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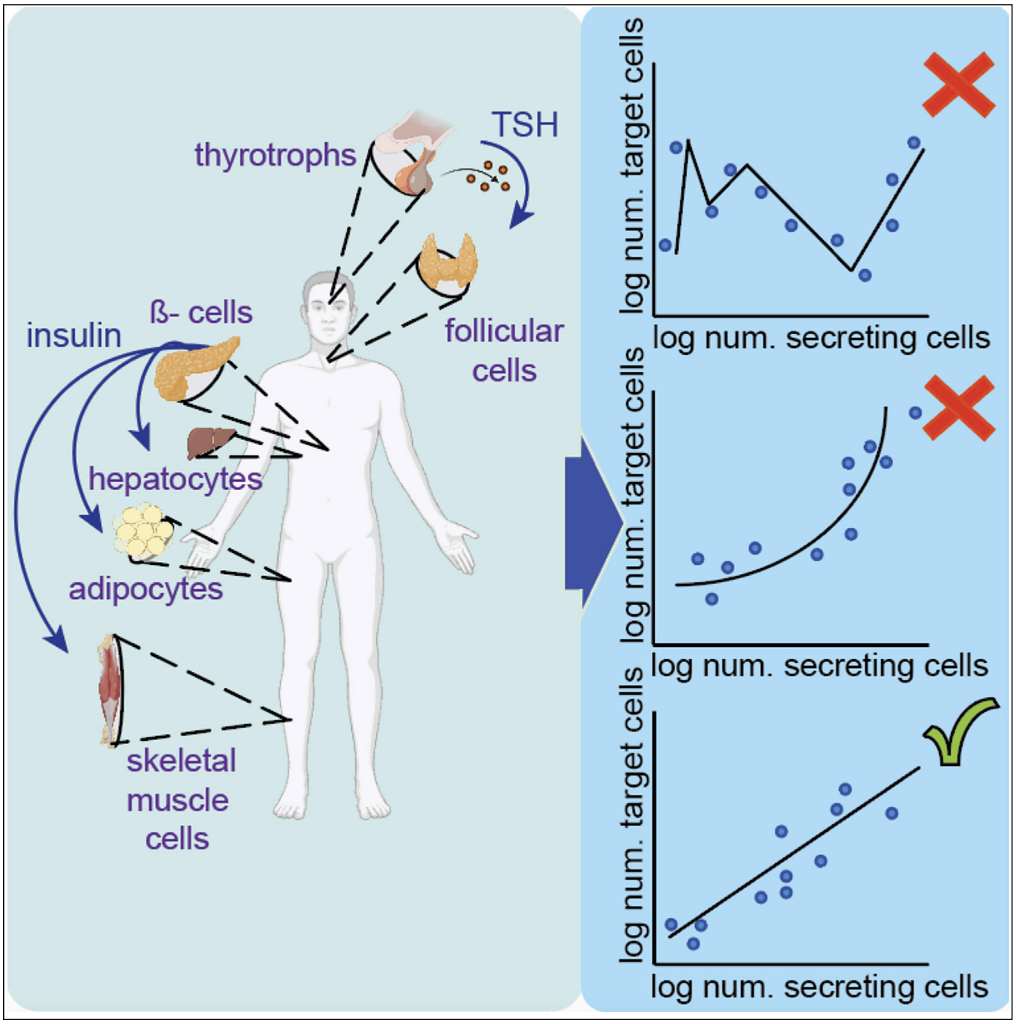

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Highlights

Hormone secreting and total target cell numbers are proportional

One endocrine cell serves about 2,000 target cells

This holds across a million-fold difference in gland sizes

This suggests that cells are near maximal capacity and glands are no bigger than needed

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Article

Endocrine gland size is proportional to its target tissue size

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SUMMARY

Endocrine glands secrete hormones into the circulation to target distant tissues and regulate their functions. The qualitative relationship between hormone-secreting organs and their target tissues is well established, but a quantitative approach is currently limited. Quantification is important, as it could allow us to study the endocrine system using engineering concepts of optimality and tradeoffs. In this study, we collected literature data on 24 human hormones secreted from dedicated endocrine cells. We find that the number of endocrine cells secreting a hormone is proportional to the number of its target cells. A single endocrine cell serves approximately 2,000 target cells, a relationship that spans 6 orders of magnitude of cell numbers. This suggests an economic principle of cells working near their maximal capacity, and glands that are no bigger than they need to be.

INTRODUCTION

Hormones are regulatory molecules secreted by endocrine cells into the circulation where they affect target tissues.[1] Most hormones are secreted by dedicated endocrine cells according to specific signals. Hormones are sensed by receptors in the cells of the target tissues, and trigger metabolic, developmental and behavioral effects. Dysregulation of hormones underlies a wide range of pathologies, including diabetes, reproductive disorders, and mood disorders.[2,3]

Several specialized endocrine glands are found in humans, such as the hypothalamus and pituitary in the brain, the thyroid and parathyroid at the neck, the adrenal above the kidneys and the ovaries/testes. These secretory glands vary in size by many orders of magnitude, and so do the tissues that they target.[1,4] Some hormones are secreted from non-dedicated endocrine cells such as liver and fat cells. The primary function of these cells is not hormone secretion, and therefore they devote only part of their resources to hormone production, and the rest to their other functions.

Hormones vary in their structure, including protein/peptide, steroid, and catecholamine hormones.[1] The physiological effects of hormones are diverse, ranging from highly specific targets such as thyroid-stimulating hormone (TSH) that has a direct effect mainly on the thyroid gland,[5] to hormones that affect virtually all nucleated cells in the body such as cortisol.[1] Some hormones provide homeostasis to key metabolites, such as the parathyroid hormone (PTH) that regulates the levels of calcium in the blood,[6] whereas others control acute responses to stimuli, such as adrenaline in response to stress.[7] The range of effects of hormones in some cases is limited to a single system, such as the gut enteroendocrine hormones that facilitate digestion of food (e.g., gastrin and secretin),[8,9] whereas in other cases their effect coordinates multiple systems, such as insulin that has metabolic effects on muscle, fat, liver, and other tissues.[10,11] Endocrine systems also vary in their regulatory logic—some hormones are secreted under the control of neuronal stimulation, such as antidiuretic hormone (ADH),[12] others are secreted under the control of other hormones, such as the thyroid hormone tetraiodothyronine (T4) that is controlled by TSH[13] and yet others are secreted in response to metabolic signals, such as insulin that is secreted in response to elevated blood glucose.[14]

Extensive molecular and anatomic knowledge exists for each hormone system.[1] It is of interest to supplement this detailed knowledge with principles that relate hormone systems in a quantitative way. Such quantitative characterization can facilitate the understanding of basic principles of the endocrine system as a whole, and contribute to the field of systems endocrinology.[2]

One open question regards the diversity of sizes of endocrine glands—why do some glands have a small number of endocrine cells, such as the 120 mg parathyroid glands that total about 10^7 PTH-secreting cells[15](BNID 111609),[16] whereas other glands such as the 5.5 g adrenal cortex is a thousand times bigger with about 10^{10} cortisol-secreting cells (BNID 111609)[16–18]? Since structure and function are linked in biology,[19] the answer to this question can reveal principles regarding the function of endocrine cells and organs.

To address this, we investigated the relationship between the number of hormone-secreting cells and the total number of target cells for each hormone. We hypothesize that endocrine tissue size correlates with its target tissue size. Several possibilities exist—a slope of one would mean isometric scaling, with a fixed number of target cells served by each endocrine cell. A slope different from one means diminishing or

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increasing returns with endocrine cell number—for example, large endocrine glands might conceivably have decreased vascularization and thus each cell could serve fewer target cells than smaller glands.

RESULTS

Endocrine gland size is approximately proportional to the size of its target tissues

We considered a comprehensive set of 64 human hormones.[1,20] For each hormone, we used the literature to estimate the number of cells that secrete it. We found this information for 45 hormones. To determine the target cell types of each hormone, we used the literature to determine the cells that express high levels of the receptor for the hormone and where the hormone has a documented physiological function (Table 1). We then estimated the total number of cells in the target tissues. We derived such information for 29 hormones, which is the set of hormones considered here. Of these, 26 are secreted by a dedicated cell type, and the remaining 3 are secreted by cell types with other major functions (Figure 1).

Of the 26, we did not analyze two hormones further—thyroid hormone T3 (triiodothyronine) and noradrenaline. T3 is made from T4 (tetraiodothyronine) by deiodinases in many tissues and secreted in small amounts by the thyroid gland, and is thus an exception to most hormones whose primary source is a dedicated cell type. Noradrenaline resembles adrenaline and therefore was not included to avoid redundancy.

Details of the approach by which we estimated cell numbers are provided in the STAR Methods. In the minority of cases, we found data on the number of cells in humans in the literature. For most tissues, we calculated the number of cells after investigation of histologic slides in order to estimate the volume fraction occupied by the specific population of cells x (a number between zero and one). We used literature data on mass per cell m (grams) and total tissue mass M (grams) to estimate cell numbers $n = x\,M/m$. The calculations are detailed in the STAR Methods section.

We explored the relation between the number of secreting cells and the total number of target cells using linear regression on log cell counts (Figure 2). We find that target cell number and secreting cell number are well correlated ($R^2 = 0.89$, $p<0.0001$). The slope of the log-log regression line is 0.95 with a 95% confidence interval of (0.82,1.05). The slope is close to one, suggesting isometric scaling. The ratio of target to secreting cell numbers averages $10^{3.3\pm0.56}$. This roughly corresponds to 2,000 target cells served by each dedicated endocrine cell.

Hormones secreted by cell types with a non-endocrine major function

We next investigated hormones secreted by cell types that are not dedicated endocrine cells. We focused on the hormone insulin-like growth factor 1 (IGF-1) made primarily in the liver,[47] and the adipocyte-secreted hormones leptin and adiponectin.[60,21] These cell types have other major functions—hepatocytes secrete plasma proteins, detoxify the blood, and perform metabolic functions[61]; Adipocytes store and release fatty acids.[62]

We plot the secreting and target cell numbers for these hormones in Figure 3. The hormones lie below the regression line of Figure 2. The number of secreting cells is much larger per target cell than for the dedicated endocrine cell-types. If these hormones had obeyed the same relation as the hormones in Figure 2, they would have target cell numbers that exceed the total number of nucleated cells in the human body (dashed line in Figure 3).

DISCUSSION

We explored the relationship between the number of cells that secrete a hormone and the total number of cells in its target tissues. We find that secreting and target cell numbers are proportional to a good approximation across about 6 orders of magnitude of cell numbers. Each endocrine cell serves about 2,000 target cells. Hormones secreted by non-dedicated endocrine cells with other major functions lie below this proportionality line, such that they serve fewer target cells per secreting cell.

