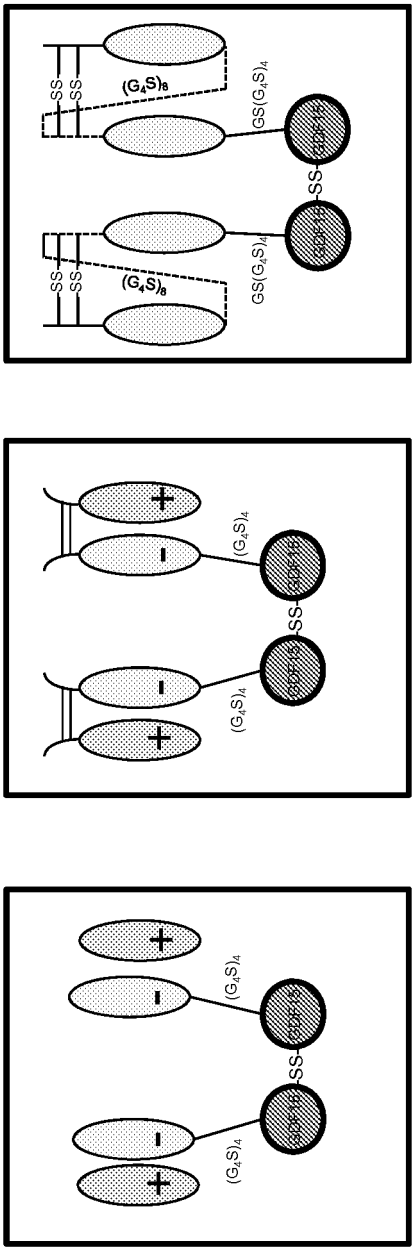
Figure 1



Dimer of DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+) construct

Dimer of CpmFc(-)-(G4S)4-GDF15:CpmFc(+) construct

Dimer of Fc-$(G_4S)_8$-Fc-$GS(G_4S)_4$-GDF15 construct

Figure 2

Evaluation of GDF15 constructs in food intake assay

Protein	ED50 (µg/kg)
DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)	8.4
DhCpmFc(+)-(G4S)4-GDF15:DhCpmFc(-)	3.6
DhCpmFc(-)-(G4S)4-GDF15(H6D):DhCpmFc(+)	7.9
DhCpmFc(+)-(G4S)4-GDF15(H6D):DhCpmFc(-)	15.5
DhCpmFc(+)-(G4S)4-GDF15(N3Q):DhCpmFc(-)	7.0
DhCpmFc(+)-GDF15:DhCpmFc(-)	21.8
DhCpmFc(+)-(G4)-GDF15:DhCpmFc(-)	12.1
DhCpmFc(+)-(G4S)2-GDF15:DhCpmFc(-)	2.4
DhCpmFc(+)-(G4Q)4-GDF15:DhCpmFc(-)	16.0
DhCpmFc(+)-(1K)-GDF15:DhCpmFc(-)	10.7
DhCpmFc(+)(L351C)-G4-GDF15:DhCpmFc(-)(L351C)	53.4
DhCpmFc(+)(S354C)-G4-GDF15:DhCpmFc(-)(Y349C)	21.1
CpmFc(+)-(G4S)4-GDF15:CpmFc(-)	87.2
Fc(G4S)8-Fc-GS(G4S)4-GDF15	16.5
Fc(G4S)3-Fc-GS(G4S)4-GDF15	25.9
Fc(G4S)5-Fc-GS(G4S)4-GDF15	30.7
hGDF15	118.7
hGDF15(H6D)	11.7

SUBSTITUTE SHEET (RULE 26)

Figure 3

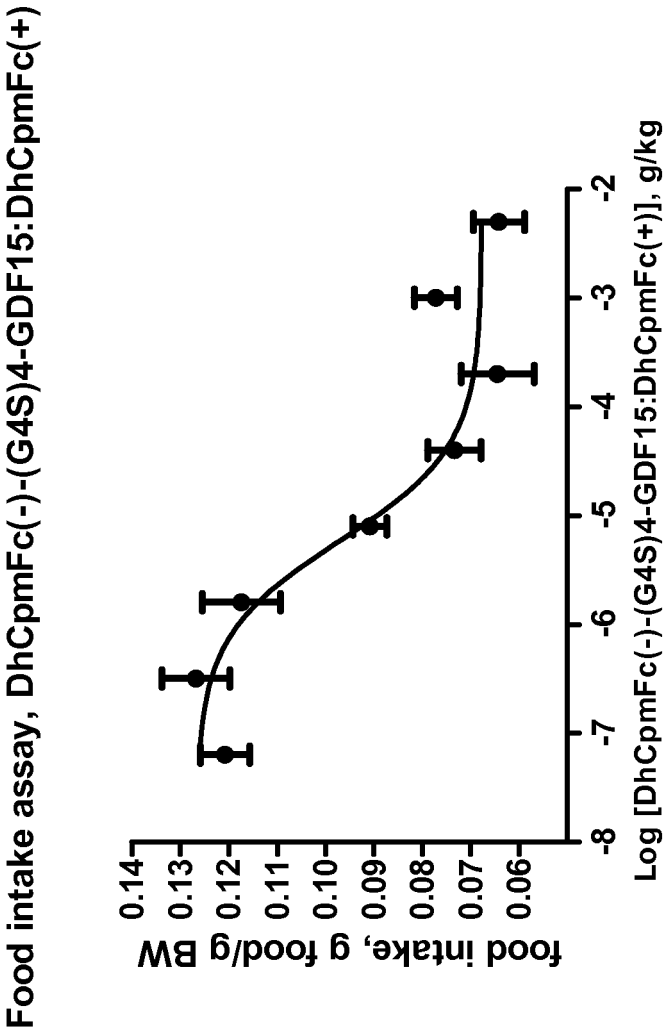

Food intake assay, DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-8
-7
-6
-5
-4
-3
-2
Log [DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)], g/kg

Figure 4

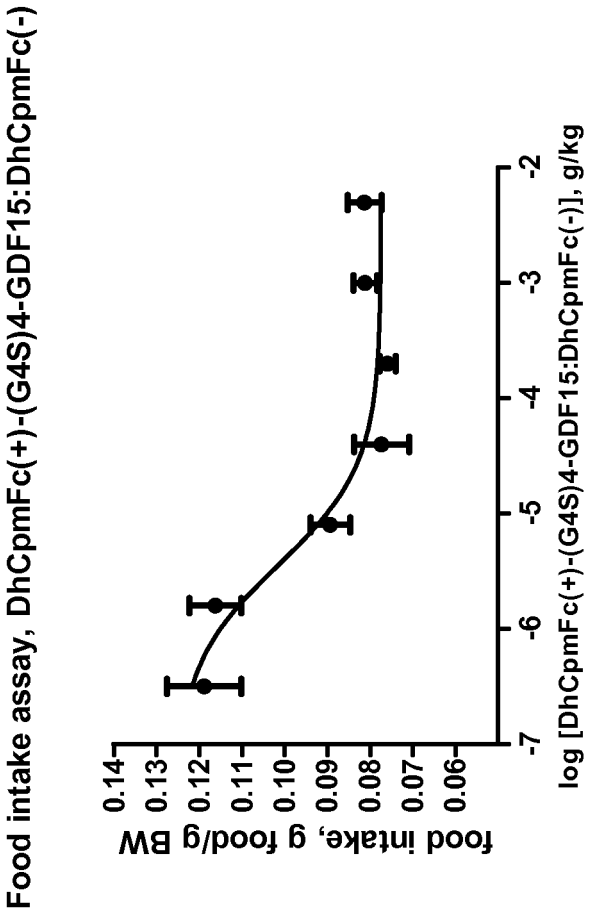

Food intake assay, DhCpmFc(+)-(G4S)4-GDF15:DhCpmFc(-)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(+)-(G4S)4-GDF15:DhCpmFc(-)], g/kg

Figure 5

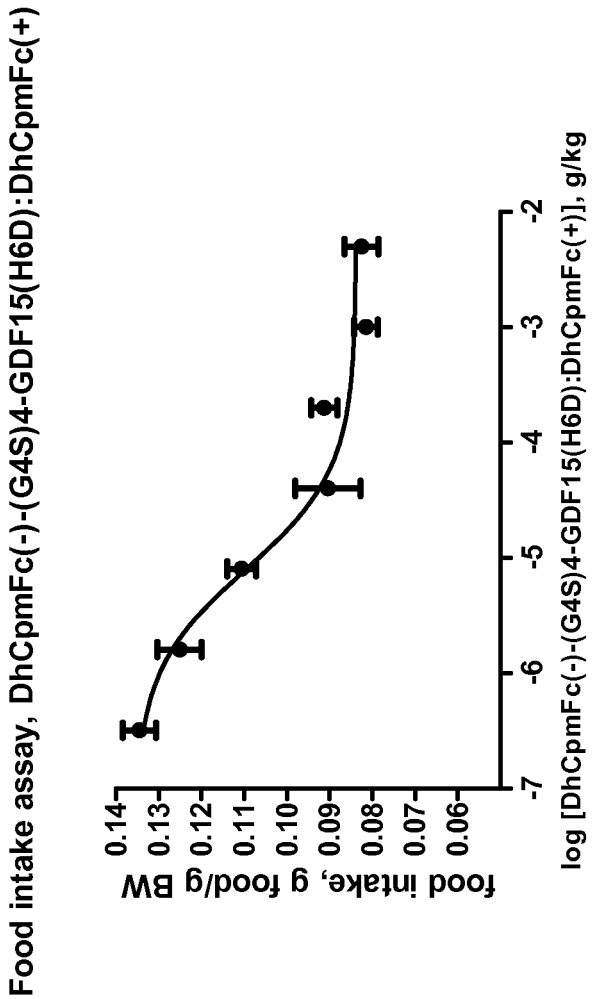

Food intake assay, DhCpmFc(-)-(G4S)4-GDF15(H6D):DhCpmFc(+)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(-)-(G4S)4-GDF15(H6D):DhCpmFc(+)], g/kg

Figure 6

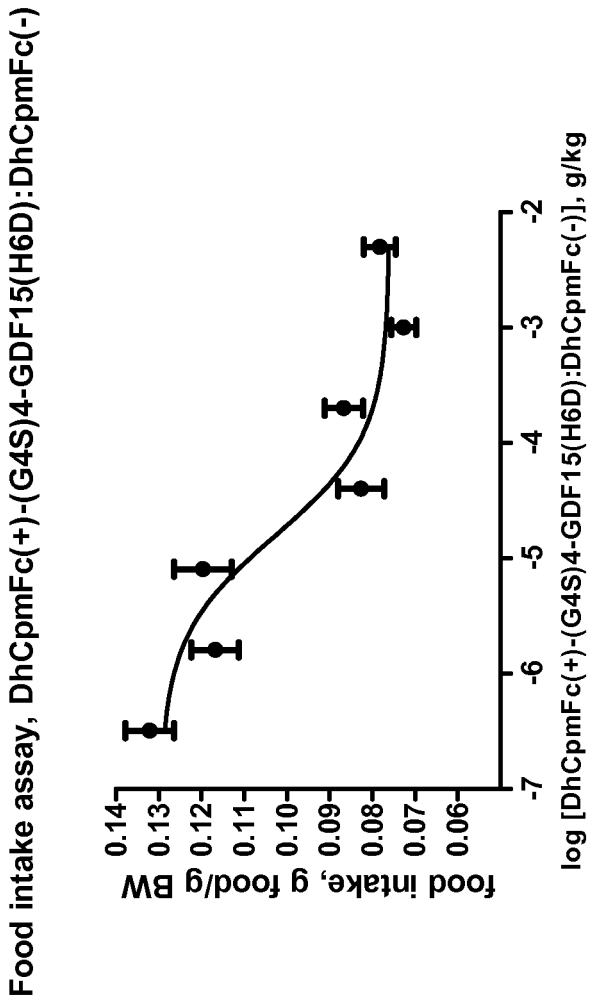

Food intake assay, DhCpmFc(+)-(G4S)4-GDF15(H6D):DhCpmFc(-)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(+)-(G4S)4-GDF15(H6D):DhCpmFc(-)], g/kg

Figure 7

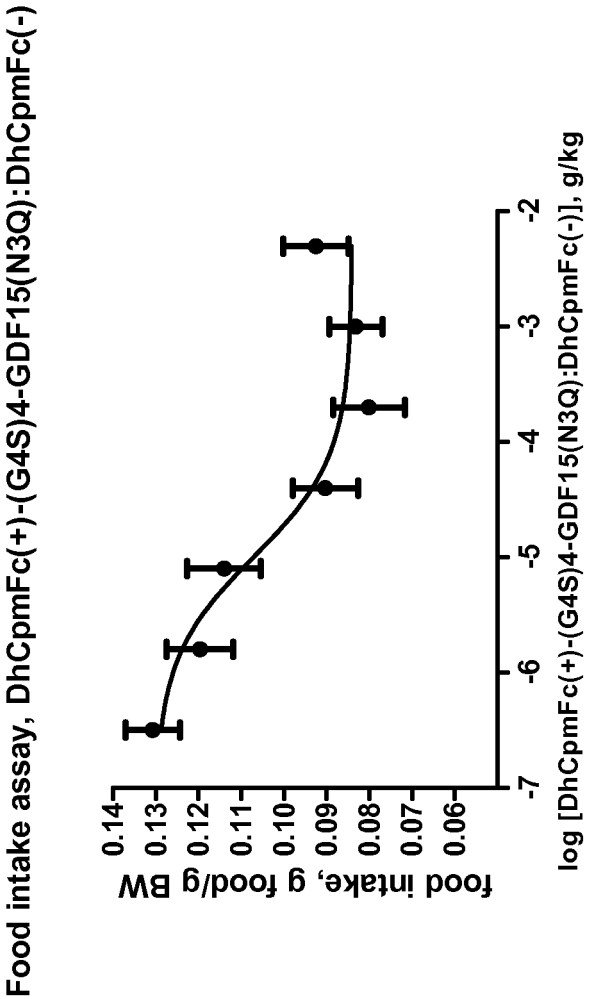

Food intake assay, DhCpmFc(+)-(G4S)4-GDF15(N3Q):DhCpmFc(-)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(+)-(G4S)4-GDF15(N3Q):DhCpmFc(-)], g/kg

Figure 8

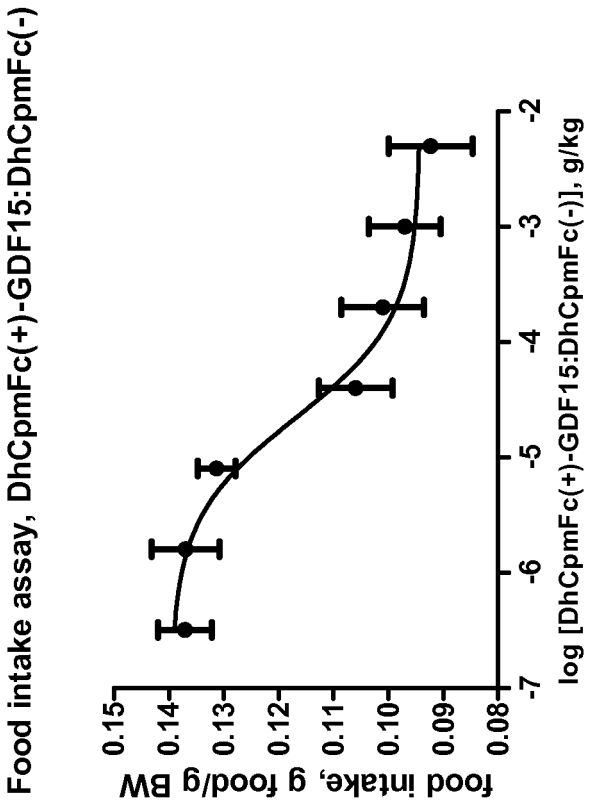

Food intake assay, DhCpmFc(+)-GDF15:DhCpmFc(-)
food intake, g food/g BW
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
-7
-6
-5
-4
-3
-2
log [DhCpmFc(+)-GDF15:DhCpmFc(-)], g/kg

Figure 9

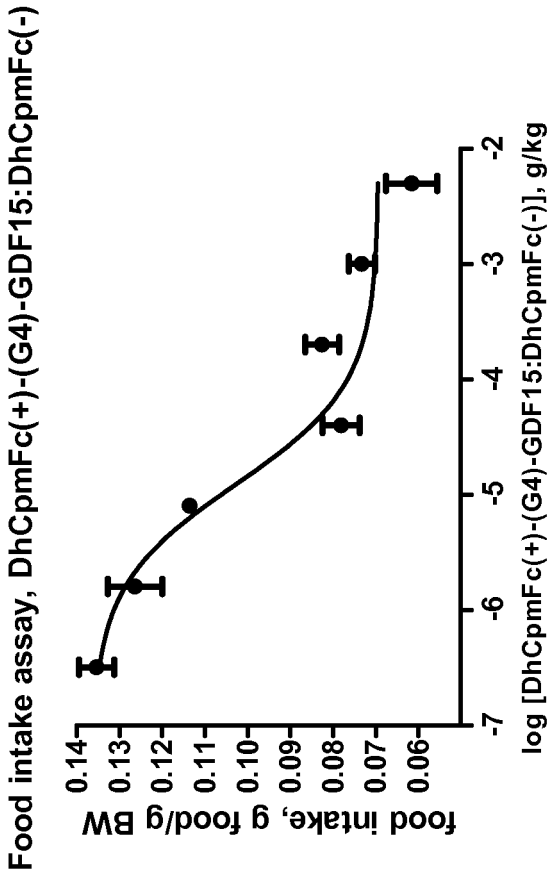

Food intake assay, DhCpmFc(+)-(G4)-GDF15:DhCpmFc(-)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(+)-(G4)-GDF15:DhCpmFc(-)], g/kg

