Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Trends in Neuroendocrinology*

Molecular genetics of hypothalamic–pituitary–adrenal axis activity and function

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The hypothalamic–pituitary–adrenocortical (HPA) axis is a major neuroendocrine system involved in the regulation of numerous physiological processes and in adaptation to stress. A wide range of variability can be observed in all the components of the system, and the contribution of genetic factors has been shown in the central regulation of the axis, the production of glucocorticoid hormones by the adrenal cortex, their bioavailability, and the efficiency of their action at the level of receptor and postreceptor mechanisms. Numerous molecular polymorphisms have been described that contribute to physiological variation as well as to HPA axis-related pathological conditions. Although most studies focus on single gene polymorphisms, future studies should aim to integrate the different sources of variation into a systems genetic model to take into account the strong interdependence of the different components of the axis.

Keywords: HPA axis; genetics; glucocorticoid receptor; corticosteroid-binding globulin; sensitivity to ACTH

Introduction

The glucocorticoid hormones cortisol and/or corticosterone are secreted by the adrenal gland cortices under the control of pituitary adrenocorticotropic hormone (ACTH), which is stimulated by neuropeptides (corticotrophin-releasing hormone [CRH] and arginine vasopressin [AVP]) from the paraventricular nucleus of the hypothalamus.[1] Although it has been studied primarily in the context of stress, the hypothalamic–pituitary–adrenal (HPA) axis is a major neuroendocrine system with a wide range of functions in developmental, metabolic, cardiovascular, immune, and neurobiological processes. As a consequence, HPA axis dysfunction is involved in the physiopathology of numerous pathological conditions that range from metabolic syndrome, obesity, and cardiovascular and immune diseases to drug intake and mood disorders, just to cite a few.[2] A large individual variation in HPA axis activity has been described and results from the interaction of several factors, such as early experiences,[3] that can be passed across generations,[4] previous history of life events,[5] and genetic influences.[6–8]

Genetics and HPA axis activity

The contribution of genetic factors to HPA axis activity is well-established. In humans, twin studies have shown that most parameters of HPA axis function are highly heritable, although divergent results can be found due to the intrinsic variability of the HPA axis (such as pulsatile secretion, that is itself subject to genetic variation[9,10]) and its exquisite sensitivity to environmental and procedural factors.[8,11] In experimental animals, large differences have been described among inbred strains of laboratory rodents[12] or genetic stocks of domestic species.[13] Divergent genetic selection for the response of the HPA axis to various stimuli (restraint, cold, confinement, and social stress) has been successful in a wide range of species (chicken, turkey, quail, finch, duck, trout, and, more recently, mouse[14]). The response to

doi: 10.1111/j.1749-6632.2010.05902.x

selection is usually very strong, with realized heritability between 0.4 and 0.5 (see Ref. 13 for review). Numerous sources of genetic variability have been described in HPA axis-related genes, but this review will be limited to the peripheral part of the HPA axis, including the production of glucocorticoid hormones by the adrenal cortex, the mechanisms regulating the bioavailability of the hormones, and the efficiency of the receptors that have been most investigated. Interested readers are referred to recently published review papers for a more comprehensive list of molecular polymorphisms, including in genes regulating the central control of the HPA axis (brain neurotransmitter systems, regulatory peptides, and their receptors).[6,8]

Molecular bases of genetic variation in HPA axis activity

Production of glucocorticoid hormones by the adrenal cortex

The production rate of cortisol is primarily regulated by the sensitivity of the adrenal cortex to ACTH, which may be driven by adrenal innervation.[15,16] Hennessy and collaborators[17] demonstrated in pigs that the adrenal response to ACTH is variable among individuals but stable across time for a given animal. Similar differences in cortisol secretion were shown in response to CRH,[18] physical exercise, or insulin-induced hypoglycemia,[19] although the ACTH response was not different among individuals; therefore, the effect must have been due to adrenal sensitivity to ACTH. Metabolic clearance of cortisol bears no relationship with the response to ACTH.[20] Altogether, these data demonstrate that adrenal sensitivity to ACTH is a key index of individual differences in HPA function. This was confirmed in humans by Bertagna and collaborators, who coined the expression "adrenal phenotype."[21,22] The adrenal response to ACTH is highly heritable as shown in pigs ($h^2 = 0.51$),[23] and divergent lines of turkey could be selected on the basis of their response to ACTH injection, with a realized heritability of 0.28.[24] Differential gene expression studies in pigs[25–28] and chickens[29] have produced a list of candidate genes related to differences in sensitivity to ACTH.

