

**Supplementary Table S1.** Osmolarity in supplemented media culture adjusted with different glucose and mannitol concentrations

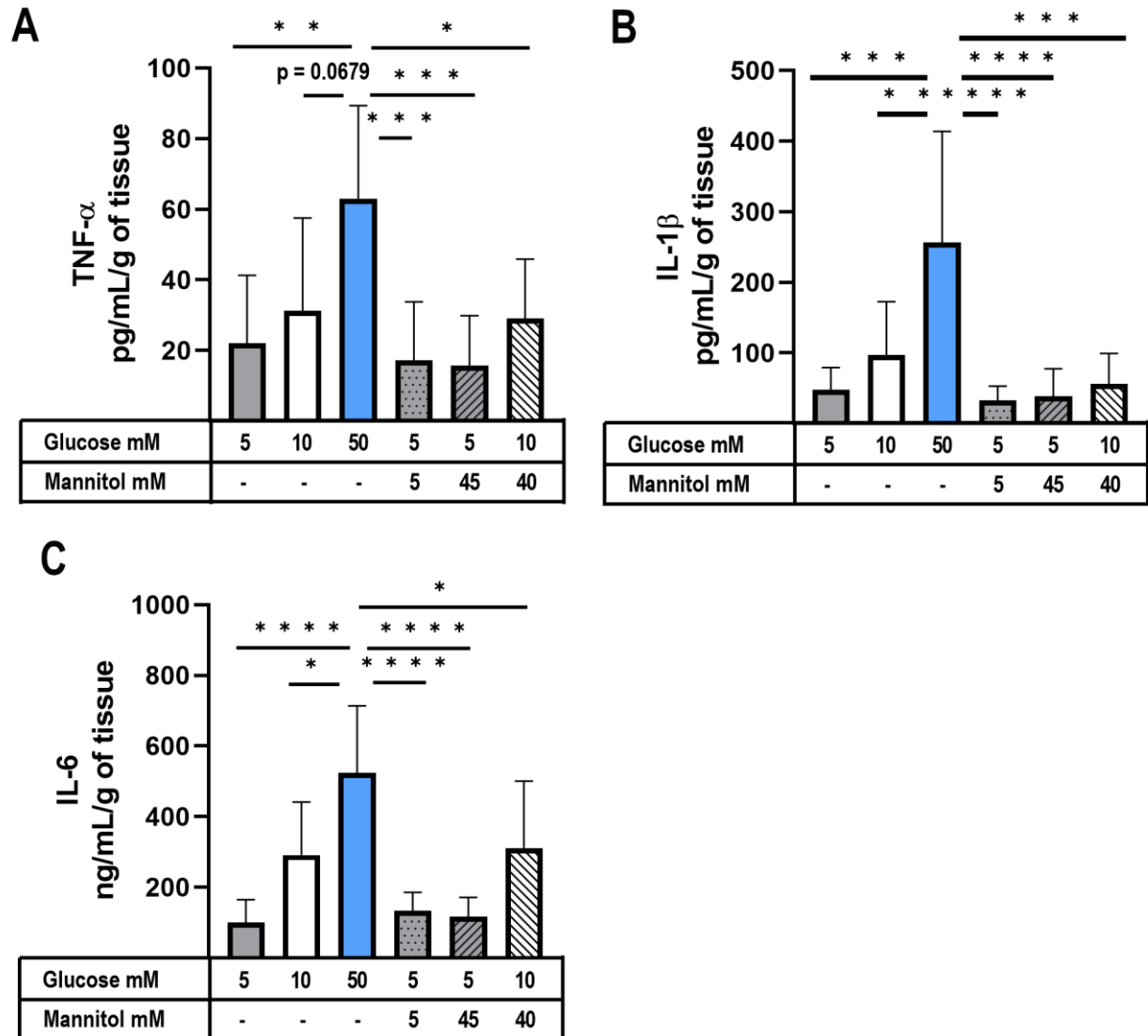
Treatment	mOsm	Osmolarity should be equivalent to
5 mM glucose	316	
10 mM glucose	320	
50 mM glucose	353	
5 mM glucose + mannitol 5 mM	320	10 mM glucose
10 mM glucose + mannitol 40 mM	346	50 mM glucose

Media base was DMEM low-glucose + 10% FBS + 1% sodium pyruvate + 1% penicillin/streptomycin