Figure 10

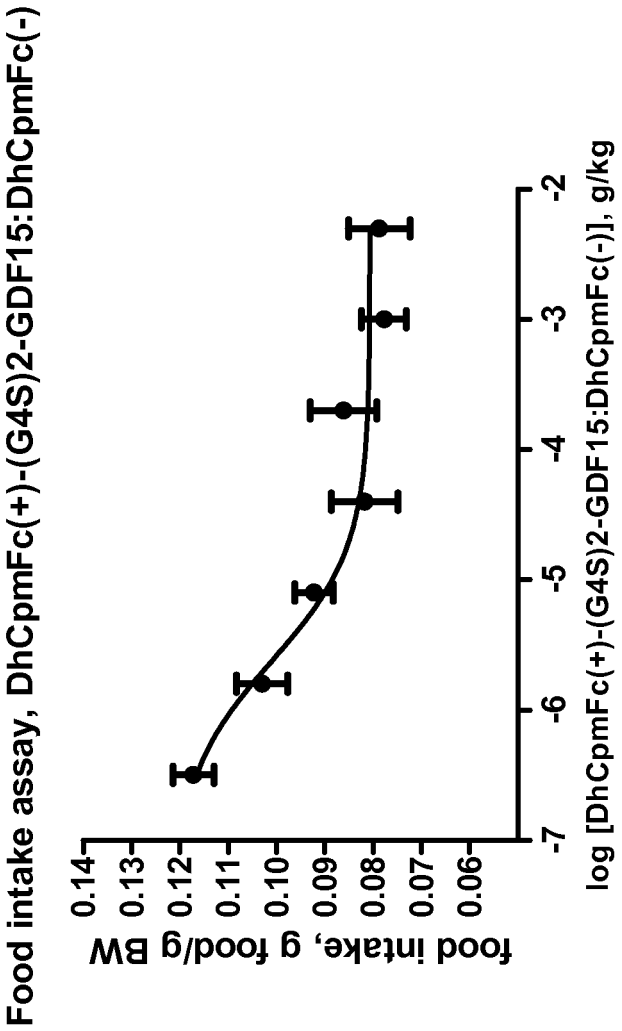

Food intake assay, DhCpmFc(+)-(G4S)2-GDF15:DhCpmFc(-)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(+)-(G4S)2-GDF15:DhCpmFc(-)], g/kg

Figure 11

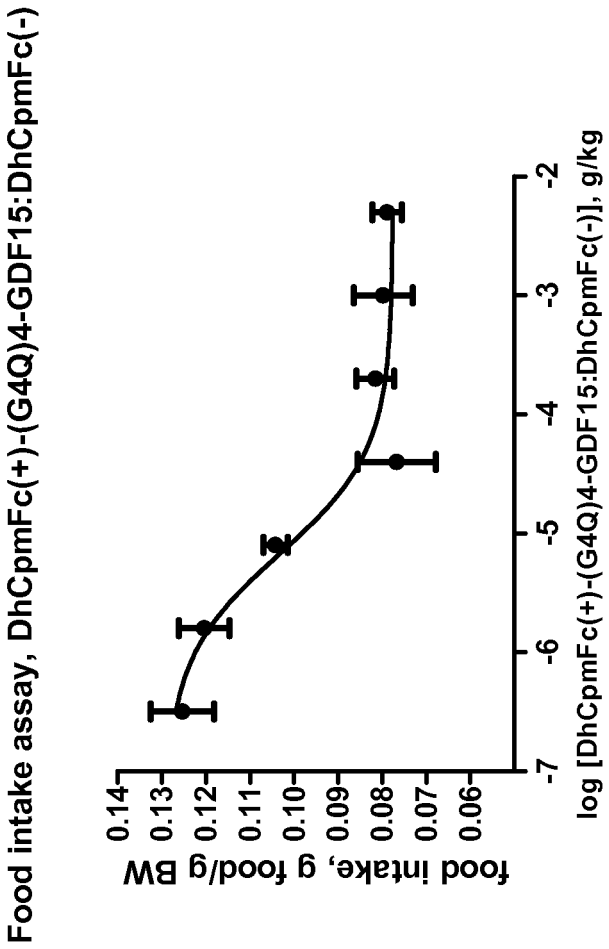

Food intake assay, DhCpmFc(+)-(G4Q)4-GDF15:DhCpmFc(-)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(+)-(G4Q)4-GDF15:DhCpmFc(-)], g/kg

Figure 12

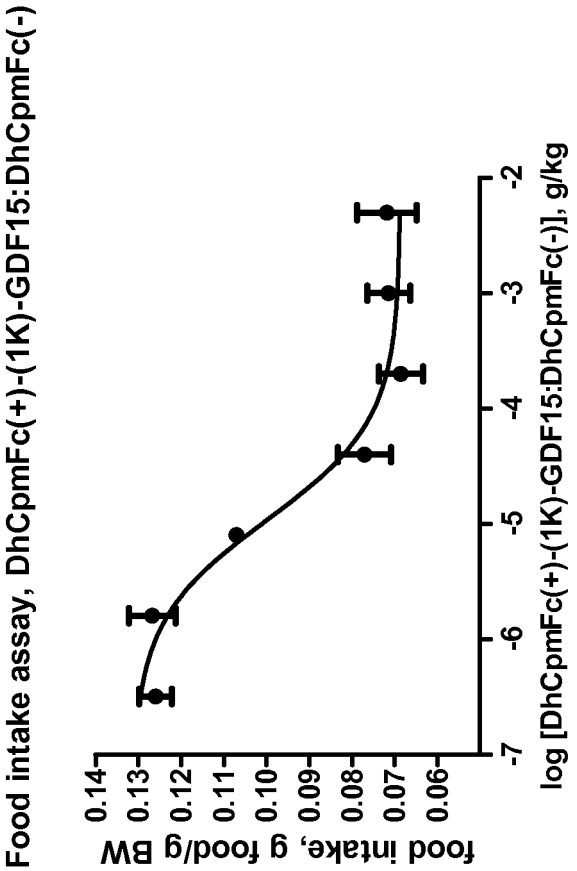

Food intake assay, DhCpmFc(+)-(1K)-GDF15:DhCpmFc(-)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(+)-(1K)-GDF15:DhCpmFc(-)], g/kg

Figure 13

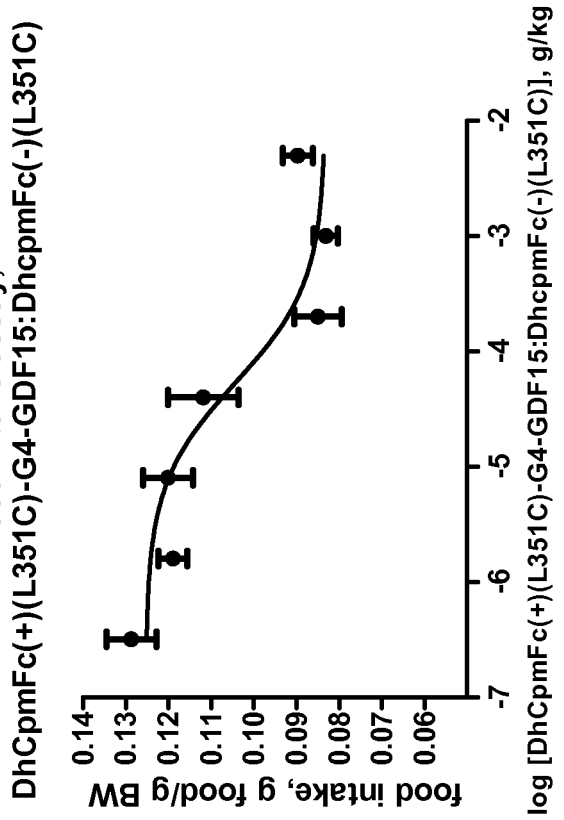

Food intake assay,
DhCpmFc(+)(L351C)-G4-GDF15:DhcpmFc(-)(L351C)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(+)(L351C)-G4-GDF15:DhcpmFc(-)(L351C)], g/kg

Figure 14

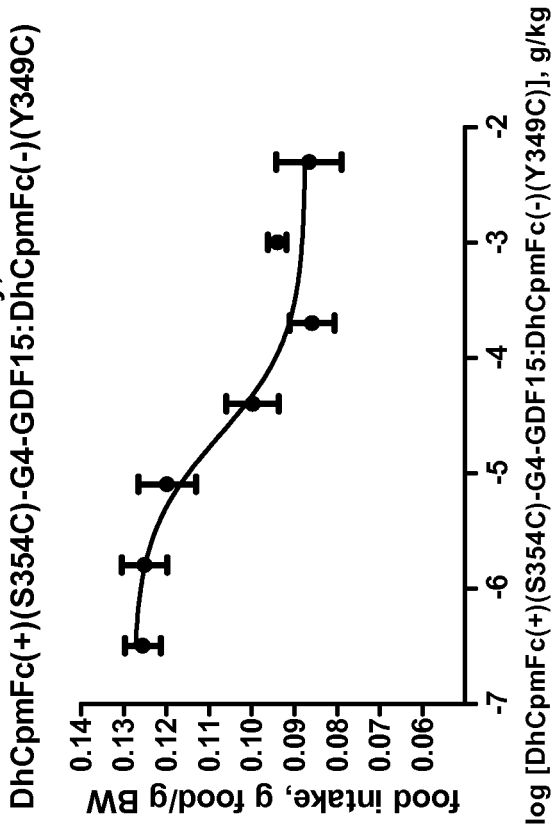

Food intake assay,
DhCpmFc(+)(S354C)-G4-GDF15:DhCpmFc(-)(Y349C)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [DhCpmFc(+)(S354C)-G4-GDF15:DhCpmFc(-)(Y349C)], g/kg

Figure 15

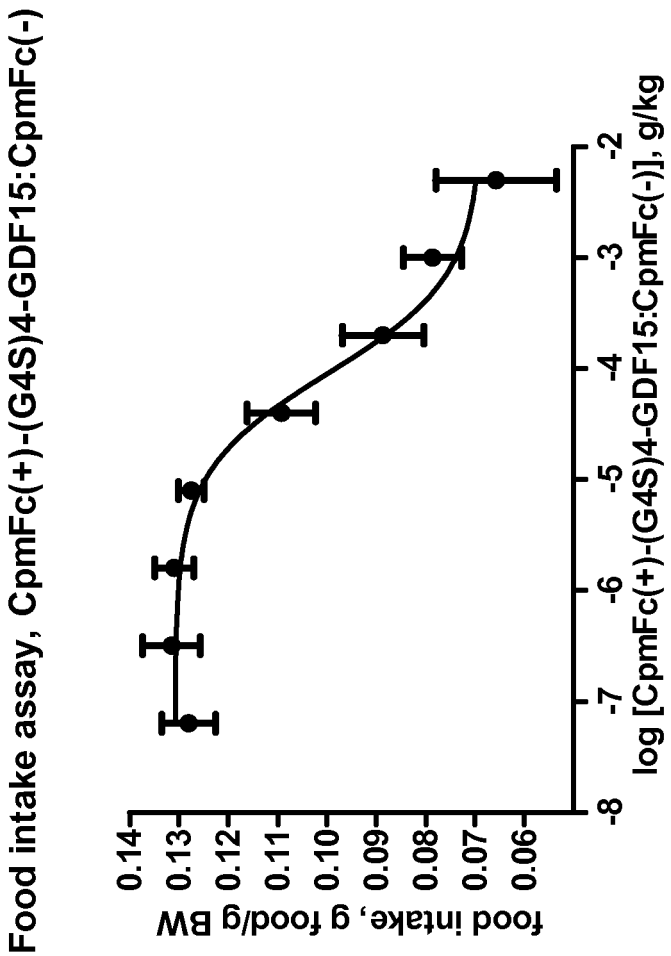

Food intake assay, CpmFc(+)-(G4S)4-GDF15:CpmFc(-)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-8
-7
-6
-5
-4
-3
-2
log [CpmFc(+)-(G4S)4-GDF15:CpmFc(-)], g/kg

Figure 16

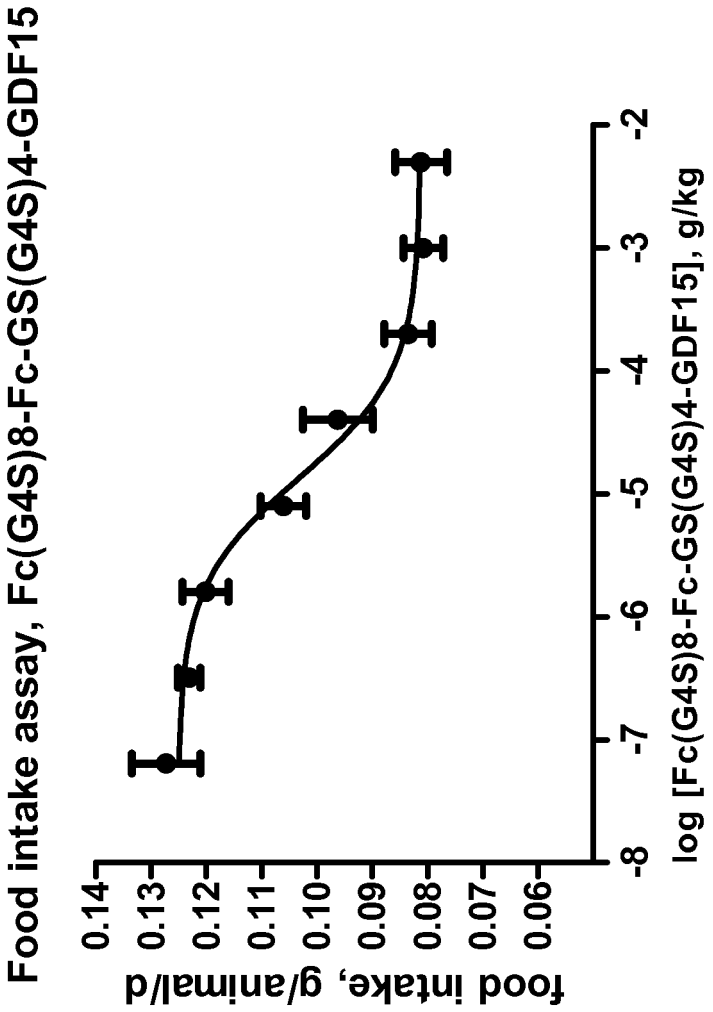

Food intake assay, Fc(G4S)8-Fc-GS(G4S)4-GDF15
food intake, g/animal/d
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-8
-7
-6
-5
-4
-3
-2
log [Fc(G4S)8-Fc-GS(G4S)4-GDF15], g/kg

Figure 17

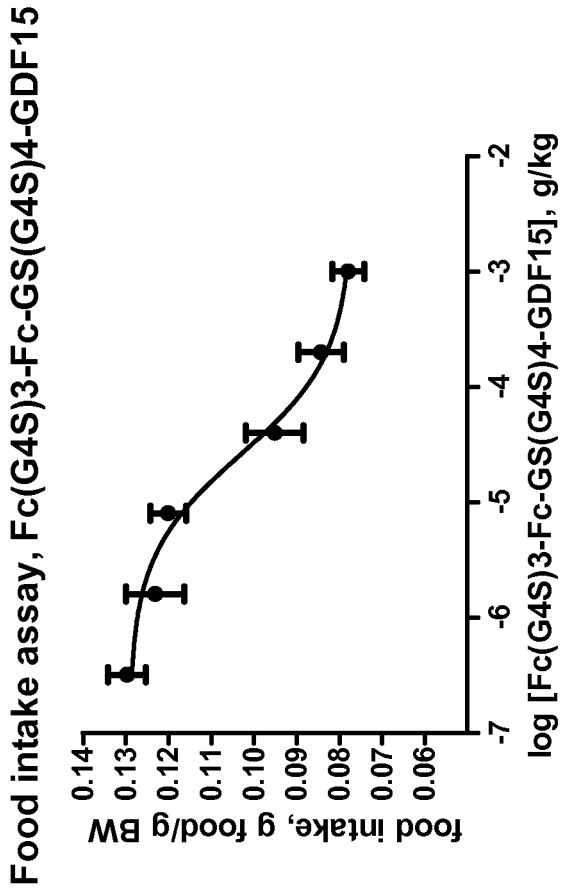

Food intake assay, Fc(G4S)3-Fc-GS(G4S)4-GDF15
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [Fc(G4S)3-Fc-GS(G4S)4-GDF15], g/kg