Bioavailability of glucocorticoid hormones

An important part of HPA genetic variability occurs at the level of glucocorticoid hormone availability. This has been clearly shown for corticosteroid-binding globulin (CBG), also called transcortin. This glycoprotein is found in plasma and forms a high-affinity complex with cortisol or corticosterone, leaving only 5–10% of active free circulating glucocorticoids. Animal genetic studies, using nonhypothesis-driven strategies, have found that the gene encoding CBG (SerpinA6) was the most important genetic factor explaining glucocorticoid levels variability, in particular after stress. In pigs, genetic variation in CBG gene impacts fat deposition, muscle content, and some parameters of meat quality (reviewed in Ref. 30). In human, rare CBG functional variants have been described, leading to hypotension, fatigue, and chronic pain and, in some cases, obesity and depressed mood.[31] Animal models of CBG genetic deficiency display glucocorticoid hyporesponsiveness.[32,33] Association studies conducted between CBG gene polymorphisms and chronic fatigue syndrome or obesity showed a moderate but significant effect of CBG gene variations (reviewed in Ref. 31). Recently, significant genetic associations were found between several single nucleotide polymorphisms (SNPs) of the SerpinA6 gene and chronic widespread pain as well as the number of pain sites in a cohort of 994 patients.[34]

Other important factors regulating glucocorticoid availability are 11 beta-hydroxysteroid dehydrogenase (11β-HSD) enzymes. The type 1 (11β-HSD1) allows the regeneration of cortisol (or corticosterone) from inert cortisone (or 11 dehydrocorticosterone) and is present in various tissues of the body—including liver, adipocytes, bones, and brain—acting as an intracellular glucocorticoid amplifier. It is also involved in the regulation of the axis.[35,36] The type 2 enzyme (11β-HSD2) has a localization restricted to mineralocorticoid-responsive tissues and the feto-placental unit; it allows the reverse reaction, metabolizing glucocorticoids to inert compounds. Mutations in the gene encoding 11β-HSD2 explained a rare inherited form of human hypertension called "apparent mineralocorticoid excess" in which cortisol, in addition to aldosterone, acts on the mineralocorticoid receptor (MR) in kidney causing hypertension and hypokalemia. Most 11β-HSD1-deficient states are not due to mutations in the gene encoding 11β-HSD1 but in the gene encoding hexose-6-phosphate dehydrogenase that provides NADPH necessary for 11β-HSD1 reductase activity; these patients are

thus said affected of "apparent cortisone reductase deficiency." Several noncoding polymorphisms in the gene encoding 11β-HSD1 have been used in association studies following animal studies and show a role of 11β-HSD1 in obesity and cognitive performances. None of these polymorphisms is associated with obesity in human cohorts, but they have been linked to the increased risk of diabetes and hypertension in two populations. An association study between 11β-HSD1 polymorphisms and lifetime cognitive changes gave negative results.[37] Recently, polymorphisms in 11β-HSD1 have been found to be associated with osteoporosis in postmenopausal women.[38]

Transduction mechanisms

The adrenocortical hormone receptors (glucocorticoid receptor [GR] and MR), members of the nuclear receptor subfamily 3 (Nr3c1 and Nr3c2, respectively), are proteins with three distinct functional regions: the N-terminal transactivation domain, the central zinc-finger DNA-binding domain, and the C-terminal ligand-binding domain. They increase or decrease the expression of a large number of genes in many tissues via complex cell- and gene-specific mechanisms. Alterations in any of the molecular mechanisms of GR action may lead to alterations in tissue sensitivity to glucocorticoids (either resistance or hypersensitivity) (see for review Refs. 39 and 40). The GR is the protein product of one gene on human chromosome 5 (5q31–32); this gene is highly polymorphic[41] and its mutations are the primary cause of inherited forms of glucocorticoid sensitivity abnormalities and acquired glucocorticoid resistance in acute lymphoblastic leukemia.

