Pflugers Arch - Eur J Physiol (2013) 465:585–594
DOI 10.1007/s00424-013-1248-6

INVITED REVIEW

Sex-dependent pathophysiology as predictors of comorbidity of major depressive disorder and cardiovascular disease

S. A. Tobet · R. J. Handa · J. M. Goldstein

Received: 31 January 2013 / Revised: 6 February 2013 / Accepted: 7 February 2013 / Published online: 16 March 2013

Abstract There is a strong and growing literature showing that key aspects of brain development may be critical antecedents of adult physiology and behavior or may lead to physiological and psychiatric disorders in adulthood. Many are significantly influenced by sex-dependent factors. Neurons of the paraventricular nucleus (PVN) of the hypothalamus occupy a key position in regulating homeostatic, neuroendocrine, and behavioral functions. This brain area is a critical link for our understanding of the etiology of a number of disorders with components ranging from mood to feeding and energy balance and to autonomic nervous system regulation. Thus, based on common brain circuitry, the PVN may be a critical anatomical intersection for understanding comorbidities among depression, obesity, and cardiovascular risk. Historically, the majority of approaches to brain development examine neuronal, glial, and vascular factors independently, with notably less emphasis on vascular contributions. The realization that the PVN undergoes a unique vascular developmental process places added value on discerning the cellular and molecular mechanisms that drive its late-onset angiogenesis and further implications for neuronal differentiation and function. This has ramifications in humans for understanding chronic, and sometimes fatal, comorbidities that share sex-dependent biological bases in development through functional and anatomical intersections with the hypothalamus.

Keywords Depression · Cardiovascular disease · Sex differences · Hypothalamus · Prenatal stress · Comorbidity

Introduction

The comorbidity of major depressive disorder (MDD) and risk for cardiovascular disease (CVD) have a prevalence of approximately 20 % [5, 25, 48, 76] and are expected be the leading cause of disability worldwide by 2020 [68, 90]. Although CVD is generally considered a "man's disease," since the overall rate is higher in men [59], in fact, CVD is the number 1 cause of death in women in the USA, and the comorbidity of MDD and CVD is twice the rate in women than men [27, 67]. MDD has a significantly higher prevalence

S. A. Tobet
Department of Biomedical Sciences and School of Biomedical Engineering, Colorado State University, 1617 Campus Delivery, Fort Collins, CO 80523, USA
e-mail: Stuart.Tobet@colostate.edu

R. J. Handa
Department of Basic Medical Sciences, University of Arizona College of Medicine, 425 North 5th Street, Phoenix, AZ 85004, USA

J. M. Goldstein
Department of Psychiatry, Harvard Medical School, Boston, MA, USA

J. M. Goldstein
Department of Medicine, Harvard Medical School, Boston, MA, USA

J. M. Goldstein
Connors Center for Women's Health and Gender Biology, Brigham and Women's Hospital (BWH), One Brigham Circle, 1620 Tremont Street BC-3-34, 3rd Floor, Boston, MA 02120, USA

J. M. Goldstein (✉)
Department of Psychiatry, Brigham and Women's Hospital (BWH), One Brigham Circle, 1620 Tremont Street BC-3-34, 3rd Floor, Boston, MA 02120, USA
e-mail: jill_goldstein@hms.harvard.edu

J. M. Goldstein
Department of Medicine, Brigham and Women's Hospital (BWH), One Brigham Circle, 1620 Tremont Street BC-3-34, 3rd Floor, Boston, MA 02120, USA

in women (twofold) than men [51, 52] and MDD is an independent risk factor for the development and progression of coronary artery disease [5, 25, 50, 69]. Numerous prospective studies indicate significantly elevated risks of coronary heart disease, myocardial infarction, or cardiac death among participants with depression [74, 75, 91]. Depression predicts first cardiovascular events even among otherwise healthy people, particularly in women [91], with a risk of 1.5-fold to 6-fold.

Obesity is associated with MDD and CVD, although the direction of effects is controversial. Elevated body mass index (BMI) is significantly associated with anhedonia and depression, particularly in women, even when controlling for other demographic variables [6, 13, 36]. Individuals with MDD typically have a higher BMI prior to the onset of depressive symptoms and a history of weight fluctuation, with some evidence that these individuals, particularly women, demonstrate increased appetite, overeating, and craving of carbohydrates, particularly in response to stress [7, 79, 82].

Although population-level studies have demonstrated substantial sex differences in comorbidities with major public health implications worldwide, the pathways to explaining comorbidity is unclear. In part, this may be due to a lack of investigative focus in general on explaining sex differences in diseases. However, it also may be due to the fact that many investigators studying the heart and associated vascular system and/or adiposity rarely think about the brain and neuroscience perspectives and vice versa. Moreover, studies focused on CVD and MDD generally begin in adulthood.