Figure 18

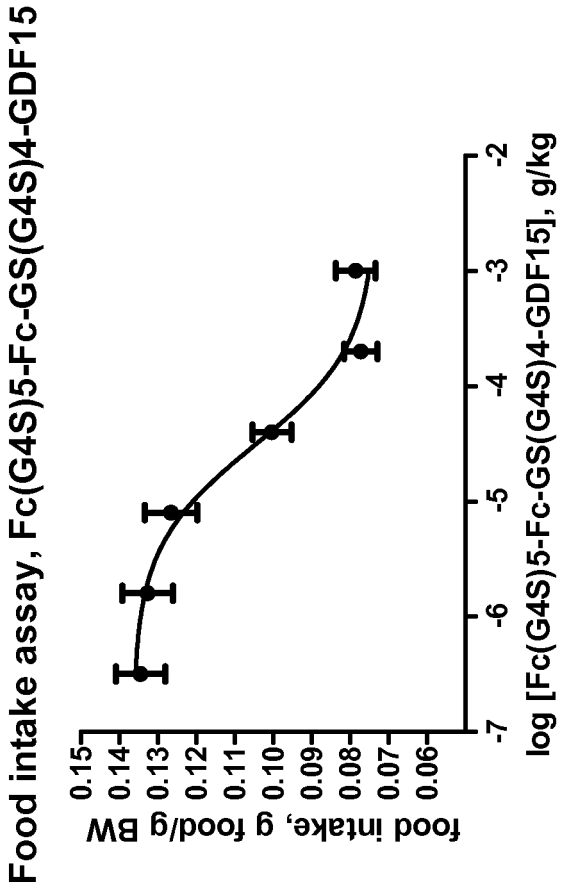

Food intake assay, Fc(G4S)5-Fc-GS(G4S)4-GDF15
food intake, g food/g BW
0.15
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [Fc(G4S)5-Fc-GS(G4S)4-GDF15], g/kg

Figure 19

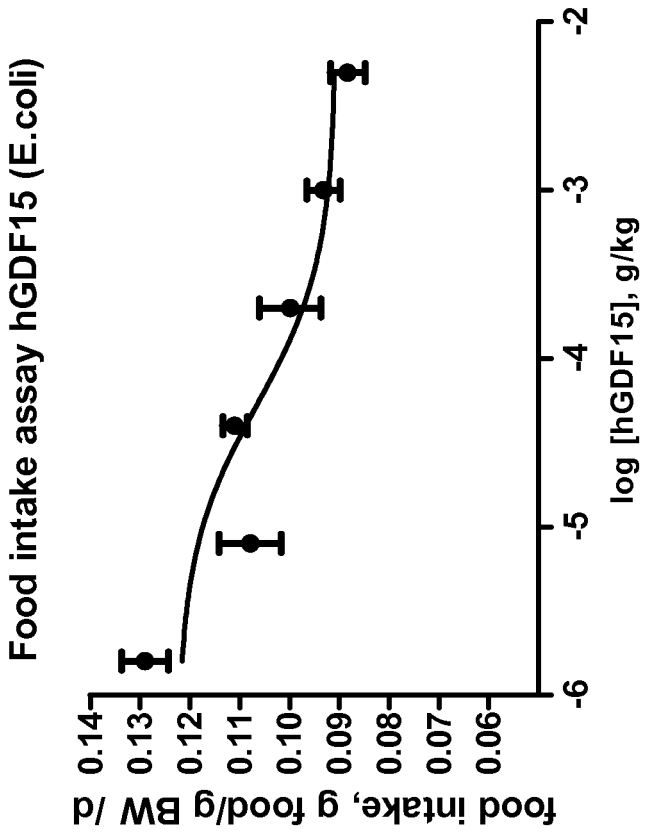

Food intake assay hGDF15 (E.coli)
food intake, g food/g BW /d
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-6
-5
-4
-3
-2
log [hGDF15], g/kg

Figure 20

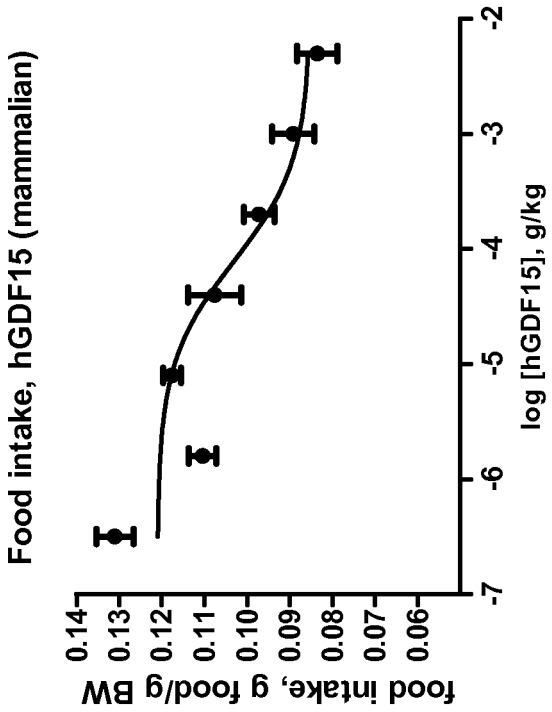

Food intake, hGDF15 (mammalian)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [hGDF15], g/kg

Figure 21

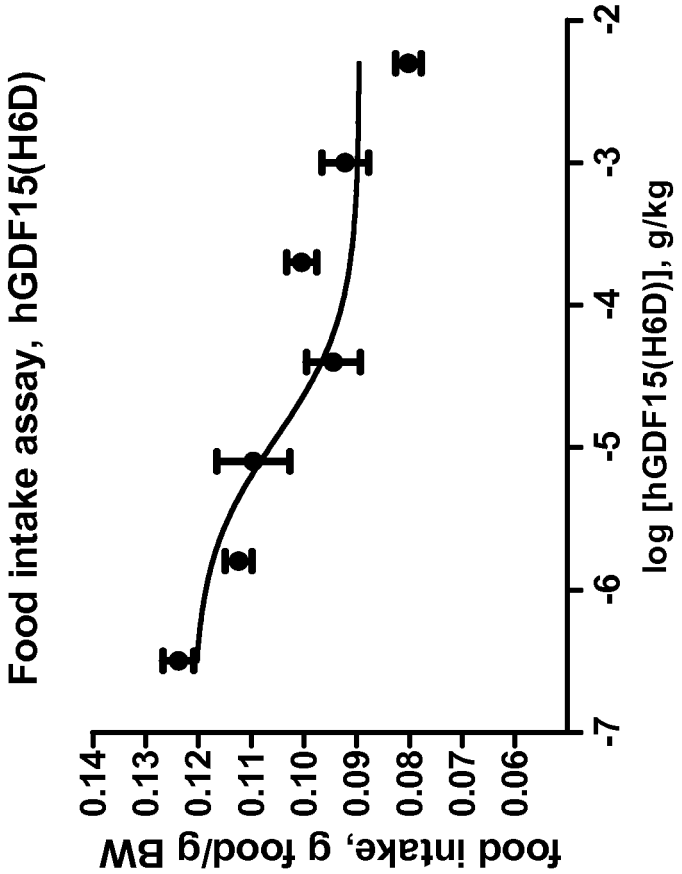

Food intake assay, hGDF15(H6D)
food intake, g food/g BW
0.14
0.13
0.12
0.11
0.10
0.09
0.08
0.07
0.06
-7
-6
-5
-4
-3
-2
log [hGDF15(H6D)], g/kg

Figure 22

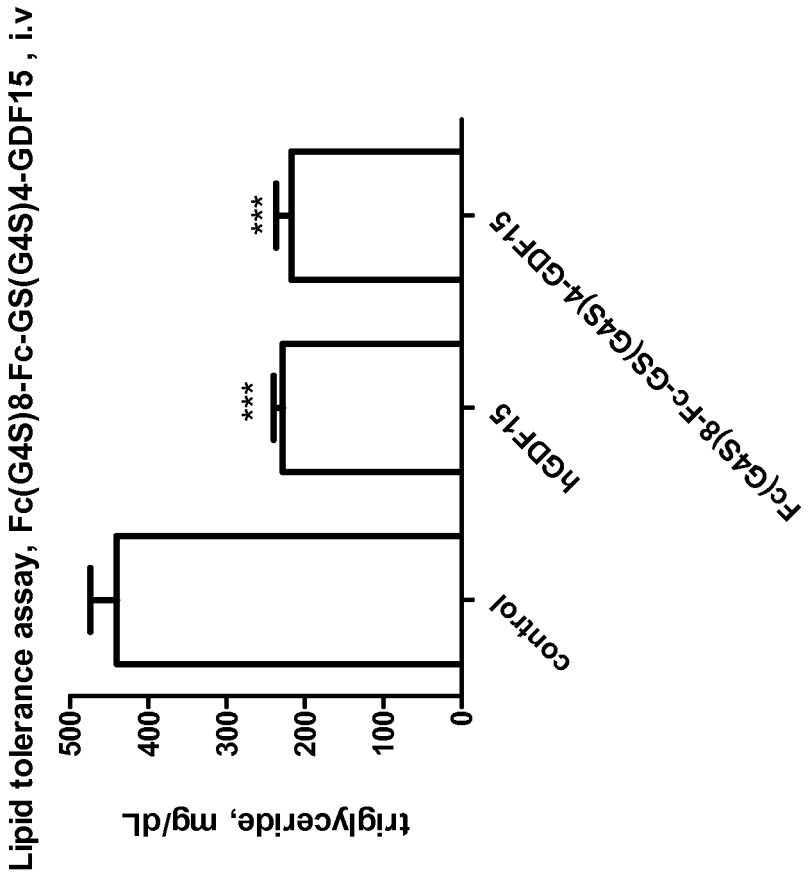

Lipid tolerance assay, Fc(G4S)8-Fc-GS(G4S)4-GDF15 , i.v
triglyceride, mg/dL
500
400
300
200
100
0
control
hGDF15
Fc(G4S)8-Fc-GS(G4S)4-GDF15
***
***

Figure 23

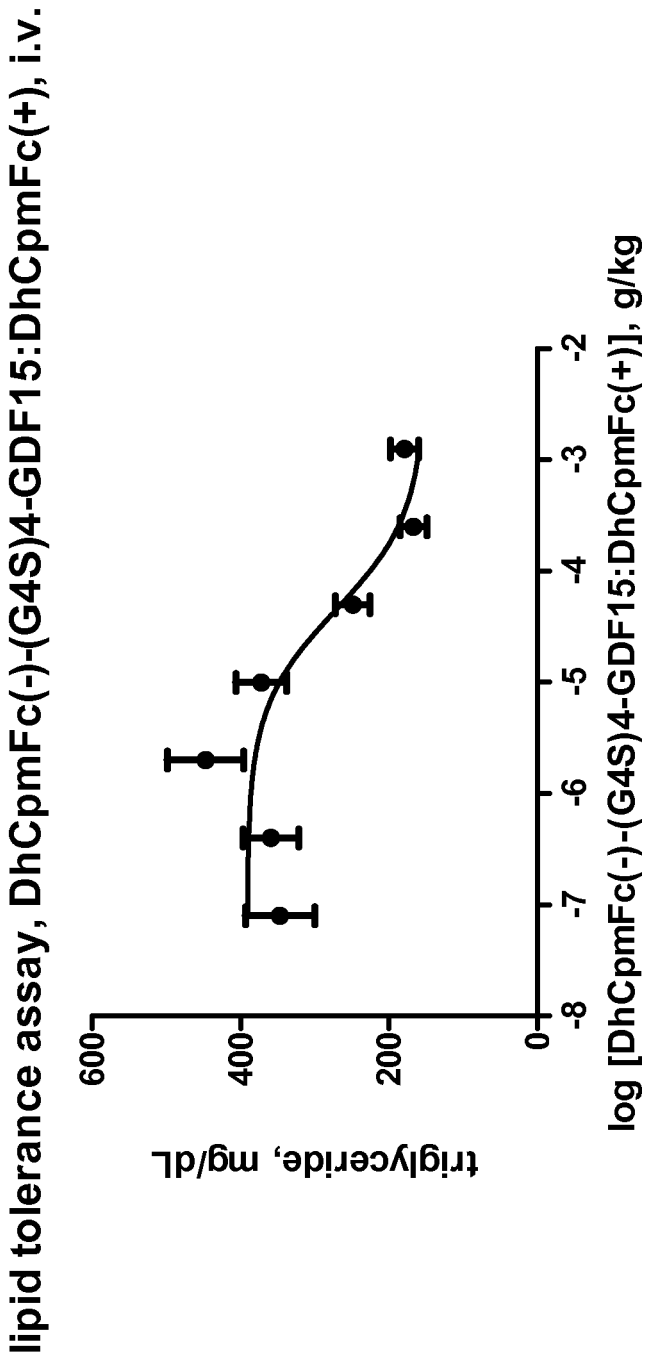

lipid tolerance assay, DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+), i.v.
triglyceride, mg/dL
600
400
200
0
-8
-7
-6
-5
-4
-3
-2
log [DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)], g/kg

Figure 24

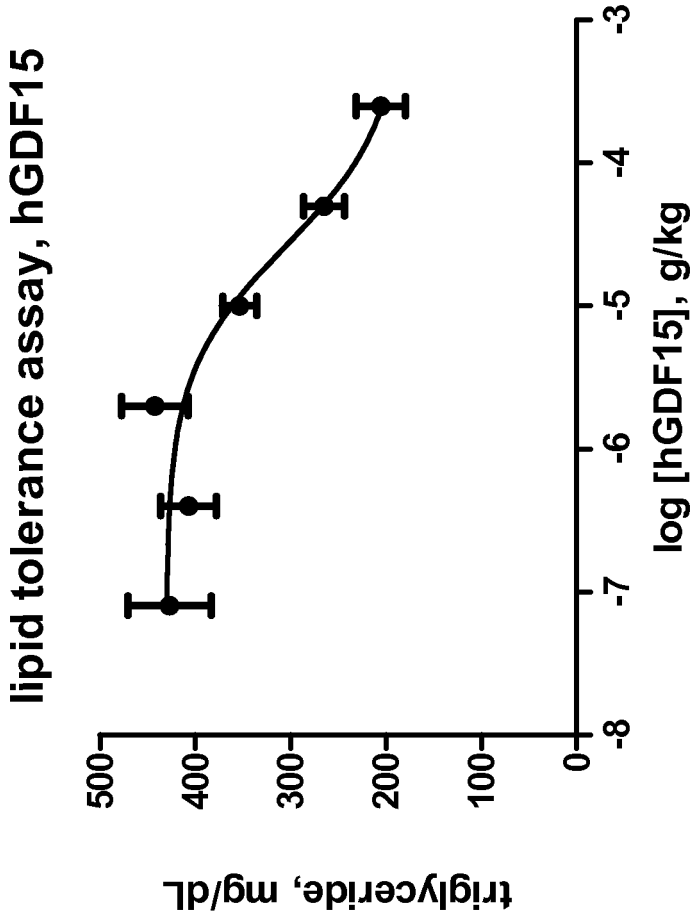

lipid tolerance assay, hGDF15
triglyceride, mg/dL
500
400
300
200
100
0
-8
-7
-6
-5
-4
-3
log [hGDF15], g/kg

Figure 25

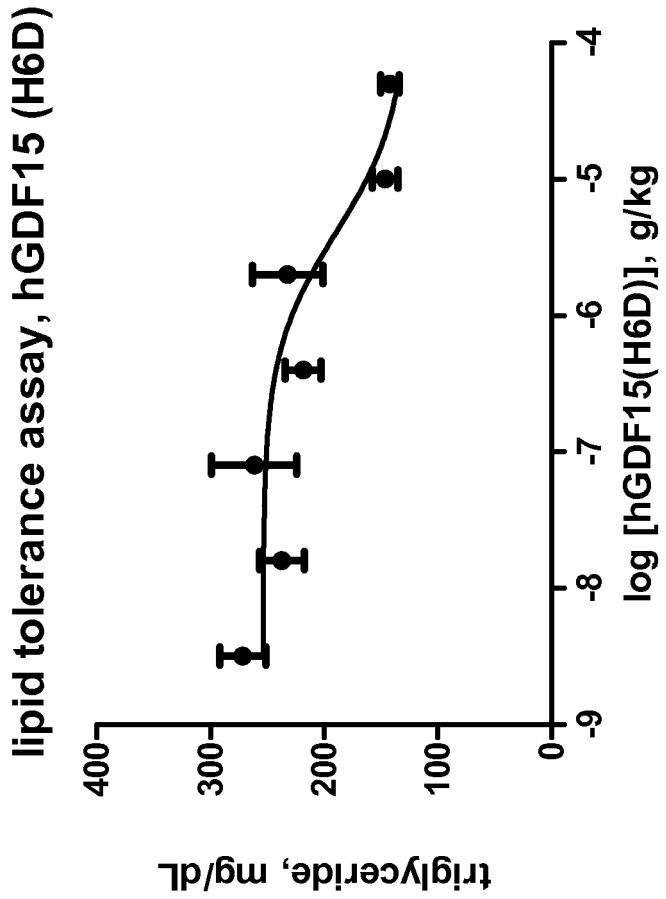
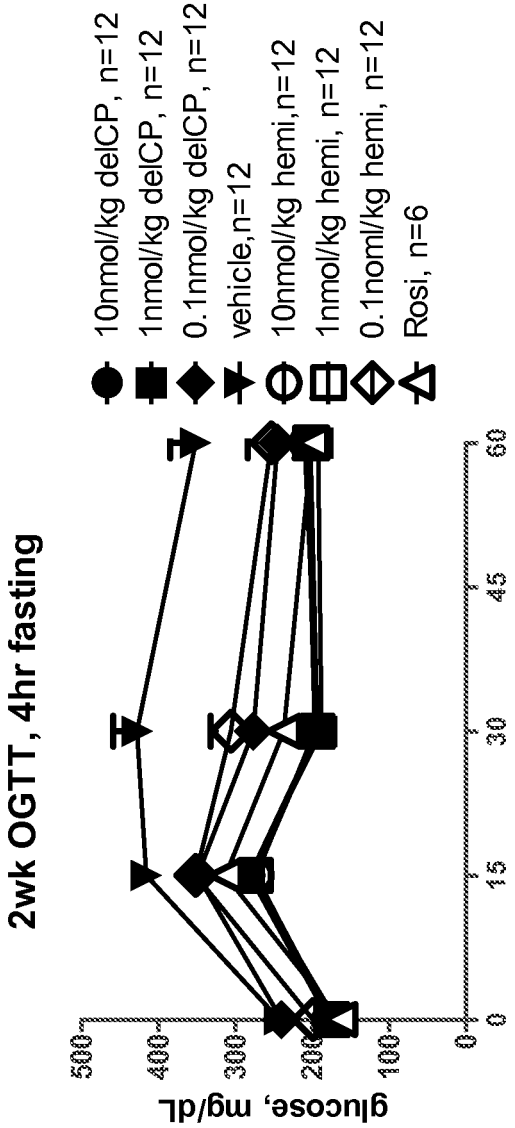

lipid tolerance assay, hGDF15 (H6D)
triglyceride, mg/dL
400
300
200
100
0
-9
-8
-7
-6
-5
-4
log [hGDF15(H6D)], g/kg

