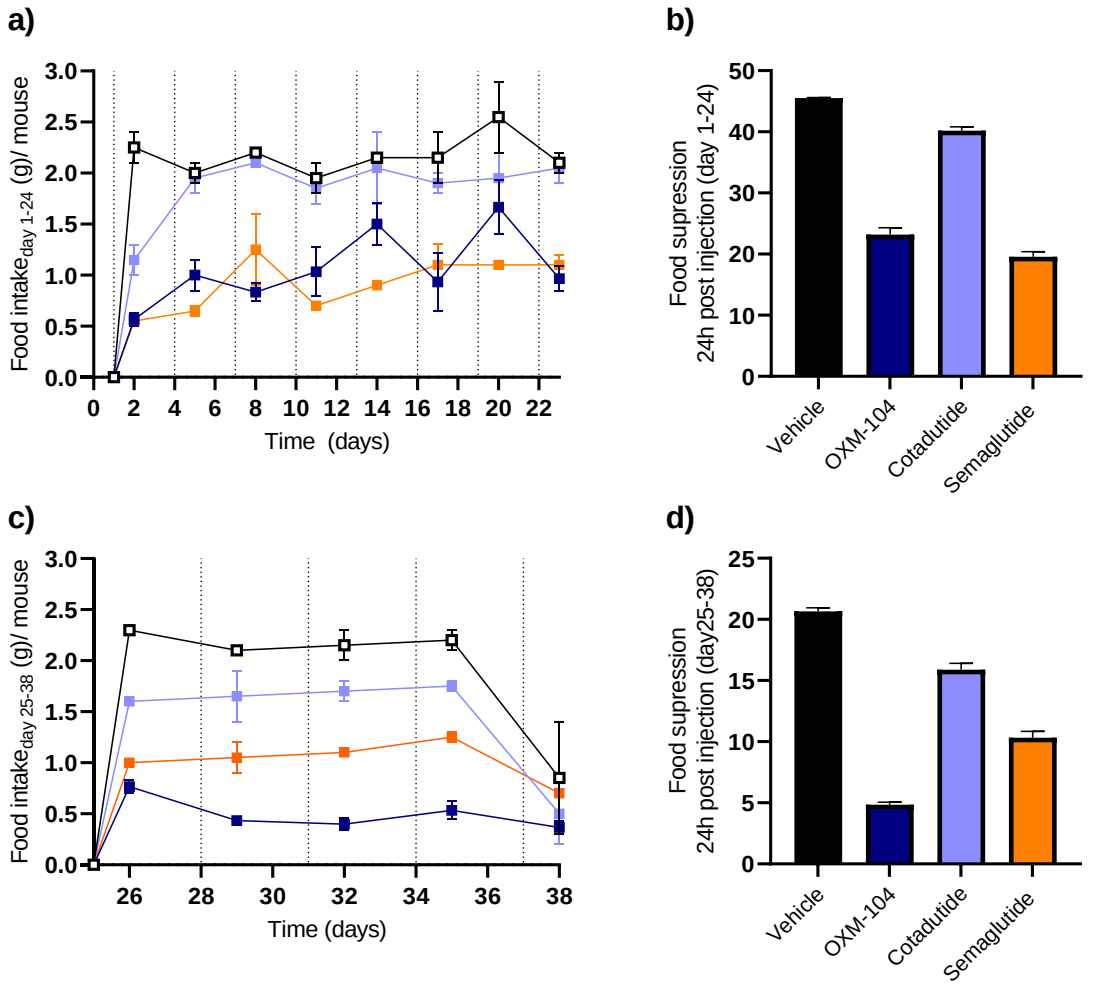

Figure S1 Effects of OXM-104, cotadutide and semaglutide on food suppression. Mice receiving OXM-104 (n=10), cotadutide (n=10) and semaglutide (n=10) for 38 days. In the first 24 days, OXM-104 and semaglutide were dosed at 30 nmol/kg, whereas cotadutide was dosed at 10 nmol/kg. From day 25 doses were increased 3-fold, corresponding to 90 nmol/kg for OXM-104 and semaglutide and 30 nmol/kg for cotadutide. Food intake (g)/mouse before and after dose increase shown in (a and c). AUC graphs representing food intake 24 hours after dosing with OXM-104 and benchmark peptides; day 1-24 (b) and day 25-38 (d). Data are presented as mean ± SEM.

Acute test of OXM-104 and semaglutide in MSNASH/PcoJ mice

24 male MS NASH mice (6-7 weeks of age upon arrival) were introduced to GAN-diet for 24 days prior to study start. Animals were randomly allocated into treatment groups according to body weight (n=8 animals/group). To explore the acute effects on body weight and caloric intake, mice received a single subcutaneous administration with either vehicle, OXM-104 (30 nmol/kg) or semaglutide (30 nmol/kg). Animals were fasted for 5-hours before administration, and body weight and caloric intake were monitored daily over a 72h period with ad libitum access to food and water.

