Glucocorticoid and Adrenergic Receptor Distribution Across Human Organs and Tissues: A Map for Stress Transduction

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ABSTRACT

Objective: Psychosocial stress is transduced into disease risk through energy-dependent release of hormones from the hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes. The levels of glucocorticoid and adrenergic hormones, together with the sensitivity of tissues to their signaling, define stress responses. To understand existing pathways responsible for the psychobiological transduction of stressful experiences, we provide a quantitative whole-body map of glucocorticoid and adrenergic receptor (AR) expression.

Methods: We systematically examined gene expression levels for the glucocorticoid receptor (GR), α- and β-ARs (AR-α1B, AR-α2B AR-β2, and AR-β3), across 55 different organs using the Human Protein Atlas and Human Proteome Map datasets. Given that mitochondria produce the energy required to respond to stress, we leveraged the Human Protein Atlas and MitoCarta3.0 data to examine the link between stress hormone receptor density and mitochondrial gene expression. Finally, we tested the functional interplay between GR activation and AR expression in human fibroblast cells.

Results: The GR was expressed ubiquitously across all investigated organ systems, whereas AR subtypes showed lower and more localized expression patterns. Receptor co-regulation, meaning the correlated gene expression of multiple stress hormone receptors, was found between GR and AR-α1B, as well as between AR-α1B and AR-α2B. In cultured human fibroblasts, activating the GR selectively increased AR-β2 and AR-α1B expression. Consistent with the known energetic cost of stress responses, GR and AR expressions were positively associated with the expression of specific mitochondrial pathways.

Conclusions: Our results provide a cartography of GR and AR expression across the human body. Because stress-induced GR and AR signaling triggers energetically expensive cellular pathways involving energy-transforming mitochondria, the tissue-specific expression and co-expression patterns of hormone receptor subtypes may in part determine the resilience or vulnerability of different organ systems.

Key words: stress hormone receptor, glucocorticoid receptor, adrenergic receptor, psychoneuroendocrinology, mitochondria, allostatic load.

INTRODUCTION

Stressful psychological experiences are transduced into physiological changes through the action of hormones on target cells and organs. The psychobiological stress response occurs particularly when an individual feels that environmental demands and exposures exceed their "adaptative capacity" (1). In the 1910s, Walter Cannon described the "emotional stimulation of adrenal secretion"—catecholamines—as a key endocrine factor in this brain-body axis (2). Subsequently, Hans Selye showed that stressful experiences triggered another kind of adrenal secretion, the peripheral release of the glucocorticoid hormones cortisol and corticosterone (3). Selye noted two hallmarks of stressful experiences: adrenal hyperactivity associated with increased release of glucocorticoids and catecholamines, and atrophy of lymphoid tissues of the immune system, which must have the ability to sense and respond to these stress signals. Over subsequent decades, the functional consequences of stress hormones on the immune system have been well described (4), including reliable changes in immune function and downstream consequences such as increased susceptibility to infections (5), slowed wound healing (6), and other psychoneuroimmunological processes that affect organs and tissues throughout the human body (7,8).

AR = adrenergic receptor, **AR-α1B** = adrenergic receptor α1B, **AR-α2B** = adrenergic receptor α2B, **AR-β2** = adrenergic receptor β2, **AR-β3** = adrenergic receptor β3, **CNS** = central nervous system, **Dex** = dexamethasone, **GR** = glucocorticoid receptor, **HPA** = -hypothalamic-pituitary-adrenal, **mtDNA** = mitochondrial DNA, **nTPM** = normalized transcript per million, **SAM** = sympathetic-adrenal-medullary

All main organ systems are known to be acutely or chronically responsive to stress exposure, including the brain, heart, airways, liver, kidneys, and the primary/secondary immune tissues. In turn, the sensitivity of these tissues to neuroendocrine stress mediators

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may account for the association of life stress with an increased risk of numerous conditions, such as psychiatric disorders, cardiovascular disease, asthma, and immune-related disorders (9–12). With regard to physiological responses to acute stress, the "fight or flight" response involves changes such as elevated heart rate to increase blood flow to the skeletal muscles, reduced blood flow to the digestive system, and glucose release from the liver (13). Collectively, these and other recalibrations fuel the energetically demanding stress response (14). Within cells, all of these hormone-mediated changes are powered by ATP produced mostly through mitochondrial respiration (15,16). Because mitochondria produce the energy and signals that enable the body to adapt to stress (17), there is a direct connection between stress responses and mitochondrial biology (14,18). Moreover, mitochondria contain their own maternally inherited DNA, which can be influenced by stress signaling, as will be discussed further hereinafter.

Although the physiological responses resulting from stress involve a wide range of organs and tissues, not all organ systems are equally responsive to the activation of stress pathways. One factor that may underlie differential responses of target organs to stress signals, and therefore the extent to which they are impacted by stress, is the variable expression of the receptors that sense and communicate stress signals across the organism.

Although many studies of stress psychobiology evaluate these pathways separately, the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes operate in tandem to transduce psychosocial stress into peripheral physiological responses (19). The coordinated activation of these two pathways is understood to be adaptive, producing responses precisely of the right nature and magnitude to face specific environmental stressors (19,20). Activation of these pathways coordinated by the brain involves the release of glucocorticoids and catecholamines, which bind to their respective receptors in or on target cells (9).

The primary glucocorticoid hormone released in primates is cortisol, which binds to the glucocorticoid receptor (GR). When activated by glucocorticoids, the GRs move from the cytoplasm into the nucleus and mitochondria where they affect the transcription of DNA into RNA (21,22), modulating the expression of both nuclear and mitochondrial genes that catalyze a range of physiological responses (15,23). The role of the GR in transducing psychosocial stress into biological changes has been documented extensively, particularly in the immune system and brain (24–26).

The SAM axis acts in parallel with the HPA axis (9). The SAM axis activates rapidly in response to psychosocial stress, resulting in the release of the catecholamines epinephrine and norepinephrine from sympathetic nerve terminals within tissues and from the adrenal medulla into peripheral circulation. On target cells, catecholamines bind to a broad family of adrenergic receptors (ARs) located on cell membranes. The nine known human ARs are classified into α and β types, which are further divided into numbered subtypes (27,28). The AR subtypes AR-α1B, AR-α2B, AR-β2, and AR-β3 have been shown to be involved in transducing psychosocial stress into biologically relevant effects (29–34).

