**Supplemental Table 1:** **Effect of GLP-1/GIP/glucagon triple agonism on circulating levels of selected markers in female and fat mass-matched male mice.** Concentration of leptin, triglycerides, non-esterified free fatty acids (NEFAs), FGF21, L-alanine:2-oxoglutarate aminotransferase (ALT), and aspartate aminotransferase (AST) in plasma of 6 hours-fasted female and fat mass-matched male mice treated daily with vehicle, 5 nmol/kg or 10 nmol/kg of the triagonist (age 9 months; ♀ *n* = 5-10; ♂ *n* = 6-8 per group). Leptin, triglycerides, and NEFAs were measured at study day 22, FGF21, ALT, and AST at study day 27. Data represent mean ± s.e.m. \**P* < 0.05, \*\**P* < 0.01, \*\*\**P* < 0.001, determined by two-way ANOVA comparing vehicle with compound injections in both sexes. $*P* < 0.05 determined by two-way ANOVA comparing both sexes. ANOVA was followed by Tukey *post hoc* multiple comparison analysis to determine statistical significance.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Females | | | Males | | |
| **Treatment** | **Vehicle** | **5 nmol/kg** | **10 nmol/kg** | **Vehicle** | **5 nmol/kg** | **10 nmol/kg** |
| Leptin (ng/ml) | 13.88 ± 1.96 | 4.75 ± 1.42\* | 3.76 ± 1.20\*\* | 12.78 ± 2.26 | 7.23 ± 2.03 | 3.55± 0.53\* |
| Triglycerides (mg/dl) | 96.27 ± 4.9 | 91.57 ± 6.4 | 105.74 ± 6.8 | 98.73 ± 4.8 | 87.09 ± 6.5 | 85.62 ± 6.6 |
| NEFAs (mM) | 1.01 ± 0.09$ | 1.34 ± 0.14 | 2.06 ± 0.17\*\*\* | 1.60 ± 0.11 | 1.42 ± 0.08 | 1.54 ± 0.18 |
| FGF21 (pg/ml) | 238.7 ± 44.4 | 637.3 ± 167.2\* | 429.4 ± 66.0 | 290.5 ± 64.4 | 427.0 ± 68.4 | 307.9 ± 45.8 |
| ALT (U/l) | 31.61 ± 9.08 | 12.21 ± 3.92 | 11.56 ± 3.65\* | 18.61 ± 4.56 | 9.50 ± 2.51 | 5.43 ± 0.99 |
| AST (U/l) | 33.92 ± 8.68 | 22.48 ± 6.00 | 17.65 ± 4.22 | 30.53 ± 8.98 | 35.95 ± 12.76 | 30.87 ± 6.47 |