Figure 26

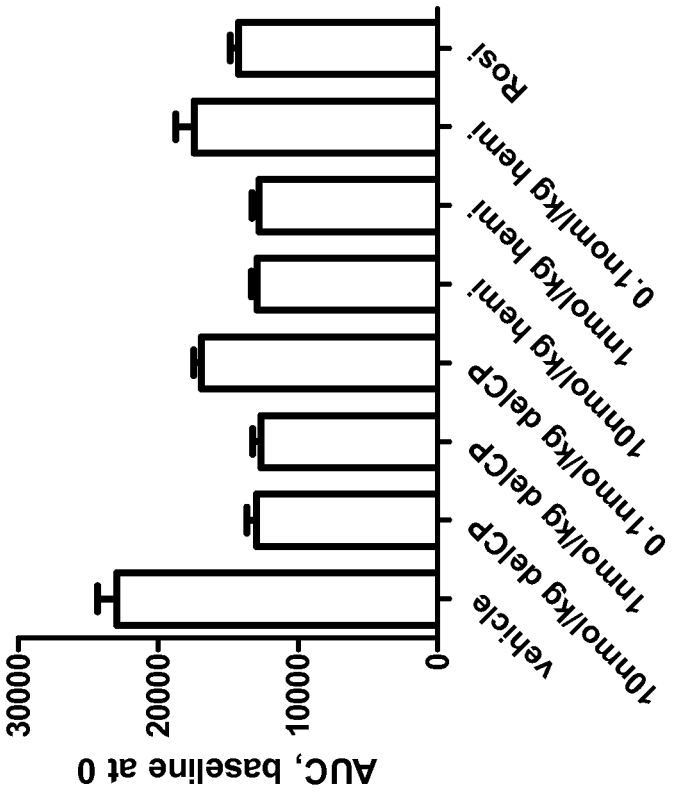


	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 0.1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
0min	*	ns	ns	ns	*	ns	ns
15min	****	****	ns	****	****	ns	**
30min	****	****	****	****	****	****	****
60min	****	****	****	****	****	***	****

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

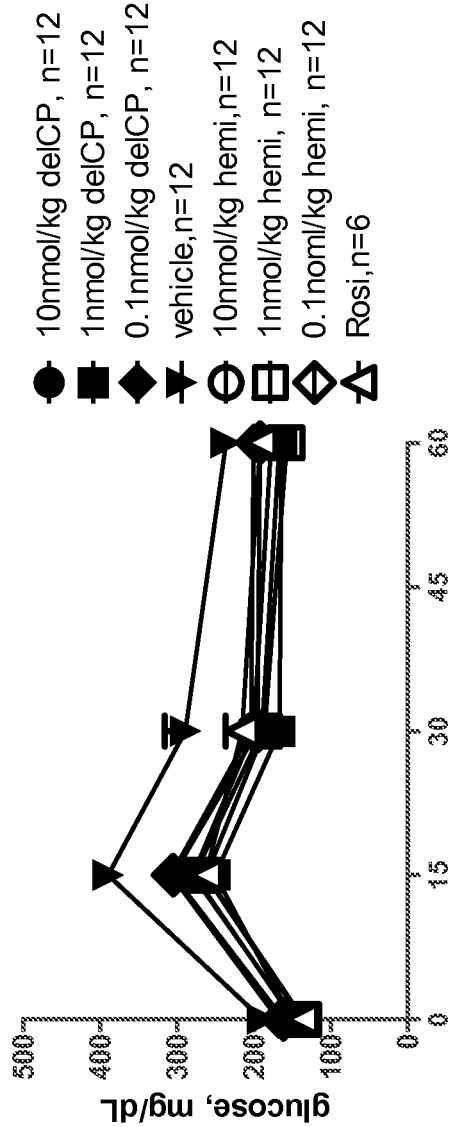
delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

Figure 27



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

Figure 28

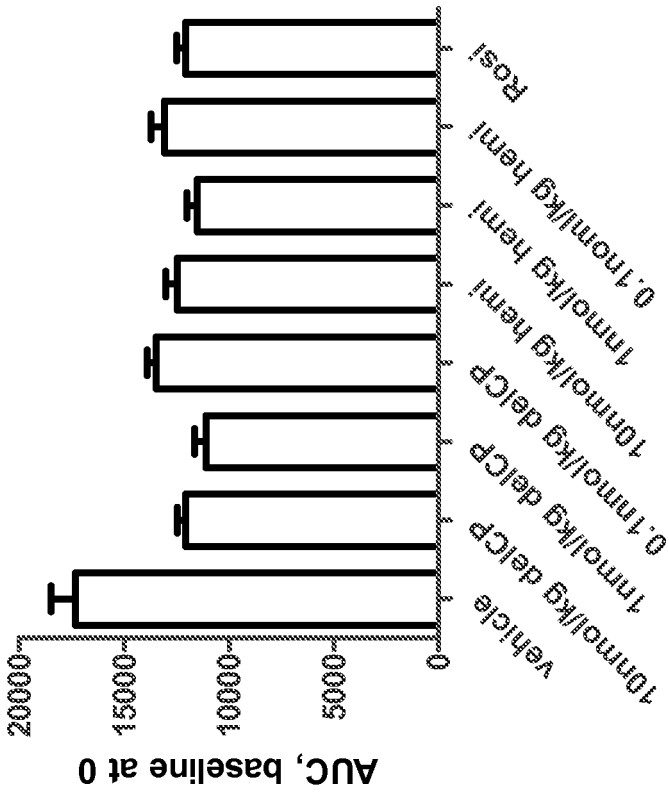


	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 0.1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
0min	ns	ns	ns	ns	ns	ns	ns
15min	****	****	****	****	****	****	****
30min	****	****	****	****	****	****	*
60min	**	**	ns	*	***	ns	ns

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

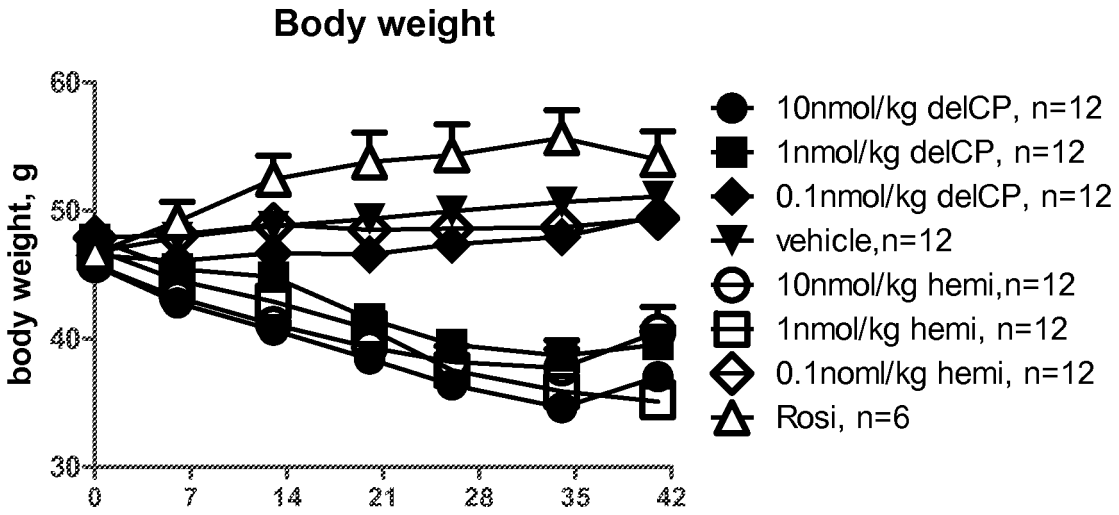
delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

Figure 29



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

Figure 30



	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 0.1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
d0	ns	ns	ns	ns	ns	ns	ns
d6	**	ns	ns	*	ns	ns	ns
d13	****	ns	ns	****	***	ns	ns
d20	****	****	ns	****	****	ns	ns
d26	****	****	ns	****	****	ns	ns
d34	****	****	ns	****	****	ns	ns
d41	****	****	ns	****	****	ns	ns

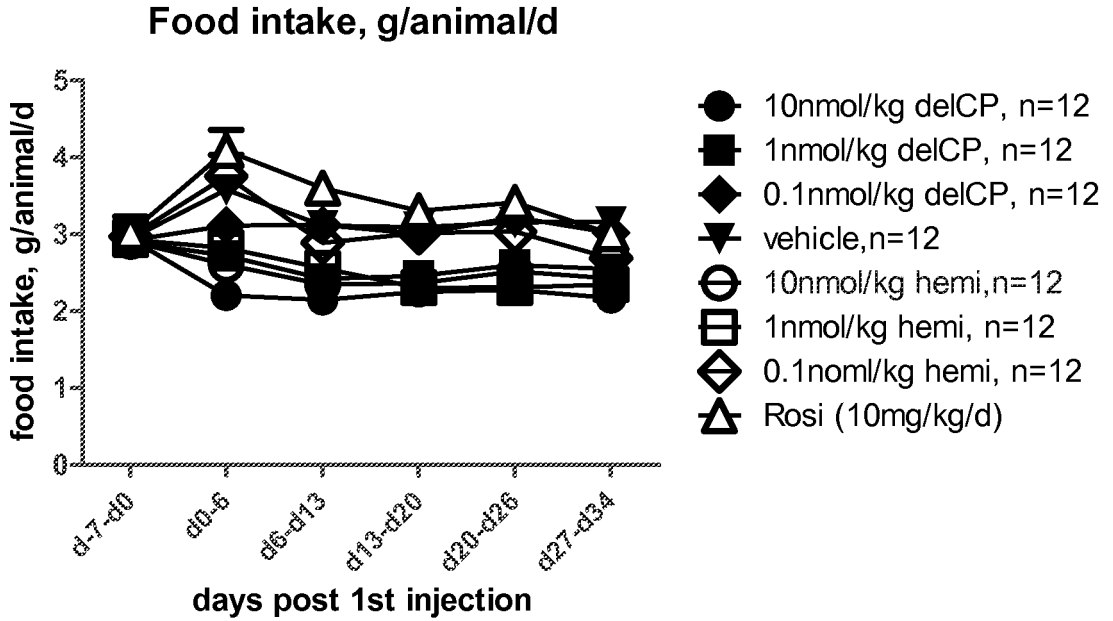
* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

SUBSTITUTE SHEET (RULE 26)

SUBSTITUTE SHEET (RULE 26)

Figure 31



Last injection on d28

	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 0.1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
d-7-d0	ns	ns	ns	ns	ns	ns	ns
d0-6	****	*	ns	***	*	ns	ns
d6-d13	**	ns	ns	ns	ns	ns	ns
d13-d20	**	ns	ns	*	**	ns	ns
d20-d26	*	ns	ns	ns	*	ns	ns
d27-d34	**	ns	ns	*	*	ns	ns

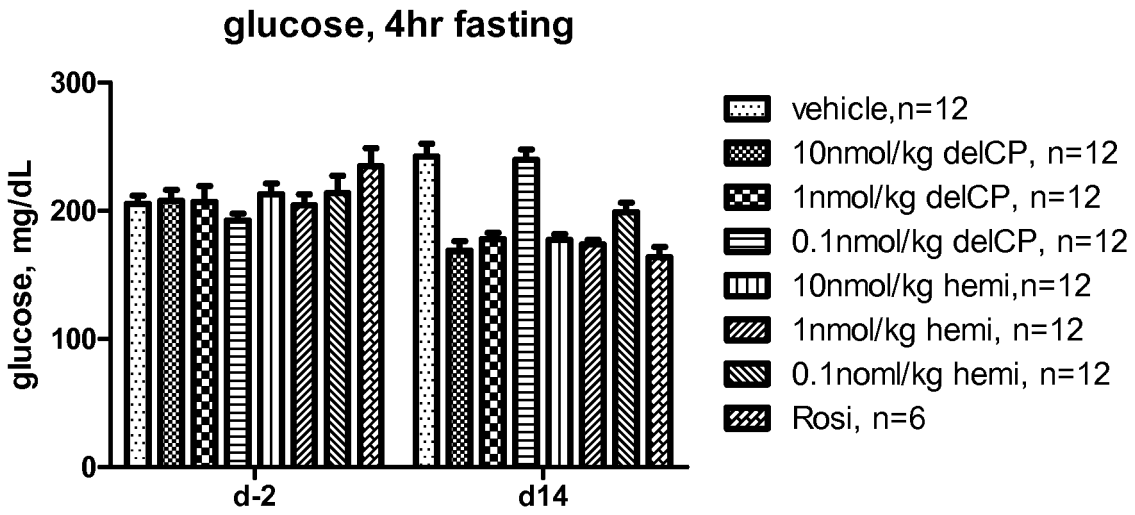
* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)

hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

SUBSTITUTE SHEET (RULE 26)

Figure 32

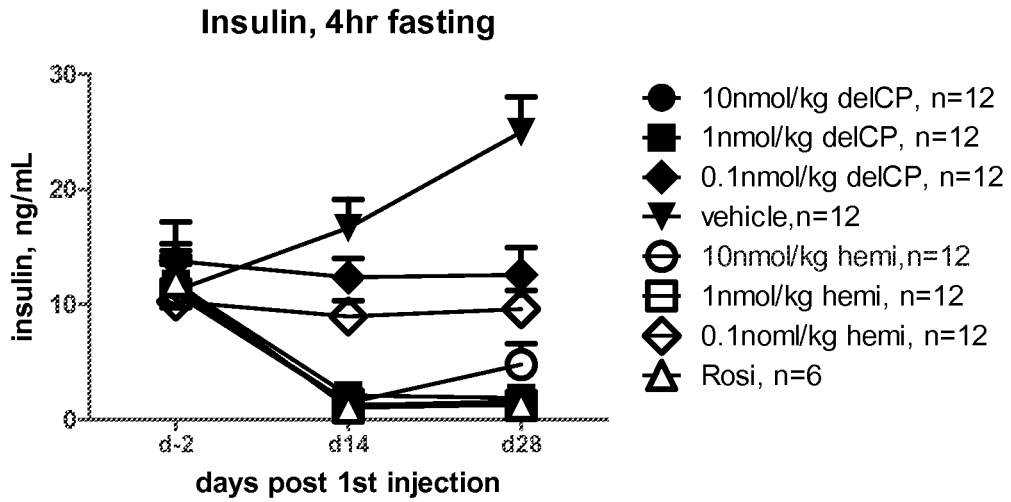


	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 0.1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
d-2	ns	ns	ns	ns	ns	ns	ns
d14	****	****	ns	****	****	**	****

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

Figure 33



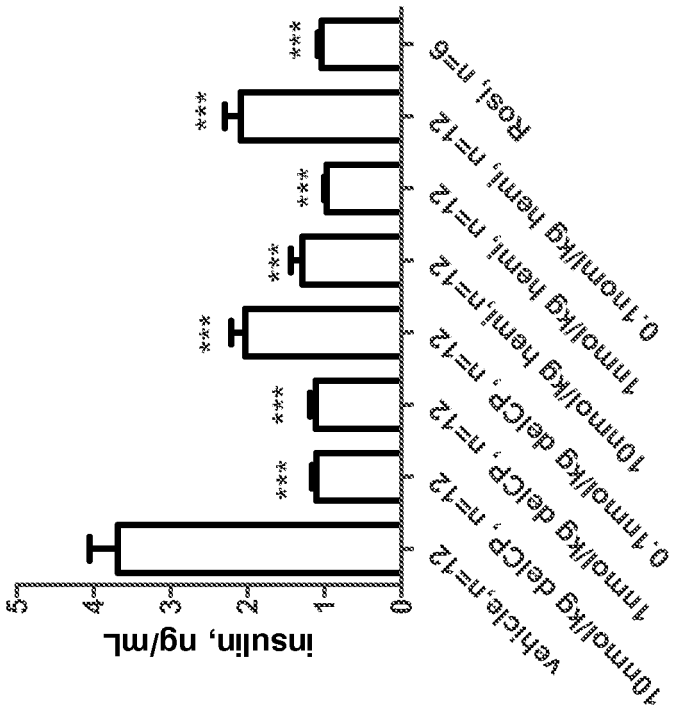
	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 0.1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
d-2	ns	ns	ns	ns	ns	ns	ns
d14	****	****	ns	****	****	ns	****
d28	****	****	****	****	****	****	****

