gp.genomicpress.com

Genomic Psychiatry

OPEN

BREVIA

Varying levels of interleukin 1 receptor antagonist (*Il1rn*) gene expression affect circulating leptin concentrations and fat distribution

© The Author(s), 2025. This article is under exclusive and permanent license to Genomic Press

Genomic Psychiatry; https://doi.org/10.61373/gp025l.0056

The relationship between leptin and interleukin 1 receptor antagonist (IL1RA) is critical to the understanding of obesity's low-grade chronic inflammatory state. IL1RA antagonizes the proinflammatory effects of IL1, dampens systemic inflammation markers, and in clinical trials improved glycemic control in type 2 diabetes. We show that leptin levels decreased relative to the number of *Il1rn* copies in mice overexpressing IL1RA; these mice have altered white fat distribution with decreased epididymal and retroperitoneal fat tissue masses. They also have increased IL1RA plasma levels and insulin sensitivity. Recombinant IL1RA may be a novel treatment strategy for metabolic syndrome by improving resistance to leptin and insulin.

Low-grade chronic metabolic inflammation is as a pivotal shared pathophysiological feature of neurodegenerative diseases and cognitive deficits as well as obesity, insulin resistance, and progression toward type 2 diabetes (T2D) (1). Increased levels of proinflammatory cytokines, such as interleukin 1B (IL1B), can contribute to pancreatic ß-cell destruction leading to T1D and to insulin resistance (2, 3). IL1 receptor antagonist (IL1RA), a naturally occurring endogenous antagonist for the proinflammatory effects of IL1A and IL1B, is increased severalfold in obesity with concentrations that are correlated with leptin levels (4). IL1RA appears to regulate adipogenesis, energy expenditure, and intake. Its elevated levels in obesity may contribute to obesity-associated outcomes, including leptin resistance (5). The complex interplay between IL1RA and leptin suggests that these molecules engage in bidirectional communication affecting inflammatory and metabolic pathways. Despite the use of recombinant human IL1RA in the treatment of rheumatoid arthritis and in trials for treating T2D, where it improved glycemic control, ß-cell function, and systemic inflammation (6), the net long-term IL1RA effects on metabolism are not well understood.

Using a unique approach of varying exposure to IL1RA levels based on transgenic mouse models with different copy numbers of the secreted form of the *Il1rn* (7), we investigated the effects of IL1RA on adipose tissue function. All experiments used male mice aged 10–14 weeks, acknowledging the sexual dimorphism in fat distribution and leptin biology. As an initial exploratory study, we focused on males, though future studies should examine sex-specific responses to IL1RA overexpression. This transgenic approach allows for investigation of dose-dependent effects that would be difficult to achieve with pharmacological administration, where IL1RA levels fluctuate rapidly after