Primary hereditary glucocorticoid resistance is a rare disorder that causes slightly elevated plasma ACTH levels and increased circulating cortisol concentrations without symptoms of Cushing's syndrome. Symptoms of this disorder stem from increased serum concentrations of androgens and mineralocorticoids resulting from adrenocortical overstimulation by the elevated plasma ACTH levels. The phenotype spectrum is large, from clinically severe to forms limited to biochemical abnormalities.[42]

Less dramatic but more frequent than the primary hereditary glucocorticoid resistance is the variation of interindividual response to pharmacological glucocorticoid administration.[43,44] Functional polymorphisms within the GR gene explain, at least partly, this population variation of sensitivity.[39] Glucocorticoid sensitivity does not depend on GRs only. For instance, the results of different tests of glucocorticoid sensitivity (postdexamethasone cortisol levels, lipopolysaccharide-induced interleukin 6 secretion, and skin blanching) are not correlated,[45] suggesting a tissue-specific regulation by various molecular components of the receptor-activated pathway (concentrations, mutations, or polymorphism of chaperones and cofactors, etc.). The latter would explain both inter- and intraindividual variations. Indeed, some GR polymorphisms differentially affect transactivation and transrepression by differently combining to other proteins; this would lead to various consequences in different tissues.[46] Some work has been done on variations of glucocorticoid sensitivity due to chaperone or cochaperone gene polymorphisms. For instance, alteration of heat shock protein 90 (hsp90) in mice modifies GR function,[47] and polymorphisms in HSP have been associated with pathological conditions in humans (e.g., Ref. 48). The cochaperone FKBP5 is responsible for resistance to glucocorticoid action in New World monkeys, and, in humans, polymorphisms of the FKBP5 gene are associated with a relative GR resistance.[49] Dysregulation of the HPA system is a consistent finding in patients suffering from major depression. A neuroendocrine functioning test combining dexamethasone suppression and CRH stimulation shows an enhanced release of cortisol and ACTH compared to normal subjects probably because of reduced hypothalamic feedback sensitivity for glucocorticoids. Interestingly, a normalization of the HPA axis dysregulation occurs in remitters but not in nonremitters after a few weeks of antidepressant treatment.[50] The large range of responses in this test in depressed patients is influenced by several factors, such as gender and treatment.[51] A higher number of recurrent episodes and more prominent somatic symptoms are correlated with a more dysregulated HPA axis, which suggests that there may be distinct subtypes of patients with depression who could be distinguished according to their HPA axis status. For instance, polymorphisms in the angiotensin-converting enzyme gene have been associated with a genotype-dependent difference in the magnitude of the Dex-CRH.[52] Additionally, the GR BclI and ER22/23EK polymorphisms are associated with

susceptibility to develop major depression, and ER22/23EK polymorphisms are associated with a faster clinical response to antidepressant treatment.[53]

Functional consequences of genetic variation

Metabolism

Genetic variability in HPA axis function influences feeding behavior, metabolism, and energy expenditure.[54] Glucocorticoids were first described for their implication in carbohydrate metabolism, that is, a GR-dependent release of glucose from hepatic and muscle stores in order to supply the "fight or flight" response of the body to face environmental challenges. They also induce insulin resistance directly by perturbing insulin signal transduction and indirectly by promoting visceral fat deposition and loss of lean mass. The interplay between the HPA axis and metabolic disorders may also be mediated by inflammatory processes that play an active role in the pathogenesis of obesity and are regulated by glucocorticoids.[55] As a result, via both MR and GR, glucocorticoids stimulate preadipocyte differentiation, favor accumulation of fat, and drive adipose tissue distribution.[56,57] Cushing's syndrome in humans and animals illustrates the link between high glucocorticoid levels and accumulation of central fat at the expense of subcutaneous fat.

Most models described for their vulnerability to metabolic disorders also show some alterations in HPA axis function. For instance, in leptin-resistant Zucker rats, the reactivation of active glucocorticoids by 11β-HSD1 is decreased in liver but increased in visceral fat.[55] Altered CBG levels were also described in these rats and in an obese chicken line.[30] In rodents, obesity models induced either by genetic alterations (*ob/ob*, *db/db*, *fa/fa*, etc.) or by environmental pressure in vulnerable strains (glutamate treatment, diet, chronic stress, etc.) are improved by adrenalectomy (ADX) on the one hand, or by GR,[58] MR, or 11β-HSD1 blockade on the other hand.[55] Inbred rodent strains that spontaneously differ for both metabolic and corticotropic traits are relevant tools to investigate the relationships between the genetic variability of HPA axis and energy metabolism. As an example, BN and LOU/C rat strains are both characterized by their leanness and successful aging and share peculiarities in their HPA axis function, that is, low glucocorticoid levels across the circadian cycle and, after restraint or metabolic stress,[59,60] insensitivity to ADX, and high MR and GR sensitivity to their agonists.[57,60,61] We also showed that LOU/C rats were resistant to diet-induced obesity (DIO).[57,62] On the other hand, the F344 inbred rat strain, whose HPA axis is hyperactive and hyperreactive to stress, is vulnerable to DIO and was proposed as a relevant model of the unfavorable effects exerted by glucocorticoids via GR on food preference for high-calorie diets, abdominal fat deposition, insulin resistance, and other deleterious consequences of visceral obesity.[57]