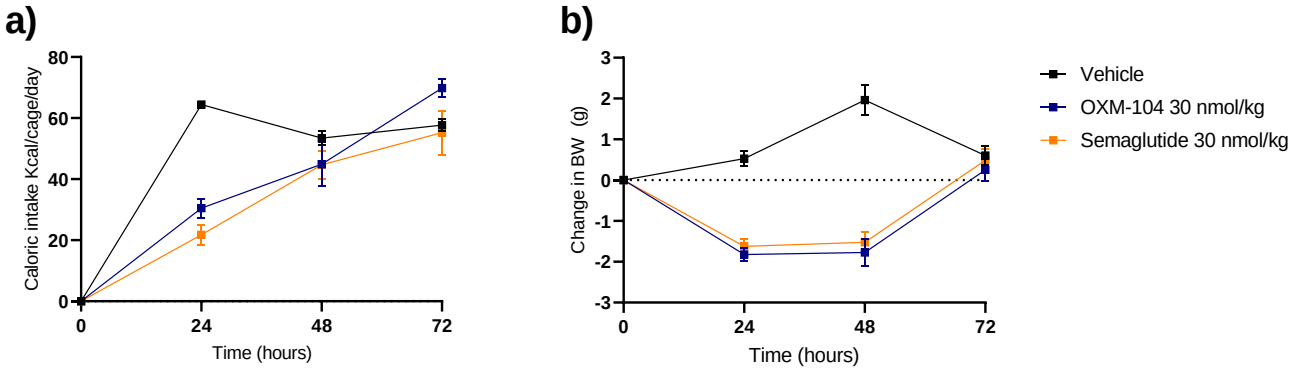

Figure S2. Acute effect of OXM-104 and Semaglutide on caloric intake and body weight after a single injection. Following a 5h fast, male MSNASH mice were administered vehicle (n=8), OXM-104 (n=8) or semaglutide (n=8) at 30nmol/kg. Caloric intake (a) and body weight change (b) were monitored once-daily for 72 hours.

Absolute AT weights	C57BL6 mice					
	Inguinal (g±SEM)		Perirenal (g±SEM)		Liver (g±SEM)	
Vehicle	1.3	0.09	0.8	0.05	1.2	0.07
PF-OXM-104	0.8$^{**\#}$	0.1	0.3$^{***\#}$	0.04	1.0*	0.09
OXM-104	0.4***	0.04	0.1***	0.02	1.1	0.05
Cotadutide	0.7***	0.1	0.4***	0.07	0.9	0.06
Semaglutide	0.8***	0.11	0.4***	0.07	0.9**	0.04
Chow control	0.1**	0.01	0.05***	0.01	0.9*	0.05
AT weights relative to body weight	Inguinal (g/kg±SEM)		Perirenal (g/kg±SEM)		Liver (g/kg±SEM)	
Vehicle	29.6	1.8	17.7	1.0	26.6	1.1
PF-OXM-104	21.3$^{\#}$	1.4	7.7***	0.9	24.3$^{\#\#\#}$	3.1
OXM-104	12.0****	1.0	4.0***	0.4	37.3***	1.5
Cotadutide	19.6**	2.3	9.5***	1.5	29.8	2.4
Semaglutide	20.5**	2.1	11.4**	1.8	25.7	0.9
Chow control	2.4***	0.4	2.0***	0.5	39.9***	1.5

Table S1 Adipose tissue depots and liver weights in female obese (C57BL6) mice following 38 days treatment with OXM-104, cotadutide, semaglutide, PF-OXM-104, and age-matched lean controls. Weights of inguinal and perirenal adipose tissue (AT) depots and liver presented in absolute term (g) and relative to body weights (g/kg). (n=10) for all groups except for PF-OXM-104 and chow control; (n=5). Statistical analysis between groups was evaluated by an ordinary one-way ANOVAs with Tukey's multiple comparisons test. *** p<0.001 compared to vehicle mice. # p<0.05 ### p<0.001 when compared to OXM-104. Data are presented as mean ± SEM.