The relationship we have discussed is a question of scaling and allometry,[64,65] which is a widely studied topic including the mechanisms that generate it.[66] We find essentially isometric scaling of the sizes of glands and their targets (power law of one). This is scaling between different organ systems within the same species (human). Most studies of scaling concern the relation between different species. For example, endotherm organ sizes scale with body mass with isometry for fat and subisometry for brain and other organs (power laws smaller than 1).[67,68] Fractional scaling laws are found for metabolic rate and other properties with organism mass across species.[69]

The proportionality of the number of secreting and target cells may stem from a maximal hormone production rate per endocrine cell. This suggests that gland size evolved to be large enough to serve the size of its target tissues and no larger.

According to this principle, hormones secreted as a secondary function of a cell type (which has a non-endocrine major function) should lie below the line—the secreting cell number should be much larger than its predicted target size. We find that this is the case for hormones secreted by fat (e.g., leptin that targets mainly the brain[50]) and liver (IGF-1, targeting almost all nucleated cells in the body[48]) that have secreting cell numbers of $10^{10} - 10^{11}$ cells; their targets, however, are much smaller than the $10^{13} - 10^{14}$ cells that would be predicted by the proportionality line in Figure 2. This exceeds the total number of nucleated cells in humans, about 5×10^{12} cells.[63]

The current study focused on cell number. It would be intriguing to explore whether linear scaling is seen when considering total cell mass instead of cell number. This is because cells can vary in mass. Muscle cells, fat cells, and neurons can be hundreds of times more massive than a typical cell.[16] The proportionality in terms of number of cells may indicate that an important factor is gene regulation rather than cytoplasmic

Table 1. Hormone-secreting and target cell numbers

Hormone	Secreting cell	Major target tissues	Secreting cell number	Total target cell number
Adiponectin (secreted from non-dedicated endocrine cells)	Adipocytes[21]	Mainly skeletal muscle cells and hepatocytes (liver)[21]	5.2×10^{10} (L)	skeletal muscle cells: 1.4×10^{11} (H,L) hepatocytes: 2×10^{11} (H,L)
Adrenaline	Chromaffin cells (adrenal medulla)[7,22]	All nucleated cells in the body[23]	2×10^{9} (H,L)	5×10^{12} (L)
Adreno-corticotropic hormone (ACTH)	Corticotrophs (anterior pituitary)[17]	Adrenal cortex (mostly zona fasciculata and zona glomerulosa)[17]	10^{7} (L)	5×10^{9} (H, L)
Aldosterone	Zona glomerulosa (adrenal cortex)[24]	Epithelial cells in the distal tubules and collecting ducts of the kidneys, cardiomyocytes, and cardiac fibroblasts[25]	6×10^{8} (H,L)	Epithelial cells in the distal tubules and collecting ducts of the kidneys: 4×10^{10} (H,L), cardiac fibroblasts- 3×10^{10} (H,L), cardiac myocytes: 2.5×10^{9} (L)
Androgen (male)	Leydig cells (testicles)[26]	Adipocytes, skeletal muscle cells, several brain areas, seminiferous ducts epithelial cells, Leydig cells and epididymis glandular cells, glandular cells inside seminal vesicle[27–30]	10^{9} (H,L)	Adipocytes: 5.2×10^{10} (L), skeletal muscle cells: 1.4×10^{11} (H,L) As these two population of cells outnumber the other target tissues by several orders of magnitude, we used their combined number as the number of target cells
Cholecystokinin (CCK)	I-cells located mostly in the duodenum and jejunum[31]	Pancreatic acinar cells, cholangiocytes in the liver and gallbladder smooth muscle cells[32]	3.3×10^{8} (L,H)	Pancreatic acinar cells: 9×10^{9} (H,L), cholangiocytes in the liver: 8×10^{9} (L), smooth muscle cells in the gallbladder, 1.5×10^{10} (H,L)
Corticotropin-releasing hormone (CRH)	Parvocellular neurosecretory cells (in the paraventricular nucleus of the hypothalamus)[33]	Corticotrophs (anterior pituitary)[34]	10^{4} (L)	10^{7} (L)
Cortisol	Zona fasciculata (adrenal cortex)[4]	All nucleated cells in the body[35]	4.5×10^{9} (H,L)	5×10^{12} (L)
Estrogen—female	Granulosa cells of the ovaries[36]	Vagina, fallopian tubes, uterine endometrium, uterine cervix, breast, smooth muscle, zona reticularis of the adrenal glands and endothelial cells[30]	9.3×10^{8} (H,L)	Vagina: 1.5×10^{9} (H,L), fallopian tubes: 2×10^{10} (H,L), uterine endometrium: 2.4×10^{10} (H,L), uterine cervix: 2×10^{9} (H,L), breast- 3.5×10^{11} (H,L), smooth muscle: $\sim 3 \times 10^{9}$ (L), zona reticularis: 0.6×10^{9} (H,L), endothelial cells: 6×10^{11} (L)
Estrogen—male	Leydig cells (testicles)[37]	Testicles, seminal vesicles, prostate, penis and endothelial cells[38]	Leydig cells- 10^{9} (H,L)	Testicles: 5.5×10^{9} (H,L), seminal vesicles: 7×10^{6} (H,L), prostate: 5.5×10^{9} (H,L), penis: 8×10^{10} (H,L), endothelial cells: 6×10^{11} (L)
Follicle-stimulating hormone (FSH)—female	Gonadotrophs (anterior pituitary)[39]	Granulosa cells (ovaries), secretory endometrium during the luteal phase (uterus)[40]	4×10^{6} (L)	Granulosa cells: 9.3×10^{8} (H,L), secretory endometrium during the luteal phase: 1.6×10^{10} (H,L)
Follicle-stimulating hormone (FSH)—male	Gonadotrophs (anterior pituitary)[39]	Sertoli cells (testicles)[41]	4×10^{6} (L)	10^{9} (H,L)
Gastrin	G-cells (stomach)[42]	Parietal cells (stomach), acinar cells (pancreas)[8]	10^{7} (L)	Parietal cells: 10^{9} (L), pancreatic acinar cells: 9×10^{9} (H,L)

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Table 1. *Continued*

Hormone	Secreting cell	Major target tissues	Secreting cell number	Total target cell number
Glucagon	Alpha cells (pancreas)[43]	Hepatocytes (liver)[44]	6.3×10^{8} (L)	2×10^{11} (L)
Gonadotropin-releasing hormone (GnRH)	Medial preoptic nucleus (hypothalamus)[45]	Gonadotrophs (pituitary)[45]	1.7×10^{3} (L)	4×10^{6} (H,L)
Growth hormone (GH)	Somatotrophs (pituitary)[46]	Hepatocytes (liver) and adipocytes[30]	4×10^{7} (L)	Hepatocytes: 2×10^{11} (L), adipocytes: 5.2×10^{10} (L)
Insulin-like growth factor 1 (IGF-1) (secreted from non-dedicated endocrine cells)	Hepatocytes (liver)[47]	All nucleated cells in the body[48]	2×10^{11} (L)	5×10^{12} (L)
Insulin	Beta cell (pancreas)[10,11,49]	Hepatocytes (liver), skeletal muscle cells and adipocytes[10,11,49]	10^{9} (L)	6×10^{11} (L,H)
Leptin (secreted from non-dedicated endocrine cells)	Adipocytes[50]	Hypothalamus[50]	5.2×10^{10} (L)	2×10^{7} (H,L)
Luteinizing hormone (LH)—female	Gonadotrophs (anterior pituitary)[51]	Theca cells (ovaries), interstitial and mature granulosa cells (ovaries)[52]	4×10^{6} (L)	Ovarian theca cells and interstitial and mature granulosa cells 3×10^{9} (H,L)
Luteinizing hormone (LH)—male	Gonadotrophs (anterior pituitary)[51]	Leydig cells (testicles)[52]	4×10^{6} (L)	10^{9} (H,L)
Progesterone—female	Granulosa cells after ovulation (ovary)[53]	Fallopian tubes, uterine endometrium, uterine cervix, breast and smooth muscle[30]	9.3×10^{8} (H,L)	Fallopian tubes: 2×10^{10} (H,L), uterine endometrium: 2.4×10^{10} (H,L), uterine cervix: 2×10^{9} (H,L), breast: 3.5×10^{11} (H,L), smooth muscle cells: $\sim 3 \times 10^{9}$ (L)
Prolactin	Lactotrophs (anterior pituitary)[54]	Mammary gland cells (breast), β-cells (pancreas), adipocytes, B cells and T cells (immune system)[54]	1.2×10^{7} (L)	Breast mammary cells: 3.5×10^{11} (H,L), pancreatic β-cells: 10^{9} (L), adipocytes- 5.2×10^{10} (L), B cells: 10^{11} (L), T cells: 4×10^{11} (L)
Secretin	S-cells (duodenum)[55]	Parietal cells (stomach), ductal cells (pancreas) and cholangiocytes[56–58]	2.8×10^{7} (H,L)	Parietal cells: 10^{9} (L), pancreatic ductal cells: 10^{10} (L), cholangiocytes: 8×10^{9} (L)
Thyrotropin-releasing hormone (TRH)	Parvocellular neurosecretory cells (located in the paraventricular nucleus of the hypothalamus)[59]	Thyrotrophs (anterior pituitary)[59]	10^{4} (L)	4×10^{6} (L)
Thyrotropin-stimulating hormone (TSH)	Thyrotrophs (anterior pituitary)[46]	Follicular cells (thyroid gland)[5]	4×10^{6} (L)	2.5×10^{9} (H,L)
Thyroxine (T4)	Follicular cells (thyroid)[5]	All nucleated cells in the body[13]	4×10^{6} (L)	5×10^{12} (L)

L: cell number estimate found in literature, see "STAR Methods" for references, H: cell number estimated from histology, see "STAR Methods" for references. Calculations of the number of cells are detailed in the "STAR Methods" section.

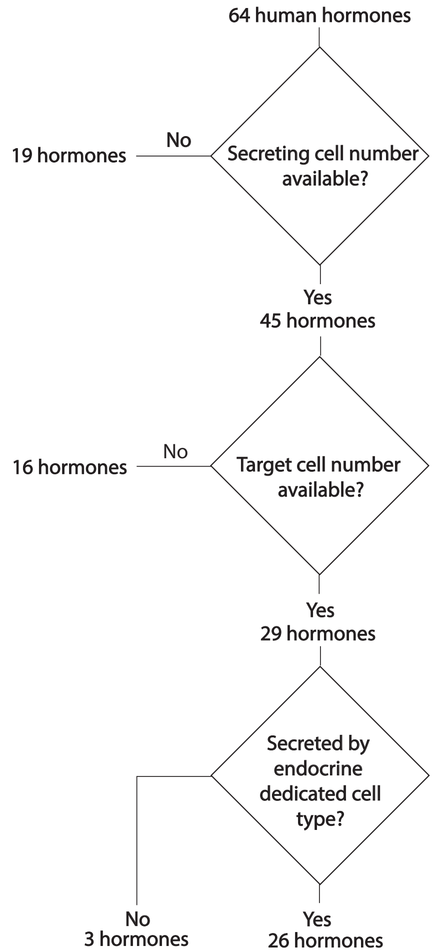

Figure 1. Hormone selection process

biomass effects. In this regard, tissues with multinucleated cells, such as osteoclasts and aged liver cells, may result in deviations from proportionality, which is a direction for future research.