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

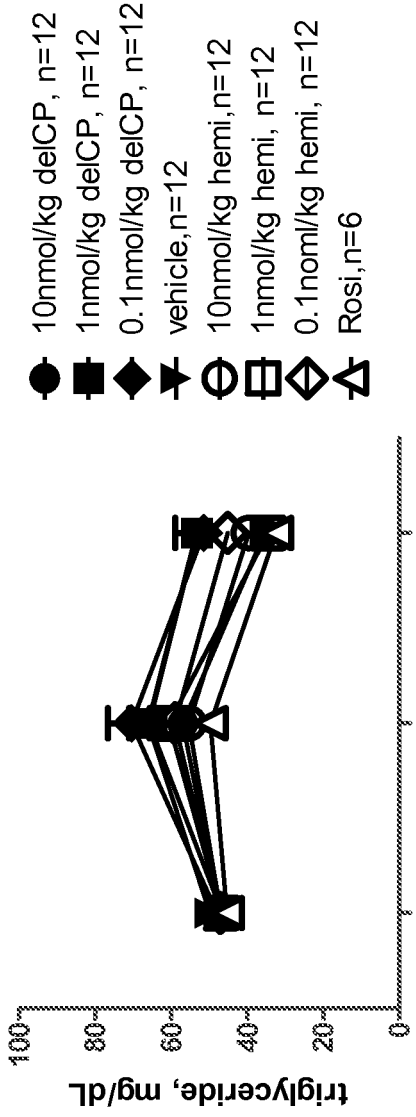
SUBSTITUTE SHEET (RULE 26)

Figure 34



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

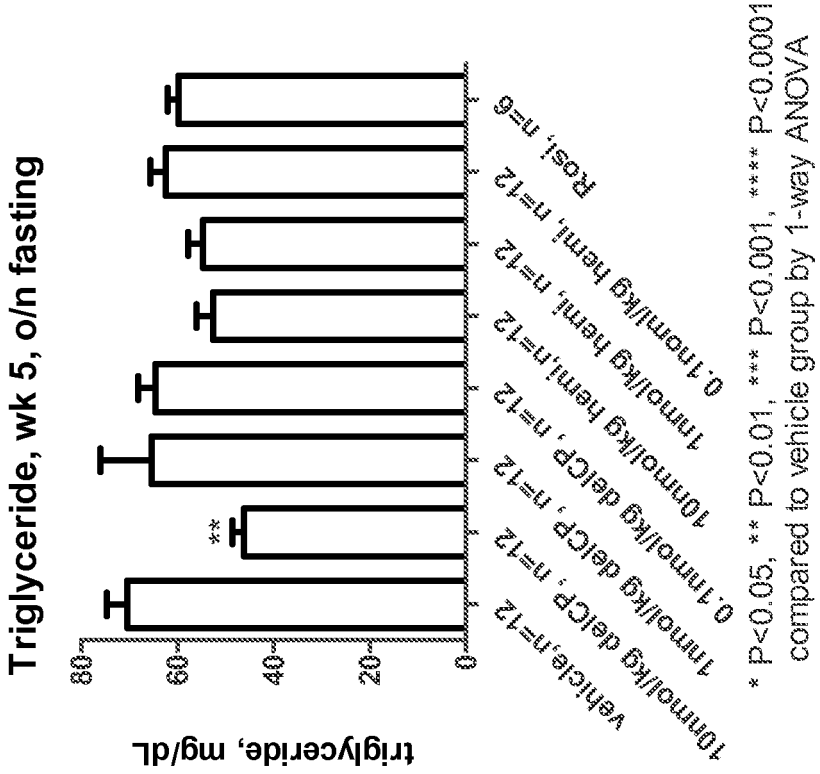
Figure 35



	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 0.1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
d-2	ns	ns	ns	ns	ns	ns	ns
d14	ns	ns	ns	ns	ns	ns	ns
d28	*	ns	ns	ns	*	ns	*

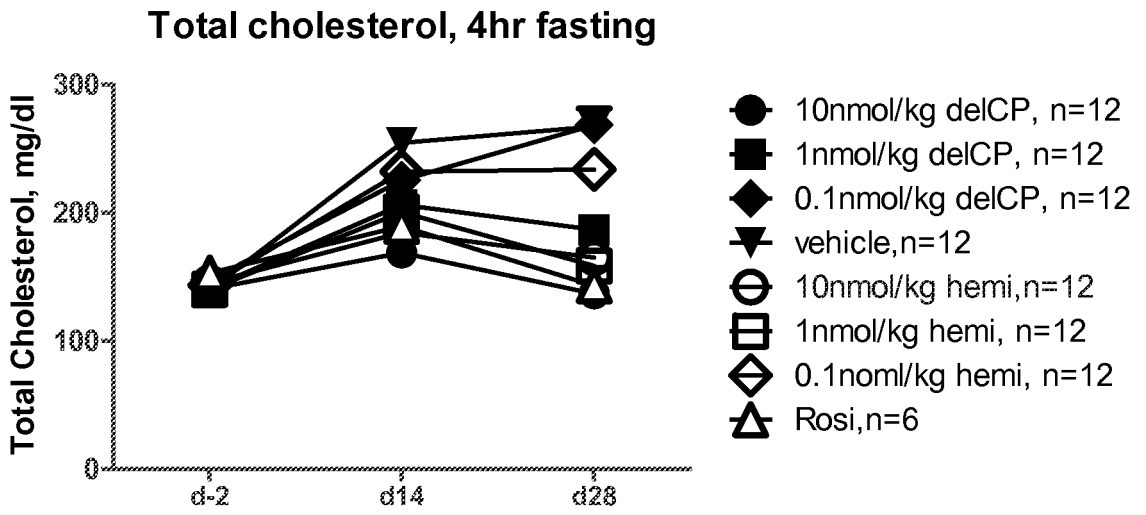
* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

Figure 36



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

Figure 37



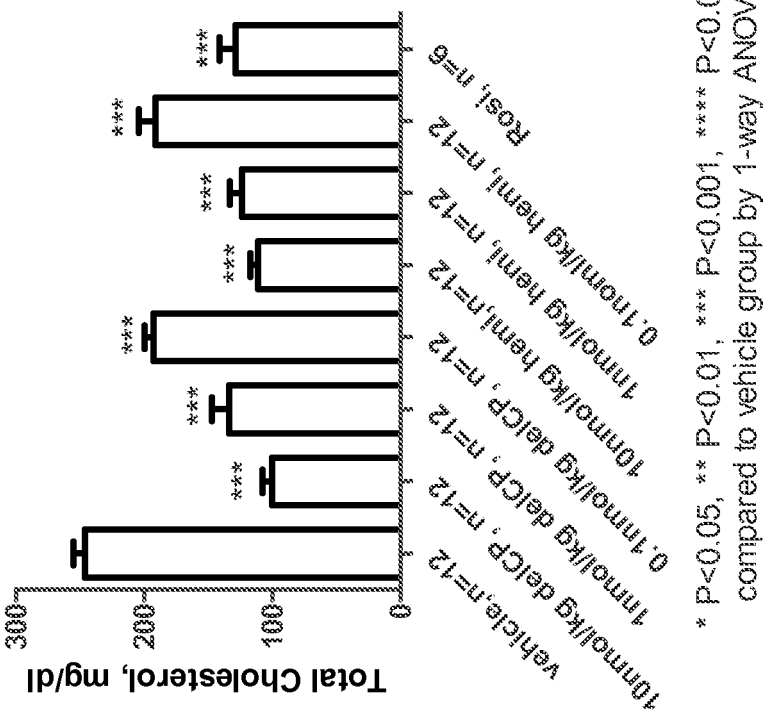
	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 0.1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
d-2	ns	ns	ns	ns	ns	ns	ns
d14	****	*	ns	****	**	ns	**
d28	****	****	ns	****	****	ns	****

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

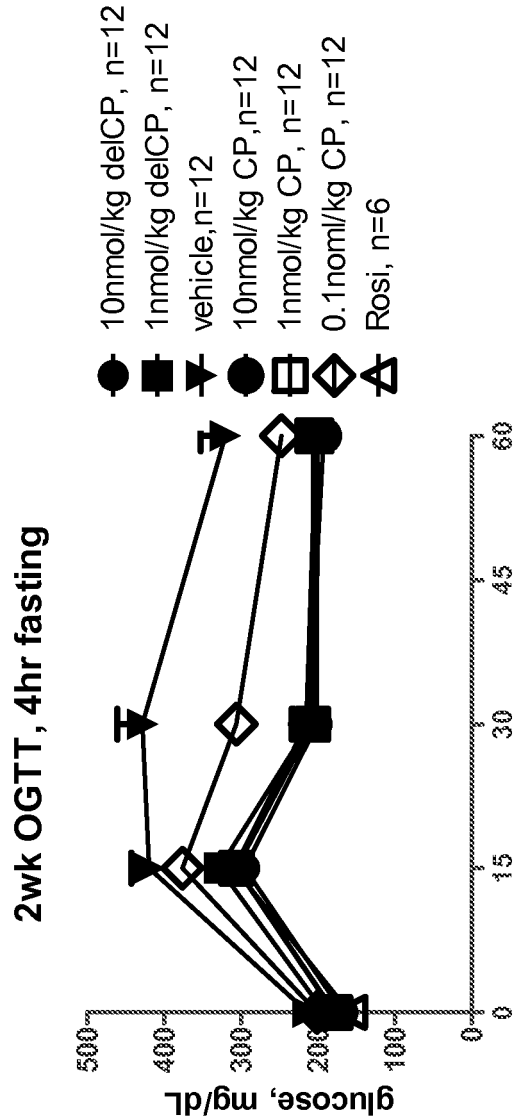
SUBSTITUTE SHEET (RULE 26)

Figure 38



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
hemi: Fc(G4S)8-Fc-GS(G4S)4-GDF15

Figure 39

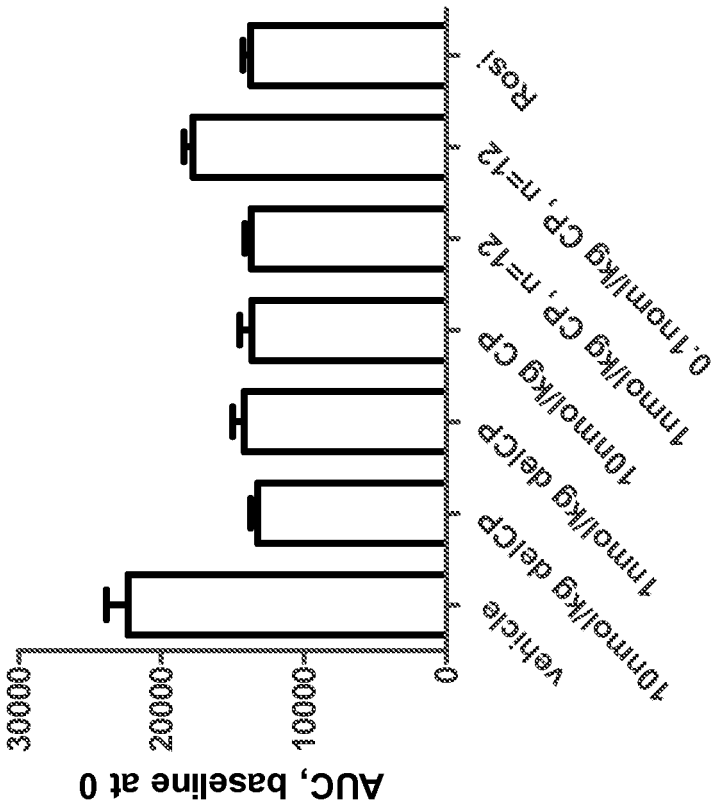


	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 10nmol/kg CP	vehicle vs 1nmol/kg CP	vehicle vs 0.1noml/kg CP	vehicle vs Rosi
0min	ns	ns	ns	ns	ns	ns
15min	****	***	****	****	ns	**
30min	****	****	****	****	****	****
60min	****	****	****	****	*	***

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

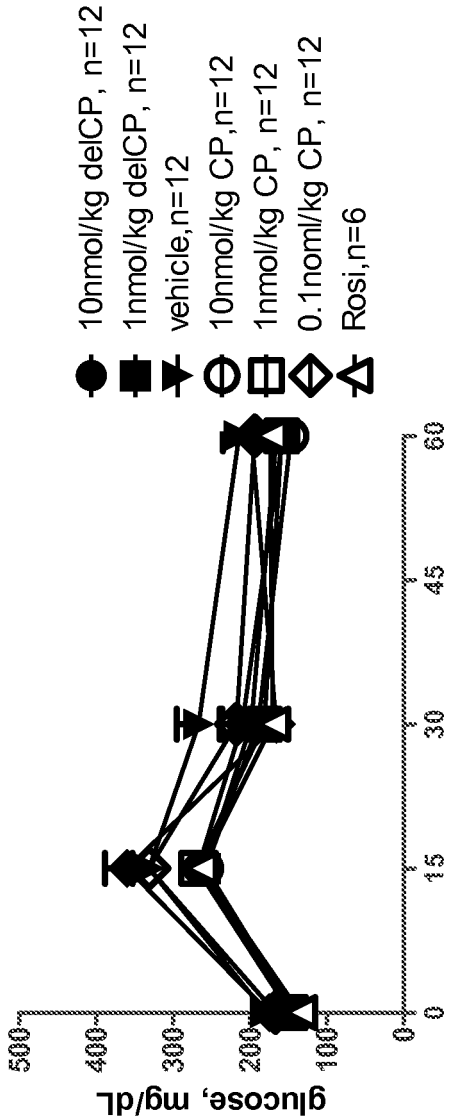
delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

Figure 40



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

Figure 41

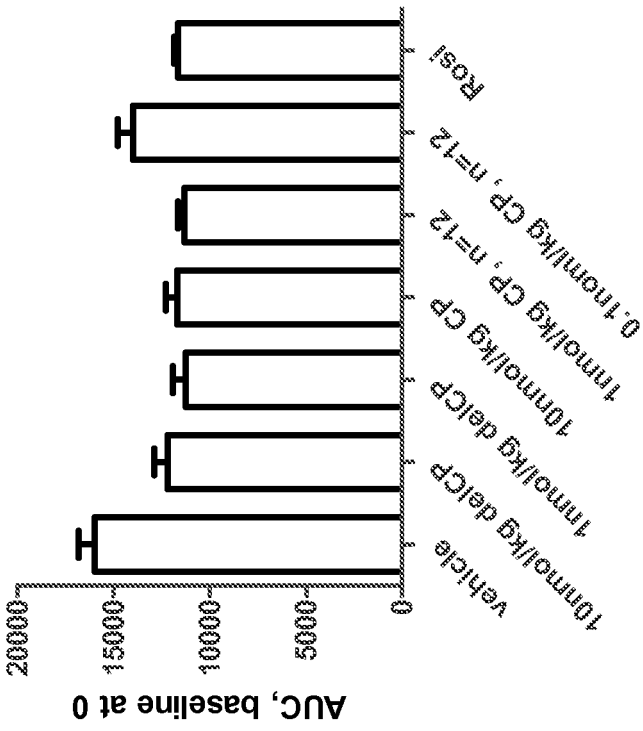


	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 10nmol/kg CP	vehicle vs 1nmol/kg CP	vehicle vs 0.1noml/kg CP	vehicle vs Rosi
0min	ns	ns	ns	ns	ns	ns
15min	*	*	**	*	ns	ns
30min	ns	*	**	***	ns	**
60min	ns	ns	*	ns	ns	ns

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

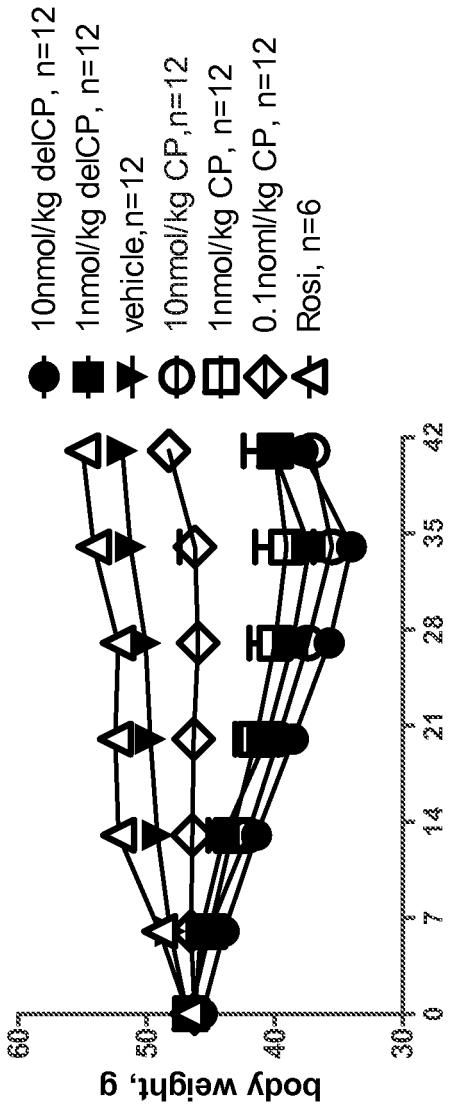
delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