Selection studies also support the fact that metabolic characteristics are generally coinherited with HPA axis-related traits. Rats from the Sprague–Dawley outbred strain that were selectively bred for either their vulnerability or resistance to DIO show alterations in their central pathways mediating stress responses.[63] DIO-prone rats showed a lower hippocampal density of GR than DIO-resistant rats regardless their diets. After exposure to an acute stress, chow-fed DIO-susceptible rats gained less weight, while their high fat-fed counterparts gained more weight and had higher feed efficiency and plasma leptin levels than their unstressed controls. On the other hand, compared to DIO-resistant rats, DIO-prone rats appeared less responsive to the effects of a high fat diet or chronic unpredictable stress on plasma corticosterone. The weight gain of DIO-resistant rats was affected neither by stress nor by diets.[64] Selection studies can reveal the complexity underlying interactions between HPA axis and metabolism by the diversity of corticotropic functional patterns possibly involved in metabolic disorders. For instance, mice selected for their greater visceral fat content showed unexpectedly reduced circulating and intraadipose glucocorticoid levels, but a higher functional activity of glucocorticoids in liver than their lean counterparts.[65] To our knowledge, rodent substrains selected for their sensitivity to environmental stress (high responders versus low responders, e.g., Ref. 14) and that may differ in their body weights have not been investigated yet for their metabolic profiles or their vulnerability to metabolic disorders.

In heterogeneous populations, either natural (humans, outbred rodent strains, or domestic animals) or experimental (F2 intercross in rodents), strong statistical correlations have been found between corticotropic and metabolic traits.[30] Moreover, in some

quantitative trait loci (QTL) studies, HPA axis measures and metabolic traits shared common genetic influences. For instance, glucose dysregulation-related loci overlapped with HPA axis-related loci on chromosomes 3, 5, and 7 in a F2 WKYxF344 rat intercross.[66] Other QTL studies also suggest the involvement of candidate genes related to corticotropic function in metabolic traits in humans, pigs, or rodents.[67] In mice, the GR locus was associated with adiposity[68] and the CBG locus with growth, body weight, adiposity, and insulin levels.[30] In the same way, the gene coding for 11β-HSD1 is a potential candidate in a major QTL influencing plasma glucose, body weight, and fat levels in F2 NZOxB6 mice.[69]

Neurobiological processes

The consequences of genetic variation of the HPA axis at the level of the central nervous system have been determined in various studies. In rats and mice, a CAG repeat number polymorphism, leading to a variable length of polyglutamine track, has been described within the gene encoding the GR. A study reported association between this polymorphism (GR16q) and low corticosterone response to stress as well as reduced locomotor activity and increased anxiety,[70] but experimental biases were noted in this report.[71] In an independent study, the effect of the same polymorphism was examined on mice exposed to a water-immersion restraint stress. The GR16q male mice were found to have more gastric lesions, a delayed corticosterone peak response, and slower recovery to the stress. Altered cytokines and hsp70 levels were also reported for the GR16q mice.[72]