This review argues the position that sex differences in MDD–CVD comorbidity (and associated metabolic syndrome disorders arising from conditions such as obesity) originate in part from pathogenic processes initiated in fetal development that involve shared pathophysiology between the brain, the vascular system, and the central nervous system control of the heart, food intake, and energy balance. Fetal origins of MDD, CVD, and obesity independently implicate "prenatal stress models" of hypothalamic–pituitary–adrenal (HPA) axis circuitry disruption. At the population-level, there is higher risk in women regarding shared fetal antecedents to comorbidity of MDD and poor autonomic nervous system (ANS) deficits (a significant CVD risk factor) [27], which implicates prenatal inflammatory and adrenal hormonal abnormalities. At the in vivo brain imaging level, fetal disruptions of HPA circuitry development are significantly associated with sex differences in adult brain activity deficits and hormonal dysregulation in MDD alone [28] that, in pilot work, were significantly associated with ANS dysregulation [41]. Previous work on the fetal programming of CVD risk alone, although not focused on sex differences, suggested that adverse fetal exposures cause HPA abnormalities and elevated blood pressure and blood glucose levels, implicating glucocorticoid receptors [77, 94]. Much of the work in model animals, including our own [12, 23, 65, 101], demonstrated possible pathways in MDD involved in the disruption of maternal gestational glucocorticoids on nerve and angiogenic growth factors [brain derived nerve growth factor (BDNF/trkB), vascular endothelial and insulin growth factors (VEGF and IGF-1)], gonadal hormones, and gamma aminobutyric acid (GABA) and on neuronal and vascular development of HPA axis regions, such as the hypothalamic paraventricular nucleus (PVN). The PVN, which is one of the most highly vascularized regions in the brain [1], is important for regulating many homeostatic, neuroendocrine, and behavioral functions and has been associated with the etiology of affective disorders, such as MDD. Furthermore, the PVN is an essential component of brain circuitries important for feeding and energy balance and serves to regulate the ANS which is critical for appropriate cardiovascular responses. Thus, the PVN may lie at a critical crossroad for understanding comorbidities among depression, CVD, and related metabolic syndromes associated with obesity.

The neurobiological model proposed here (Fig. 1) to explain sex differences in MDD–CVD comorbidity is that excess maternal gestational glucocorticoids (an indicator of "prenatal stress") disrupt GABA signaling in conjunction with growth factors (VEGF, IGF-1, and BDNF) and gonadal hormones, leading to sex-specific alterations in neuronal and vascular development in HPA axis brain regions (such as the PVN) that are sexually dimorphic and implicated in MDD and CVD risk through the ANS and the vasculature. Given the substantial comorbidity worldwide, a common fetal cause will have important implications for the prevention or attenuation of disability in many countries, particularly in women.

The problem of comorbidity

It is common to consider various diseases or disorders from unitary perspectives, i.e., so-called silo'ed investigative approaches within specific fields of medicine. The missions of the National Institutes of Health are predicated on the unitary approach to the study of a number of disorders. For example, the National Institute of Mental Health (NIMH) focuses on depressive disorders, while the National Institute of Diabetes and Digestive and Kidney Diseases focuses on obesity and diabetes and the National Institute of Heart, Lung, and Blood focuses on CVDs. It is likely that there are instances where these various disorders occur due to independent etiologies. However, the central theme of this review is that the greater risk, and perhaps more prevalent problem and greater expense to the healthcare system, lies in the comorbidity of one or more disorders that are found together in symptom clusters. This view of shared