Figure 42



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

Figure 43



Last injection on d28, wash-out ongoing

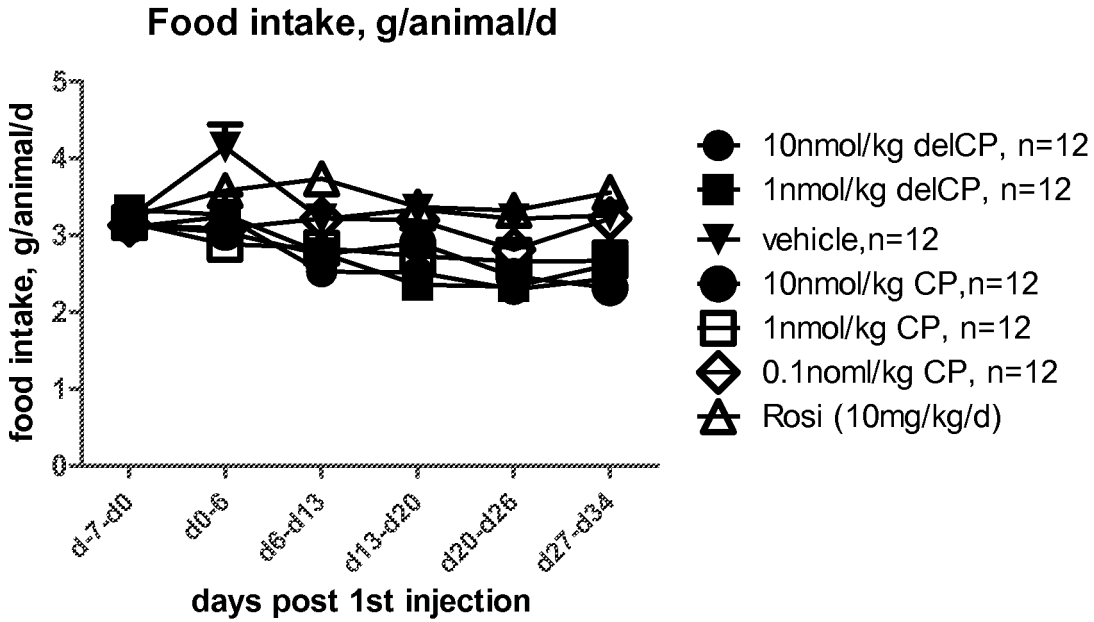
	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 10nmol/kg CP	vehicle vs 1nmol/kg CP	vehicle vs 0.1noml/kg CP	vehicle vs Rosi
d0	ns	ns	ns	ns	ns	ns
d6	ns	ns	ns	ns	ns	ns
d13	****	*	***	**	ns	ns
d20	****	****	****	****	ns	ns
d26	****	****	****	****	ns	ns
d34	****	****	****	****	ns	ns

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)

CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

Figure 44



Last injection on d28

	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 10nmol/kg CP	vehicle vs 1nmol/kg CP	vehicle vs 0.1noml/kg CP	vehicle vs Rosi
d-7-d0	ns	ns	ns	ns	ns	ns
d0-6	**	**	****	****	***	ns
d6-d13	**	ns	ns	ns	ns	ns
d13-d20	*	**	ns	ns	ns	ns
d20-d26	****	**	**	ns	ns	ns
d27-d34	ns	ns	*	ns	ns	ns

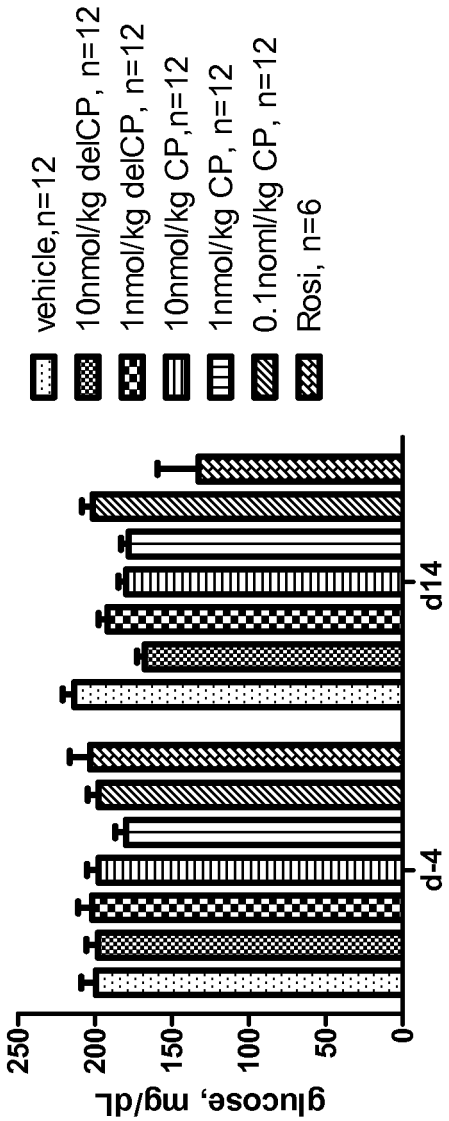
* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)

CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

SUBSTITUTE SHEET (RULE 26)

Figure 45



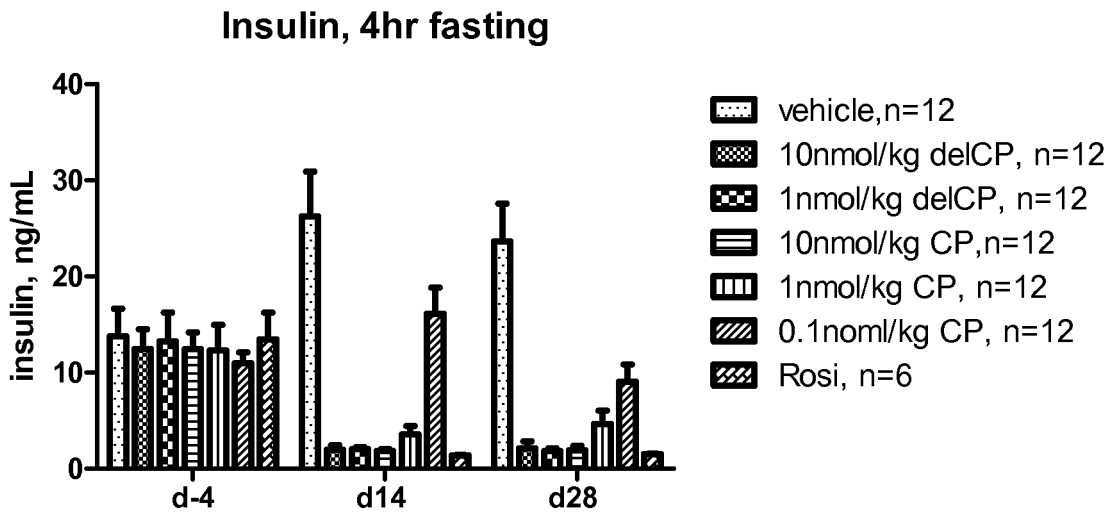
	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
d-4	ns	ns	ns	ns	ns	ns
d14	***	ns	*	*	ns	****

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

SUBSTITUTE SHEET (RULE 26)

Figure 46

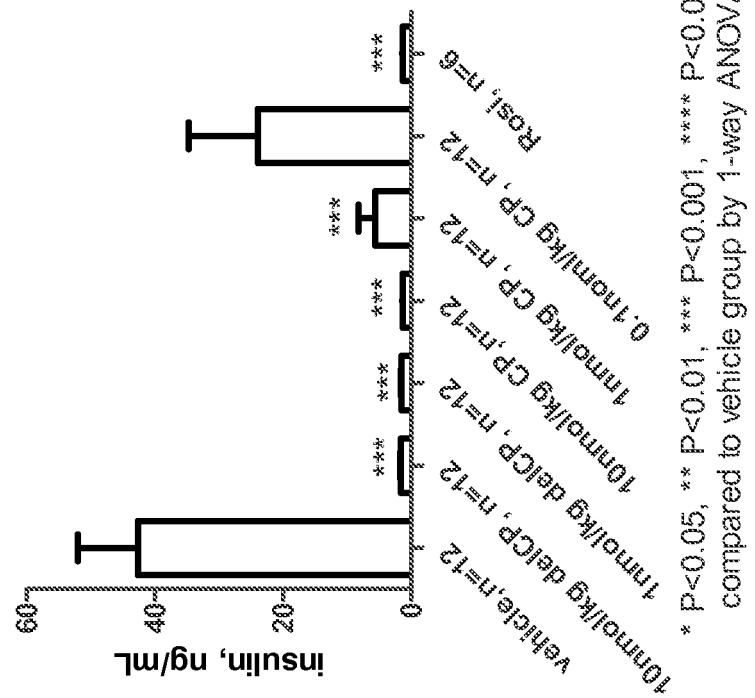


	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
d-4	ns	ns	ns	ns	ns	ns
d14	****	****	****	****	*	****
d28	****	****	****	****	****	****

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

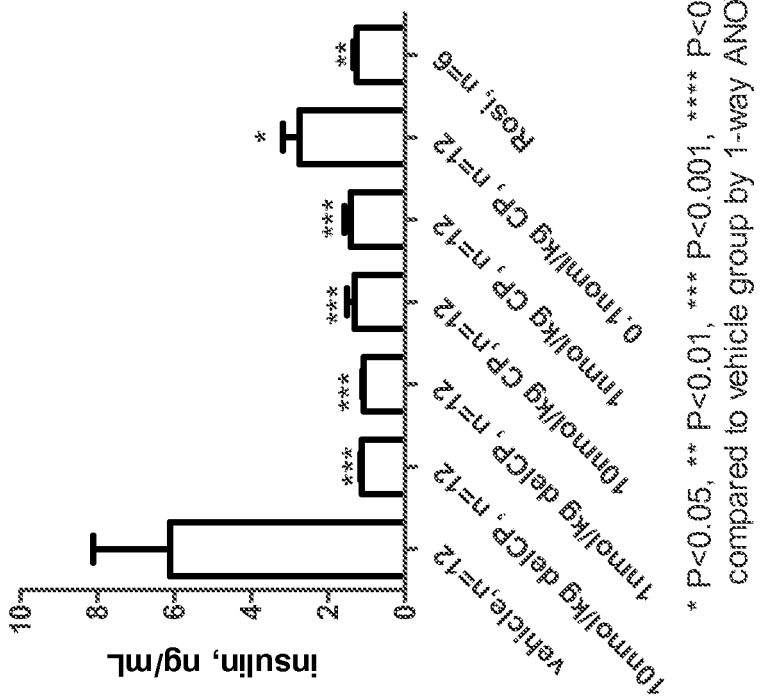
delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

Figure 47



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

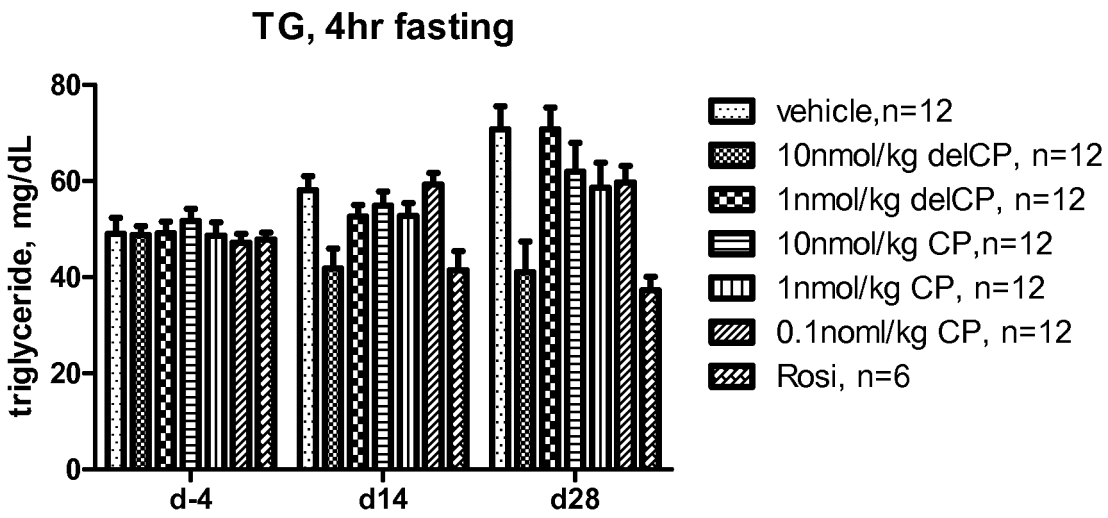
Figure 48



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

SUBSTITUTE SHEET (RULE 26)

Figure 49

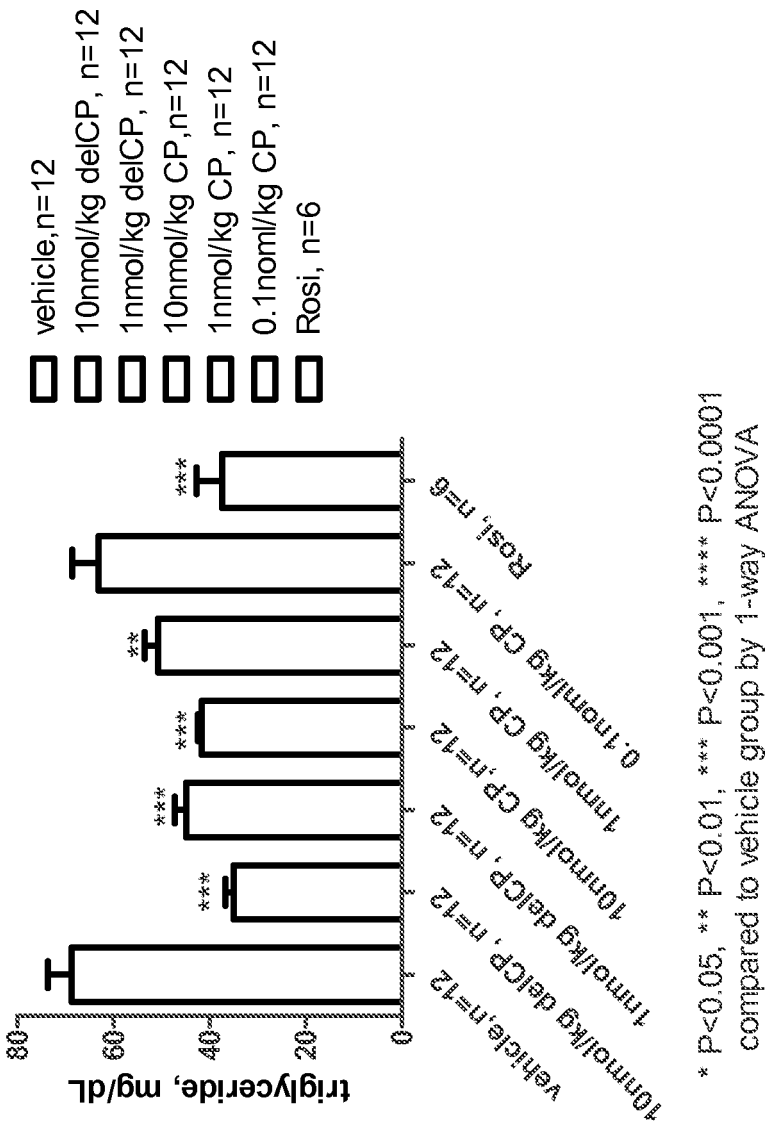


	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
d-2	ns	ns	ns	ns	ns	ns
d14	*	ns	ns	ns	ns	ns
d28	****	ns	ns	ns	ns	****

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

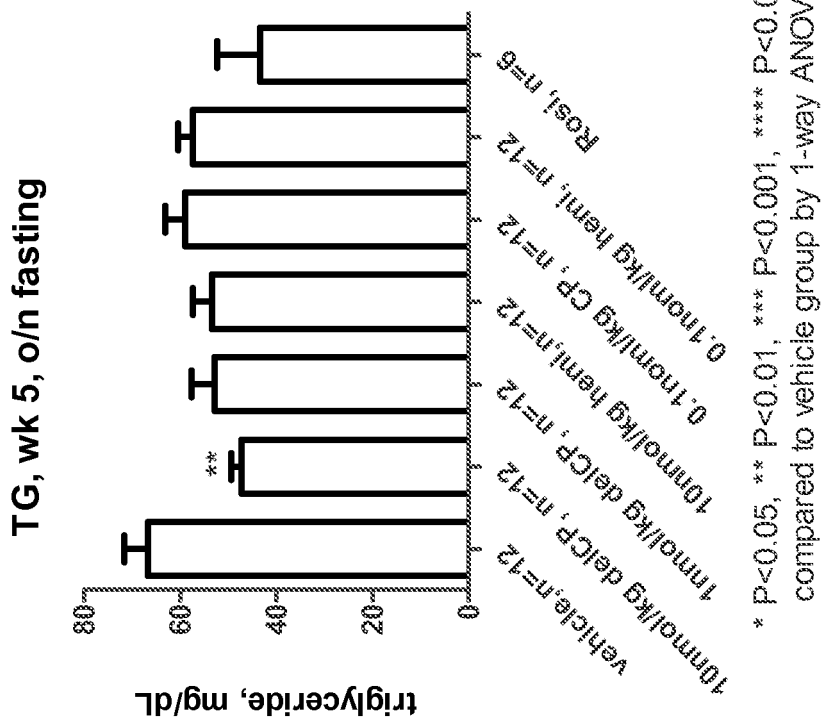
delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