When activated, adrenergic and GRs trigger energy-intensive molecular and physiological responses including increases in heart rate, vasodilation/constriction altering blood pressure, gene expression changes, and changes in neuronal excitability (35). Mitochondria also contribute to the stress response by metabolizing catecholamines, in addition to transforming the energy needed to power brain adaptations resulting from AR signaling during the stress response (36). Mitochondria perform multiple functions beyond energy transformation including vitamin metabolism, nucleotide synthesis for DNA replication and telomere maintenance, hormone and neurotransmitter synthesis, and more (37). From the point of view of the cell, mitochondria sit at the interface of the external environment and the internal (epi)genome. Many of these mitochondrial functions are likely responsible for transducing stressors and the resulting neuroendocrine signals into the molecular changes that contribute to stress pathophysiology (38).

Therefore, defining the mitochondrial pathways most strongly (or weakly) associated with GR and AR expression may provide insights or future targets to understand the psychobiological mechanisms responsible for the biological embedding of psychosocial stress. Moreover, it is possible that tissues that are particularly sensitive to stress and undergo significant changes in response to stress may also contain higher mitochondrial content to power these responses. On this basis, we can expect a functional connection between stress hormone signaling and mitochondrial regulation in target tissues, although this question has not been systematically examined in humans. Therefore, we will evaluate the link between overall mitochondrial gene expression (as a poor proxy for mitochondrial content), specific functional pathways within mitochondria, and the expression of the stress hormone receptors to better understand the bioenergetics of the stress response among human tissues.

Without receptors for glucocorticoids and catecholamines to convey messages carried by HPA and SAM axis signaling molecules, cells of the brain, immune system, digestive tract, and other organ systems would not be able to sense and respond to stressors. Therefore, variations in the density of these receptors across organs may help to identify systems that are likely to be more responsive and/or vulnerable to acute and chronic stress. To explore the molecular basis for stress transduction across the human body, we leveraged publicly available datasets and live cell experiments to systematically quantify the RNA and protein expression of stress hormone receptors across human tissues, identify co-regulation between specific receptor subtypes (when more of one receptor subtype is associated with higher levels of another receptor), and evaluate associations between GR and AR expression and mitochondrial gene expression. Our results provide a quantitative map of neuroendocrine stress hormone receptors across human tissues.

METHODS

Data Extraction

Stress hormone receptors were selected based on evidence linking specific receptor types to the transduction of psychosocial stress (29–34). Using the Human Protein Atlas, we systematically examined gene expression levels (RNA) for the GR, α-adrenergic receptors (AR-α1B and AR-α2B), and β-adrenergic receptors (AR-β2 and AR-β3) across different organs (n = 55) (39). For RNA expression, we used the Human Protein Atlas consensus tissue gene dataset with consensus normalized transcriptomics data determined from the HPA RNA-seq dataset (normal tissue samples from n = 95 individuals) and the Genotype-Tissue Expression (GTEx) Project RNA-Seq dataset (n = 948 donors, n = 17,382 total samples) (40–43). Human Protein Atlas data can be downloaded at https://www.proteinatlas.org/about/download.

For our analyses, organs were grouped into systems based on functional similarities, including the immune system (n = 5, e.g.,

spleen, lymph nodes, thymus), brain and central nervous system (CNS, $n = 15$, e.g., amygdala, cerebellum, cortex), digestive ($n = 8$, e.g., stomach, colon, duodenum), reproductive ($n = 10$, e.g., ovary, cervix, testis), glandular ($n = 5$, e.g., parathyroid gland, salivary gland, adrenal gland), anabolic ($n = 2$, liver and kidney), striated muscle ($n = 2$, skeletal muscle and heart muscle), and other systems ($n = 8$).

For stress hormone receptor protein expression, we used the Human Proteome Map dataset with protein expression levels determined by high-resolution Fourier-transform mass spectrometry for adult tissues ($n = 17$), placenta, and immune cell subtypes ($n = 6$) (44). Postmortem samples of "histologically normal" human tissues were pooled from three individuals before analysis (44). Immune cells (monocytes, natural killer cells, B cells, $CD8^+$ T cells, and $CD4^+$ T cells) were isolated from blood samples from healthy volunteers (44). AR-β3 protein data were not detected. Human Proteome Map data can be downloaded at http://www.humanproteomemap.org/download.php.

Cellular Life Span Gene Expression Analysis to Glucocorticoid Stimulation

The glucocorticoid-treated fibroblast gene expression data were analyzed from Ref. (45) using the following approach. Briefly, primary dermal fibroblasts (human skin cells) harvested from three unrelated healthy donors were cultured throughout their replicative life span, passaging every ~5 days either in untreated condition (without any stress simulation) or chronically treated with the GR agonist dexamethasone (Dex; 100 nM; to mimic the cell signaling that would occur in conditions of repeated stress). Cells were collected and RNA was isolated at 8 to 11 time points for each donor and used for RNA sequencing. The data were processed and expressed as normalized transcript per million (nTPM) as described in Ref. (45). To obtain a stable estimate of AR gene expression for each donor, target AR nTPMs were averaged across all time points. Refer to Ref. (45) for greater detail.

Analyses of Mitochondrial Content and Functional Pathways

To extract mitochondrial genes to evaluate the connection between the energetically costly stress hormone receptor expression and the energy-producing mitochondria, the Human Protein Atlas normalized tissue consensus dataset (42,46) was mapped to the human MitoCarta3.0 (47) gene list (1136 mitochondrial genes). For each tissue, a transcription-based index of mitochondrial gene expression was calculated from the average expression of all normalized (nTPM) mitochondrial transcripts, including the 37 mitochondrial DNA (mtDNA)–encoded genes. One mitochondrial gene was not found in the Human Protein Atlas dataset, namely, TSTD3. In addition, a score for MitoCarta-annotated mitochondrial pathways (149 MitoPathways) was calculated for each tissue and used in regression analyses with each stress hormone receptor. Each of these pathways represents a particular aspect of mitochondria biology (e.g., energy transformation, calcium regulation, steroid hormone synthesis), which we examine to consider whether sensitivity to stress hormone signaling (as indicated by greater receptor expression) was associated with higher or lower expression of genes involved in particular mitochondrial functions and behaviors across the body. First, the specific gene set of each pathway was extracted. Next, a tissue-specific unweighted MitoPathway gene expression score was calculated by taking the average expression of the specific mitochondrial gene set of each pathway.

