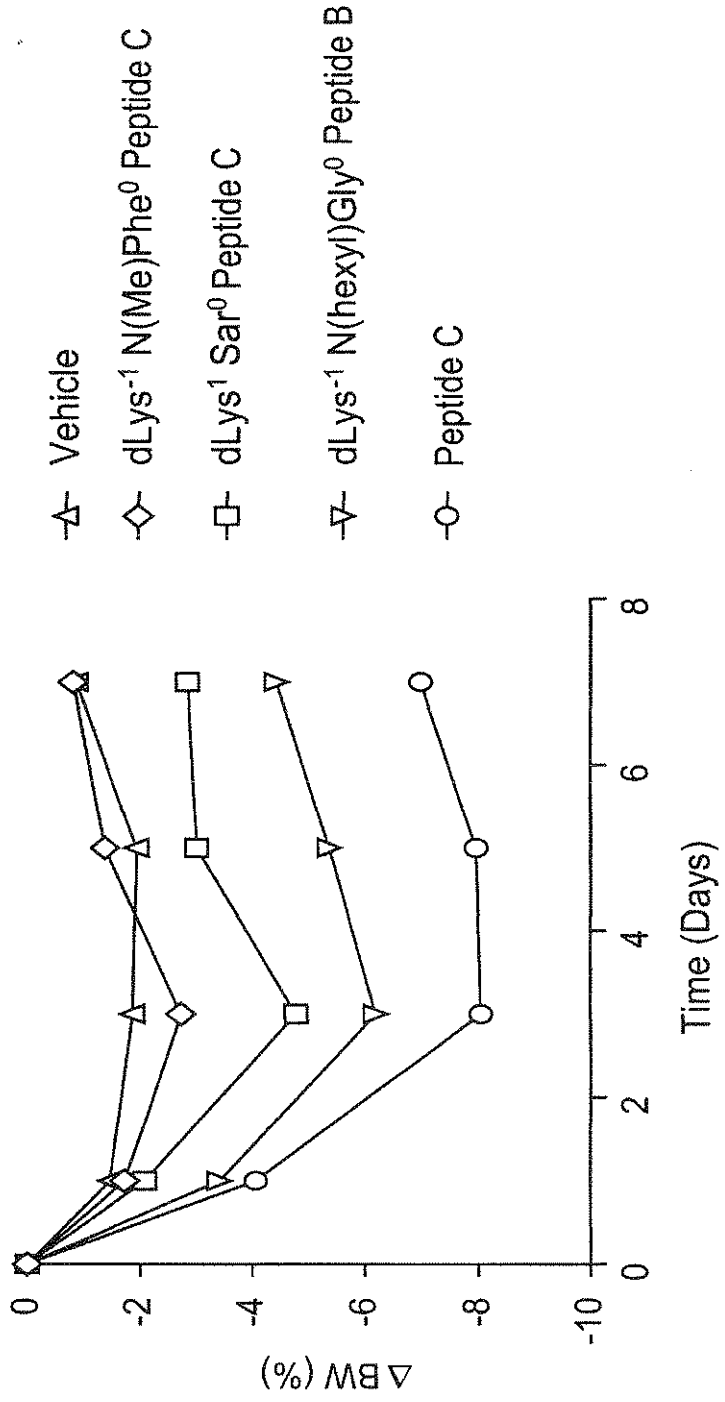

Change in Body Weight as a Function of Prodrug (10 nmol/kg)
Vehicle
dLys-1 N(Me)Phe0 Peptide C
dLys1 Sar0 Peptide C
dLys-1 N(hexyl)Gly0 Peptide B
Peptide C
Δ BW (%)
0
-2
-4
-6
-8
-10
0
2
4
6
8
Time (Days)