A number of neurobiological phenotypes have been studied in mice selectively bred by Touma and collaborators for extremes in stress reactivity.[14] In the original article, the three mouse lines (HR/IR/LR) selected for divergent plasma corticosterone response to restraint stress were found to differ in exploratory drive and depression-like behavior. The low reactivity (LR) line displayed a passive coping style compared to the control IR line, while the high reactivity (HR) line showed a hyperactive/agitated phenotype. Furthermore, the LR line showed more aggressiveness in the attack latency test.[14] These lines were further characterized by studying sleep-endocrine regulation. The HR line displayed reduced amplitude of the circadian glucocorticoid rhythm due to elevated trough levels and increased rapid eye movement (REM) and decreased non-REM sleep as well as slow-wave activity. The LR line was not different from IR except for a higher proportion of slow-wave sleep across the day.[73] In terms of cognitive performance, the HR line showed deficits in hippocampus-dependent memory tests associated with decreased brain-derived nerve growth factor levels in hippocampus. Conversely, the LR line showed increased cognitive performances compared to the control line IR but only in males.[74] This study was pursued by the examination of the performance of the three lines in a reversal learning task and of latent inhibition in a conditioned taste aversion paradigm. Cognitive deficits were confirmed in the HR line that showed perseveration in the reversal learning task and disrupted latent inhibition. These deficits were associated with an altered dopaminergic system.[75] Overall, these mouse lines, genetically selected for divergent HPA axis reactivity, accumulate several neurobiological alterations, whether the HPA axis is hyper- or hypo-functioning. The genes underlying the differences between the HR, IR, and LR lines remain to be identified, but these results clearly show that genetic variations in HPA axis reactivity may be part of individual differences in behavioral reactivity.

Genetic association studies in clinical practice

The HPA axis, because of its implications in stress-responsiveness, has been extensively studied in depression. At least four studies have reported evidence for associations between the risk for developing major depressive disorders and GR gene SNPs associated with reduced sensitivity to glucocorticoids (mainly ER22/23EK and *Bcl*I SNPs) (see Ref. 76 for review). Furthermore, ER22/23EK polymorphism is associated with a better cognitive function in depressed patients but also in elderly subjects.[77] Alleles associated with increased expression of FKBP5 that lead to GR resistance are overrepresented in individuals with major depression, as well as in bipolar disorder and posttraumatic stress disorder.[49] Molecular polymorphisms in the CRH receptor genes have also been associated with depression, suicidality, and the influence of child maltreatment or abuse to predict adult depression.[78,79]

The other major fields for implications of genes involved in HPA axis sensitivity and reactivity are metabolism and obesity. In overfeeding situation, BclI polymorphism of the GR

gene is associated with increase atherogenic profile, including increase body weight, blood pressure, and cholesterol level, as well as visceral fat.[80] An association exists between SNP in exon 9β and multiple blood pressure measures in European-Americans.[58] In a group of elderly subjects, van Rossum and collaborators[81] found that carriers of the ER22/23EK allele are relatively more resistant to the effects of glucocorticoids with respect to the sensitivity of the adrenal feedback mechanism than noncarriers, resulting in a better metabolic health profile. They also found that the *Bcl*I SNP is associated with body mass index in the elderly, with the G allele associated with hypersensitivity to glucocorticoids and loss of lean mass during aging.[8] More recently, this G allele in *Bcl*I polymorphism was suggested to increase vulnerability to fat deposition in youngsters in obesity-promoting environment.[82] A polymorphism in the MR gene was also associated with divergences in stress responsiveness, body composition, and adipocyte biology in young hypertensive subjects.[83] We studied CBG gene polymorphism in premenopausal obese women regarding fat mass distribution. We found that the correlation between salivary cortisol after dexamethasone suppression test and waist-to-hip ratio differs with a CBG gene polymorphism that might modulate the influence of the HPA axis on the fat mass distribution in this population.[84] Even if no link was noted between *Hsd11b1* genotype and susceptibility to obesity in two European populations, a weak association was measured with visceral fat deposition, particularly in women,[85] supporting expression studies in humans and molecular studies in rodents.[86] Small body size at birth and preterm birth are known to be associated with abdominal fat accumulation and insulin resistance. In a birth cohort study, a common GR haplotype was associated with lower birth weight and length. This haplotype modified the association of length at birth with adult glucose tolerance and HPA function phenotypes.[87] In a second birth cohort study that included 19-year-old survivors born prematurely, carriers of the 23K variant presented with better postnatal catch-up growth and lower insulin resistance than noncarriers, suggesting a protective effect of this polymorphism.[88]