The number of cells in many endocrine glands is not constant over time in adults. Regulatory circuits can increase and decrease the number of cells in a controlled way.[70] For example, TSH can cause thyroid cells to proliferate, causing goiter.[71] Similarly, adreno-corticotropic hormone (ACTH) can cause proliferation of adrenal cortex cells.[72] These gland-mass control circuits have recently been analyzed and shown to provide compensation ability to endocrine circuits.[70–72] Cell population size can grow and shrink, and thus secrete more and less hormone respectively, to compensate for changes in physiological parameters.[2] These changes, however, are much smaller than the range of gland sizes studied here, and thus should not strongly affect the proportionality in Figure 2.

It would be interesting to compare these results in humans with other organisms—if scaling is found in several different organisms, one may hypothesize that it is a universal feature of endocrine systems. Current data on cell counts in mice and other organisms are not sufficiently extensive. Repeating the present analysis in other organisms is thus a challenge for future work. Recent advances signal the availability of large scale data in other species in the near future, such as a study on the hormone network of the mouse lemur.[73]

It would also be interesting to explore a given organism at different developmental stages, at different ages and across states of health and disease.

In summary, despite the diversity in hormone biology, a regularity emerges in which secreting cell number is proportional to the total cell number of the hormone's target tissues. This suggests a fixed capacity of production per endocrine cell, where an endocrine cell serves about 2,000 target cells. It would be interesting to explore additional principles to deepen our understanding of systems endocrinology.

Limitations of the study

This study used data from the literature or from histologic slides for the number of secreting and target cells, without differentiating between sexes or other possible confounders because of the limited amount of data available. It may be problematic to fit a statistical model such as

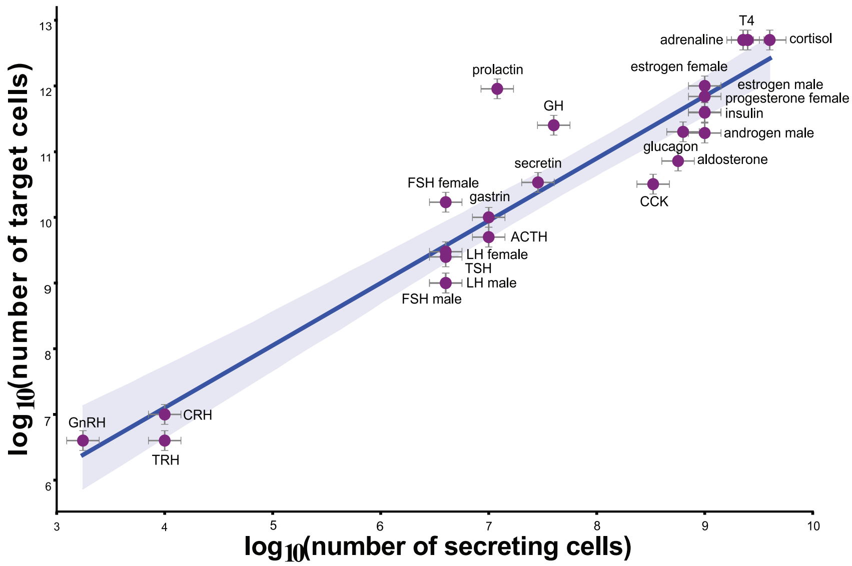

Figure 2. The number of cells that secrete a hormone is approximately proportional to the total number of its target cells
Secreting versus target cell numbers for 24 hormones secreted by dedicated cell types. Regression line and 95% CI are shown in blue, $R^2 = 0.89$, $p<0.0001$. The slope of the log-log regression line is 0.95 with a 95% confidence interval of (0.82,1.05), which suggests isometric scaling. The ratio of target to secreting cell numbers averages $10^{3.3\pm0.56}$. This roughly corresponds to 2,000 target cells served by each dedicated endocrine cell. Error bars represent a log normal noise model with a dispersion factor of two. ACTH, adrenocorticotropic hormone; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T4, tetraiodothyronine.

linear regression to means as if they were raw data, an issue known as "aggregated data analysis" or "ecological regression" that in some cases can lead to biases.[74–78] Since data are scarce, we could not estimate the distribution of values in the population; future work on cell numbers from many individuals can help to address this.

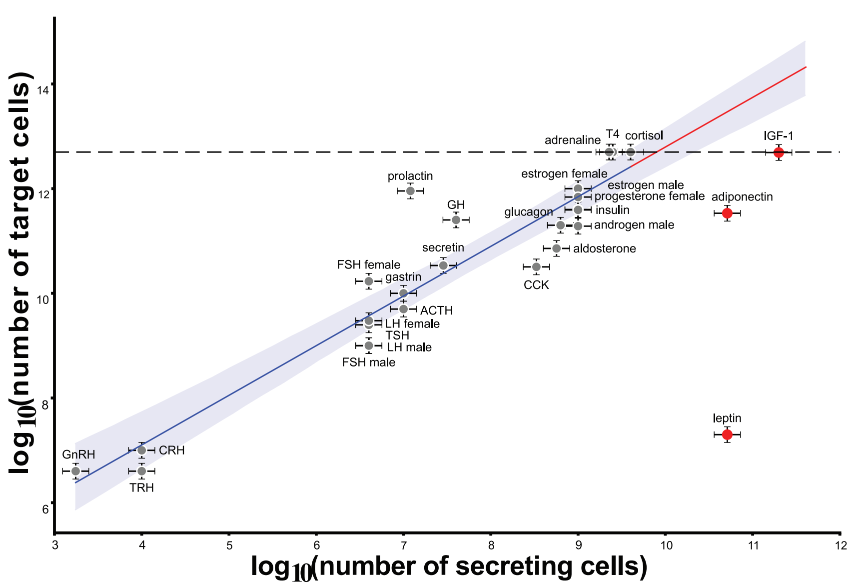

Figure 3. Secreting versus target cell numbers for hormones secreted by cell types that have other major functions
The hormones IGF-1, adiponectin and leptin are shown in red, the hormones of Figure 2 in gray. Dashed line is the total number of nucleated cells in the human body,[63] and the regression line was extrapolated using the regression in Figure 2 (red). Error bars represent log normal variation with dispersion of 2. ACTH, adrenocorticotropic hormone; CCK, cholecystokinin; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; T4, tetraiodothyronine.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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- METHOD DETAILS
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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2024.110625.

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AUTHOR CONTRIBUTIONS

Conceptualization: M.R. and U.A.; methodology: M.R. and U.A.; software: M.R., T.M., and D.S.G.; formal analysis: M.R., D.S.G., A.M., and U.A.; data curation: M.R.; writing: M.R. and U.A.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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REFERENCES

1. Melmed, S., Auchus, R.J., Goldfine, A.B., Rosen, C.J., and Kopp, P.A. (2019). Williams Textbook of Endocrinology, 14th edition (Elsevier).
2. Alon, U. (2023). Systems Medicine: Physiological Circuits and the Dyamics of Disease (Chapman and Hall/CRC).
3. Molina, P. (2006). Endocrine Physiology (LANGE Physiology Series) (McGraw-Hill Medical).
4. Hall, J.E., and Hall, M.E. (2021). Guyton and Hall Textbook of Medical Physiology, 14th edition (Elsevier).
5. Parmentier, M., Libert, F., Maenhaut, C., Lefort, A., Gérard, C., Perret, J., Van Sande, J., Dumont, J.E., and Vassart, G. (1989). Molecular cloning of the thyrotropin receptor. Science *246*, 1620–1622. https://doi.org/10.1126/science.2556796.
6. Goltzman, D. (2018). Physiology of Parathyroid Hormone. Endocrinol. Metab. Clin. North Am. *47*, 743–758. https://doi.org/10.1016/j.ecl.2018.07.003.
7. Adrenaline - an overview | ScienceDirect Topics https://www.sciencedirect.com/topics/chemistry/adrenaline.
8. Prosapio, J.G., Sankar, P., and Jialal, I. (2023). Physiology, Gastrin. In StatPearls (StatPearls Publishing).
9. DiGregorio, N., and Sharma, S. (2023). Physiology, Secretin. In StatPearls (StatPearls Publishing).
10. De Meyts, P. (2000). The Insulin Receptor and Its Signal Transduction Network. In Endotext, K.R. Feingold, B. Anawalt, M.R. Blackman, A. Boyce, G. Chrousos, E. Corpas, W.W. de Herder, K. Dhatariya, J. Hofland, and K. Dungan, et al., eds. (MDText.com, Inc.).
11. Obesity: Facts, Figures, Guidelines https://www.wvdhhr.org/bph/oehp/obesity/section1.htm.
12. Sukhov, R.R., Walker, L.C., Rance, N.E., Price, D.L., and Young, W.S. (1993). Vasopressin and oxytocin gene expression in the human hypothalamus. J. Comp. Neurol. *337*, 295–306. https://doi.org/10.1002/cne.903370210.
13. Shahid, M.A., Ashraf, M.A., and Sharma, S. (2022). Physiology, Thyroid Hormone. In StatPearls (StatPearls Publishing).
14. Nakrani, M.N., Wineland, R.H., and Anjum, F. (2023). Physiology, Glucose Metabolism. In StatPearls (StatPearls Publishing).
15. Yeh, R., Tay, Y.-K.D., Dercle, L., Bandeira, L., Parekh, M.R., and Bilezikian, J.P. (2020). A Simple Formula to Estimate Parathyroid Weight on 4D-CT, Predict Pathologic Weight, and Diagnose Parathyroid Adenoma in Patients with Primary Hyperparathyroidism. AJNR. Am. J. Neuroradiol. *41*, 1690–1697. https://doi.org/10.3174/ajnr.A6687.
16. Milo, R., Jorgensen, P., Moran, U., Weber, G., and Springer, M. (2010). BioNumbers—the database of key numbers in molecular and cell biology. Nucleic Acids Res. *38*, D750–D753. https://doi.org/10.1093/nar/gkp889.
17. Neville, A.M., and O'Hare, M.J. (1981). The Human Adrenal Cortex: Pathology and Biology- An Integrated Approach. Springer-Verlag (Berlin and Heidelberg).
18. Ross, M.H., and Pawlina, W. (2011). Histology: A Text and Atlas: with Correlated Cell and Molecular Biology (Wolters Kluwer/Lippincott Williams & Wilkins Health).