FIG. 12

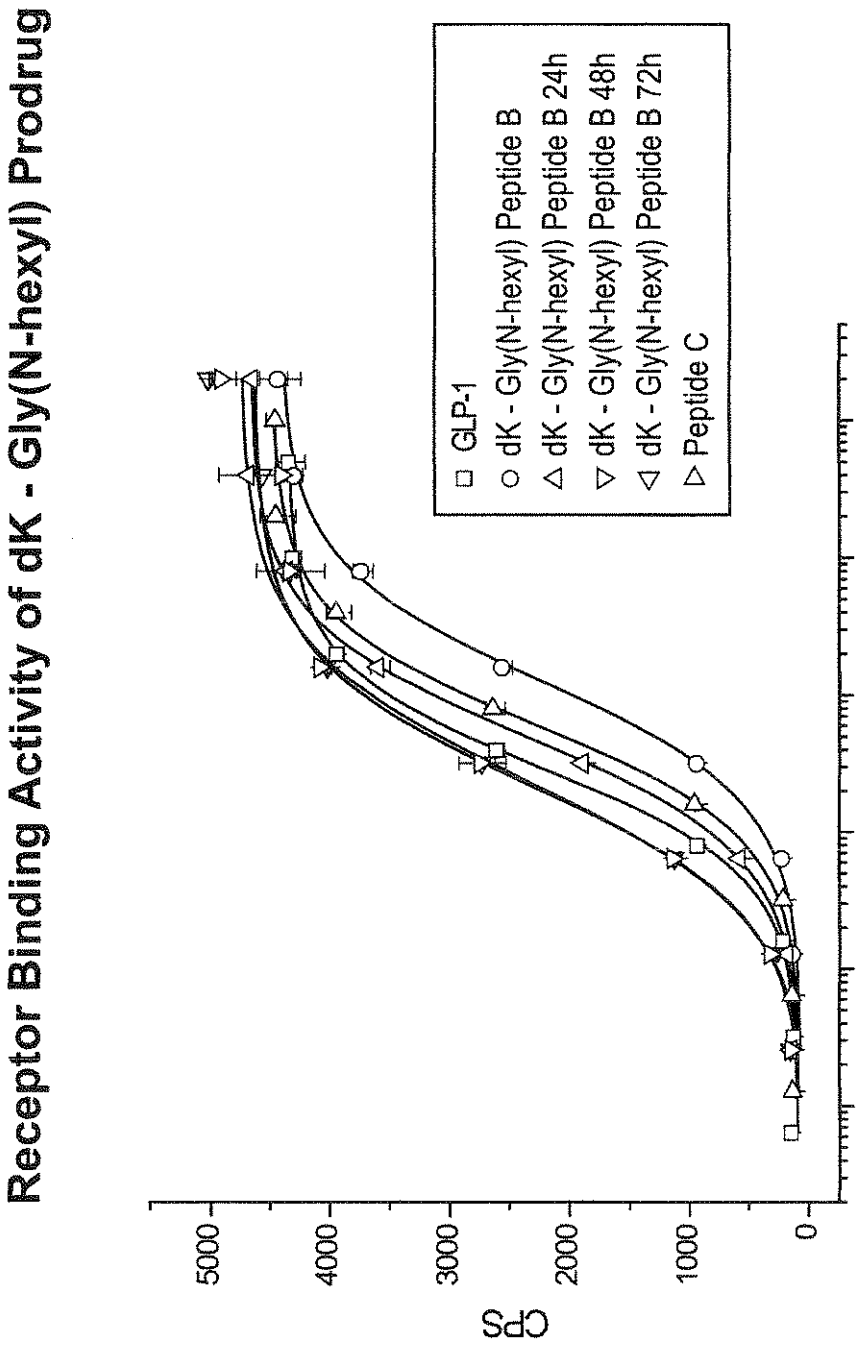

Receptor Binding Activity of dK - Gly(N-hexyl) Prodrug
GLP-1
dK - Gly(N-hexyl) Peptide B
dK - Gly(N-hexyl) Peptide B 24h
dK - Gly(N-hexyl) Peptide B 48h
dK - Gly(N-hexyl) Peptide B 72h
Peptide C
CPS
0
1000
2000
3000
4000
5000
1E-4
1E-3
0.01
0.1
1
10
Concentration, nM