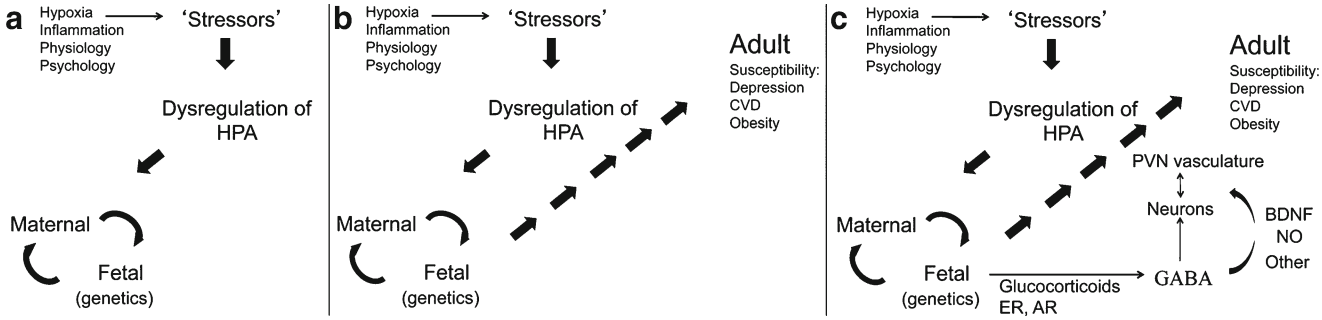

Fig. 1 Prenatal stress model of sex-dependent risk for comorbidity. This figure shows schematically the progressive influence of external stressors to the mother on her HPA axis function (**a**), in addition to maternal–fetal interactions to influence adult susceptibility to disorder (**b**). Mechanisms that may play roles in the fetal compartment include steroid hormone receptors that could impact sex differences (estrogen and androgen receptors (*ER* and *AR*) and glucocorticoids (and their receptors)). These transcription factors may impact the function of neurotransmitters (e.g., GABA), neuromodulators (nitric oxide [*NO*]), or growth factors (e.g., BDNF, VEGF, IGF) on neuronal, glial, or vascular compartments in the PVN (**c**)

pathophysiology has been espoused by NIMH [44], although this view is restricted to disorders of the brain and not the comorbidities of brain disorders with general medical disorders. This review addresses the comorbidity of MDD and CVD and associated syndromes with emphasis on sex differences in the risk of each, underscoring the fact that the comorbidity of these disorders occurs more commonly in women.

In considering developmental origins of disorders that cluster together, there are at least two major etiological pathways to consider. One way is to postulate a general linear model in which one disorder helps trigger another one, resulting in several disorders in the same individual (see Fig. 2a). For example, depression might arise—cause unknown, leading to overeating and obesity as downstream consequences. Obesity might then cause a cascade of medical problems leading to CVD. In a similar way, the sequence might start with obesity leading to depression, which may in turn lead to cardiovascular risk. Just as likely is that a cardiovascular problem that would lead to depression and then subsequent obesity. An alternative possibility to a linear model is a nonlinear model which is at the heart of this review. The perspective of this review is that all of these disorders have a shared biological substrate that provides a basis for an increased likelihood of several disorders arising in the same individual (see Fig. 2b). Shared biological substrates could be envisioned on at least three levels: anatomical, molecular/biochemical, and genetic.

Anatomy as a shared biological substrate for causation

If one were to go through a list of brain structures or regions to identify those that are linked to a constellation of disorders that included depression, obesity, and cardiovascular risk, it is likely that the hypothalamus would be one of the key identified regions. It is also likely that the list would include the amygdala and/or the hippocampus. These are not disconnected regions, but rather players in a key brain circuit described many years ago by Papez [71]. However, only recently has this circuit become accessible to analysis by human in vivo magnetic resonance imaging (MRI) techniques that have demonstrated its importance in a number of disorders of the brain [31, 32, 40, 42, 62].

Of particular interest for this review, one location within the hypothalamus is notable for its role in signaling from the brain directly to the periphery. This locus, the PVN, contains neurons that control behavior, neuroendocrine, and autonomic function. Specifically, neurons in regions of the PVN direct the HPA axis that controls much of what is considered the stress response. Other neurons in the PVN are considered preautonomic and project to brainstem and spinal cord areas that control the ANS. Still other PVN neurons project to sites that can control behaviors, such as feeding. These features are discussed further below.

The PVN lies at the dorsal limit of the classical hypothalamus flanking the top of the third ventricle. It has been implicated in a broad array of homeostatic and behavioral functions ranging from neuroendocrine and cardiovascular functions to affective, ingestive, and defensive behaviors (reviewed in [38, 85]). Depending upon the species, functional groups of PVN neurons can be defined based on cellular characteristics, position, or chemical phenotype. Each of these subdivisions has been associated with specific functions (e.g., [10]). While there is some controversy regarding the degree to which the PVN may be subdivided in humans, it seems likely that subdivisions exist based on several criteria [53, 62]. This is consistent with findings of subgroup-selective cell loss in particular human disorders (e.g., [4, 9]).

Neurons of the PVN express a number of receptors for steroid hormones and from this arises the potential for sex differences in PVN function that could be driven by circulating sex steroid hormones. Moreover, steroid hormone