Absolute AT weights	MSNASH mice							
	Inguinal (g±SEM)		Epididymal (g±SEM)		Perirenal (g±SEM)		Liver (g±SEM)	
Vehicle	0.6	0.05	0.8	0.02	0.8	0.04	4.8	0.2
PF-OXM-104	0.4 $^{\#}$	0.04	0.8$^{\#\#}$	0.1	0.9$^{\#\#\#}$	0.1	3.2$^{**\#\#\#}$	0.2
OXM-104	0.2***	0.03	0.4**	0.04	0.3***	0.1	1.9***	0.1
Cotadutide	0.5	0.1	0.7	0.1	0.6	0.1	2.5***	0.1
Semaglutide	0.5	0.03	0.9	0.04	0.8	0.04	3.4***	0.6
Chow control	0.2 **	0.1	1.1	0.3	0.4	0.1	4.0***	0.2
AT weights relative to body weight	Inguinal (g/kg±SEM)		Epididymal (g/kg±SEM)		Perirenal (g/kg±SEM)		Liver (g/kg±SEM)	
Vehicle	13.3	0.4	15.9	0.6	15.1	0.6	94.0	2.7
PF-OXM-104	9.4	1.0	17.9 $^{\#\#\#}$	1.5	18.8$^{\#\#\#}$	1.2	68.5***	2.9
OXM-104	6.8*	0.6	11.2***	0.9	8.9**	1.3	59.9***	2.4
Cotadutide	10.8	1.0	16.6	0.7	14.0	1.5	59.3***	1.5
Semaglutide	11.7	0.7	19.3*	0.7	16.6	0.7	36.8***	9.5
Chow control	10.4	2.4	48.1***	10.8	18.0	4.2	82.1***	18.6
FBG	Baseline (mmol/L±SEM)				Study end (mmol/L±SEM)		Change in FBG (mmol/L±SEM)	
Vehicle	14.2	0.7			12.1	0.5	-2.9	1.0
PF-OXM-104	12.6	1.3			10.6$^{\#\#}$	0.3	-2.0	1.1
OXM-104	11.9	0.6			4.9***	0.2	-6.9	0.8
Cotadutide	12.4	0.6			10.0	0.4	-2.4	0.7
Semaglutide	11.9	0.8			12.2	0.3	0.3	0.9
Chow control	9.2	0.6			9.7	0.4	0.5	0.4
Study end plasma insulin	Study End (ng/mL±SEM)							
Vehicle	14.1	1.6						
PF-OXM-104	4.6***	0.6						
OXM-104	2.9***	0.7						
Cotadutide	5.4***	0.8						
Semaglutide	7.4**	0.9						
Chow control	3.7***	0.7						

Table S 2 Adipose tissue depots weights, liver weights, FBG levels, and plasma insulin in male obese NASH mice following 50 days treatment with OXM-104, cotadutide, semaglutide, PF-OXM-104, and age-matched chow control. Weights of inguinal, epididymal, and perirenal adipose tissue depots and liver presented in absolute terms (g) and relative to body weights (g/kg). Statistical analysis between groups was evaluated by an ordinary one-way ANOVA with Tukey's multiple comparisons test (inguinal, Epididymal AT relative to body weight, perirenal relative to body weight and liver weights; absolute and relative to body weight and changes in ALP levels) or a Kruskal-Wallis test with Dunn's multiple comparison test (Inguinal AT relative to body weight, epididymal AT, perirenal AT and plasma insulin). (n=19; OXM-104), (n=15; cotadutide), (n=16; semaglutide), (n=8; PF-OXM-104), (n=15; vehicle) and (n=4; chow control). * p<0.05 ** p<0.01 *** p<0.001 compared to vehicle. # p<0.05 ### p<0.001 when compared to PF-OXM-104. Data are presented as mean ± SEM.

Absolute AT weights	db/db mice							
	Inguinal (g±SEM)		Epididymal (g±SEM)		Perirenal (g±SEM)		Liver (g±SEM)	
Vehicle	1.3	0.1	0.7	0.03	0.8	0.03	3.2	0.1
OXM-104	1.3	0.1	0.6	0.05	0.4***	0.1	1.8***	0.2
Cotadutide	1.3	0.3	0.9	0.2	0.5	0.1	3.7	0.7
Semaglutide	1.4	0.1	0.7	0.03	0.7	0.03	2.5	0.1
AT weights relative to body weight	Inguinal (g/kg±SEM)		Epididymal (g/kg±SEM)		Perirenal (g/kg±SEM)		Liver (g/kg±SEM)	
Vehicle	24.2	1.2	12.4	0.5	14.4	0.9	59.4	4.4
OXM-104	30.4*	1.8	15.6*	0.9	10.3**	1.2	42.8*	5.5**
Cotadutide	28.9	5.9	20.2***	4.1	12.5	2.7	82.6	16.5
Semaglutide	28.3	2.2	14.5	0.6	14.3	0.7	49.8	2.0

Table S 3 Adipose tissue depots and liver weights in male db/db mice following 50 days of treatment with OXM-104, cotadutide and semaglutide. Weights of inguinal, epididymal, and perirenal adipose tissue depots and liver presented in absolute term (g) and relative to body weights (g/kg). (n=13; OXM-104), (n=7; cotadutide), (n=14; semaglutide) and (n=16; vehicle). Statistical analysis between groups was evaluated by an ordinary one-way ANOVAs with Tukey's multiple comparisons test * p<0.05 ** p<0.01 *** p<0.001 compared to vehicle. Data are presented as mean ± SEM.