FIG. 13A

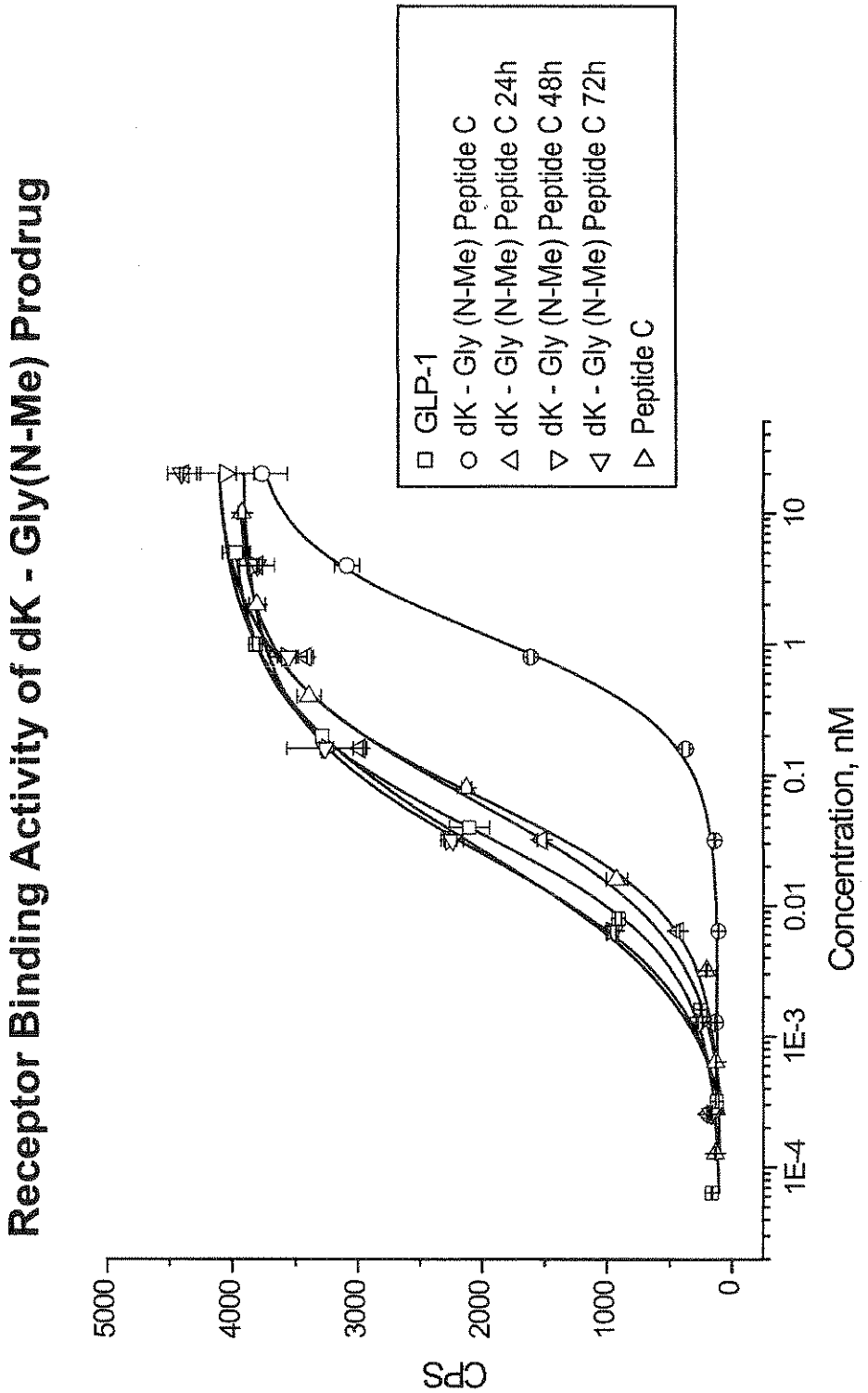

Receptor Binding Activity of dK - Gly(N-Me) Prodrug
GLP-1
dK - Gly (N-Me) Peptide C
dK - Gly (N-Me) Peptide C 24h
dK - Gly (N-Me) Peptide C 48h
dK - Gly (N-Me) Peptide C 72h
Peptide C
CPS
5000
4000
3000
2000
1000
0
1E-4
1E-3
0.01
0.1
1
10
Concentration, nM