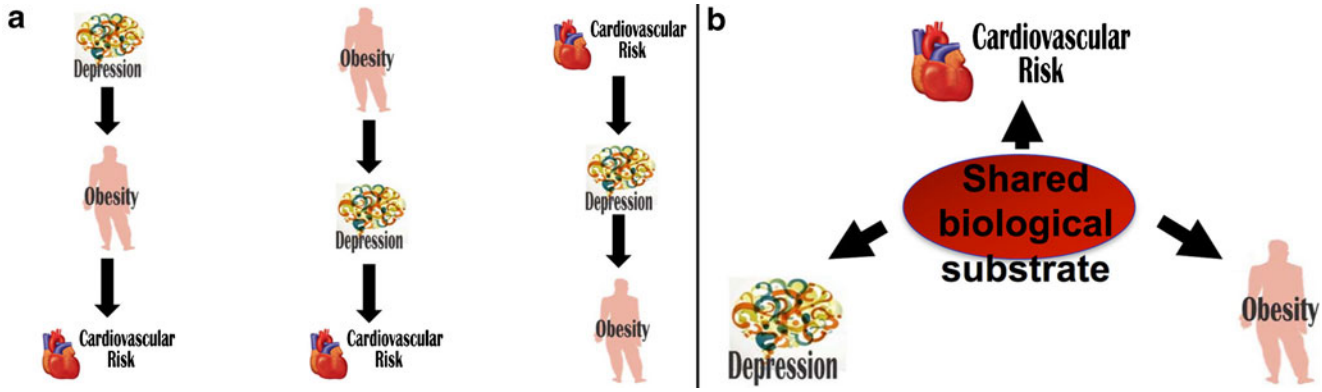

Fig. 2 Sequential (**a**) versus shared (**b**) biological pathways to comorbidity. **a** Sequential pathways to comorbidity in which one disorder may lead to others. The disorders are such that any one of them may be able to trigger steps towards the others. **b** Shared biological pathway to comorbidity in which an underlying biological problem can contribute to the onset of each of the disorders at the same time

receptors are among the markers that indicate different zones within the PVN.

For example, cell groups reportedly contain immunoreactive estrogen receptors-α (ir-ERα), ERβ, androgen receptors, or glucocorticoid receptors (e.g., [80, 83, 84]). Immunoreactive neurotransmitters (e.g., corticotropin-releasing hormone (CRH), arginine vasopressin (AVP), oxytocin (OXY) [2, 85]) and other proteins, including calbindin and nNOS [65], also characterize specific regions of the nucleus (see Fig. 3). To the extent that the neurons expressing these molecules are stereotypic for particular zones in the developing PVN and controlled by key developmental factors, they may be useful biomarkers for future analyses of pathology as well as normal function.

Defects in the healthy development of the PVN provide an anatomical basis to predict shared comorbidity for disorders related to the functions of neurons normally located in or around the PVN. A number of mechanisms may lead to potential long-term alterations in PVN function that may or may not also be sex-dependent. These include changes in gene expression, cell death, connectivity, neuronal phenotypes or positions thereof, or relationships to unique vasculature. Further, environmental stimuli in development (e.g., obstetric complications or chronic social/psychological stress) may cause changes in gene expression within neurons of the PVN, in response to a common circulating factor (such as glucocorticoids), and perhaps as a function of epigenetic marks that are placed on DNA in response to such stimuli [11, 12]. For example, we and others demonstrated that perinatal exposure of rats to the synthetic glucocorticoid, dexamethasone, change the methylation state of the BDNF gene [11, 43] and/or the levels of prepro-thyrotropin-releasing hormone (TRH) [12]. In a similar fashion, levels of maternal behavior can alter the adult expression of glucocorticoid receptor [93] and ER [16]. In many cases, such influences may be sex-dependent with responses more prevalent in females.

Disruptive events in development can also lead to apoptotic (or possibly necrotic) cell death within specific subdivisions of the PVN or the neighboring region [101]. Changes in the incidence of cell death, whether increases or decreases, can have long-lasting effects on neural circuitry. For example, it has been demonstrated that prenatal exposure of rats to stress caused an increase in cell death in the fetal PVN [89], with greater levels in the female. Correspondingly, fetal exposure to dexamethasone caused increases in apoptotic cell numbers in areas that project to the PVN, such as CA1, CA3, and peri-PVN [101]. There are many connections into the PVN and the surrounding region, and increased or decreased stimulation along any of these pathways, either during development or relative to later plasticity, may cause long-term changes in PVN function. This can be due to changes in inputs from intrahypothalamic or extrahypothalamic areas or changes in synaptogenesis in the PVN itself. For example, chronic variable stress may impact synapse formation in the PVN [22, 37] that might also be reflected as sex differences in synaptophysin-containing terminals [14].

Neurogenesis and neuron migration are classic mechanisms for neural development in general. Specific stimuli may cause changes in the location of neuron phenotypes within the PVN because of altered birth or migration [65]. For example, we demonstrated that loss of $GABA_B$ receptor function by either genetic or pharmacological means (during fetal development) resulted in cells that express ERα being located more laterally in the PVN in females only. Such a change (like for phenotype or apoptosis) might be useful in predicting alterations in PVN-mediated functions that underlie the development of a sex-related disorder. Interestingly, the loss of $GABA_B$ receptor functioning also disrupted the positions of cells containing ir-ERα in and around the ventromedial nucleus [64], but not in a sex-dependent manner. These findings suggest the importance of developmental timing and region-specificity for the identification of sex-specific outcomes.