Statistical Analyses

Organ systems–level RNA differences were quantified using Hedges g, a standardized measure of effect size, which guards against bias from small sample sizes (48). Independent-samples t tests were used to compare average gene expression of GR in different organ systems (CNS versus immune, CNS versus digestive, CNS versus reproductive). The Welch correction was applied for the comparison of GR expression in CNS and digestive tissues because the standard deviations differed significantly. Because of their exploratory nature, the t test p values were not adjusted for multiple comparisons. Nonparametric correlation (Spearman r) was performed to assess co-regulation between stress hormone receptors' RNA expression and between mitochondrial pathway scores and stress hormone receptor RNA expression, using the Bonferroni correction to adjust for multiple comparisons. The cutoff for the high and low mitochondrial expression groups was set at 500 nTPM, and a nonparametric Mann-Whitney U test was conducted to evaluate between-group differences. The effect of GR stimulation on ARs gene expression in human fibroblasts was tested using a mixed-effects model, using all time points available across the life span of each cell line to derive a stable estimate of expression level for each gene. χ^2 Tests were used to compare the observed proportions of positive and negative correlations between mitochondrial pathways and stress hormone receptor expression compared with the proportions expected by chance (50:50). All analyses were performed in Prism (version 9), Excel (version 16.59), and R version 4.2.0 (2022-04-22)—"Vigorous Calisthenics."

RESULTS

Our primary objective was to investigate differential expression of genes that encode the GR and ARs that respond to activation of the HPA and SAM stress pathways across human organs (Figure 1A). To accomplish this, we first analyzed transcriptomic (RNA sequencing) data from the Human Protein Atlas (42,46,49) and proteomic data from the Human Proteome Map (44), combining expression data across 55 different human tissues and six immune cell subtypes (Figure S1A, Supplemental Digital Content 1, http://links.lww.com/PSYMED/B2). We confirmed the sensitivity of these data and our ability to discriminate between genes expressed by all nucleated cells in the body (e.g., the cytoskeletal element actin [*ACTB*]) and those expressed more selectively, such as the serotonin receptor (*HT2RA*) in CNS neurons, or the B-cell marker *CD19* expressed exclusively in immune tissues (Figure S1B). The results confirmed our ability to sensitively discriminate genes expressed either ubiquitously or restricted to only one or a few tissues.

GR and ARs Are Expressed Heterogeneously Across Organ Systems

Our systematic survey showed that GR is expressed across all investigated organ systems, theoretically enabling every human tissue to respond to cortisol (Figure 1B). Comparing organ systems with one another, striated muscles had the highest GR expression (average expression of 34.9 normalized RNA transcript per million [nTPM]), consistent with the role of glucocorticoids in muscle metabolism (50). The immune system exhibited the second highest average GR expression, 64.4% higher than the CNS (Hedges $g = 1.70$, $p = .003$, independent-sample t test, Welch