FIG. 13B

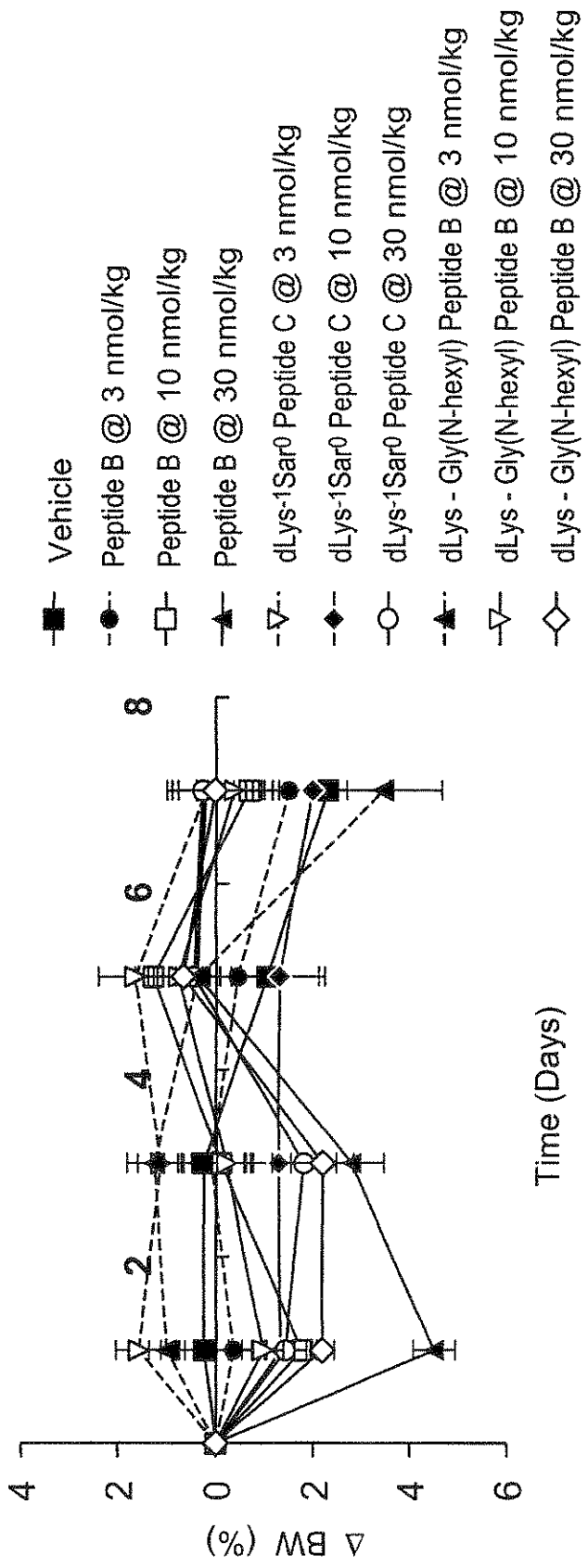

Change in Body Weight as a Function of Prodrug and Prodrug Concentration
Vehicle
Peptide B @ 3 nmol/kg
Peptide B @ 10 nmol/kg
Peptide B @ 30 nmol/kg
dLys-1Sar0 Peptide C @ 3 nmol/kg
dLys-1Sar0 Peptide C @ 10 nmol/kg
dLys-1Sar0 Peptide C @ 30 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 3 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 10 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 30 nmol/kg
Time (Days)
Δ BW (%)
0
2
4
6
8
4
2
0
2
4
6