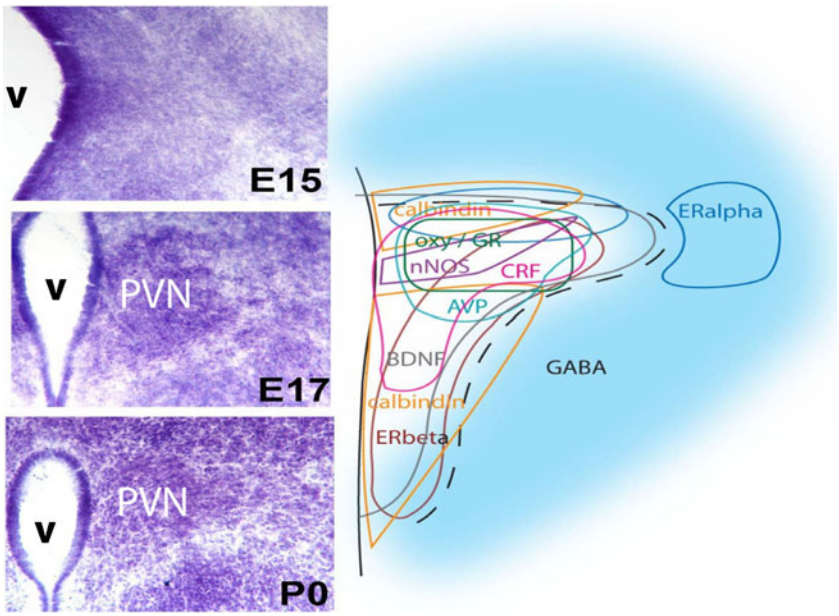

Fig. 3 Molecular complexity of PVN neurons. Developmental sequence for Nissl (thionin stain) architecture of the PVN of the hypothalamus in mice (*left*) is contrasted with the complex molecular heterogeneity of PVN neurons across the nucleus (*right*). The molecular phenotypes of many PVN neurons are already in place by embryonic day 15 (*E15*), even though the nucleus is not yet viewable based on cell density (*left*). The PVN emerges from the background of cells along the third ventricle (*v*) as a cell-poor zone opens up around the nascent nucleus between *E15* and *E17*. By birth at postnatal day 0 (*P0*), the medial to lateral extent of the PVN on one side is about 400 μm

The vast majority of approaches to brain development examine neuronal, glial, and vascular factors independently, with notably less emphasis on vasculogenesis. Surprisingly, the extensive vascularity of the PVN [1, 92] occurs late in hypothalamic development. Thus, changes in vascular density or function within the PVN [23] provide another anatomical substrate to help explain shared comorbidities. The healthy development of brain vasculature proceeds through the invasion of vascular sprouts from the pial vessels towards the central ventricles. Subsequently, finer branches form via secondary angiogenic processes. Hypoxia is considered a major driving force in promoting the formation of new vessels. However, for PVN development, the region is fully vascularized at birth similar to the rest of the forebrain. By the second postnatal week, a striking increase in vascularization is readily discernible [23, 66]. Whatever drives the increased vascularity does so over a period of time when the PVN receives similar blood flow as the rest of the hypothalamus and presumably sufficient oxygen. Thus, postnatal angiogenesis in the PVN (which is associated with later prenatal human development) may be driven by neural signals as suggested by the term "angioneurins" [99], but intrinsic to the unique environment and components of the PVN. Our preliminary studies in mice (Frahm et al., unpublished observations) suggest that the mRNAs of known angiogenic factors or receptors, such as VEGF, BDNF, and the BDNF receptor TrkB, have a postnatal developmental time course in the neonatal PVN in rodents (and prenatal in humans), consistent with a role in driving angiogenesis. Important for the PVN is the fact that neural activity may impact the development of the vasculature, since $GABA_B$ receptor signaling caused a 20 % decrease in vascular characteristics of length or branch points [23].

Studies of the neurovascular unit suggest that the blood–brain barrier (BBB) may be a variable that may be particularly important in highly vascularized regions like the PVN. Given the several-fold greater density of blood vessels in the PVN, any disruption of BBB function will make the PVN appear selectively vulnerable compared to many other brain regions. In development, there is debate as to when the BBB "closes" or begins to regulate the flow of macromolecules into and out of the brain parenchyma. In general, significantly more information is needed on the maturation and regulation of BBB function in all brain areas, including the PVN. Studies are just beginning to illuminate regulators of BBB development in the region of the PVN. Our results suggest that perinatal GABAergic [23] or glucocorticoid (Frahm and Tobet, unpublished results) treatments may influence BBB development. Evidence currently exists for both sex-dependent glucocorticoid [73] and reproductive hormone [96] influences on some aspects of BBB function, such as permeability and expression of molecular pumps.