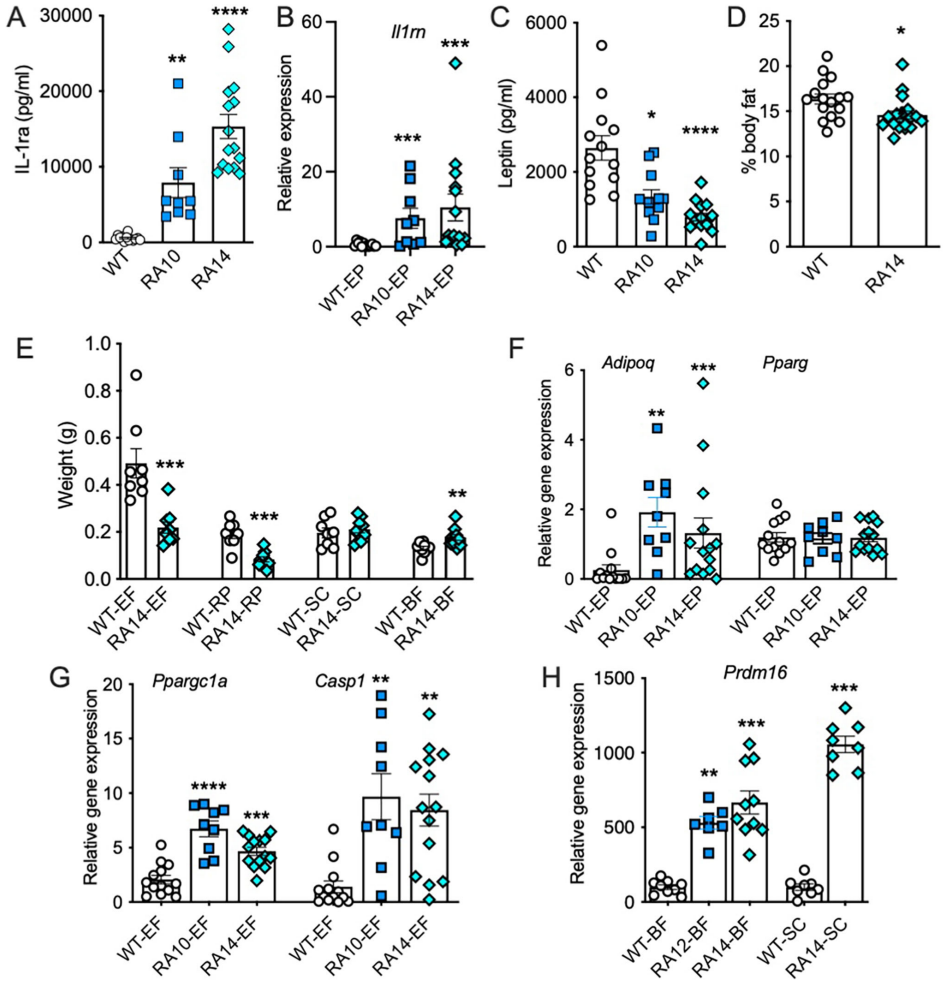

Figure 1. IL1RA overexpression alters fat depot weight and function. Comparing to wild-type (WT) mice, mice expressing a total of 10 (RA10) and 14 (RA14) copies of the *Il1rn* had: (A) higher plasma IL1RA levels and (B) significantly increased *Il1rn* gene expression in the EF (epididymal fat pad); and (C) decreased plasma leptin levels. (D) Dual-energy X-ray absorptiometry (DXA) scan showed decreased body fat percentage in RA14 mice. (E) RA14 mice showed decreased fat tissue mass in the EF and retroperitoneal fat (RF), unchanged subcutaneous fat (SC), and decreased brown fat (BF). (F) IL1RA-overexpressing mice had increased *Adipoq* expression and unchanged *Pparg* expression in the EF. *Ppargc1a* and *Casp1* mRNA expression were increased in the EF of mice overexpressing IL1RA. (G) *Prdm16* expression was increased in BF and SC of IL1RA-overexpressing mice. Columns and error bars = means ± sem; $n > 8$/group; one-way ANOVA or Kruskal–Wallis test and post hoc test (A, B, C, F, G, and BF data in H); Student *t*-test or Mann–Whitney test (D, E, and SC data in G); asterisks depict significant differences compared to WT mice; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$; $^{*****}P < 0.0001$.

Received: 7 April 2025. Revised: 4 May 2025. Accepted: 23 May 2025.
Published online: 10 June 2025.

Downloaded from https://prime-pdf-watermark.prime-prod.pubfactory.com/ at 2025-06-15 via Open Access. CC BY-NC-ND 4.0. https://creativecommons.org/licenses/by-nc-nd/4.0/

dosing. The sustained and genetically regulated elevation of IL1RA provides a model that more closely mimics constitutive overexpression than intermittent therapy. Compared to wild-type (WT) mice, these mice have very high levels of circulating IL1RA (Figure 1A) and significantly increased *Il1rn* gene expression (Figure 1B). Their leptin levels were decreased relative to the copy number of *Il1rn* (Figure 1C), possibly through IL1RA-mediated suppression of NFκB signaling in adipocytes. IL1RA-overexpressing mice had decreased percentage of body fat (Figure 1D) and a decrement in percentage of body fat with decreased epididymal fat (EF) pad and retroperitoneal fat (RF) masses, and increased brown fat (BF) weight (Figure 1E). Their EF adipose tissue showed increased *Adipoq* (adiponectin) gene expression, which is consistent with enhanced insulin sensitivity and glucose uptake (Figure 1F). However, the adipogenic transcription factor *Pparg* expression was unchanged. Adipose tissue *Ppargc1a* [peroxisome proliferator-activated receptor gamma (PPARG) coactivator 1 alpha] expression was also increased, implying increased mitochondrial activity (8). Caspase 1 (*Casp1*) mRNA was increased in the adipose tissue, suggesting adipocyte differentiation (Figure 1F). IL1RA-overexpressing mice also had increased *Pdrm16* (PR domain containing 16) expression in BF and subcutaneous fat (SC) (Figure 1G). PRDM16 is an essential regulator of thermogenesis and induces BF formation (9). Congruent with published work and compared to WT mice, IL1RA-overexpressing mice have normal weight (7), increased insulin sensitivity, reflected in decreased glucose level in the intraperitoneal insulin sensitivity test, and decreased circulating insulin and C-peptide levels. Additionally insulin content in pancreatic ß-cell islets was decreased (Supplemental Figure).