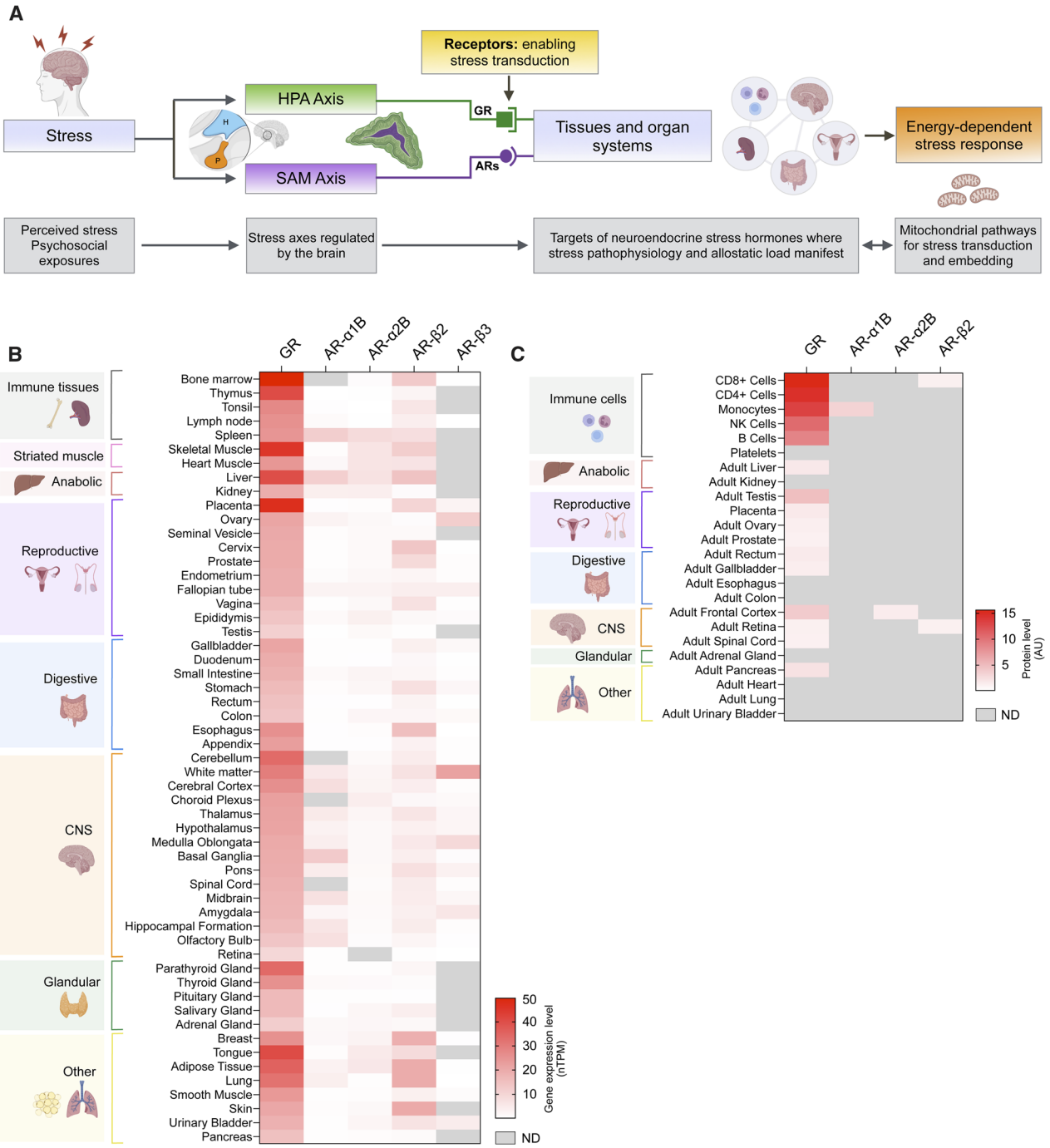

FIGURE 1. Stress hormone receptors transduce experiences of psychosocial stress to tissues; heatmaps of glucocorticoid and adrenergic receptor RNA and protein expression. A, The two major pathways with receptors enabling the transduction of psychosocial stress are illustrated here: the HPA and the SAM axes. The signaling hormones from these axes act on target organs by binding to GR and AR, which mobilize energy-dependent responses sustained by mitochondrial energy production and signaling. B, Heatmap of glucocorticoid and adrenergic receptor RNA expression (in nTPM) in different human tissue types (n = 55), grouped by organ system, highlighting the heterogeneous expression of different receptor subtypes across major organ systems. Note the high expression of the GR in all sampled tissues. C, Heatmap of glucocorticoid and adrenergic receptor protein expression (in AU) across tissue types (n = 17 adult tissues, n = 8 immune cell types), grouped by organ system (or cell type in the case of immune cells), showing the greater abundance of GR in a wider range of tissue types (Data from Uhlén et al. (39) and Kim et al. (44)). ARs = adrenergic receptors; AR-α1B = adrenergic receptor α1B; AR-α2B = adrenergic receptor α2B; AR-β2 = adrenergic receptor β2; AR-β3 = adrenergic receptor β3; AU = arbitrary units; CNS = central nervous system; GR = glucocorticoid receptor; HPA = hypothalamic pituitary adrenal; ND = not detectable; nTPM = normalized transcript per million; SAM = sympathoadrenomedullary. Color image is available online only at the *Psychosomatic Medicine* website.

correction), digestive ($g = 1.83$, $p = .039$), and reproductive organs ($g = 1.18$, $p = .040$). Among individual tissues, the bone marrow (49.8 nTPM) and the placenta (47.3 nTPM) contained the highest GR expression, consistent with the well-described glucocorticoid sensitivity of the immune system and placenta (51,52).

Relative to GR, AR subtypes showed, on average, 9.8-fold lower expression across all organ systems ($p = 6.09 \times 10^{-72}$, analysis of variance, $F = 167.8$). In regard to α-AR subtypes, AR-α1B gene expression was, on average, highest in anabolic tissues, with especially high levels detected in the liver, where catecholamines are well known to stimulate gluconeogenesis (the synthesis of glucose) (53). The CNS also had high AR-α1B RNA levels, particularly in the basal ganglia and cerebral cortex. AR-α2B transcripts were detected at low levels in all tissue types, except the retina, and its expression was highest in the spleen, liver, and striated muscles.

In regard to β-AR subtypes, AR-β2 transcripts were expressed ubiquitously, although at lower levels than GR (3.9-fold lower on average). In contrast to α-ARs, AR-β2 had the highest expression in the skin, lung, and adipose tissue. AR-β3 was only expressed in 69% of tissues, although it was expressed at high levels in the ovaries and some isolated brain regions, including white matter tracts and the medulla.

The expression levels of all stress hormone receptors in each tissue type are detailed in Table S1, Supplemental Digital Content 2, http://links.lww.com/PSYMED/A992, along with the additive expression of the five examined GR and ARs. These results emphasize the particularly robust expression of stress hormone receptors in metabolic, CNS, and immune tissues, consistent with the known physiological responses that these organ systems undergo in response to acute stress.

GR and AR Receptor Protein Abundance

To be functionally active, the RNA transcripts discussed previously must be translated into protein receptors at the cell surface. Thus, although protein abundance is technically more difficult to measure than RNA, it represents the most direct assessment of a tissue's molecular sensing machinery. Similar to the patterns observed for RNA, the GR protein was detected in the largest variety of tissues, including all reproductive and CNS tissues (Figure 1C). GR was detected at highest levels in immune cells (except platelets, which have no nucleus), providing the molecular basis for the immune system's glucocorticoid sensitivity. All ARs showed significantly lower and more restricted protein expression, consistent with patterns observed at the RNA level. Compared with average GR protein levels, AR-α1B was 96% lower, AR-α2B was 98% lower, and AR-β2 was 97% lower. AR-α1B protein was only detected in monocytes, whereas AR-α2B was only detected in the adult frontal cortex. AR-β2 protein was expressed in $CD8^+$ T cells and in the adult retina. AR-β3, likely of very low abundance, was not detected in any of the examined tissues. The protein abundance for all examined receptors and tissues is detailed in Table S2, Supplemental Digital Content 2, http://links.lww.com/PSYMED/A992.

GR and ARs Co-regulation Across Tissues

Under some conditions, psychosocial stress differentially activates the HPA and SAM axes, with SAM responses occurring more rapidly than HPA responses. To examine if these pathways may functionally interact in target tissues, we next tested if tissues that express more GRs also express more ARs, and if tissues that express more of one AR subtype also express more of other AR subtypes. Our nonparametric correlation-based co-regulation analysis of gene expression across 55 tissues showed that organs that expressed higher levels of GR transcripts also generally expressed higher levels of AR-β2 receptor RNA (Spearman $r = 0.50$, $p = .0009$, Bonferroni-corrected), but not other ARs (Figure 2A). Tissues like the bone marrow, skin, and placenta express high levels of both receptors, potentially providing particularly high sensitivity to both glucocorticoids and catecholamines (Figure 2B). Although less robust, AR-α1B and AR-α2B also showed a significant correlation ($r = 0.46$, $p = .004$, Bonferroni-corrected), with the spleen and liver expressing particularly high levels of both receptors (Figure 2C). The high expression levels of these two ARs would be expected to confer heightened sensitivity to catecholamine signaling.

GR Signaling Upregulates AR Expression in Vitro

Given their established association, we wanted to examine if the co-regulation of GR and ARs means that these receptors influence the expression of one another at the cellular level. To do so, we leveraged an in vitro gene expression (RNA sequencing) dataset of primary human fibroblasts treated with Dex, a synthetic glucocorticoid that acts as an agonist and activates the GR (Figure 2D) (45). In this cellular in vitro system, as in most human tissues, GR was the most highly expressed receptor, and all ARs were expressed at considerably lower levels. This result and other molecular features, such as DNA methylation patterns found by Sturm et al. (54), mirror measurements in human tissues, providing evidence of external validity for this in vitro cellular system. Using this live human cell model, we can therefore test if activating one stress signaling pathway causally influences the other pathway.

