Activation of the Hypothalamic-Pituitary-Adrenal axis by exogenous and endogenous GDF15

Irene Cimino¹,¹⁵, Hanna Kim²,¹⁵, YC Loraine Tung¹, Kent Pedersen³, Debra Rimmington¹, John A. Tadross¹,⁴, Sara N. Kohnke¹, Ana Neves-Costa⁵, André Barros⁵, Stephanie Joaquim², Don Bennett⁶, Audrey Melvin¹, Samuel M. Lockhart¹, Anthony J. Rostron⁷,⁸, Jonathan Scott⁷, Hui Liu⁹, Keith Burling¹⁰, Peter Barker¹⁰, Menna R. Clatworthy¹¹,¹²,¹³, E-Chiang Lee⁹, A. John Simpson⁷, Giles S.H. Yeo¹, Luis F. Moita⁵,¹⁴, Kendra K. Bence², Sebastian Beck Jørgensen³,¹⁶, Anthony P. Coll¹,¹⁶, Danna M. Breen²,¹⁶ and Stephen O’Rahilly¹,¹⁶,¹⁷, *

¹Metabolic Research Laboratories, Wellcome Trust-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge CB2 0QQ, UK;
²Internal Medicine Research Unit, Pfizer Inc, 1 Portland Avenue, Cambridge, MA, USA;
³Global Obesity and Liver Disease Research, Novo Nordisk A/S, Maaloev, Denmark
⁴Department of Pathology, University of Cambridge, Cambridge CB2 1QP, UK
⁵Innate Immunity and Inflammation Laboratory, Instituto Gulbenkian de Ciência, 2780-156 Oeiras, Portugal;
⁶Biostatistics, Early Clinical Development, Pfizer Inc, 1 Portland Street, Cambridge, MA, USA;
⁷Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne, UK;
⁸Integrated Critical Care Unit, Sunderland Royal Hospital, South Tyneside and Sunderland NHS Foundation Trust
⁹The Bennet Building (B930), Babraham Research Campus, Kymab Ltd., Cambridge CB22 3AT UK
¹⁰Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK;
¹¹Molecular Immunity Unit, Department of Medicine, University of Cambridge, Cambridge, UK;
¹²Cambridge Institute of Therapeutic Immunology and Infectious Diseases, University of Cambridge, Cambridge, UK;
¹³Cellular Genetics, Wellcome Sanger Institute, Hinxton, UK.
¹⁴Instituto de Histologia e Biologia do Desenvolvimento, Faculdade de Medicina, Universidade de Lisboa, 1649-004 Lisboa, Portugal.

¹⁵These authors contributed equally
¹⁶Senior author
¹⁷Lead Contact
* correspondence: so104@medschl.cam.ac.uk (S.O.R.)
SI Appendix Fig. S1. GDF15 acute administration/leptin level/anti-GFRAL validation

(A–B) Mouse Study 12 (MS12): acute effect of human recombinant GDF15 administration on (A) endogenous corticosterone and human GDF15 (B) plasma concentration at 1 h.

(C–D) Mouse Study 13–14 (MS13–14): (C) Corticosterone serum level 30 min after human recombinant GDF15 injection at standard housing condition in mice. (D) Leptin serum concentration 1 h post human recombinant GDF15 injection in mice.

(E–F) Mouse Study 15 (MS15) Validation of GFRAL blocking antibody (anti-GFRAL) in mice. Percentage change in (E) food intake and (F) body weight in the 24 h following human recombinant GDF15 administration. Data are expressed as mean ± SEM, n = 6–8 per group. **p < 0.01, ***p < 0.001, ****p < 0.0001, for MS12-13-14 data were analysed by unpaired Student’s t-test, for MS15 by ANOVA.
SI Appendix Fig. S2. GDF15 infusion validation  Rat Study 1 (RS1): (A) Timeline of GDF15 administration and blood collection in the experiment (B) Daily food intake of rats continuously intravenous infused with vehicle or human GDF15. (C) Body weights prior to (day 0) and after continuous intravenous infusion (day 6) with vehicle buffer or human recombinant GDF15. Data are expressed as mean ± SEM, n = 6. *p < 0.05, ***p < 0.001, and ****p < 0.0001 by ANOVA.
Supplementary figure 3 (related to figure 3). mouse corticosterone study

MS 5: LPS

(A) Mouse Study 5 (MS5): Time course of (A) mouse GDF15 and (B) corticosterone serum concentrations at baseline (time=0) and at 2, 6 and 8 h after LPS (0.5 mg/kg) injection in mice. (C-E) Human Study 1 (HS1): Cytokine levels after LPS treatment in healthy human subjects. For MS5 data are expressed as mean ± SEM, n = 4-5 per group. *p < 0.05, **p < 0.01, ***p < 0.001 by ANOVA. For HS1 data are expressed as mean ± SEM, n = 11. *p < 0.05, ***P<0.001 by one-way repeated measures with post-hoc Dunnett’s test to compare each timepoint with baseline.

SI Appendix Fig. S3. Time course of GDF15 and corticosterone in the LPS model
(A-B) Mouse Study 5 (MS5): Time course of (A) mouse GDF15 and (B) corticosterone serum concentrations at baseline (time=0) and at 2, 6 and 8 h after LPS (0.5 mg/kg) injection in mice. (C-E) Human Study 1 (HS1): Cytokine levels after LPS treatment in healthy human subjects. For MS5 data are expressed as mean ± SEM, n = 4-5 per group. *p < 0.05, **p < 0.01, ***p < 0.001 by ANOVA. For HS1 data are expressed as mean ± SEM, n = 11. *p < 0.05, ***P<0.001 by one-way repeated measures with post-hoc Dunnett’s test to compare each timepoint with baseline.