19. Michael, J. (2021). What do we mean when we talk about "structure/function" relationships? Adv. Physiol. Educ. *45*, 880–885. https://doi.org/10.1152/advan.00108.2021.
20. UpToDate (2023 (UpToDate Inc.). https://www.uptodate.com/home.
21. Straub, L.G., and Scherer, P.E. (2019). Metabolic Messengers: Adiponectin. Nat. Metab. *1*, 334–339. https://doi.org/10.1038/s42255-019-0041-z.
22. Verberne, A.J.M., Korim, W.S., Sabetghadam, A., and Llewellyn-Smith, I.J. (2016). Adrenaline: insights into its metabolic roles in hypoglycaemia and diabetes. Br. J. Pharmacol. *173*, 1425–1437. https://doi.org/10.1111/bph.13458.
23. adrenaline | PMG Biology https://pmgbiology.com/tag/adrenaline/.
24. Curnow, K.M., Tusie-Luna, M.T., Pascoe, L., Natarajan, R., Gu, J.L., Nadler, J.L., and White, P.C. (1991). The product of the CYP11B2 gene is required for aldosterone biosynthesis in the human adrenal cortex. Mol. Endocrinol. *5*, 1513–1522. https://doi.org/10.1210/mend-5-10-1513.
25. Lombès, M., Alfaidy, N., Eugene, E., Lessana, A., Farman, N., and Bonvalet, J.P. (1995). Prerequisite for cardiac aldosterone action. Mineralocorticoid receptor and 11 beta-hydroxysteroid dehydrogenase in the human heart. Circulation *92*, 175–182. https://doi.org/10.1161/01.cir.92.2.175.
26. Vasta, V., Shimizu-Albergine, M., and Beavo, J.A. (2006). Modulation of Leydig cell function by cyclic nucleotide phosphodiesterase 8A. Proc. Natl. Acad. Sci. USA *103*, 19925–19930. https://doi.org/10.1073/pnas.0609483103.
27. Singh, R., Artaza, J.N., Taylor, W.E., Braga, M., Yuan, X., Gonzalez-Cadavid, N.F., and Bhasin, S. (2006). Testosterone inhibits adipogenic differentiation in 3T3-L1 cells: nuclear translocation of androgen receptor complex with beta-catenin and T-cell factor 4 may bypass canonical Wnt signaling to down-regulate adipogenic transcription factors. Endocrinology *147*, 141–154. https://doi.org/10.1210/en.2004-1649.
28. Sinha-Hikim, I., Taylor, W.E., Gonzalez-Cadavid, N.F., Zheng, W., and Bhasin, S. (2004). Androgen receptor in human skeletal muscle and cultured muscle satellite cells: up-regulation by androgen treatment. J. Clin. Endocrinol. Metab. *89*, 5245–5255. https://doi.org/10.1210/jc.2004-0084.
29. Zuloaga, D.G., Puts, D.A., Jordan, C.L., and Breedlove, S.M. (2008). The role of androgen receptors in the masculinization of brain and behavior: what we've learned from the testicular feminization mutation. Horm. Beyond Behav. *53*, 613–626. https://doi.org/10.1016/j.yhbeh.2008.01.013.
30. Sjöstedt, E., Zhong, W., Fagerberg, L., Karlsson, M., Mitsios, N., Adori, C., Oksvold, P., Edfors, F., Limiszewska, A., Hikmet, F., et al. (2020). An atlas of the protein-coding genes in the human, pig, and mouse brain. Science *367*, eaay5947. https://doi.org/10.1126/science.aay5947.
31. Cholecystokinin - an overview | ScienceDirect Topics https://www.sciencedirect.com/topics/medicine-and-dentistry/cholecystokinin.
32. Liddle, R.A. (1997). Cholecystokinin cells. Annu. Rev. Physiol. *59*, 221–242. https://doi.org/10.1146/annurev.physiol.59.1.221.
33. Kim, J.S., Han, S.Y., and Iremonger, K.J. (2019). Stress experience and hormone feedback tune distinct components of hypothalamic CRH neuron activity. Nat. Commun. *10*, 5696. https://doi.org/10.1038/s41467-019-13639-8.
34. Allen, M.J., and Sharma, S. (2022). Physiology, Adrenocorticotropic Hormone (ACTH). In StatPearls (StatPearls Publishing).
35. Endocrine gland/https://www.gla.ac.uk/external/EBF/EndocrineTable.html.
36. Granulosa Cell - an overview | ScienceDirect Topics https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/granulosa-cell.
37. Carreau, S., Bouraima-Lelong, H., and Delalande, C. (2011). Estrogens in male germ cells. Spermatogenesis *1*, 90–94. https://doi.org/10.4161/spmg.1.2.16766.
38. Russell, N., and Grossmann, M. (2019). MECHANISMS IN ENDOCRINOLOGY: Estradiol as a male hormone. Eur. J. Endocrinol. *181*, R23–R43. https://doi.org/10.1530/EJE-18-1000.
39. Anterior Pituitary - an overview | ScienceDirect Topics https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/anterior-pituitary.
40. La Marca, A., Carducci Artenisio, A., Stabile, G., Rivasi, F., and Volpe, A. (2005). Evidence for cycle-dependent expression of follicle-stimulating hormone receptor in human endometrium. Gynecol. Endocrinol. *21*, 303–306. https://doi.org/10.1080/09513590500402756.
41. Asatiani, K., Gromoll, J., Eckardstein, S.V., Zitzmann, M., Nieschlag, E., and Simoni, M. (2002). Distribution and function of FSH receptor genetic variants in normal men. Andrologia *34*, 172–176. https://doi.org/10.1046/j.1439-0272.2002.00493.x.
42. Rehfeld, J.F. (1998). The new biology of gastrointestinal hormones. Physiol. Rev. *78*, 1087–1108. https://doi.org/10.1152/physrev.1998.78.4.1087.
43. Müller, T.D., Finan, B., Clemmensen, C., DiMarchi, R.D., and Tschöp, M.H. (2017). The New Biology and Pharmacology of Glucagon. Physiol. Rev. *97*, 721–766. https://doi.org/10.1152/physrev.00025.2016.
44. Glucagon Receptor - an overview | ScienceDirect Topics https://www.sciencedirect.com/topics/neuroscience/glucagon-receptor.
45. Jayes, F.C., Britt, J.H., and Esbenshade, K.L. (1997). Role of gonadotropin-releasing hormone pulse frequency in differential regulation of gonadotropins in the gilt. Biol. Reprod. *56*, 1012–1019. https://doi.org/10.1095/biolreprod56.4.1012.
46. Le Tissier, P.R., Hodson, D.J., Lafont, C., Fontanaud, P., Schaeffer, M., and Mollard, P. (2012). Anterior pituitary cell networks. Front. Neuroendocrinol. *33*, 252–266. https://doi.org/10.1016/j.yfrne.2012.08.002.
47. Laron, Z. (2001). Insulin-like growth factor 1 (IGF-1): a growth hormone. Mol. Pathol. *54*, 311–316. https://doi.org/10.1136/mp.54.5.311.
48. Zapf, J., and Froesch, E.R. (1986). Insulin-Like Growth Factors/Somatomedins: Structure, Secretion, Biological Actions and Physiological Role. Hormone Res. *24*, 121–130.
49. What is the strongest muscle in the human body? Libr. Congr. Wash. DC 20540 USA. https://www.loc.gov/item/what-is-the-strongest-muscle-in-the-human-body/.
50. Baskin, D.G., Hahn, T.M., and Schwartz, M.W. (1999). Leptin sensitive neurons in the hypothalamus. Horm. Metab. Res. Horm. Stoffwechselforschung Horm. Metab *31*, 345–350. https://doi.org/10.1055/s-2007-978751.
51. Stamatiades, G.A., and Kaiser, U.B. (2018). Gonadotropin regulation by pulsatile GnRH: Signaling and gene expression. Mol. Cell. Endocrinol. *463*, 131–141. https://doi.org/10.1016/j.mce.2017.10.015.
52. Luteinizing Hormone Receptor - an overview | ScienceDirect Topics https://www.sciencedirect.com/topics/neuroscience/luteinizing-hormone-receptor.
53. Granulosa Cells: Hormones, Function & Anatomy Clevel. Clin. https://my.clevelandclinic.org/health/body/22528-granulosa-cells.
54. Gorvin, C.M. (2015). The prolactin receptor: Diverse and emerging roles in pathophysiology. J. Clin. Transl. Endocrinol. *2*, 85–91. https://doi.org/10.1016/j.jcte.2015.05.001.
55. Afroze, S., Meng, F., Jensen, K., McDaniel, K., Rahal, K., Onori, P., Gaudio, E., Alpini, G., and Glaser, S.S. (2013). The physiological roles of secretin and its receptor. Ann. Transl. Med. *1*, 29. https://doi.org/10.3978/j.issn.2305-5839.2012.12.01.
56. Banales, J.M., Huebert, R.C., Karlsen, T., Strazzabosco, M., LaRusso, N.F., and Gores, G.J. (2019). Cholangiocyte pathobiology. Nat. Rev. Gastroenterol. Hepatol. *16*, 269–281. https://doi.org/10.1038/s41575-019-0125-y.
57. Whitmore, T.E., Holloway, J.L., Lofton-Day, C.E., Maurer, M.F., Chen, L., Quinton, T.J., Vincent, J.B., Scherer, S.W., and Lok, S. (2000). Human secretin (SCT): gene structure, chromosome location, and distribution of mRNA. Cytogenet. Cell Genet. *90*, 47–52. https://doi.org/10.1159/000015658.
58. Costanzo, L.S. (2006). Physiology, 3rd ed. (Saunders Elsevier).
59. Ghamari-Langroudi, M., Vella, K.R., Srisai, D., Sugrue, M.L., Hollenberg, A.N., and Cone, R.D. (2010). Regulation of thyrotropin-releasing hormone-expressing neurons in paraventricular nucleus of the hypothalamus by signals of adiposity. Mol. Endocrinol. *24*, 2366–2381. https://doi.org/10.1210/me.2010-0203.
60. Cammisotto, P.G., and Bendayan, M. (2007). Leptin secretion by white adipose tissue and gastric mucosa. Histol. Histopathol. *22*, 199–210. https://doi.org/10.14670/HH-22.199.
61. Gong, J., Tu, W., Liu, J., and Tian, D. (2022). Hepatocytes: A key role in liver inflammation. Front. Immunol. *13*, 1083780. https://doi.org/10.3389/fimmu.2022.1083780.
62. Church, C., Horowitz, M., and Rodeheffer, M. (2012). WAT is a functional adipocyte? Adipocyte *1*, 38–45. https://doi.org/10.4161/adip.19132.
63. Sender, R., Fuchs, S., and Milo, R. (2016). Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol. *14*, e1002533. https://doi.org/10.1371/journal.pbio.1002533.
64. James, H., and Brown, G.B.W. (2000). Scaling in Biology (Oxford University Press).
65. Reiss, M.J. (1989). The Allometry of Growth and Reproduction, 1st ed. (Cambridge University Press).
66. West, G. (2017). Scale- The universal laws of growth, innovation, sustainability, and the