In line with our correlational findings in the human body, we found that experimentally inducing GR signaling increased expression levels for two of the four ARs examined but had no effect on two (Figure 2E). Dex induced AR-α1B expression by 360% ($p = 1.84 \times 10^{-8}$, mixed-effects model, $F = 257.0$) and AR-β2 expression by 221% ($p = 4.68 \times 10^{-7}$, $F = 130.2$). The functional induction of AR-β2 by GR activation corroborates and supports the in vivo evidence that GR and AR-β2 are co-regulated across human tissues. This finding indicating that GR signaling stimulates AR-α1B and AR-β2 expression is consistent with a functional interplay among the HPA and SAM axes at the level of target tissues.

AR-α1B And AR-α2B Transcripts Are Positively Associated With Mitochondrial Gene Expression

Given that the stress response consumes energy mostly provided by mitochondria (16), we systematically assessed the relationship between GR and AR receptors and all known mitochondrial genes in the tissue gene expression data (42,46,49). Mitochondrial gene expression was estimated for each tissue type by taking the average gene expression of all mitochondrial genes, based on the MitoCarta3.0 database (47,55). Estimated tissue mitochondrial expression was positively associated with AR-α1B (Spearman $r = 0.47$, $p = .0003$, Bonferroni-corrected) and with AR-α2B gene expression ($r = 0.55$, $p = .0009$, Bonferroni-corrected; Figures 3A, B), indicating that tissues with more of these ARs express mitochondrial genes at higher levels.

The distributions of our index of mitochondrial expression for AR-α1B and AR-α2B were bimodal, indicating two main groups of tissues with either low or high mitochondrial gene expression. We therefore took a different approach, comparing AR-α1B and

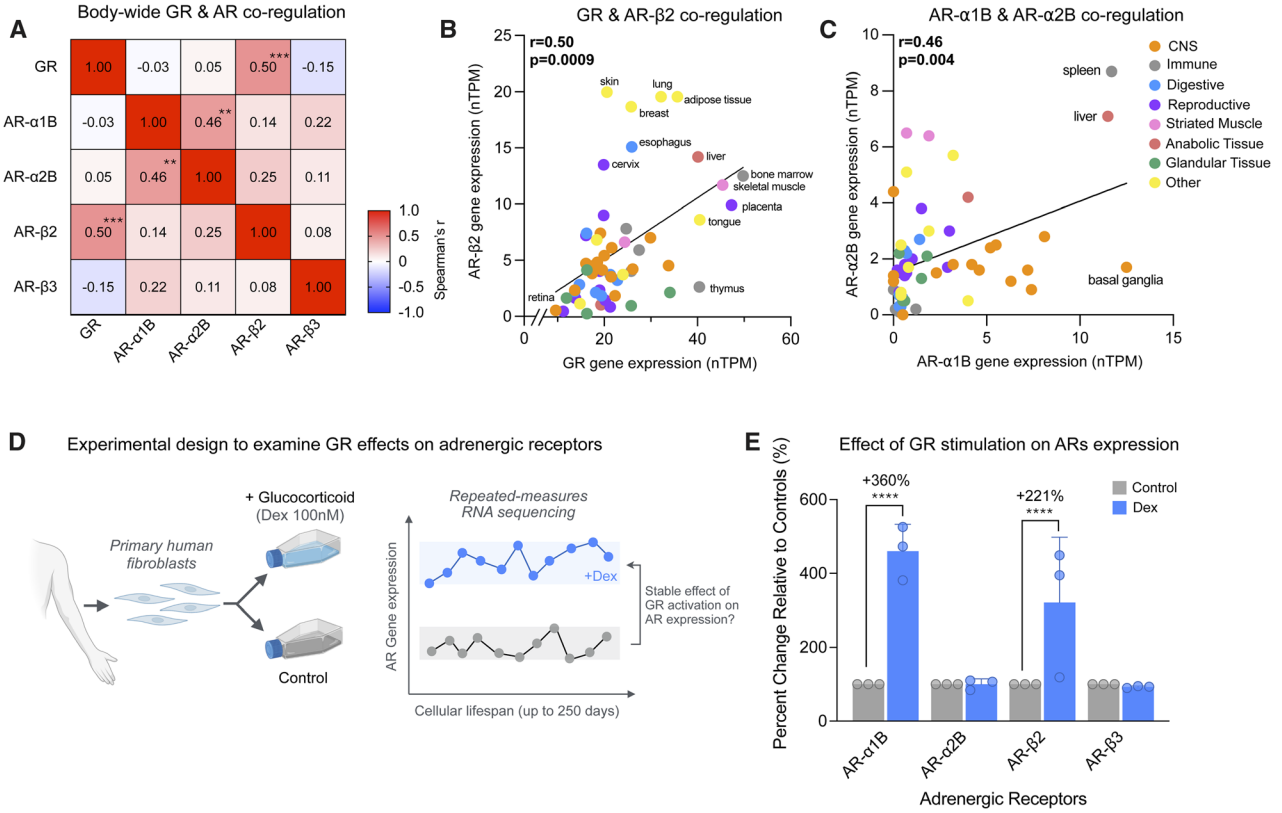

FIGURE 2. Co-regulation and functional interaction of stress hormone receptor expression. A, Correlation matrix of GR and AR RNA expression, showing significant correlations between GR and AR-β2, as well as between AR-α1B and AR-α2B. Scatterplots of GR and AR-β2 RNA expression (B) and of AR-α1B and AR-α2B (C), which showed significant positive correlations. Tissues expressing more of one receptor tend to express more of the other. D, Schematic of study design where primary skin cells (dermal fibroblasts) are obtained from forearm and cultured in vitro, followed by longitudinal gene expression analysis across the cellular life span. The average of all time points for each donor was taken as a measure of stable lifetime gene expression for each AR, compared with the values in the untreated (control) culture of the same donor. E, Effect of Dex (100 nM), a GR agonist, on the gene expression of ARs in $n = 3$ fibroblast lines (healthy controls 1, 2, 3), demonstrating how chronic GR stimulation induces a significant increase in the expression of two specific ARs. Data are means ± SEM, normalized to control from Sturm et al. (45). Statistics from Spearman rank correlation with Bonferroni correction (A, B) and mixed-effects model (D), $*p < .05$, $**p < .01$, $***p < .001$, $****p < .0001$. AR = adrenergic receptor; AR-α1B = adrenergic receptor α1B; AR-α2B = adrenergic receptor α2B; AR-β2 = adrenergic receptor β2; AR-β3 = adrenergic receptor β3; CNS = central nervous system; Dex = dexamethasone; GR = glucocorticoid receptor; nTPM = normalized transcript per million. Color image is available online only at the *Psychosomatic Medicine* website.