Some inflammatory or autoimmune diseases have been investigated with regard to the involvement of HPA-related polymorphisms. Overall, no major impact has been described. In asthma, polymorphisms of the GR gene do not seem to be associated with the existence of the disease nor to the response to inhaled glucocorticoids.[89] Patients with multiple sclerosis and carrying the haplotype *TthIII*I, ER22/23EK, and 9β have a more aggressive disease course.[90] Polymorphisms of the gene STIP1 coding for a protein associated to the chaperone hsp70 in the GR complex is associated with improved lung function in asthmatic patients with inhaled corticosteroids treatment.[91] Another hsp polymorphism has been related to uveitis in sarcoidosis.[92] Polymorphisms of importin-13, a nuclear transport receptor mediating GR translocation to the nucleus, have been associated to variations of airway hyperresponsiveness.[93]

The influence of variations of HPA-related genes in tumors has also been investigated. The N363S polymorphism of the GR gene is overrepresented in patients with bilateral adrenal incidentalomas.[94] No clear increased risk has been described for malignant tumors. However, polymorphisms of the GR gene may affect the efficiency of the glucocorticoid treatment and the outcome of childhood acute lymphoblastic leukemia.[95]

Implications in farm animal breeding: production traits and robustness

Cortisol has mainly negative effects on production traits in livestock. In pigs, growth rate and feed efficiency decrease as the adrenal response to ACTH increase.[96] Residual feed intake, which is the difference between an animal's actual intake and its expected intake based on its live weight and growth rate over a specified period of time, is positively correlated with serum cortisol concentrations after injection of ACTH in rams.[97] In chickens, chronic administration of ACTH reduces weight gain and feed efficiency.[98] In line with the metabolic effect of cortisol that favors the accretion of lipids in fat at the expense of proteins from muscle and others tissues,[56] an increase of cortisol production, as measured by cortisol urinary levels, decreases carcass leanness.[99,100]

On the contrary, cortisol may have positive effects on robustness. Knap[101] defines robustness as "the ability to combine a high production potential with resilience to stressors, allowing for unproblematic expression of a high production potential in a wide variety of environmental conditions"

(p. 764). Robustness can then be considered as the capacity for an animal to cope with environmental challenges, while maintaining his production level. For example, Leenhouwers *et al.*[102] suggested that higher physiological maturity of piglets with high estimated breeding values for piglet survival is due to the higher average plasma cortisol concentration in these animals. Cortisol has also complex influences on the immune system and inflammatory processes.[103] Finally, Michel *et al.*[104] showed that the rats with the highest corticotrope response to heat exposure showed the best adaptive response, with a lower body temperature increase and hemoconcentration as well as reduced brain inflammation. These studies confirm that animals showing a strong response of the HPA axis to a stressful situation may adapt better. The relationship between HPA axis and robustness needs further investigation, especially in the actual context of global warming (heat stress) and with the reduction of human intervention during the different phases of breeding (newborn survival and resistance to parasitic infections).

During the last 30 years, fast growth and the reduction of carcass fat content were the main objectives of genetic selection in pigs. The consequences on stress-responsive systems were analyzed in a study comparing progeny from sires born either in 1977 (frozen semen) or in 1998.[105] We found a correlation between cortisol production and fatness within populations, and a significant reduction of cortisol production between 1977 and 1988. This indirect counter-selection of the HPA axis activity may be responsible for the negative trends observed on robustness traits, such as newborn survival. Therefore, the HPA axis appears to be a tradeoff factor between production and robustness traits. In order to optimize selection by improving farm animal robustness, it would be interesting to increase HPA axis activity without compromising productivity.[13] Marker-assisted selection—based on the knowledge of molecular mechanisms influencing HPA axis activity—will be the most efficient strategy as robustness is a global measure that includes many different traits that are difficult to measure routinely.

Conclusion

Many molecular polymorphisms have been described in the components of the HPA axis, with strong consequences on the functioning of the system and its numerous physiological targets, leading to large individual variation with wide physiopathological implications. Up to now, most studies have focused on single genes, and this quest is not yet exhaustive. However, the HPA axis is highly regulated so that each source of variation may influence other components of the axis. For instance, we showed in mice that a larger increase of plasma corticosterone to stress may reflect a reduced efficiency of the hormone transduction mechanisms rather than a strong response of the axis as a whole,[12] so that individual differences in single traits must be interpreted with much care. Furthermore, several sources of genetic variability are usually found in the same model,[61] but very little is known about the interactions among the different sources of variation within the axis and how they eventually compensate for or potentate each other. A more global systems genetics approach is needed for a better understanding of the system as a whole to integrate its physiopathological consequences.

Conflicts of interest

The authors declare no conflicts of interest.

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