pace of life in organisms, Cities, Economies, and Companies (Penguin Press).
67. Antoł, A., and Kozłowski, J. (2020). Scaling of organ masses in mammals and birds: phylogenetic signal and implications for metabolic rate scaling. ZooKeys *982*, 149–159. https://doi.org/10.3897/zookeys.982.55639.
68. Martin, R.D. (1996). Scaling of the Mammalian Brain: the Maternal Energy Hypothesis. Physiology *11*, 149–156. https://doi.org/10.1152/physiologyonline.1996.11.4.149.
69. West, G.B., Woodruff, W.H., and Brown, J.H. (2002). Allometric scaling of metabolic rate from molecules and mitochondria to cells and mammals. Proc. Natl. Acad. Sci. USA *99*, 2473–2478. https://doi.org/10.1073/pnas.012579799.
70. Karin, O., Swisa, A., Glaser, B., Dor, Y., and Alon, U. (2016). Dynamical compensation in physiological circuits. Mol. Syst. Biol. *12*, 886. https://doi.org/10.15252/msb.20167216.
71. Korem Kohanim, Y., Milo, T., Raz, M., Karin, O., Bar, A., Mayo, A., Mendelson Cohen, N., Toledano, Y., and Alon, U. (2022). Dynamics of thyroid diseases and thyroid-axis gland masses. Mol. Syst. Biol. *18*, e10919. https://doi.org/10.15252/msb.202210919.
72. Karin, O., Raz, M., Tendler, A., Bar, A., Korem Kohanim, Y., Milo, T., and Alon, U. (2020). A new model for the HPA axis explains dysregulation of stress hormones on the timescale of weeks. Mol. Syst. Biol. *16*, e9510. https://doi.org/10.15252/msb.20209510.
73. Consortium, T.T.M., Ezran, C., Liu, S., Ming, J., Guethlein, L.A., Wang, M.F.Z., Dehghannasiri, R., Olivieri, J., Frank, H.K., Tarashansky, A., et al. (2022). Mouse lemur transcriptomic atlas elucidates primate genes, physiology, disease, and evolution. Preprint at bioRxiv. https://doi.org/10.1101/2022.08.06.503035.
74. Roumeliotis, S., Abd ElHafeez, S., Jager, K.J., Dekker, F.W., Stel, V.S., Pitino, A., Zoccali, C., and Tripepi, G. (2021). Be careful with ecological associations. Nephrology *26*, 501–505. https://doi.org/10.1111/nep.13861.
75. Cragg, J.J., Kramer, J.L.K., Borisoff, J.F., Patrick, D.M., and Ramer, M.S. (2019). Ecological fallacy as a novel risk factor for poor translation in neuroscience research: A systematic review and simulation study. Eur. J. Clin. Invest. *49*, e13045. https://doi.org/10.1111/eci.13045.
76. Loney, T., and Nagelkerke, N.J. (2014). The individualistic fallacy, ecological studies and instrumental variables: a causal interpretation. Emerg. Themes Epidemiol. *11*, 18. https://doi.org/10.1186/1742-7622-11-18.
77. Bonovas, S., and Piovani, D. (2023). Simpson's Paradox in Clinical Research: A Cautionary Tale. J. Clin. Med. *12*, 1633. https://doi.org/10.3390/jcm12041633.
78. Ameringer, S., Serlin, R.C., and Ward, S. (2009). Simpson's Paradox and Experimental Research. Nurs. Res. *58*, 123–127. https://doi.org/10.1097/NNR.0b013e318199b517.
79. Rapoport, B., and McLachlan, S.M. (2007). The Thyrotropin Receptor in Graves' Disease. Thyroid® *17*, 911–922. https://doi.org/10.1089/thy.2007.0170.
80. Philips, R., and Milo, R. (2015). Cell Biology by the Numbers (Garland Science).
81. Ross, M.H., Reith, E.J., and Romrell, L.J. (1989). Histology: A Text and Atlas (Williams & Wilkins).
82. Adrenal Gland - an overview. ScienceDirect Topics https://www.sciencedirect.com/topics/medicine-and-dentistry/adrenal-gland.
83. Trouillas, J., Guigard, M.P., Fonlupt, P., Souchier, C., and Girod, C. (1996). Mapping of corticotropic cells in the normal human pituitary. J. Histochem. Cytochem. *44*, 473–479. https://doi.org/10.1177/44.5.8627004.
84. Adrenal Medulla- Structure- Function-Pathology https://teachmephysiology.com/endocrine-system/adrenal-glands/adrenal-medulla/.
85. Molina, D.K., and DiMaio, V.J.M. (2012). Normal organ weights in men: part II-the brain, lungs, liver, spleen, and kidneys. Am. J. Forensic Med. Pathol *33*, 368–372. https://doi.org/10.1097/PAF.0b013e31823d29ad.
86. Tirziu, D., Giordano, F.J., and Simons, M. (2010). Cell Communications in the Heart. Circulation *122*, 928–937. https://doi.org/10.1161/CIRCULATIONAHA.108.847731.
87. Walpole, S.C., Prieto-Merino, D., Edwards, P., Cleland, J., Stevens, G., and Roberts, I. (2012). The weight of nations: an estimation of adult human biomass. BMC Publ. Health *12*, 439. https://doi.org/10.1186/1471-2458-12-439.
88. Frontera, W.R., and Ochala, J. (2015). Skeletal muscle: a brief review of structure and function. Calcif. Tissue Int. *96*, 183–195. https://doi.org/10.1007/s00223-014-9915-y.
89. Tabula Sapiens Consortium, Jones, R.C., Karkanias, J., Krasnow, M.A., Pisco, A.O., Quake, S.R., Salzman, J., Yosef, N., Bulthaup, B., Brown, P., et al. (2022). The Tabula Sapiens: A multiple-organ, single-cell transcriptomic atlas of humans. Science *376*, eabl4896. https://doi.org/10.1126/science.abl4896.
90. Cadot, B., Gache, V., and Gomes, E.R. (2015). Moving and positioning the nucleus in skeletal muscle – one step at a time. Nucleus *6*, 373–381. https://doi.org/10.1080/19491034.2015.1090073.
91. Sender, R., and Milo, R. (2021). The distribution of cellular turnover in the human body. Nat. Med. *27*, 45–48. https://doi.org/10.1038/s41591-020-01182-9.
92. DSc, S.S.P. (2015). Gray's Anatomy: The Anatomical Basis of Clinical Practice.
93. Morgan, R.G., Schaeffer, B.K., and Longnecker, D.S. (1986). Size and number of nuclei differ in normal and neoplastic acinar cells from rat pancreas. Pancreas *1*, 37–43. https://doi.org/10.1097/00006676-198601000-00008.
94. Schaefer, J.H. (1926). The normal weight of the pancreas in the adult human being: A biometric study. Anat. Rec. *32*, 119–132. https://doi.org/10.1002/ar.1090320204.
95. Ogoke, O., Oluwole, J., and Parashurama, N. (2017). Bioengineering considerations in liver regenerative medicine. J. Biol. Eng. *11*, 46. https://doi.org/10.1186/s13036-017-0081-4.
96. Wang, Z., Faria, J., van der Laan, L.J.W., Penning, L.C., Masereeuw, R., and Spee, B. (2022). Human Cholangiocytes Form a Polarized and Functional Bile Duct on Hollow Fiber Membranes. Front. Bioeng. Biotechnol. *10*, 868857. https://doi.org/10.3389/fbioe.2022.868857.
97. (2003). Chapter 8 Supraoptic and paraventricular nucleus (SON, PVN). In Handbook of Clinical Neurology The Human Hypothalamus: Basic and Clinical Aspects, D.F. Swaab, ed. (Elsevier), pp. 163–237. https://doi.org/10.1016/S0072-9752(03)80015-5.
98. How much do fallopian tubes weigh? - Alexa Answers https://alexaanswers.amazon.com/question/7557Q56tRkNuZKn6hlMCol.
99. 27.2 Anatomy and Physiology of the Female Reproductive System - Anatomy and Physiology. OpenStax https://openstax.org/books/anatomy-and-physiology/pages/27-2-anatomy-and-physiology-of-the-female-reproductive-system.
100. Leissner, K.H., and Tisell, L.E. (1979). The weight of the human prostate. Scand. J. Urol. Nephrol. *13*, 137–142. https://doi.org/10.3109/00365597909181168.
101. Silber, S. (2018). Adult Testis Anatomy. In Fundamentals of Male Infertility, S. Silber, ed. (Springer International Publishing), pp. 19–21. https://doi.org/10.1007/978-3-319-76523-5_3.
102. Chai, C.K. (1956). Seminal Vesicle Growth as a Function of Androgen Stimulation in Mice. Am. J. Physiol. *186*, 463–467. https://doi.org/10.1152/ajplegacy.1956.186.3.463.
103. The average human penis weighs approx. 160 grams. (2016). r/Showerthoughts. www.reddit.com/r/Showerthoughts/comments/5j5pnp/the_average_human_penis_weighs_approx_160_grams/.
104. How Many Muscles Are in the Human Body? Plus a Diagram https://www.healthline.com/health/how-many-muscles-are-in-the-human-body#types-of-muscles.
105. Simoni, M., Gromoll, J., and Nieschlag, E. (1997). The follicle-stimulating hormone receptor: biochemistry, molecular biology, physiology, and pathophysiology. Endocr. Rev. *18*, 739–773. https://doi.org/10.1210/edrv.18.6.0320.
106. Ovary, animal and human. Britannica https://www.britannica.com/science/ovary-animal-and-human.
107. Royston, C.M., Polak, J., Bloom, S.R., Cooke, W.M., Russell, R.C., Pearse, A.G., Spencer, J., Welbourn, R.B., and Baron, J.H. (1978). G cell population of the gastric antrum, plasma gastrin, and gastric acid secretion in patients with and without duodenal ulcer. Gut *19*, 689–698.
108. Naik, S.R., Bajaj, S.C., Goyal, R.K., Gupta, D.N., and Chuttani, H.K. (1971). Parietal Cell Mass in Healthy Human Stomach. Gastroenterology *61*, 682–685. https://doi.org/10.1016/S0016-5085(19)33431-6.
109. Cabrera, O., Berman, D.M., Kenyon, N.S., Ricordi, C., Berggren, P.-O., and Caicedo, A. (2006). The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. Proc. Natl. Acad. Sci. USA *103*, 2334–2339. https://doi.org/10.1073/pnas.0510790103.
110. Scharfmann, R., Staels, W., and Albagli, O. (2019). The supply chain of human pancreatic β cell lines. J. Clin. Invest. *129*, 3511–3520. https://doi.org/10.1172/JCI129484.
111. Roa, J., and Tena-Sempere, M. (2018). Unique Features of a Unique Cell: The Wonder World of GnRH Neurons. Endocrinology *159*, 3895–3896. https://doi.org/10.1210/en.2018-00870.
112. Jit, I., and Sanjeev. (1991). Weight of the testes in Northwest Indian adults. Am. J. Hum. Biol. *3*, 671–676. https://doi.org/10.1002/ajhb.1310030618.