AR-α2B expression levels between the two groups of tissues (Figures 3A, B; insets). Consistent with the nonparametric correlation analysis, tissues with higher estimated mitochondrial expression, such as the heart muscle, cerebral cortex, skeletal muscle, and liver, had higher expression of both AR-α1B and AR-α2B. Thus, tissues endowed with high stress hormone receptor density also invest a larger proportion of their transcriptome for mitochondria and may therefore harbor commensurately higher capacity for energy production and other mitochondrial functions.

Stress Hormone Receptors Are Associated With Specific Mitochondrial Pathways

To systematically examine whether the expression of GR and AR receptors was associated with specific mitochondrial pathways, we correlated the five stress hormone receptors observed across 55 human tissues with each of the 149 well-defined mitochondrial functional pathways in MitoCarta3.0 (47). For each receptor, this yielded 149 nonparametric Spearman ρ correlation coefficients, which we ranked from the highest to lowest. In Figures 3C and D, each point on the plot represents a correlation value for a specific AR or GR, with 1 of 149 mitochondrial pathways. Positive correlations between a stress hormone receptor and a particular mitochondrial pathway are shown in red, whereas negative correlations are shown in blue. For this analysis, if there is no association between the expression of GR/ARs and mitochondrial pathways, the distribution would be centered around zero and follow a Gaussian distribution (i.e., small positive and negative tails, reflecting the null hypothesis; Figure 3C).

The results showed that for all receptors except AR-β3, the distributions of stress receptor-MitoPathway correlations were positively skewed. This means that there were significantly more mitochondrial pathways positively associated with GR and ARs than expected by chance (range, 45%–97%; average, 71%, versus 50% expected by chance; $p = .0008$, $\chi^2 = 11.17$; Figure 3D). Thus,