Our findings support the hypothesis that obesity and metabolic syndrome may be autoinflammatory conditions in which endogenous IL1RA levels, though present, are insufficiently high to restore insulin and leptin sensitivity. Administration of human recombinant IL1RA is an approved treatment for autoinflammatory disorders, such as rheumatoid arthritis. Previous studies with these transgenic mouse lines demonstrated that elevated IL1RA expression reduces systemic inflammation markers, including circulating IL1A and IL1B, and dampens IL1 signaling. While we did not measure serum adiponectin levels, the enhanced adiponectin gene expression suggests a potential mechanism for improved metabolic profiles via enhanced glucose uptake and fatty acid oxidation. The inverse relationship between IL1RA copy number and leptin levels observed in our study indicates a dose-dependent effect that could be leveraged therapeutically. The effects on fat depot distribution, with decreased white fat and increased thermogenic capacity in BF, suggest that IL1RA influences not only total adiposity but also the qualitative aspects of fat metabolism. We suggest that pharmacological doses of recombinant IL1RA may be beneficial for treating metabolic syndrome by decreasing leptin and insulin resistances; its administration should take in consideration the nocturnal peak of endogenous leptin (10).

Neuro-immune interactions, including IL1RA-leptin signaling, offer therapeutic targets beyond weight regulation. The neuro-immune axis (11, 12) modulates brain pathways relevant to metabolic and neurodegenerative disorders, suggesting potential applications for treating cognitive decline and depression alongside obesity and diabetes.

Data Availability

All data needed to evaluate the conclusions in the paper are present in the paper and supplemental materials. Original data for gene expression analyses (qPCR), plasma measurements (IL1RA, leptin, insulin, C-peptide), body composition (DXA scans), and tissue weights are available from the corresponding author (juliolicinio@gmail.com) upon reasonable request. The transgenic mouse lines used in this study were obtained from Dr. Emmet Hirsch, currently at University of Chicago.

Acknowledgment

We thank Lara Weaver for performing IL1RA overexpresson mouse genotyping.

Author Contributions

JL and MLW conceived and designed the study; CM and GP performed animal studies; CM performed gene expression and leptin assays; GP performed Dual-energy X-ray absorptiometry scans; CS conceived, designed, and performed pancreatic ß-cell islets studies; CM, GP, and CS analyzed data and plotted figures; JL and MLW wrote, and CM, GP, and CS edited the paper.

Funding Sources

This study was supported by the NIH (R21MH-128726 to MLW and JL) and Australian National University Institutional Funds.

Author Disclosures

The authors declare no competing interests.

Ma-Li Wong[1], Claudio Mastronardi[2], Gilberto Paz-Filho[3], Charmaine Simeonovic[4], and Julio Licinio[1]

[1] *State University of New York, Upstate Medical University, Syracuse, NY 13210, USA*

[2] *INPAC Research Group, Fundación Universitaria Sanitas, Bogotá, Colombia*

[3] *Medical & Scientific Affairs, Johnson & Johnson Innovative Medicine, NSW 2113, Australia*

[4] *Diabetes and Transplantation Immunobiology Group, Division of Immunology and Infectious Diseases, John Curtin School of Medical Research, Australian National University, Canberra, ACT 2601, Australia*