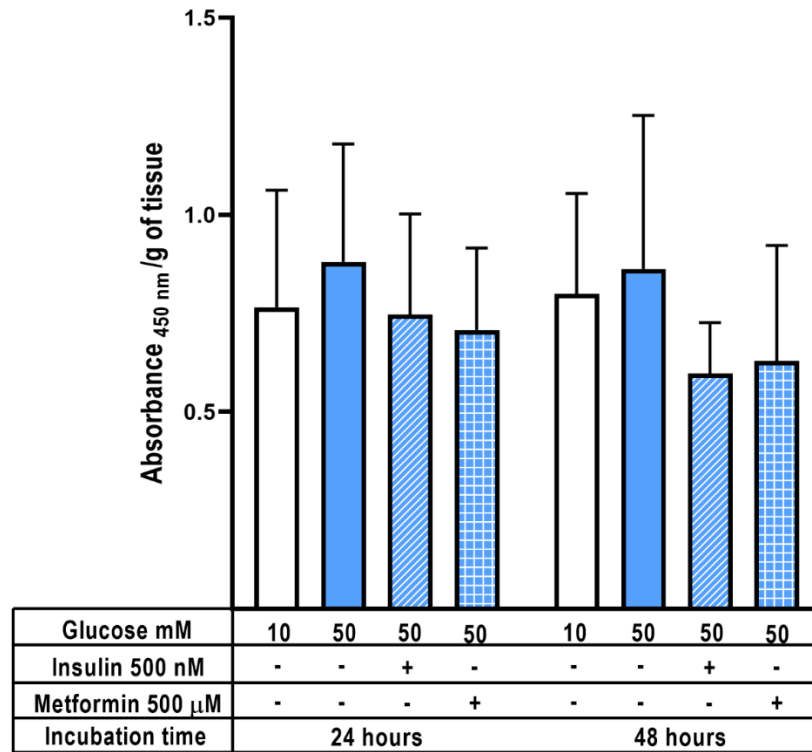
**Supplementary Table S2.** Placental adipokine secretion under normoglycemic and hyperglycemic conditions.

	<b>Visfatin</b>	<b>Chemerin</b>	<b>Adiponectin</b>	<b>Leptin</b>
<b>Glucose 10 mM</b>	10,248 (8,648 – 13,460)	9,297 (5,689 – 17,767)	28,007 (20,867 – 47,727)	425.1 (297.9 – 652.1)
<b>Glucose 50 mM</b>	7,749 (5,459 – 9,972) #	10,578 (7,857 – 18,209)	28,781 (19,823 – 51,499)	435 (270.5 – 799.3)
<b>Glucose 10 mM + Insulin 500 nM</b>	13,710 (9,978 – 19,128)	10,140 (7,604 – 16,828)	23,888 (16,372 – 39,535)	379 (271.7 – 652.1)
<b>Glucose 50 mM + Insulin 50 nM</b>	3,159 (1,972 – 5,317) *	12,278 (8,234 – 19,831)	21,039 (15,055 – 38,694)	492.9 (329.4 – 715)
<b>Glucose 50 mM + Insulin 100 nM</b>	4,327 (2,999 – 8,064) *	11,881 (8,804 – 16,323)	26,684 (20,236 – 50,233)	405.7 (312.1 – 608)
<b>Glucose 50 mM + Insulin 500 nM</b>	4,058 (2,191 – 6,727) *	11,980 (8,086 – 18,622)	33,429 (22,327 – 53,150)	343.2 (229 – 511.7)
<b>Glucose 10 mM + Metformin 500</b>	11,777 (8,575 – 14,692)	6,187 (3,381 – 12,603)	27,641 (18,569 – 48,020)	410.6 (329 – 756.7)
<b>Glucose 50 mM + Metformin 125</b>	8,893 (5,200 – 12,345)	9,240 (4,345 – 15,842)	34,539 (19,751 – 55,366)	334.9 (240 – 495.4)
<b>Glucose 50 mM + Metformin 250</b>	6,348 (3,605 – 9,766)	7,714 (5,211 – 14,340)	27,952 (20,368 – 63,250)	618.9 (265.8 – 838.6)
<b>Glucose 50 mM + Metformin 500</b>	6,171 (3,084 – 9,905)	8,871 (4,611 – 15,371)	35,553 (20,667 – 60,592)	334.9 (211.6 – 465.5)

Visfatin, chemerin, leptin, and adiponectin levels are shown in pg/mL/ g of tissue. #,  $p < 0.05$  vs Glucose 10 mM. \*,  $p < 0.05$  vs Glucose 50 mM.  $n = 6 - 7$  independent experiments in triplicate. One-way ANOVA (Kruskal-Wallis test) followed by Dunn's multiple comparisons post-hoc. Data is presented as median (interquartile range).



**Supplementary Figure S1. High osmolar pressure does not increase secretion of pro-inflammatory cytokines in cultured placental explants.** Placental explants secretion of A) TNF- $\alpha$ , B) IL-1 $\beta$ , and C) IL-6. Explants were exposed to glucose and co-incubated with mannitol for 48 hours. Treatments and culture media were refreshed at 24 hours.  $n = 3$  independent experiments in triplicate. Data are presented as mean and standard deviation. One-way ANOVA followed by Tukey's multiple comparisons post-hoc due to normal distribution \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.001$ ; \*\*\*\*,  $p < 0.0001$



**Supplementary Figure S2. Insulin and metformin do not modify viability of placental explant along 48 hours of culture.** XTT cell viability assay of placental explants incubated along 48 hours with culture media adjusted with glucose 10 mM (white bar) or 50 mM (blue bar).  $n = 3$  independent experiments in triplicate. Two-way ANOVA (mixed effects analysis) followed by Tukey's multiple comparisons test. No significant differences were detected. Data is presented as mean and standard deviation.