Molecular players as shared biological substrate for causation

Hypothalamic–pituitary–adrenal axis

The HPA axis is likely best known for its role in controlling neuroendocrine stress responses [45]. Simply put, it consists of a series of feedback loops that can be studied from an anatomical and clinical basis as well as for its molecular signaling properties. Brain regions implicated in modulating stress response circuitry provide inputs to the PVN, the neuroendocrine motor pathway for the HPA axis. The brain regions that contribute to the higher-order control of HPA axis function include subregions of the amygdala, hippocampus, periaqueductal gray, medial and orbital prefrontal cortices, and anterior cingulate cortex. In brief, the regulation of the HPA axis response to a number of different stressful stimuli is gated through these various brain regions, which we demonstrated in vivo in humans using functional MRI [29, 30]. Ultimately, CRH is secreted from parvocellular PVN neurons into the hypothalamic–hypophyseal portal capillaries of the median eminence and travel to the pituitary to regulate the secretion of adrenocorticotropic hormone (ACTH) from pituitary corticotrophs. Although CRH has been considered the principal secretagogue driving anterior pituitary ACTH secretion, studies have shown that AVP can be co-released from neuroendocrine parvocellular CRH neurons to amplify the actions of CRH on pituitary release of ACTH [95]. Once secreted into the general circulation, ACTH drives the adrenal cortex to secrete the principal glucocorticoid hormone, cortisol in humans, and corticosterone in rodents and many other vertebrates.

By causing a rapid rise in plasma glucocorticoid concentrations, stress has long been considered to play a major role in causing adrenal hypertrophy, energy mobilization, alterations in the immune system, and gastrointestinal problems [78, 86]. In concert, rapid activation of preautonomic neurons in the PVN drives chromaffin cells in the adrenal medulla to rapidly release the catecholamines, epinephrine and norepinephrine, into the general circulation. These factors are also involved in the characteristic fight or flight response to stress and rapidly impact heart rate, blood pressure, and smooth muscle functions throughout the body [41]. Further, glucocorticoid release also drives adrenal medullary synthesis of the phenylethanolamine *N*-methyltransferase, which is the key enzyme responsible for transforming norepinephrine to epinephrine. The combination of glucocorticoids and epinephrine secreted in the bloodstream generate diverse responses throughout the body.

In addition to the negative feedback responses at pituitary and brain levels, glucocorticoids have many other roles in the brain [39, 57]. Glucocorticoid actions in the brain may be impacted by sex and/or interactions with hormones of the hypothalamic–pituitary–gonadal axis [11, 21, 81]. In fact, at the human in vivo brain imaging level, gonadal hormones regulate stress response circuitry, including anterior hypothalamic regions, in healthy individuals that contribute to explaining sex differences in the brain's response to stress [29, 30] and were disrupted in depression in tandem with gonadal hormone deficits [42] and ANS dysregulation [41]. Taken together, animal and human studies of the stress response circuitry suggest that many of the influences of glucocorticoids on the brain are based on changes in "chemical anatomy" that are relevant for considering potential comorbidities.

It is at the level of molecular players that the idea of shared biological substrates becomes an amplified concept. For example, one of the first thoughts about what prenatal stress can do is to provoke a chemical response as outlined previously. These chemical responses can have wide-ranging impact in the fetal compartment (see Fig. 4). In that compartment, there are strong opportunities for interactions among molecular signaling pathways in different locations. In addition to CRH, central to stress aspects of the HPA axis, there are a number of other peptides found in the PVN that have been associated with either specific or multiple human disorders and have the potential to act as the biological bases of comorbidity. For example, vasopressin and OXY have been implicated in anxiety and depression [70], cardiovascular risk [33, 98], and metabolic issues related to obesity [20, 87, 97] and eating disorders [56]. Alterations in TRH have been linked to depression [100] and CVD [54], in addition to metabolic problems [72]. In support of these findings in humans, our recent animal studies show that prenatal dexamethasone exposure can alter homologous TRH neurons in the PVN of adult rats [12].