FIG. 14

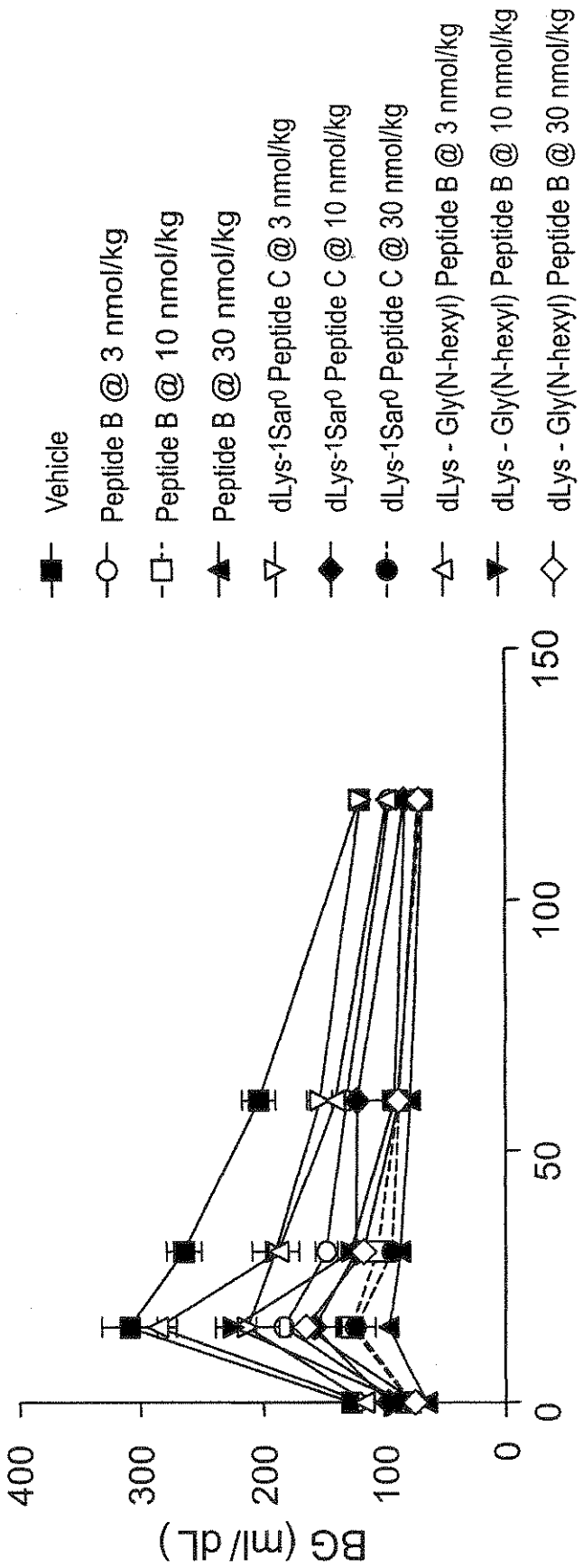

Blood Glucose Levels as a Function of Prodrug and Prodrug Concentration on Day 1
Vehicle
Peptide B @ 3 nmol/kg
Peptide B @ 10 nmol/kg
Peptide B @ 30 nmol/kg
dLys-1Sar0 Peptide C @ 3 nmol/kg
dLys-1Sar0 Peptide C @ 10 nmol/kg
dLys-1Sar0 Peptide C @ 30 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 3 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 10 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 30 nmol/kg
BG (ml/dL)
400
300
200
100
0
0
50
100
150
Time (mins)