113. Handbook of Biologically Active Peptides - 2nd Edition https://shop.elsevier.com/books/handbook-of-biologically-active-peptides/afzal-khan/978-0-12-385095-9.
114. Grapin-Botton, A. (2005). Ductal cells of the pancreas. Int. J. Biochem. Cell Biol. *37*, 504–510. https://doi.org/10.1016/j.biocel.2004.07.010.
115. Thyroid Weight - an overview. ScienceDirect Topics https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/thyroid-weight.
116. Wilson, J.L.L., Miranda, C.A., and Knepper, M.A. (2013). Vasopressin and the Regulation of Aquaporin-2. Clin. Exp. Nephrol. *17*, 751–764. https://doi.org/10.1007/s10157-013-0789–5.
117. Sekiguchi, T., Kuwasako, K., Ogasawara, M., Takahashi, H., Matsubara, S., Osugi, T., Muramatsu, I., Sasayama, Y., Suzuki, N., and Satake, H. (2016). Evidence for Conservation of the Calcitonin Superfamily and Activity-regulating Mechanisms in the Basal Chordate Branchiostoma floridae: INSIGHTS INTO THE MOLECULAR AND FUNCTIONAL EVOLUTION IN CHORDATES. J. Biol. Chem. *291*, 2345–2356. https://doi.org/10.1074/jbc.M115.664003.
118. Kragesteen, B.K., Giladi, A., David, E., Halevi, S., Geirsdóttir, L., Lempke, O.M., Li, B., Bapst, A.M., Xie, K., Katzenelenbogen, Y., et al. (2023). The transcriptional and regulatory identity of erythropoietin producing cells. Nat. Med. *29*, 1191–1200. https://doi.org/10.1038/s41591-023-02314-7.
119. Middleton, S.A., Barbone, F.P., Johnson, D.L., Thurmond, R.L., You, Y., McMahon, F.J., Jin, R., Livnah, O., Tullai, J., Farrell, F.X., et al. (1999). Shared and unique determinants of the erythropoietin (EPO) receptor are important for binding EPO and EPO mimetic peptide. J. Biol. Chem. *274*, 14163–14169. https://doi.org/10.1074/jbc.274.20.14163.
120. Plotsky, P.M., and Vale, W. (1985). Patterns of growth hormone-releasing factor and somatostatin secretion into the hypophysial-portal circulation of the rat. Science *230*, 461–463. https://doi.org/10.1126/science.2864742.
121. Frohman, L.A., and Jansson, J.O. (1986). Growth hormone-releasing hormone. Endocr. Rev. *7*, 223–253. https://doi.org/10.1210/edrv-7-3-223.
122. Slominski, A., Tobin, D.J., Shibahara, S., and Wortsman, J. (2004). Melanin pigmentation in mammalian skin and its hormonal regulation. Physiol. Rev. *84*, 1155–1228. https://doi.org/10.1152/physrev.00044.2003.
123. Klungland, H., Våge, D.I., Gomez-Raya, L., Adalsteinsson, S., and Lien, S. (1995). The role of melanocyte-stimulating hormone (MSH) receptor in bovine coat color determination. Mamm. Genome *6*, 636–639. https://doi.org/10.1007/BF00352371.
124. Tsagarakis, S., and Grossman, A. (1994). Corticotropin-releasing hormone: interactions with the immune system. Neuroimmunomodulation *1*, 329–334. https://doi.org/10.1159/000097184.
125. Auld, F., Maschauer, E.L., Morrison, I., Skene, D.J., and Riha, R.L. (2017). Evidence for the efficacy of melatonin in the treatment of primary adult sleep disorders. Sleep Med. Rev. *34*, 10–22. https://doi.org/10.1016/j.smrv.2016.06.005.
126. Zoch, M.L., Clemens, T.L., and Riddle, R.C. (2016). New Insights into the Biology of Osteocalcin. Bone *82*, 42–49. https://doi.org/10.1016/j.bone.2015.05.046.
127. Khan, M., Jose, A., and Sharma, S. (2023). Physiology, Parathyroid Hormone. In StatPearls (StatPearls Publishing)).
128. Fountain, J.H., Kaur, J., and Lappin, S.L. (2023). Physiology, Renin Angiotensin System. In StatPearls (StatPearls Publishing).
129. O'Toole, T.J., and Sharma, S. (2023). Physiology, Somatostatin. In StatPearls (StatPearls Publishing).
130. Young, J.M., and McNeilly, A.S. (2010). Theca: the forgotten cell of the ovarian follicle. Reproduction *140*, 489–504. https://doi.org/10.1530/REP-10-0094.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Number of hormone secreting and target cells	This paper	https://github.com/moriyaraz/Endocrine-gland-size-is-proportional-to-its-target-tissue-size
Software and algorithms		
Python program for analyzing the data	This paper	https://github.com/moriyaraz/Endocrine-gland-size-is-proportional-to-its-target-tissue-size

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Uri Alon (uri.alon@weizmann.ac.il).

Materials availability

This study did not generate new unique reagents.

Data and code availability

- Python code including the database needed to reconstruct the analysis and figures is provided in the GitHub repository and publically available as of the date of publication: https://github.com/moriyaraz/Endocrine-gland-size-is-proportional-to-its-target-tissue-size.
- Detailed resources and calculations of different numbers of secreting and target cells are listed below in the 'method details' section.
- Any additional information required to reanalyze the data reported in this paper is available from lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

Data regarding the identity and the number of hormone secreting and target cells in humans was collected from the literature and from a medical database.[1,18,20]

METHOD DETAILS

Analysis of endocrine systems

We aimed in this work to produce a list of all human hormones for which the number of secreting and target cells are known or could be estimated to a reasonable accuracy. Of the known human hormones,[1,20] we selected those with a well-defined cell of origin. We separately considered hormones made by dedicated cells whose major function is to produce and secrete the hormone, and hormones made by cells which have other major functions than hormone production, such as fat (adipocyte) or liver (hepatocyte) cells. We did not include hormones for which we could not find or estimate (as explained below) reliable values for the number of secreting cells. This includes oxytocin, GHRH, vasopressin, GLP, Ghrelin and motilin which we excluded.

For the remaining hormones, we searched the literature to find their target tissues. We defined the target cell types for each hormone using the following criteria: 1. Cells that express the receptor for the hormone at a high level and 2. Cells where the hormone has a documented physiological function. We excluded cell types where the receptor is expressed but no physiological function is known. This includes cases where the hormone has only known pathophysiological effects - for example TSH receptors are found in the eye orbital muscles, but have a known effect only in cases of hyperthyroidism such as Graves disease.[79] We also excluded hormones for which we could not find the specific identity of their target cell types, such as melatonin.

For hormones that were selected according to the criteria stated above, we searched the literature for the number of secreting and target cells. In cases of hormones for which we could not find an explicitly reported estimation of the secreting or target cell numbers, we used histologic slides in order to estimate the volume fraction occupied by the relevant population of cells, x (a number between zero and one). We then used literature data on mass per cell m (grams) and total tissue mass M (grams) to estimate cell numbers $n = x\,M/m$. Two independent investigators with knowledge in histology inspected the histologic slides, and in places where there was disagreement between estimations beyond a factor of 2, without the ability to reach a consensus, we did not include the hormone in the study. Also, in places where one of the investigators reported uncertainty in estimates above factor 2, the hormone was excluded. This was the case for most hormones that target the kidneys, whose complex anatomy makes the estimations of its specific cell populations difficult. In cases where we found multiple literature estimates of tissue or cell mass we used their geometric average.[80]

In Table S1 we provide a detailed list of all human hormones that we found, including explanations for those not included in Figures 2 and 3. We provide here a detailed account of the estimation process for each hormone, including hormones that were not included. For further details regarding the selection process see also Figure 1.

(1) Adrenaline- secreted from chromaffin cells in the adrenal medulla[7] and targets all nucleated cells in the body.[23] We estimated the number of chromaffin cells, $2\ 10^9$, using total adrenal mass, ≈ 8.5 *gr*, multiplied by the fraction of chromaffin cells, 0.25, estimated using the literature and histologic slides.[81,82] We used an average weight of 10^{-9} *gr* for each cell (BNID 111609).[16] The number of nucleated cells in an adult human of average height and weight is $5\ 10^{12}$.[63]

(2) Adrenocorticotropic hormone (ACTH)- secreted from corticotrophs in the anterior pituitary, and targets the adrenal cortex (mostly zona fasciculata and zona glomerulosa).[17] The number of corticotrophs, 10^7, is known from the literature.[83] We estimated the number of target cells, $5\ 10^9$, using the total weight of the adrenal glands, ≈ 8.5 *gr*,[17] multiplied by the portion that these layers of the adrenal cortex occupy from it, ≈ 0.6 *relevant layers of cortex/adrenal*, estimated from histologic slides.[81,84] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue.

(3) Aldosterone- secreted from zona glomerulosa cells in the adrenal cortex and targets epithelial cells in the distal tubules and collecting ducts of the kidneys and also cardiomyocytes and cardiac fibroblasts.[24,25] We estimated the number of zona glomerulosa cells, $6\ 10^8$, using the total weight of the adrenal glands, ≈ 8.5 *gr*,[17] multiplied by the portion that zona glomerulosa cells occupy from the adrenal glands- ≈ 0.06 *zona glumerolosa/adrenals*, estimated using histologic slides.[81,82] We estimated the number of epithelial cells in the distal tubules and collecting ducts cells in the kidneys, $4\ 10^{10}$, and the number of cardiac fibroblasts, $3\ 10^{10}$, using the weight of the organs, kidneys-240 *gr* and heart- 320 *gr* as known in the literature[85] multiplied by the portion that the relevant population of cells occupy from the entire organ- ≈ 0.15 *epithelial cells in the distal tubules and collecting ducts of the kidneys/kidneys*, ≈ 0.1 *cardiac fibroblasts/heart*, estimated from histologic slides.[81] The number of cardiac myocytes, $2.5\ 10^9$, is known in the literature.[86] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue.