Figure 50



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

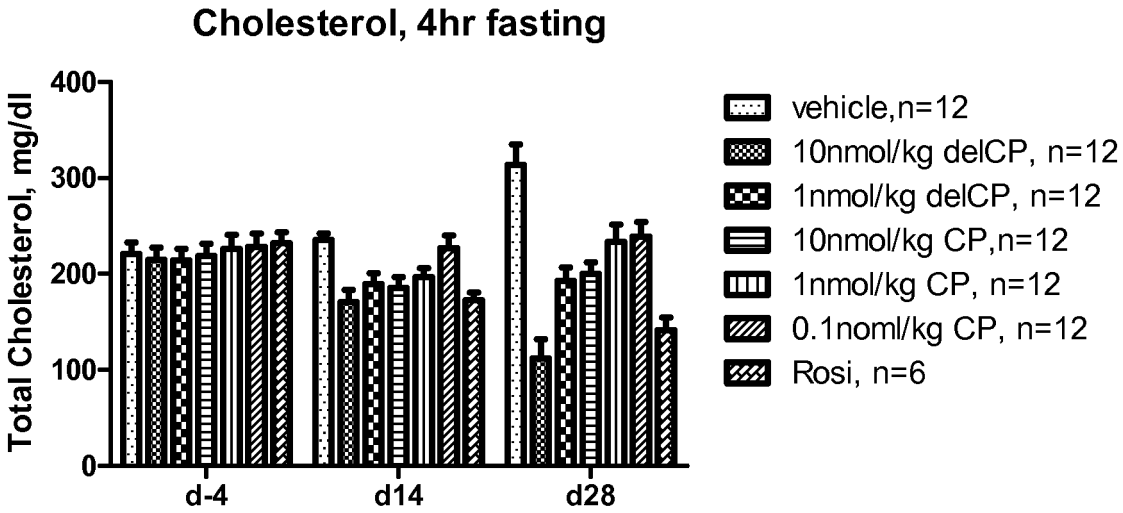
Figure 51



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

SUBSTITUTE SHEET (RULE 26)

Figure 52



* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 compared to vehicle group by 1-way ANOVA

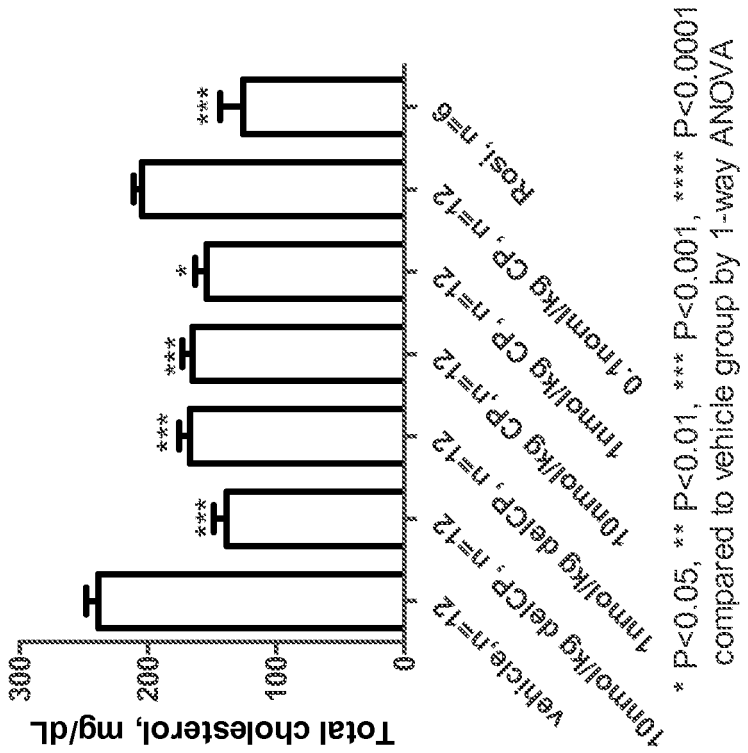
	vehicle vs 10nmol/kg delCP	vehicle vs 1nmol/kg delCP	vehicle vs 10nmol/kg hemi	vehicle vs 1nmol/kg hemi	vehicle vs 0.1noml/kg hemi	vehicle vs Rosi
d-2	ns	ns	ns	ns	ns	ns
d14	*	ns	ns	ns	ns	ns
d28	****	****	****	***	**	****

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001 by 2-way ANOVA

delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)

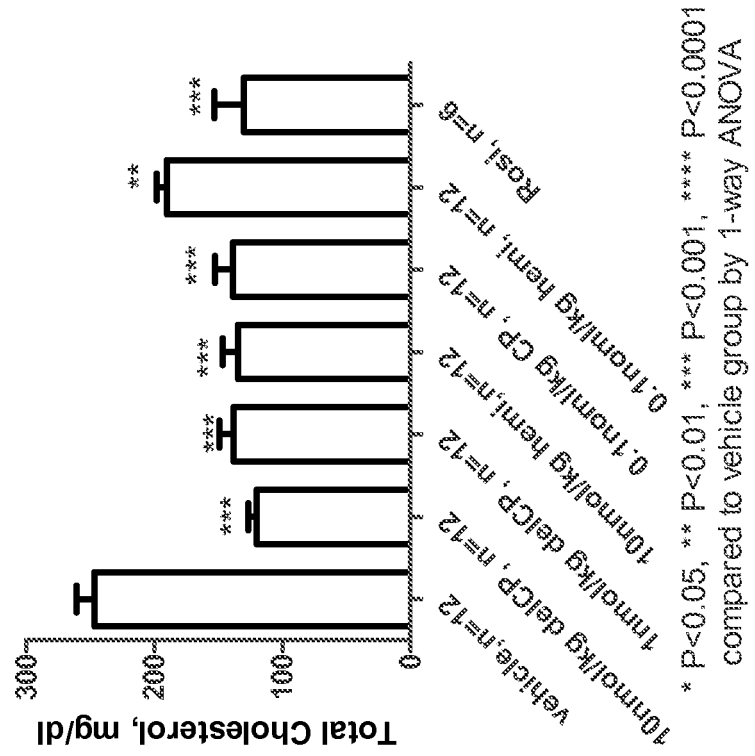
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

Figure 53



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

Figure 54



delCP: DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
CP: CpmFc(-)-(G4S)4-GDF15:CpmFc(+)

Figure 55

GDF15 Efficacy in Obese Cynomolgus Monkeys Study Design

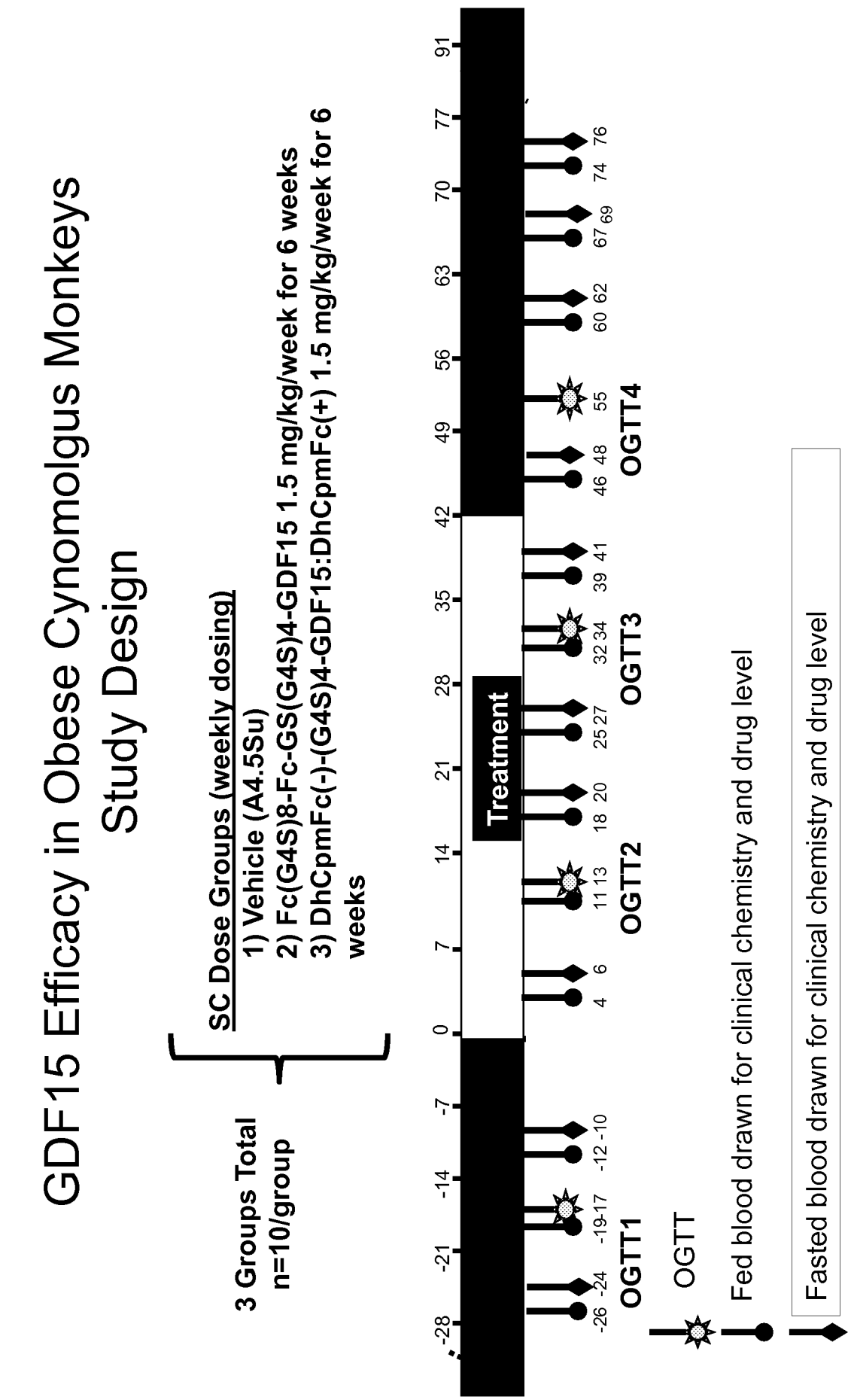
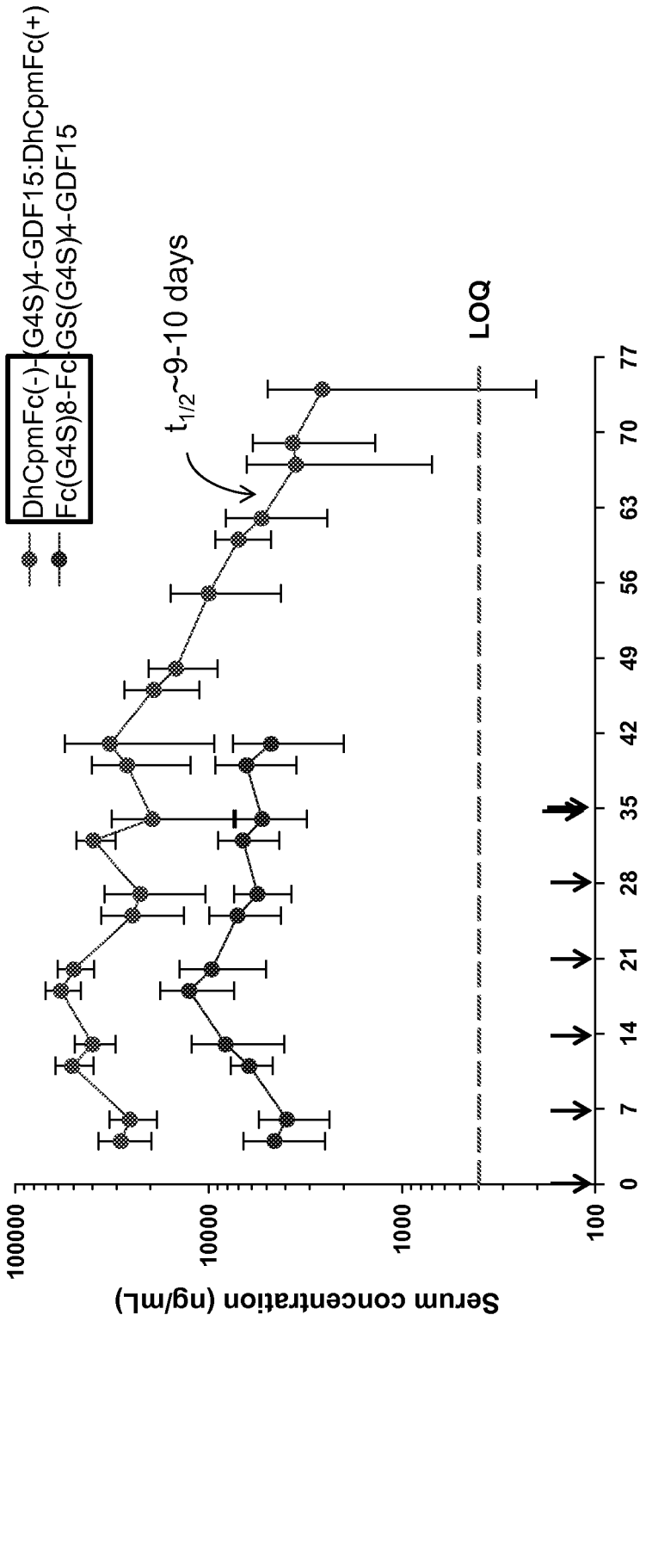


Figure 56

Drug Exposure Measurements in Cyno Study



2/10 animals in the delhingeFc-hGDF15 group suspected ADA positive (data not included post day 27)
5/10 animals in the hemiFc-hGDF15 group suspected ADA positive (data not included)
Loss of PD responses in suspected ADA-positive animals correlates with loss of drug exposure

Figure 57

Glucose AUC – OGTT (acclimation)

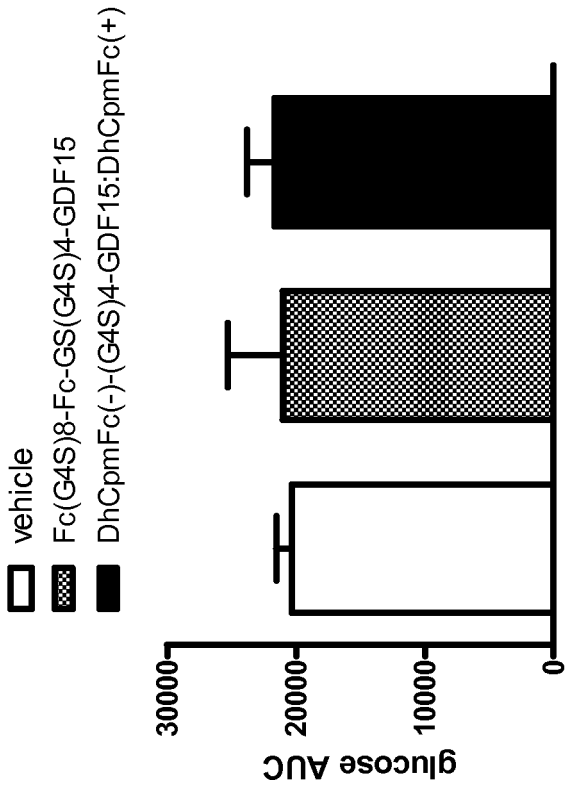


Figure 58

Glucose AUC – OGTT (treatment, week 2)

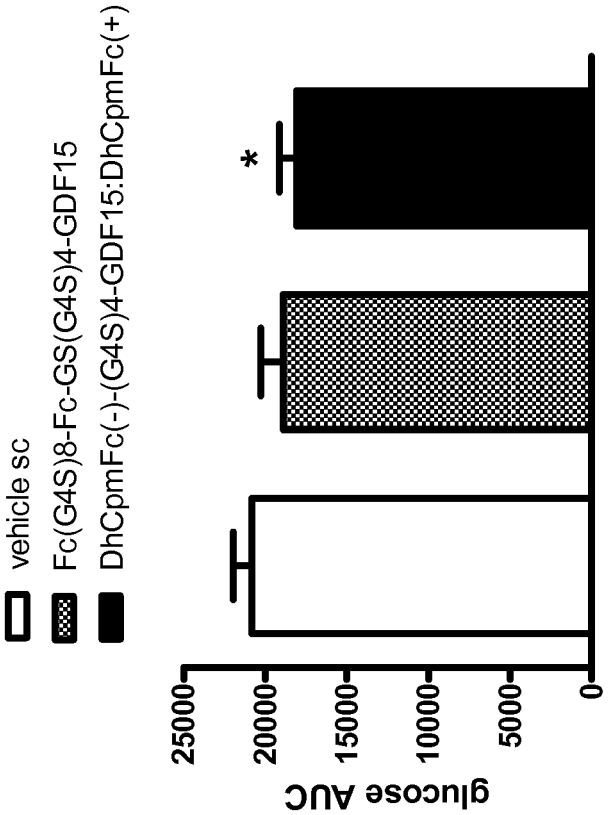


Figure 59

Glucose AUC – OGTT (treatment, week 5)

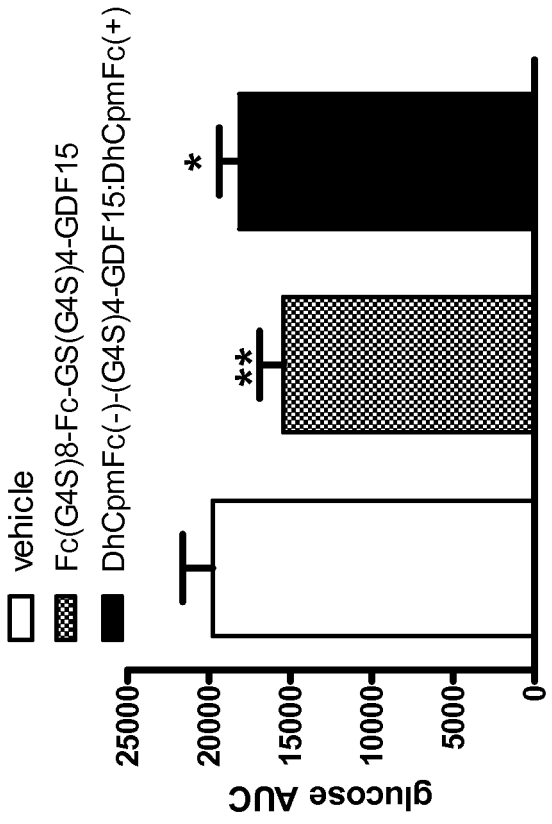


Figure 60

Glucose AUC – OGTT (washout, week 8)