FIG. 15A

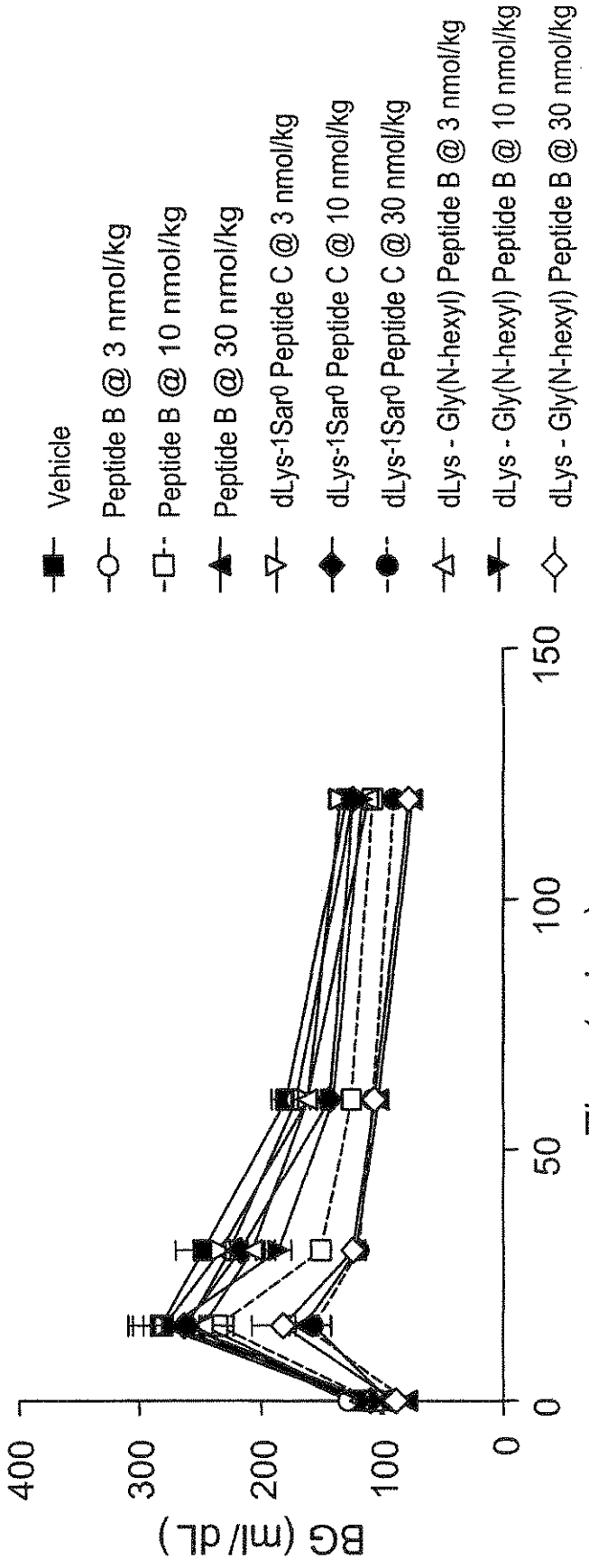

Blood Glucose Levels as a Function of Prodrug and Prodrug Concentration on Day 3
BG (mil/dL)
400
300
200
100
0
0
50
100
150
Time (mins)
Vehicle
Peptide B @ 3 nmol/kg
Peptide B @ 10 nmol/kg
Peptide B @ 30 nmol/kg
dLys-1Sar0 Peptide C @ 3 nmol/kg
dLys-1Sar0 Peptide C @ 10 nmol/kg
dLys-1Sar0 Peptide C @ 30 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 3 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 10 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 30 nmol/kg

FIG. 15B

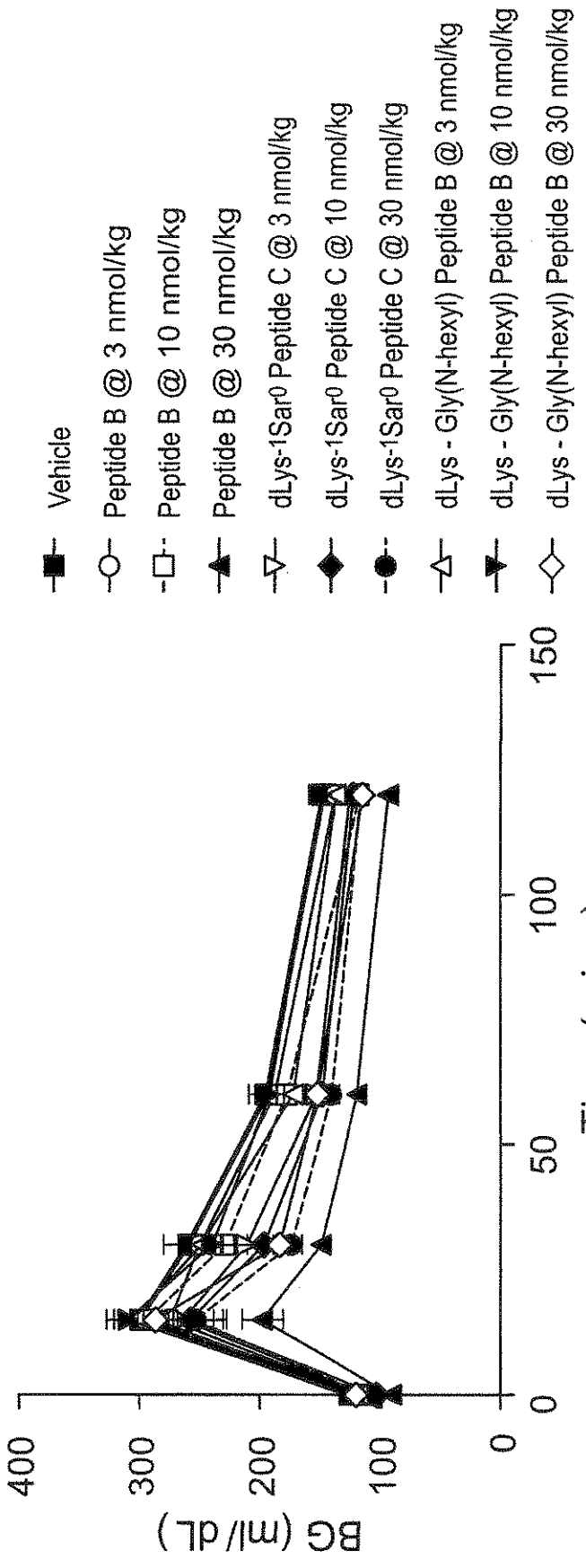

Blood Glucose Levels as a Function of Prodrug and Prodrug Concentration on Day 5
BG (ml/dL)
400
300
200
100
0
0
50
100
150
Time (mins)
Vehicle
Peptide B @ 3 nmol/kg
Peptide B @ 10 nmol/kg
Peptide B @ 30 nmol/kg
dLys-1Sar0 Peptide C @ 3 nmol/kg
dLys-1Sar0 Peptide C @ 10 nmol/kg
dLys-1Sar0 Peptide C @ 30 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 3 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 10 nmol/kg
dLys - Gly(N-hexyl) Peptide B @ 30 nmol/kg

FIG. 15C