✉ *e-mail: juliolicinio@gmail.com*

1. Rohm TV, Meier DT, Olefsky JM, Donath MY. Immunity. 2022;55(1):31–55. DOI: 10.1016/j.immuni.2021.12.013. PMID: 35021057; PMCID: PMC8773457
2. Maedler K, Sergeev P, Ris F, Oberholzer J, Joller-Jemelka HI, Spinas GA, et al. J Clin Inv. 2002;110(6):851–60. DOI: 10.1172/JCI15318. PMID: 12235117; PMCID: PMC151125
3. Tsalamandris S, Antonopoulos AS, Oikonomou E, Papamikroulis GA, Vogiatzi G, Papaioannou S, et al. Eur Cardiol. 2019;14(1):50–9. DOI: 10.15420/ecr.2018.33.1. PMID: 31131037; PMCID: PMC6523054
4. Meier CA, Bobbioni E, Gabay C, Assimacopoulos-Jeannet F, Golay A, Dayer JM. J Clin Endocrinol Metab. 2002;87(3):1184–8. DOI: 10.1210/jcem.87.3.8351. PMID: 11889184
5. Somm E, Henrichot E, Pernin A, Juge-Aubry CE, Muzzin P, Dayer JM, et al. Diabetes. 2005;54(12):3503–9. DOI: 10.2337/diabetes.54.12.3503. PMID: 16306368
6. Larsen CM, Faulenbach M, Vaag A, Ehses JA, Donath MY, Mandrup-Poulsen T. Diabetes Care. 2009;32(9):1663–8. DOI: 10.2337/dc09-0533. PMID: 19542207; PMCID: PMC2732140
7. Hirsch E, Irikura VM, Paul SM, Hirsh D. Proc Natl Acad Sci USA. 1996;93(20):11008–13. DOI: 10.1073/pnas.93.20.11008. PMID: 8855299; PMCID: PMC38274
8. Kobayashi M, Deguchi Y, Nozaki Y, Higami Y. Int J Mol Sci. 2021;22(11):6025. DOI: 10.3390/ijms22116025. PMID: 34199596; PMCID: PMC8199692
9. Seale P, Conroe HM, Estall J, Kajimura S, Frontini A, Ishibashi J, et al. J Clin Inv. 2011;121(1):96–105. DOI: 10.1172/JCI44271. PMID: 21123942; PMCID: PMC3007155
10. Licinio J, Mantzoros C, Negrao AB, Cizza G, Wong ML, Bongiorno PB, et al. Nat Med. 1997;3(5):575–579. DOI: 10.1038/nm0597-575. PMID: 9142131
11. Sternberg EM, Licinio J. Ann N Y Acad Sci. 1995;771:364–71. DOI: 10.1111/j.1749-6632.1995.tb44695.x. PMID: 8597414
12. Inserra A, Mastronardi CA, Rogers G, Licinio J, Wong M-L. Mol Neurobiol. 2019;56(6):4288–305. DOI: 10.1007/s12035-018-1359-3. PMID: 30306457; PMCID: PMC6505498

Publisher's note: Genomic Press maintains a position of impartiality and neutrality regarding territorial assertions represented in published materials and affiliations of institutional nature. As such, we will use the affiliations provided by the authors, without editing them. Such use simply reflects what the authors submitted to us and it does not indicate that Genomic Press supports any type of territorial assertions.

Open Access. This article is licensed to Genomic Press under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND 4.0). The license mandates: (1) Attribution: Credit must be given to the original work, with a link to the license and notification of any changes. The acknowledgment should not imply licensor endorsement. (2) NonCommercial: The material cannot be used for commercial purposes. (3) NoDerivatives: Modified versions of the work cannot be distributed. (4) No additional legal or technological restrictions may be applied beyond those stipulated in the license. Public domain materials or those covered by statutory exceptions are exempt from these terms. This license does not cover all potential rights, such as publicity or privacy rights, which may restrict material use. Third-party content in this article falls under the article's Creative Commons license unless otherwise stated. If use exceeds the license scope or statutory regulation, permission must be obtained from the copyright holder. For complete license details, visit https://creativecommons.org/licenses/by-nc-nd/4.0/. The license is provided without warranties.

Downloaded from https://prime-pdf-watermark.prime-prod.pubfactory.com/ at 2025-06-15 via Open Access. CC BY-NC-ND 4.0. https://creativecommons.org/licenses/by-nc-nd/4.0/