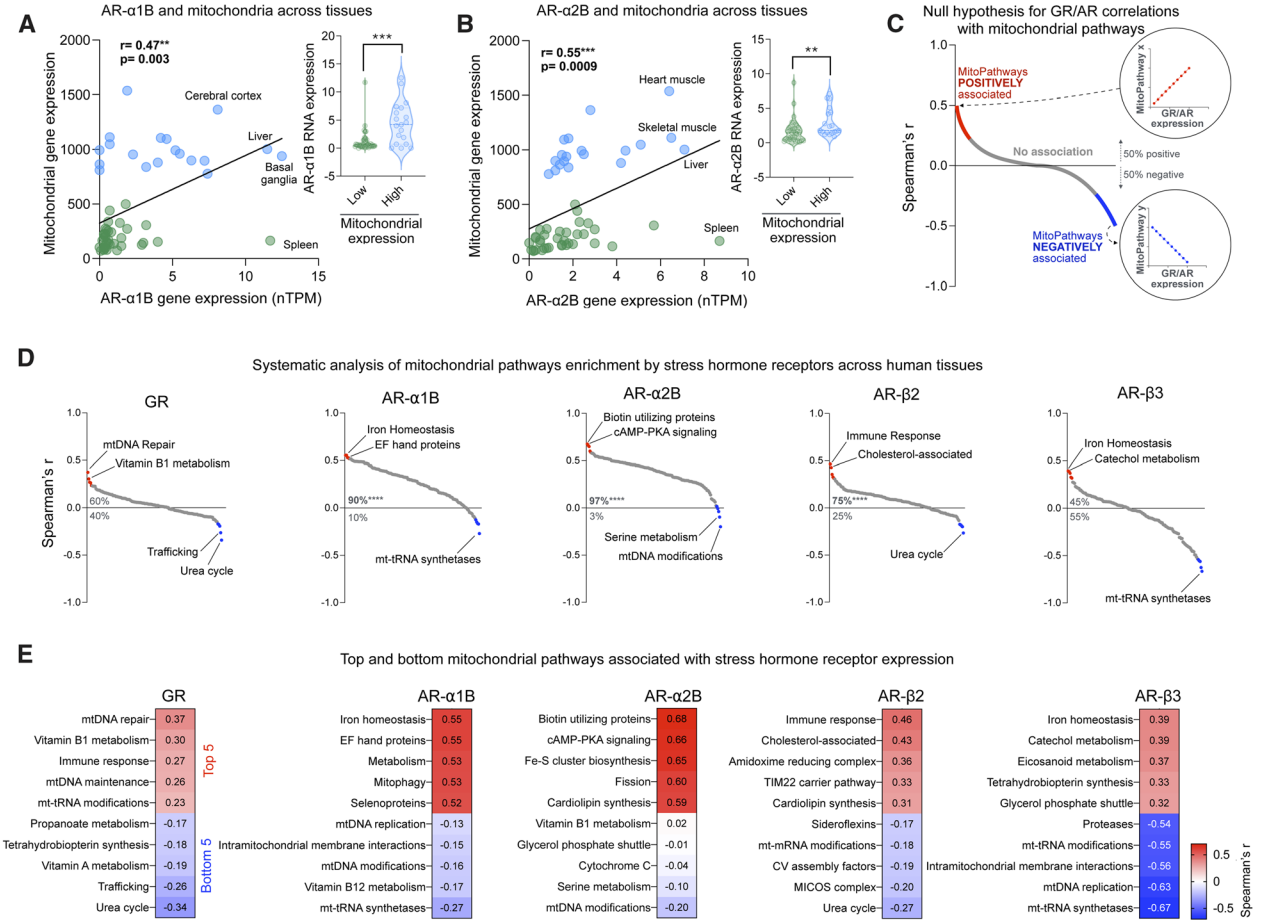

FIGURE 3. Stress hormone receptors and mitochondrial phenotypes across human tissues. A, Scatterplot of the significant correlation (Spearman *r*) between AR-α1B receptor RNA expression (nTPM) and mean mitochondrial gene expression (mean nTPM), demonstrating that tissues with higher mitochondrial expression also tend to have higher levels of this AR subtype. Inset: Violin plot of average AR-α1B RNA expression for tissues dichotomized as high versus low mean mitochondrial expression (threshold = 500 nTPM), with Mann-Whitney *U* test used to compare the two groups. B, Same as in panel A, for AR-α2B receptor. C, Null hypothesis plot of correlations between stress hormone gene expression and specific functional mitochondrial pathways (MitoPathway, $n = 149$). This panel illustrates expected results if there were no overall associations between mitochondrial pathway expression and stress hormone receptor expression, resulting in an approximately even distribution of positive, null, and negative correlations. D, Plot of correlations (Spearman *r*) between gene expression for stress hormone receptors and 149 MitoPathways. χ^2 Tests were used to compare distribution of correlations to null hypothesis distribution (50% positive and 50% negative correlations), showing that there were significantly more positive correlations than expected for the stress hormone receptor subtypes AR-α1B, AR-α2B, and AR-β2. E, Heatmaps of five most positive and most negative correlations (Spearman *r*) between stress hormone receptors and mitochondrial pathway gene expression. Statistics from Mann-Whitney test and χ^2 test, $^*p < .05$, $^{**}p < .01$, $^{***}p < .001$, $^{****}p < .0001$. AR-α1B, adrenergic receptor α1B; AR-α2B, adrenergic receptor α2B; AR-β2, adrenergic receptor β2; AR-β3, adrenergic receptor β3; nTPM, normalized transcripts per million; GR, glucocorticoid receptor. Color image is available online only at the *Psychosomatic Medicine* website.

tissues with high glucocorticoid and catecholamine receptor expression tend to express higher levels of various mitochondrial pathways, consistent with the energy cost associated with stress hormone receptor signaling (16).

Because mitochondria are complex organelles with multiple functions (37) and little is known about what aspect of their biology is linked to stress signaling, we explored which domains of mitochondrial biology were associated with each receptor. The identified mitochondrial pathways included some expected, as well as some novel stress-related mitochondrial profiles. Figure 3D illustrates the distributions of correlations, and Figure 3E shows the associated heatmaps with the five mitochondrial pathways most positively and most negatively associated with each receptor. Overall, there was little overlap between the mitochondrial profiles associated with each receptor (Figure S2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/B2), suggesting either the existence of highly receptor-specific mitochondrial profiles or the influence of confounding factors and low signal-to-noise ratio for these analyses.

Given the heterogeneity of mitochondrial functions, there is not one clear signature in the correlations between mitochondrial pathways and stress hormone receptors, but rather a variety of potentially relevant pathways. Consistent with the role of calcium

signaling downstream of ARs, tissues with high AR-α1B were enriched for mitochondrial *EF hand proteins*, and AR-α2B was enriched for mitochondrial *cyclic AMP-protein kinase A (cAMP-PKA) signaling*; both of these two pathways enable signaling within the cell using calcium. High GR expression was linked to *mtDNA repair*, which safeguards genes found within the mitochondria that are required to sustain energy transformation, in addition to *mtDNA maintenance*. This result is consistent with the energetic cost of stress and the deleterious effects of chronic GR signaling on mtDNA and genomic instability (16). AR-β2 and GR were also positively associated with the mitochondrial *immune response* pathway, which could reflect the enhancement of some parts of the immune system in response to stress (56).

Overall, these data reveal predominantly positive associations between the expression of stress hormone receptors and mitochondrial pathways, consistent with the notion that stress signaling entails energy costs at the cellular level. We have also highlighted several mitochondrial pathways that are relevant to the stress response, which were found to be positively associated with stress hormone receptor expression.

DISCUSSION

To map the signaling machinery responsible for cellular responses to the activation of the HPA and SAM pathways, which presumably enable coordinated physiological responses to psychosocial stress throughout the entire human body, we evaluated the RNA and protein expression of glucocorticoid and ARs across a wide range of organ systems. Our results demonstrate three major points. First, in contrast to ARs that are expressed at lower levels and in a more tissue-specific pattern, the GR is ubiquitously expressed and at considerably higher levels across organ systems. Second, body-wide correlations validated in live-cell experimental data show that GR and some ARs are co-regulated, meaning that tissues expressing more of one receptor subtype also tend to express more of another, consistent with their functional and genetic interactions. Finally, we find evidence that tissues with greater GR and AR density, and potentially greater sensitivity to psychosocial stress, harbor higher estimated mitochondrial content and expression of specific mitochondrial pathways. This seems in line with the energetic cost of stress responses (35), as tissues that have more stress hormone receptors and presumably are more sensitive to stress signaling will need energy transformed by mitochondria (in addition to a range of other functions performed by multifunctional mitochondria) to enact the physiological changes needed to react to stress. These findings provide a quantitative body-wide inventory of receptors involved in brain-body communication and may help to understand how stress is transduced differentially across human organ systems.

The distribution of GR and ARs across the body is the mechanism by which psychobiological stress is transduced into cellular responses. As expected, organ systems classically implicated in response to HPA activation have the highest GR levels, making them particularly sensitive and responsive to circulating glucocorticoids (13). These include the *liver*, which breaks down glycogen stores to increase blood glucose, the *skeletal muscles*, where glucocorticoids suppress glucose uptake to increase availability to other organs like the *brain*, and the adaptive *immune system*, which similarly must be rapidly suppressed to prevent overconsumption of glucose in times of stress. The immune organs and purified immune cells showed high levels of GR, especially at the protein level, which may enable particularly rapid and robust responses to HPA signaling. On the other hand, high receptor abundance also may render them more vulnerable to adaptation arising from HPA axis overactivation during chronic stress. The hypersensitivity of immune organs to stress signaling aligns with the large body of research documenting stress effects on various aspects of immunity, as evidenced by downregulation of aspects of adaptive immune function and increased susceptibility to the common cold (5,57–59). In addition, we found that the placenta exhibits substantial GR expression, indicating a high potential for GR signaling to mediate the prenatal effects and vulnerability of fetal development to maternal stress exposure (60).

Compared with GR, the lower and more localized protein expression of AR subtypes suggests that the organs responsive to stress signals conveyed by the SAM axis are more specialized or selective. For example, the AR-α1B protein was only detected in monocytes, which aligns with previous findings about the influence of AR-α1 on innate immune cells (61,62). In addition, AR-α2B protein was only identified in the adult frontal cortex, potentially rendering this brain region particularly sensitive to local or systemic catecholaminergic signals arising from psychosocial stress. These selected examples of more circumscribed AR expression may provide a biological explanation for organ-specific responses to adrenergic stimulation. However, given that the fight or flight response is known to involve the swift, coordinated reaction of a range of organs, it is also possible that the AR protein levels were simply below the detection threshold in some tissues.