(4) Androgen (male)- secreted from testicular Leydig cells[26] and targets adipocytes,[27] skeletal muscle cells,[28] several brain areas,[29] seminiferous ducts epithelial cells, Leydig cells and epididymis glandular cells located inside the testicles, and also the glandular cells located in the seminal vesicles.[30] We estimated the number of testicular Leydig cells, 10^9, using the total weight of the testicles, 11 *gr*, multiplied by the portion that they occupy from it- ≈ 0.1 *Leydig cells/testicles*, estimated from histologic slides.[81] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue. The number of adipocytes, $5.2\ 10^{10}$, is known in the literature (BNID 103488).[16] We estimated the number of skeletal muscle cells, $1.4\ 10^{11}$, using their percentage from total body mass- 40%, from which about half is occupied by stroma. Total body mass of an averaged size human adult male is ≈ 70 *kg* as known in the literature.[87–89] As muscle cells are about two orders of magnitude bigger than the average cell according to histologic slides (taking into consideration that they have hundreds of nuclei),[16,81,90] we used an average cell weight of 10^{-7} *gr* in order to calculate the number of muscle cells per given mass of tissue. Because adipocytes and skeletal muscle cells outnumber other target cell populations by several orders of magnitude, we used their combined estimated number as the estimated number of target cells.

(5) Cholecystokinin (CCK)- secreted from I cells located mostly in the duodenum and jejunum,[31] and targets pancreatic acinar cells, hepatic bile producing cells and gallbladder smooth muscle cells.[32] We estimated the number of I cells using data on their portion, $\approx 6.3\ 10^{-3}$, from all cells lining the proximal intestine, as analyzed in sections of human duodenal-jejunal junction using Visium (Itzkovitz lab, unpublished), multiplied by the number of epithelial cells lining the duodenum and jejunum, $4.78\ 10^9$ and $4.78\ 10^{10}$ respectively (explanation is supplied below), to obtain $3.3\ 10^8$ cells. We estimated the number of epithelial cells in the duodenum and jejunum using the number of epithelial cells in the small intestine, $0.11\ 10^{12}$, known in the literature,[91] multiplied by the portion occupied by the duodenum and jejunum, 0.04 and 0.4 respectively, estimated according to their length.[92] The number of pancreatic acinar cells, $9\ 10^9$, was estimated using their diameter of 20*um* and their portion from total pancreatic volume, 85%,[93] given that the weight of an adult pancreas is 100 *gr* as known from the literature.[94] The number of cholangiocytes, $8\ 10^9$, was estimated using their portion from other liver cells, which is $3-5\%$ from $2\ 10^{11}$ *cells*, according to the literature.[95,96] We estimated the number of smooth muscle cells in the gallbladder, $1.5\ 10^{10}$, using the total average weight of the gallbladder (empty from bile) which is on average 45 *gr*,[92] multiplied by the portion occupied by the muscularis layer, ≈ 0.3, estimated from histologic slides.[81] We considered an average weight of 10^{-9} *gr* for one smooth muscle cell of the gallbladder in order to calculate the number of cells per given mass of tissue, as it is about the same size as an average cell according to histologic slides.[16,81]

(6) Corticotropin-releasing hormone (CRH)- secreted from parvocellular neurosecretory cells located in the paraventricular nucleus of the hypothalamus[33] and targets corticotrophs located in the anterior pituitary.[34] The number of CRH secreting neurons, 10^4, and corticotrophs, 10^7, is known in the literature.[83,97]

(7) Cortisol- secreted from cells in the zona fasciculata of the adrenal cortex[4] and targets all nucleated cells in the body.[35] We estimated the number of cells in the zona fasciculata, $4.5\ 10^9$, using the total weight of the adrenal glands, ≈ 8.5 *gr*,[17] multiplied by the portion occupied by the zona fasciculata, ≈ 0.5 *zona fasciculata/adrenals*, estimated using histologic slides.[81] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue. The number of nucleated cells in an adult human of average height and weight is $5\ 10^{12}$.[63]

(8) Estrogen- in females, estrogen is produced mainly in granulosa cells of the ovaries[36] and targets the vagina, fallopian tubes, endometrium, uterine cervix, breast, smooth muscle, zona reticularis of the adrenal glands and endothelial cells.[30] In males

estrogen is produced in testicular Leydig cells[37] and targets the testicles, seminal vesicles, prostate, penis and endothelial cells.[38] We estimated the number of secreting and target tissue cells using the weight of each of the organs as found in the literature: ovaries- 6 *gr*, testicles- 11 *gr*, vagina- 3 *gr*, fallopian tubes- 40 *gr*, uterus- 60 *gr*, uterine cervix- 4 *gr*, breast- 700 *gr*, adrenal glands- 8.5 *gr*, seminal vesicles- 7 *mg*, prostate- 11 *gr* and penis- 160 *gr*),[16,82,98–103] multiplied by the portion occupied by the relevant population of cells (when indicated), as estimated from histologic slides: $ovarian\ granulosa\ cells - 0.15\ relevant\ tissue\ mass/\ total\ mass\ of\ ovaries$, $uterine\ endometrium - 0.4\ relevant\ tissue\ mass/total\ organ\ mass$, $uterine\ cervix - 0.05\ relevant\ tissue\ mass/total\ organ\ mass$, $breast - 0.5\ parenchyma/total\ tissue\ mass$, $adrenal\ zona\ reticularis - 0.05\ relevant\ tissue\ mass/total\ organ\ mass$, $testicular\ Leydig\ cells - 0.1\ relevant\ tissue\ mass/total\ organ\ mass$.[81] When an entire organ was involved, we included only half of its weight as it is on average the part occupied by stroma components, as known from the literature.[89] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue. Thus we obtained: granulosa cells of the ovaries- 9.3 10^8 *cells*, vagina- 1.5 10^9 *cells*, fallopian tubes- 2 10^{10} *cells*, uterine endometrium- 2.4 10^{10} *cells*, uterine cervix- 2 10^9 *cells*, breast- 35 10^{10} *cells*, zona reticularis-0.6 10^9 *cells*, testicular Leydig cells- 10^9 *cells*, testicles- 5.5 10^9 *cells*, seminal vesicles- 7 10^6 *cells*, prostate- 5.5 10^9 *cells*, penis- 8 10^{10} *cells*. The number of smooth muscle cells, $\sim 3\ 10^9$, and the number of endothelial cells, 6 10^{11}, was found in the literature.[63,104]

(9) Follicle-stimulating hormone (FSH)- secreted from gonadotrophs in the anterior pituitary.[39] In females, FSH targets ovarian granulosa cells[105] and the secretory endometrium during the luteal phase.[40] In males, FSH targets testicular sertoli cells.[41] We estimated the number of gonadotrophs using the number of corticotrophs, 10^7, and their ratios among anterior pituitary endocrine cells- $corticotroph - 10 - 15\%, gonadotrophs - 5\%$,[39] to obtain 4 10^6 *cells*. We estimated the number of target cells using the weight of the organs: ovaries- 6 *gr*, uterus- 60 *gr*, testicles- 11 *gr*, known in the literature,[99,101,106] multiplied by the portion of the relevant population of cells: $ovarian\ granulosa\ cells - 0.15\ relevant\ mass/total\ mass\ of\ ovaries$, $secretory\ endometrium\ of\ uterus - 0.25\ relevant\ mass/total\ mass\ of\ uterus$. $testicular\ sertoli\ cells - 0.1\ relevant\ mass/total\ mass\ of\ testicles$, estimated using histologic slides.[81] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue. Thus we obtained the following numbers: granulosa cells of the ovary- 9.3 10^8 *cells*, secretory endometrium during the luteal phase- 1.6 10^{10} *cells*, testicular sertoli cells- s10^9 *cell*.

(10) Gastrin- secreted from stomach G -cells[42] and targets stomach parietal cells and pancreatic acinar cells.[8] The number of stomach G-cells, 10^7, and stomach parietal cells, 10^9, is from the literature.[107,108] The number of pancreatic acinar cells, 9 10^9, was estimated using their diameter, 20*um*, their fraction from total pancreatic volume, 85%,[93] and the weight of an adult pancreas, 100 *gr*.[94] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue.

(11) Glucagon- secreted from pancreatic alpha cells[43] and targets liver hepatocytes.[44] We estimated the number of pancreatic alpha cells, 6.3 10^8, using the portion of pancreatic islets occupied by this population of cells compared to the part occupied by pancreatic beta cells, 35% : 55%,[109] using the number of pancreatic beta cells, 10^9.[110] The number of liver hepatocytes, 2 10^{11}, is from the literature.[95]

(12) Gonadotropin-releasing hormone (GnRH)- secreted from the medial preoptic nucleus of the hypothalamus and targets pituitary gonadotrophs.[45] The number of GnRH secreting neurons, 1.7 10^3, is known from the literature.[111] We estimated the number of gonadotrophs using the number of corticotrophs, 10^7,[83] and their ratios among anterior pituitary endocrine cells- $corticotroph - 10 - 15\%$, $gonadotrophs - 5\%$,[39] to obtain s4 10^6 *cell*.

(13) Growth hormone (GH)- secreted from pituitary somatotrophs[46] and targets mainly liver hepatocytes and adipocytes.[30] We estimated the number of somatotrophs using the number of corticotrophs, 10^7,[83] and their ratios among anterior pituitary endocrine cells- $corticotroph - 10 - 15\%$, $somatotrophs - 50\%$,[39] to obtain 4 10^7 *cells*. The number of liver hepatocytes and adipocytes, 2 10^{11} and 5.2 10^{10} respectively, is in the literature[95] (BNID 103488).[16]

(14) Insulin- secreted from pancreatic beta cells, and targets liver hepatocytes, skeletal muscle cells and fat cells.[10,11,49] The number of beta cells, 10^9, and liver hepatocytes, 2 10^{11}, is known in the literature.[95,109] We estimated the number of skeletal muscle cells, 1.4 10^{11}, using their percentage from total body mass, 40%, from which about half is occupied by stroma.[89] Total body mass of an averaged size human adult male is ≈ 70 *kg*.[87,88] As muscle cells are about two order of magnitude bigger than the average cell according to histologic slides (taking into consideration that they have hundreds of nuclei),[16,81,90] we used an average cell weight of 10^{-7} *gr* in order to calculate the number of muscle cells per given mass of tissue. The number of adipocytes, 5.2 10^{10}, is in the literature (BNID 103488).[16]

(15) Luteinizing hormone (LH)- secreted from gonadotrophs located in the anterior pituitary.[51] In females, LH targets ovarian theca cells and interstitial and mature granulosa cells. In males, LH targets testicular Leydig cells.[52] We estimated the number of gonadotrophs using the number of corticotrophs, 10^7,[83] and their ratios among anterior pituitary endocrine cells- $corticotroph - 10 - 15\%$, $gonadotrophs - 5\%$,[60] to obtain 4 10^6 *cells*. We estimated the number of target cells in females and males using the weight of the organs, ovaries- 6 *gr* and testicles-11 *gr*,[101,106] multiplied by the portion occupied by the relevant cells, $ovarian\ theca\ and\ interstitial\ and\ mature\ granulosa\ cells - 0.5\ relevant\ mass/total\ mass\ of\ ovary$, $testicular\ Leydig\ cells - 0.1\ relevant\ mass/total\ mass\ of\ testicles$, estimated using histologic slides.[81] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue. Thus, we obtained the following estimates: ovarian theca cells and interstitial and mature granulosa cells-3 10^9 *cells*, testicular Leydig cells- 10^9 *cells*.