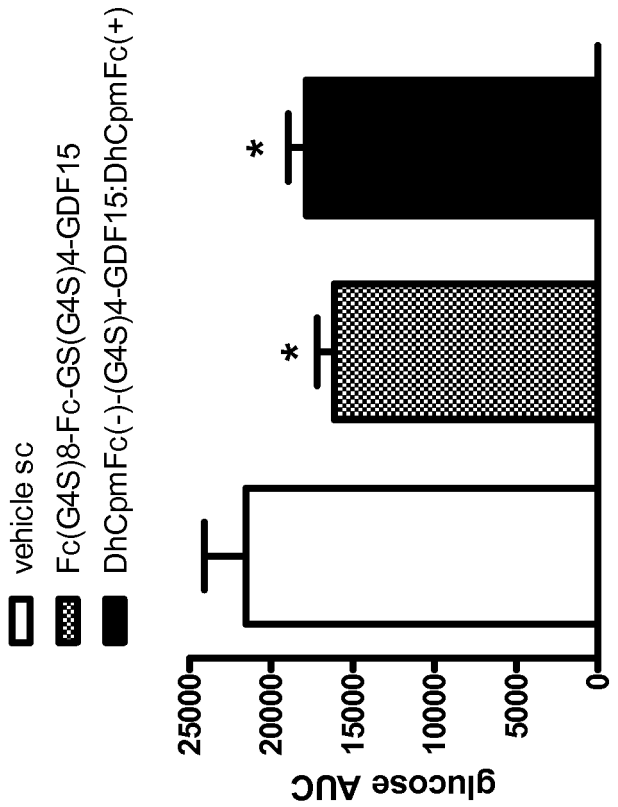


Figure 61

Insulin AUC – OGTT (acclimation)

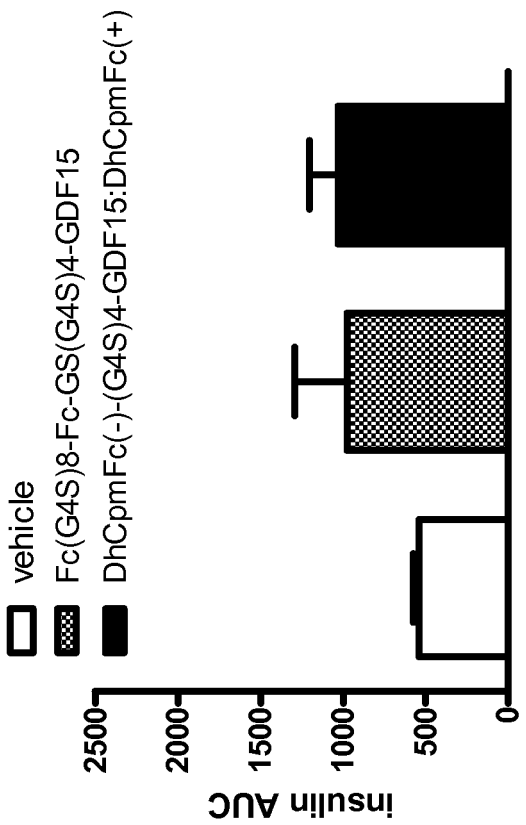


Figure 62

Insulin AUC – OGTT (treatment, week 2)

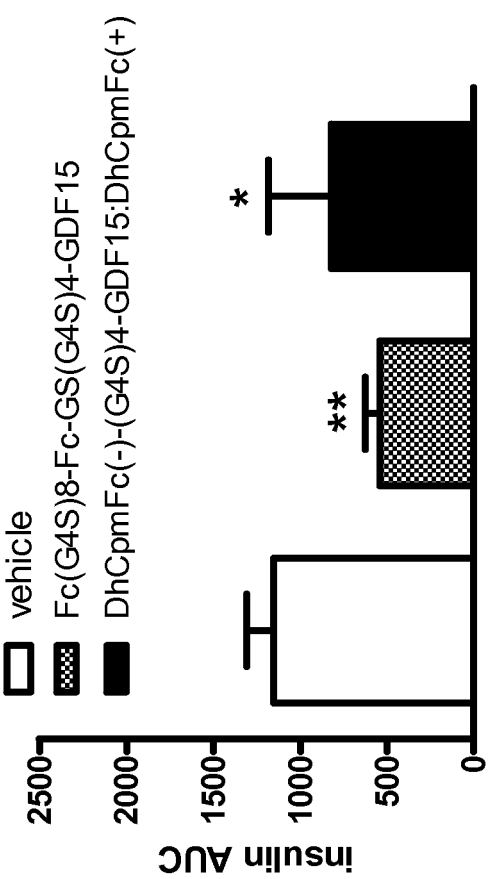


Figure 63

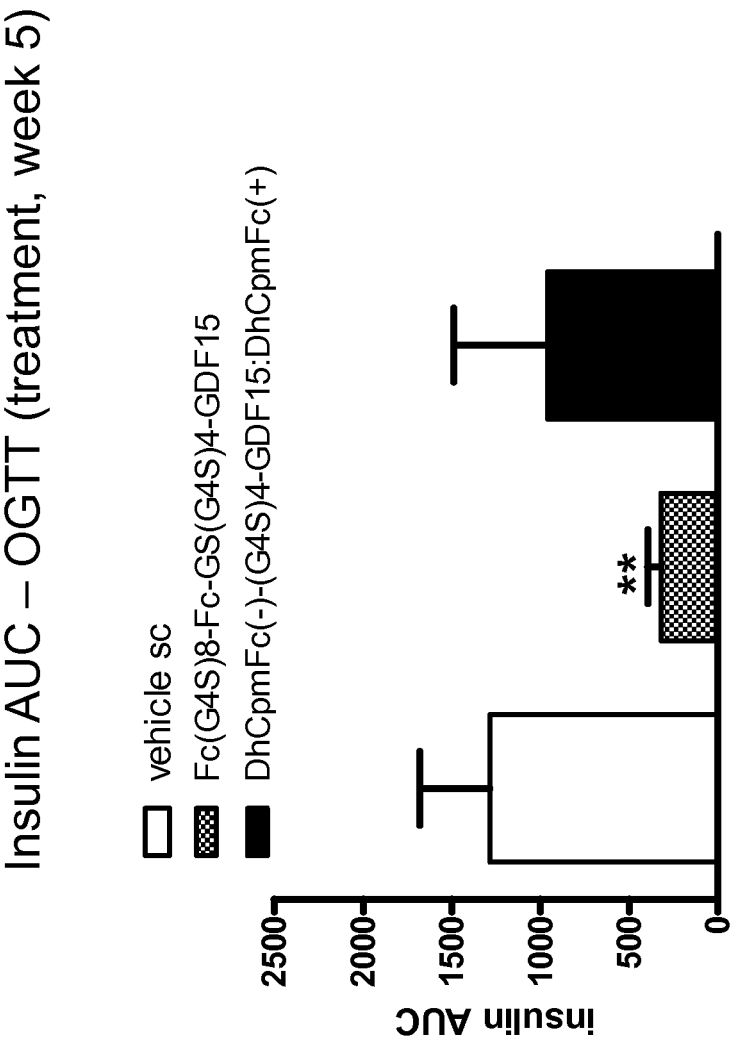

Insulin AUC – OGTT (treatment, week 5)
vehicle sc
Fc(G4S)8-Fc-GS(G4S)4-GDF15
DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
insulin AUC
2500
2000
1500
1000
500
0
**

Figure 64

Insulin AUC – OGTT (washout, week 8)

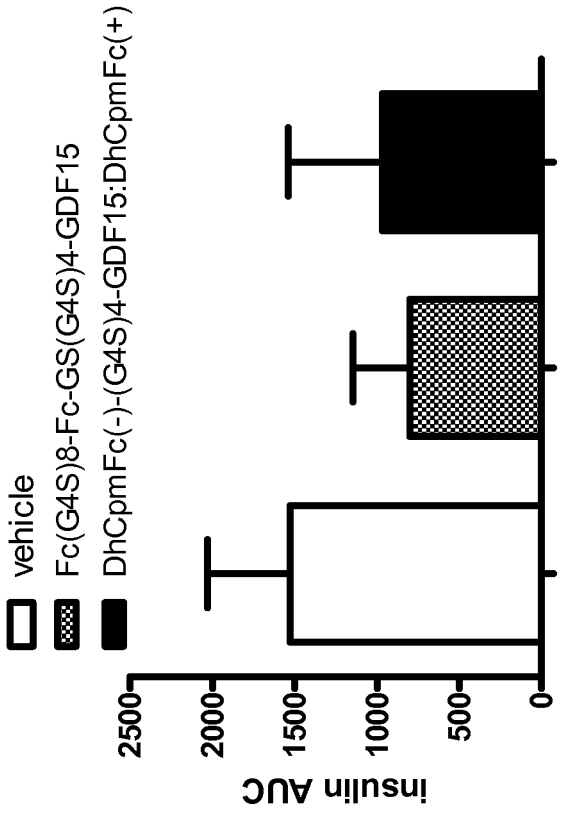


Figure 65

body weight

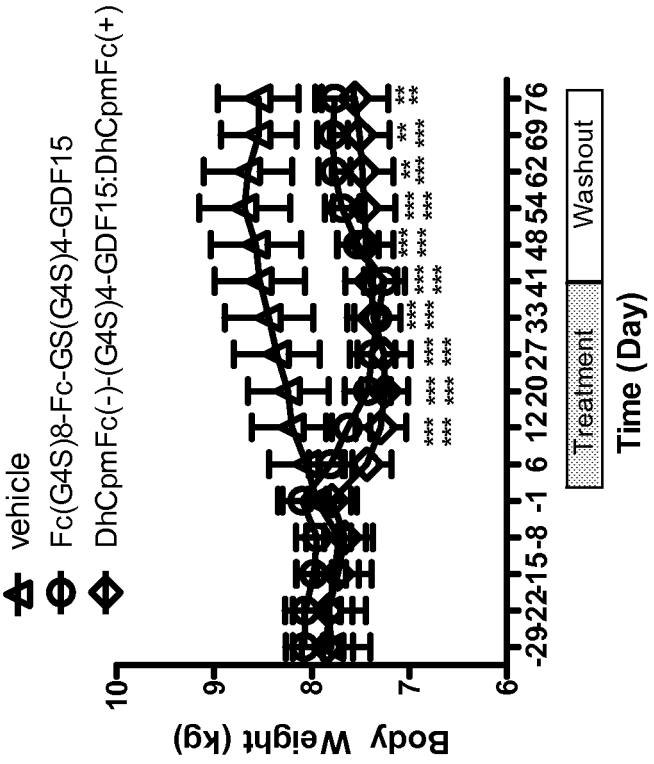


Figure 66

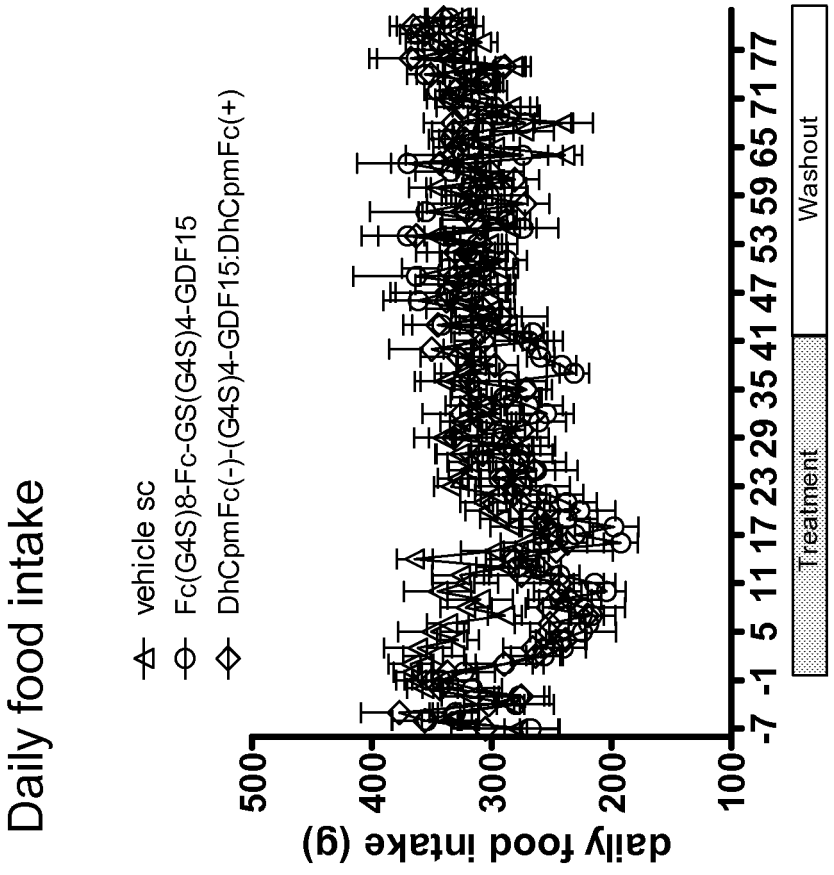

Daily food intake
vehicle sc
Fc(G4S)8-Fc-GS(G4S)4-GDF15
DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
daily food intake (g)
500
400
300
200
100
-7 -1 5 11 17 23 29 35 41 47 53 59 65 71 77
Treatment
Washout

Figure 67

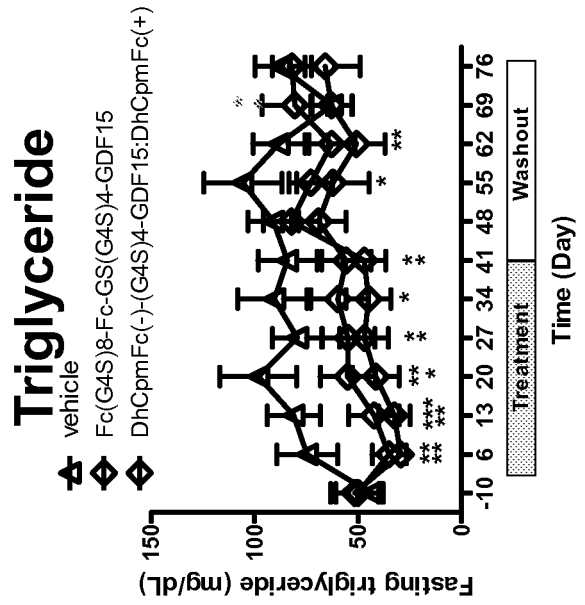
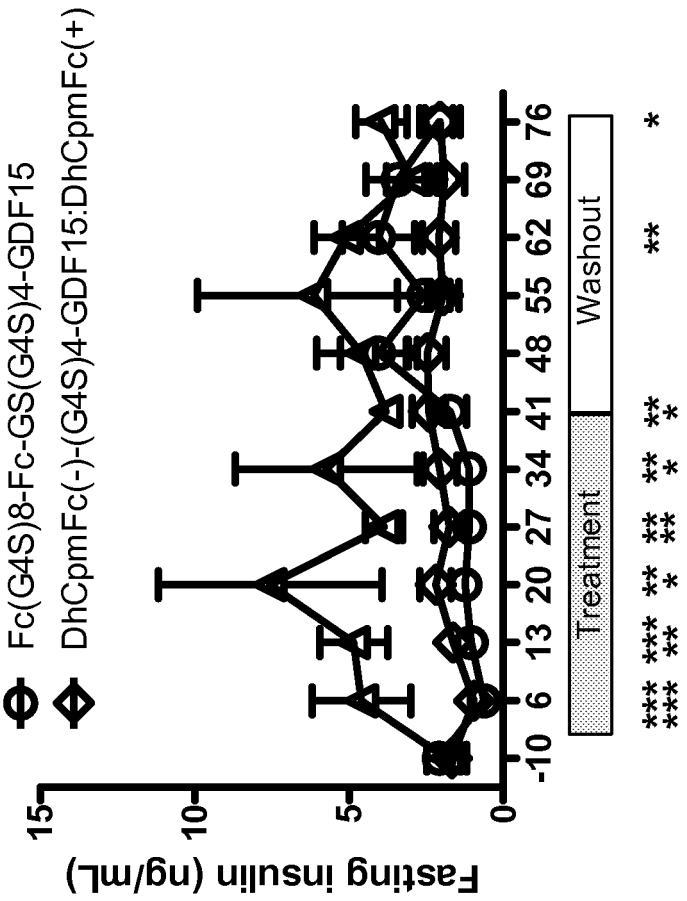

Triglyceride
vehicle
Fc(G4S)8-Fc-GS(G4S)4-GDF15
DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
Fasting triglyceride (mg/dL)
150
100
50
0
-10 6 13 20 27 34 41 48 55 62 69 76
Treatment
Washout
Time (Day)

Figure 68


Fasting insulin
vehicle
Fc(G4S)8-Fc-GS(G4S)4-GDF15
DhCpmFc(-)-(G4S)4-GDF15:DhCpmFc(+)
Fasting insulin (ng/mL)
15
10
5
0
-10 6 13 20 27 34 41 48 55 62 69 76
Treatment
Washout
*** *** ** * ** ** * ** ** *