Stress signaling axes do not act in isolation. High AR expression in a specific tissue could indicate that it is prepared to mount the *rapid* stress response that the SAM axis is responsible for, whereas high levels of GR could mean that a tissue is primed to participate in the *slower* stress response that the HPA axis generates. Our findings that GR and AR-β2 are co-regulated across human tissues suggest that some organs must be sensitive to outputs from both faster SAM and slower HPA axes. The high levels of both receptors particularly in bone marrow, placenta, liver, adipose tissue, and skin could enable either more robust or faster responses in these tissues, as well as their coordination. For example, the high levels of GR and AR-β2 in the bone marrow could be connected to the acute stress–induced redistribution of immune cells from the bone marrow into peripheral circulation in response to epinephrine and glucocorticoid signaling (56). This coordinated transduction by the HPA and SAM axis receptors could help the innate immune system efficiently prepare for infections or injuries resulting from acute stress (63). Moreover, our in vitro results demonstrating that GR stimulation increases the expression of ARs (α1B and β2) confirms a potential functional connection between the HPA and SAM pathways, where the presence of glucocorticoids leads to sensitization to catecholamine signaling, at least in some tissues. Although stress research often examines the HPA axis or the SAM axis in isolation, these findings suggest that further investigation of their coordinated activity in response to stressors is warranted.

With regard to the biology downstream from AR and GR signaling, our findings established an initial connection between GR/ARs and mitochondrial gene expression. The significant correlation of levels of both AR-α1B and AR-α2B with estimated mitochondrial content indicates that the tissues most sensitive to adrenergic stimulation may be better prepared to mount robust and rapid

energetic responses to stress. In addition, the expression of mitochondrial genes involved in the cAMP-PKA signaling pathway showed a strong positive association with AR-α2B. Given that ARs are G-protein–coupled receptors, a type of receptor that typically conveys information through cAMP-signaling pathways, the high expression of these mitochondrial pathways could imply that mitochondria contribute to signal transduction in these tissues, thereby contributing to more energetically efficient stress responses (27). In addition, the positive correlation of GR transcript expression with mtDNA repair–related mitochondrial genes suggests that stress-susceptible tissues are also preparing to repair mtDNA damage that may result from stress (16). However, there were negative associations between AR-β3 and various mitochondrial pathways, indicating that this receptor may predominantly activate other intracellular pathways less dependent on mitochondria. Overall, the diverse associations between stress hormone receptor expression and a wide range of mitochondrial pathways empirically support the general conceptual link between stress responses and mitochondrial biology (64).

In regard to psychosocial stress and its transduction within cells and tissues, our findings raise important questions about how cells and organisms balance the energy needed to respond to stress with energy availability. A recent in vitro study showed that chronic GR activation increases energy expenditure at the cellular level by 60%, and that this state of "hypermetabolism" accelerated the rate of aging over several months (16). This suggests that the activation of stress pathways may steal energy away from other protective and longevity-promoting cellular functions, possibly contributing to the damaging effects of chronic stress (35). The correlations between ARs and mitochondrial pathways reported in our study indirectly suggest that this is a possibility, but whether ARs activation could participate in stress-related increase in energy expenditure remains to be determined.

These molecular-level data also can help orient future research at the organ level, as they open up further questions about how brain-derived stress signals reach each organ system. In each organ, based on the receptor profile (i.e., what each cell and organ can sense), stress hormones may recruit distinct energy-dependent responses. Future research aiming to connect the dots between psychosocial stress and subjective experiences, the resulting systemic neuroendocrine factors, and the end-point cellular and molecular recalibrations that cause stress pathophysiology, could use the receptor expression profiles provided herein, or the mitochondrial signatures linked with each receptor, to formulate precise quantitative hypotheses about the temporality and magnitude of expected responses. Examining stress-evoked responses in individuals with genetic mitochondrial defects, or with other metabolic/energetic disorders, may also shed light on the connection between cellular energetics, mitochondria, and the psychobiological mechanisms that confer resilience or vulnerability to psychosocial stress.

One limitation of this work leveraging gene expression is the indirect assessment of the effect of stress on tissues, as this method does not capture the dynamic transcription, translation, and degradation of stress hormone receptors over time. In addition, the Human Protein Atlas and Human Proteome Map datasets did not include RNA and protein expression in the exact same set of organs and immune cells, allowing for less direct comparison between the two (RNA and protein) modalities. Also, the Human Proteome Map did not include protein levels for AR-β3, likely undetected because of its low expression level. Technically, the untargeted proteomics data were generated by mass spectrometry, which has a fairly high detection limit and may not have detected the proteins present at low levels (65). A more sensitive method could be more suitable to precisely quantify specific proteins in organs of interest (65).

We also note that our whole-body transcriptomic data reflect aggregate data across over 950 participants. Although this adds confidence that the results are generally robust, it does not permit the examination of interindividual differences. Whether individuals exhibit differences in GR and AR distribution that could contribute to the magnitude of the physiological stress response should be considered in future studies. In addition, single-cell studies of GR and AR expression are needed given the differential effects of stress on distinct cell types, such as those of the innate versus adaptive immune system, which likely coexist within the immune cells and organs sampled. Finally, some tissues showed no stress hormone receptor expression, such as platelets, despite extensive literature highlighting the way in which they are impacted by stress (66). This calls for further consideration of downstream effects of the HPA and SAM axes, as well as nonclassical mechanisms of stress transduction beyond these two well-studied types of receptors.

In conclusion, this study provides a rough cartography of canonical glucocorticoid and ARs, highlighting their high heterogeneity among organs across the human body. The resulting quantitative map of organ-specific stress hormone receptor expression (available in Tables S1 and S2, Supplemental Digital Content 2, http://links.lww.com/PSYMED/A992) provides a basis to understand the nature and magnitude of stress responses among specific organ systems, such as the immune system, that occur following the activation of neuroendocrine pathways by psychosocial stress. This analysis also demonstrates a connection between GR and ARs, as well as with mitochondrial gene expression, consistent with the notion that mitochondria and cellular energetics contribute to transduce stressful experiences into physiological responses relevant to human health.

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The authors did not preregister the research in an independent, institutional registry.

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