(16) Progesterone- in females progesterone is secreted by ovarian granulosa cells after ovulation[53] and targets the fallopian tubes, uterine endometrium, uterine cervix, breast and smooth muscle.[30] We estimated the number of secreting and target tissue cells

using the total weight of the organs: ovaries- 6 *gr*, fallopian tubes- 40 *gr*, uterus- 60 *gr*, uterine cervix- 4 *gr*, breast- 700 *gr*, as known in the literature,[16,17,98,99,101,106,112] multiplied by the portion of relevant cells: *ovarian granulosa cells* − 0.15 *relevant mass*/*total mass of organ*, *uterine endometrium* − 0.4 *relevant mass*/*total mass of organ*, *breast* − 0.5 *relevant mass* (*parenchyma*)/*total mass of organ*, using histologic slides.[81] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue. Thus we obtained the following numbers: granulosa cells of the ovaries- 9.3 10^8 *cells*, fallopian tubes- 2 10^{10} *cells*, uterine endometrium- 2.4 10^{10} *cells*, uterine cervix- 2 10^9 *cells*, breast- 35 10^{10} *cells*. The number of smooth muscle cells, ∼ 3 10^9 , is known in the literature.[63]

(17) Prolactin- secreted from pituitary lactotrophs and targets breast mammary gland cells, pancreatic β-cells, adipocytes and B- and T-cells.[54] We estimated the number of pituitary lactotrophs using the number of corticotrophs, 10^7,[83] and their ratios among anterior pituitary endocrine cells- *corticotroph* − 10 − 15%, *lactotrophs* − 15%,[39] to obtain 1.2 10^7 *cells*. We estimated the number of breast mammary cells, 3.5 10^{11}, as total breast tissue weighs about 700 *gr* on average, but only about 50% is parenchymal tissue.[89] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue. The number of pancreatic β-cells, 10^9, and adipocytes, 5.2 10^{10}, are both known in the literature (BNID 103488).[16,109] The number of B- cells and T-cells are 10^{11} and 4 10^{11} respectively, also mentioned in the literature.[63]

(18) Secretin- secreted from S cells of the duodenum, located in the intestinal glands[55] and targets the parietal cells of the stomach, ductal cells of the pancreas and cholangiocytes.[56–58] The number of S cells, 2.8 10^7, was estimated using the fraction of S cells among duodenal epithelium cells which is 0.006, as known in the literature,[113] multiplied by the number of epithelial cells in the duodenum, 4.8 10^9. We estimated the number of epithelial cell in the duodenum using the portion of the duodenum from the small intestine, 0.04 , calculated according to its length[92] multiplied by the number of epithelial cells in the small intestine, 0.11 10^{12}, known from the literature.[91] The number of stomach parietal cells, 10^9 , is known in the literature.[108] Pancreatic ductal cells are the most numerous target and amount to about 10^{10} *cells* as they comprise about 10% from the 100 *gr* weight of the pancreas.[94,114] The number of cholangiocytes, 8 10^9 , was estimated using their portion from other liver cells, which is 3 − 5% from 2 10^{11} *cells*, according to the literature.[95,96]

(19) Thyrotropin-releasing hormone (TRH)- secreted from parvocellular neurosecretory cells located within the paraventricular nucleus of the hypothalamus and targets thyrotrophs in the anterior pituitary.[59] The number of TRH secreting neurons, 10^4, is known from the literature.[97] In order to estimate the number of pituitary thyrotrophs we used the number of corticotrophs 10^7 and the proportion of endocrine cells in the anterior pituitary- *corticotroph* − 10 − 15%, *thyrotrophs* − 5%,[39] to obtain 4 10^6 *cells*.

(20) Thyrotropin-stimulating hormone (TSH)- secreted from pituitary thyrotrophs[46] and targets mainly thyroid follicular cells.[5] In order to estimate the number of pituitary thyrotrophs we used the number of corticotrophs, 10^7 , and the proportion of endocrine cells in the anterior pituitary- *corticotroph* − 10 − 15%, *thyrotrophs* − 5%,[39] to obtain 4 10^6 *cells*. In order to estimate the number of thyroid follicular cells, 2.5 10^9, we used the total weight of an average adult thyroid gland, 25 *gr*,[115] multiplied by the portion occupied by follicular cells, 0.1, as estimated from histologic slides.[81] We used an average cell weight of 10^{-9} *gr* (BNID 111609)[16] in order to calculate the number of cells per given mass of tissue.

(21) Thyroxine (T4)- secreted from thyroid follicular cells[5] and targets all nucleated cells in the body.[13] In order to estimate the number of pituitary thyrotrophs we used the number of corticotrophs, 10^7, and the proportion of endocrine cells in the anterior pituitary- *corticotroph* − 10 − 15%, *thyrotrophs* − 5%,[39] to obtain 4 10^6 *cells*. The number of nucleated cells in an adult human of average height and weight is 5 10^{12}.[63] Note that T3 is made from T4 by deiodinases in many tissues, and is secreted in small amounts by the thyroid; hence it is unlike T4 and not included in Figure 1.

Examples of main hormones not included in Figure 2.

(1) Antidiuretic hormone (ADH, also known as vasopressin)- secreted from magnocellular neurosecretory cells in the posterior pituitary (neuronal projections that arise in the parvocellular neurosecretory neurons in the hypothalamus) and targets cells in the kidneys and in blood vessels.[12,116] Estimation of most cellular components in the kidneys is difficult as they are highly variable between different individuals and because their spatial structure makes their estimation from histologic slides very difficult.

(2) Adiponectin (included in Figure 2)- secreted from adipocytes and targets mainly skeletal muscle cells and liver hepatocytes.[21] As the main function of adipocytes isn't endocrine, we did not include the hormone in Figure 2. Because the number of secreting and target cells is known from the literature, we included the hormone in Figure 3.

(3) Calcitonin- secreted from thyroid parafollicular cells and targets osteoclasts in the bone and tubular cells in the kidneys.[1,117] Estimation of most cellular components in the kidneys is difficult as they are highly variable between different individuals and because their spatial structure makes their estimation from histologic slides very difficult.

(4) Enteroendocrine hormones (list not provided here)- from this family of hormones, we included only those for which we could supply a fare estimation for the population of secreting cells, as their estimation was challenging due to lack of information in the literature regarding the portion they occupy in relation to other gastrointestinal epithelial cells.

(5) Erythropoietin- secreted from extraglomerular mesangial cells in the kidney (Norn cells)[118] and targets erythroid progenitor cells in the bone marrow.[119] Estimation of most cellular components in the kidneys is difficult as they are highly variable between different individuals and because their spatial structure makes their estimation from histologic slides very difficult.

(6) Growth Hormone- Releasing Hormone (GHRH)- secreted from neurosecretory cells in the arcuate nucleus of the hypothalamus and targets somatotrophs located in the anterior pituitary.[120,121] We could not find literature sources for the number of GHRH secreting neurons in humans.
(7) Insulin-like growth factor 1 (IGF-1) (included in Figure 3)- secreted from liver hepatocytes[47] and targets almost all nucleated cells in the body.[48] As the main function of liver hepatocytes isn't endocrine, we did not include the hormone in Figure 1. Because the number of secreting and target cells is known from the literature, we included the hormone in Figure 3.
(8) Leptin (included in Figure 2)- secreted by adipocytes and targets neurons located in the hypothalamus.[50] As the main function of adipocytes isn't endocrine, we did not include the hormone in Figure 1. Because the number of secreting and target cells is known from the literature, we included the hormone in Figure 3.
(9) Melanocyte- Stimulating hormone (MSH)- secreted from corticotrophs in the anterior pituitary[122] and targets melanocytes located in the skin, hair follicles, and eyes. Other target cells are located in the immune system and in the brain.[123,124] Estimating the types and numbers of cells which respond to MSH (other than melanocytes) was challenging with a high degree of uncertainty.
(10) Melatonin- secreted from pinealocytes in the pineal gland and targets the CNS and peripheral tissues.[125] We were not able to find the specific types and number of target cells in the literature.
(11) Osteocalcin- secreted from osteoblasts and targets different populations of cells in the bone, pancreas, adipose tissue, testes, brain and the central nervous system.[126] We could not find the number of secreting cells in the literature or estimate it due to the complex microscopic anatomy of the human bone.
(12) Oxytocin- secreted from special hypothalamic neurons that project to the posterior pituitary,[92] and targets different populations of cells in the uterus, breast mammary glands, brain, kidneys and cardiovascular system.[1] The number of secreting neurons could not be found or estimated from the literature.
(13) Parathyroid hormone (PTH)- secreted by chief cells in the parathyroid glands and targets different populations of cells in the bone, kidneys and in the intestinal tract.[127] Estimation of most cellular components in the kidneys is difficult as they are highly variable between different individuals and because their spatial structure makes their estimation from histologic slides very difficult.
(14) Renin- secreted by kidney juxtaglomerular cells and targets kidney proximal tubule cells, among cells from other tissues.[128] Estimation of most cellular components in the kidneys using histological slides is difficult due to their spatial structure.
(15) Somatostatin- secreted mostly from cells in several areas of the central nervous system, their number could not be found in the literature, and targets different populations of cells in the gastrointestinal tract, pancreas, pituitary, etc.[129]
(16) Testosterone- secreted from testicular Leydig cells in men[26] and from ovarian theca cells in women[130] and targets different populations of cells in the reproductive tract and also in bones, brain, skin, blood vessels, etc,[1] their exact type and number was difficult to estimate.

QUANTIFICATION AND STATISTICAL ANALYSIS

Cell number analysis

We used linear regression with 95% confidence interval in order to model the relationship between the number of hormone secreting cells and their target cells (columns 4 and 5 in Table 1). We added noise to the data, using a lognormal noise model with a dispersion factor of two according to the guidelines of.[16] We used bootstrapping by sampling the data with returns, which provided a 95% confidence interval for the slope. Statistical details are provided in Figure legend 2 and in the 'results' section. We used Python version number 3.9.12. for statistical analysis.

Python notebook which contains the code needed for the statistical analysis is provided in the GitHub repository: https://github.com/moriyaraz/Endocrine-gland-size-is-proportional-to-its-target-tissue-size.