Genetics as a shared biological substrate for causation

As a shared biological substrate for causation, genetics can be considered a special molecular/biochemical case. The search for genetic associations has typically been for specific disorders, although some have begun to investigate shared genetic pathways related to comorbidities [63]. One way to consider genetic predisposition is to consider mutations that either prevent the synthesis of a functional protein or more often provide for the synthesis of a protein with suboptimal function. For example, Val66Met is an amino acid substitution in BDNF that compromises, but does not eliminate, BDNF signaling [17]. This amino acid substitution has been linked to CRH homeostatis [46] and to multiple psychiatric disorders [47]. However, a recent meta-analysis suggests that, by examining the literature as a whole, the linkage of BDNF variants alone to MDD may be less promising than previously thought [34] and may need to be thought of in the context of epigenetic effects of environmental exposures on the regulation of BDNF, as

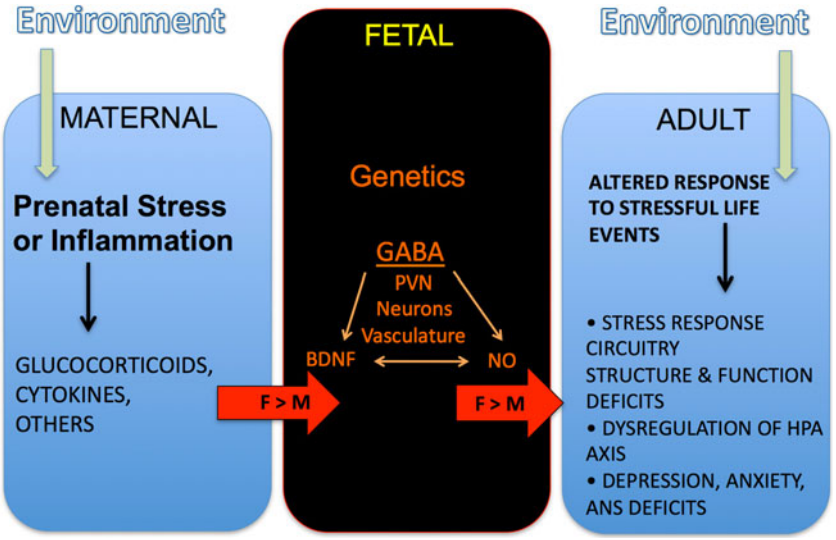

Fig. 4 Impact of maternal conditions on sex-dependent brain development and outcomes. This schematic illustrates the tripartite nature of maternal impact on fetal development resulting in an adult offspring that responds differentially to specific stimuli. Sex differences arise at multiple points in the process

with studies of gene–environment interactions in MDD with the serotonin receptor transporter or other genes and early childhood adversity [15, 49].

Combining biological substrates for causation

The simplest combination of causes for comorbidity might predict a location in the brain that participates in the regulation of several components of multiple disorders and/or has some unique molecular/biochemical properties that were partially accounted for by the expression of specific genes of interest. There is a long history of research on the interaction of HPA axis dysregulation and disorders from the perspective of fetal antecedents to these disorders that includes MDD, CVD, and obesity [3, 26, 28, 35]. During brain development, glucocorticoids may influence GABAergic mechanisms, as has been shown in adulthood [61, 88]. There is a significant link between GABA and morphogenetic roles in brain development. Several neurotransmitter systems have been suggested as neurotrophic factors or morphogens in various brain regions [8, 55] including GABA, serotonin, dopamine, and endogenous opiates. Important for the current discussion, defects in GABA signaling have been found in animal models of depression [18, 19, 60] in addition to humans with MDD [24] and CVD [58]. Moreover, as we have demonstrated, the distribution of GABAergic elements may be essential for the final cytoarchitectural arrangement of cellular elements in the region of the PVN [65]. Viewed sequentially (as in Fig. 1), exposure to stressors of any type during development may cause activation of the HPA axis (Figs. 1a and 4). This will lead to a number of humoral signals exchanged between the maternal and fetal compartments that ultimately result in changes in brain structure and function leading to adult susceptibility to disorders. These include depression, cardiovascular risk, or metabolic imbalances leading to obesity (Figs. 1b and 4). Potential mechanisms of action operating in the fetal compartment include the interactions of steroid hormone receptors regulating responses to neurotransmitters (e.g., GABA) or growth factors (e.g., BDNF, VEGF, IGF) in the context of neurons, glia, or vasculature in the PVN (Figs. 1c and 4).

Currently, there is reasonable evidence to implicate several key factors in the etiology of comorbid disorders. From the anatomical perspective, the PVN occupies a notable location that mediates functions at the heart of a number of disorders. It is the site in the brain where neurons involved in controlling HPA function lose negative feedback control in MDD. It may be interesting to note that other areas of focus for comorbidities include the hippocampus, amygdala, and portions of the cerebral cortex that also signal transsynaptically to regulate PVN activity, as demonstrated in our studies activating this circuitry in vivo [29, 30, 42]. From the molecular perspective, brain GABA and stress-related release of glucocorticoids have notable ties to fetal antecedent actions with long-term consequences for neuronal circuitry and function. From the genetic perspective, it is difficult to find strong gene linkages to particular disorders. However, there have been several studies to connect alterations in GABA signaling genes, glucocorticoid signaling related genes, and the BDNF gene to increased likelihood of several disorders. There is currently much less evidence relating changes in angiogenic genes to multiple disorders, but the number of studies is growing as investigators learn to specifically focus on such markers. Viewing the evidence through a prism that highlights sex differences will likely help clarify results that may be conflicting or insufficiently powerful because genetic sex or differences in sex steroid hormones were not considered in the model.

Acknowledgments The ideas in this review emanated from research on a translational (human to animal) program project that was supported by the Office for Research on Women's Health (ORWH) and National Institute of Mental Health (ORWH-NIMH P50 MH082679; principal investigators: Goldstein, Tobet, and Handa; http://mddscor.bwh.harvard.edu). Additionally, it was in part supported by NIMH-NHLBI R01 MH074679 (principal investigator: Goldstein). We are very grateful for the funding support and to our incredible research teams at Brigham and Women's Hospital (Clinical Neuroscience Laboratory for Sex Differences in the Brain (http://cnl-sd.bwh.harvard.edu), Colorado State University, and University of Arizona College of Medicine.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ambach G, Palkovits M (1974) Blood supply of the rat hypothalamus. II. Nucleus paraventricularis. Acta Morphol Acad Sci Hung 22:311–320
2. Armstrong WE, Warach S, Hatton GI, McNeill TH (1980) Subnuclei in the rat hypothalamic paraventricular nucleus: a cytoarchitectural, horseradish peroxidase and immunocytochemical analysis. Neuroscience 5(11):1931–1958
3. Asztalos E (2012) Antenatal corticosteroids: a risk factor for the development of chronic disease. J Nutr Metab 2012:930591. doi:10.1155/2012/930591
4. Bao AM, Hestiantoro A, Van Someren EJ, Swaab DF, Zhou JN (2005) Colocalization of corticotropin-releasing hormone and oestrogen receptor-alpha in the paraventricular nucleus of the hypothalamus in mood disorders. Brain 128:1301–1313
5. Barefoot JC, Helms MJ, Mark DB, Blumenthal JA, Califf RM, Haney TL, O'Connor CM, Siegler IC, Williams RB (1996) Depression and long-term mortality risk in patients with coronary artery disease. Am J Cardiol 78:613–617
6. Barry D, Pietrzak RH, Petry NM (2008) Gender differences in associations between body mass index and DSM-IV mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Ann Epidemiol 18:458–466
7. Beauregard M, Leroux JM, Bergman S, Arzoumanian Y, Beaudoin G, Bourgouin P, Stip E (1998) The functional neuroanatomy of major depression: an fMRI study using an emotional activation paradigm. Neuroreport 9:3253–3258
8. Behar TN, Li YX, Tran HT, Ma W, Dunlap V, Scott C, Barker JL (1996) GABA stimulates chemotaxis and chemokinesis of embryonic cortical neurons via calcium-dependent mechanisms. J Neurosci 16:1808–1818
9. Bernstein HG, Stanarius A, Baumann B, Henning H, Krell D, Danos P, Falkai P, Bogerts B (1998) Nitric oxide synthase-containing neurons in the human hypothalamus: reduced number of immunoreactive cells in the paraventricular nucleus of depressive patients and schizophrenics. Neuroscience 83:867–875
10. Biag J, Huang Y, Gou L, Hintiryan H, Askarinam A, Hahn JD, Toga AW, Dong HW (2012) Cyto- and chemoarchitecture of the hypothalamic paraventricular nucleus in the C57BL/6J male mouse: a study of immunostaining and multiple fluorescent tract tracing. J Comp Neurol 520:6–33. doi:10.1002/cne.22698
11. Carbone DL, Handa RJ (2012) Sex and stress hormone influences on the expression and activity of brain-derived neurotrophic factor. Neuroscience. doi:10.1016/j.neuroscience.2012.10.073
12. Carbone DL, Zuloaga DG, Lacagnina AF, McGivern RF, Handa RJ (2012) Exposure to dexamethasone during late gestation causes female-specific decreases in core body temperature and prepro-thyrotropin-releasing hormone expression in the paraventricular nucleus of the hypothalamus in rats. Physiol Behav 108:6–12. doi:10.1016/j.physbeh.2012.07.010
13. Carpenter KM, Hasin DS, Allison DB, Faith MS (2000) Relationships between obesity and DSM-IV major depressive disorder, suicide ideation, and suicide attempts: results from a general population study. Am J Public Health 90:251–257
14. Carvalho-Netto EF, Myers B, Jones K, Solomon MB, Herman JP (2011) Sex differences in synaptic plasticity in stress-responsive brain regions following chronic variable stress. Physiol Behav 104:242–247. doi:10.1016/j.physbeh.2011.01.024
15. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301(5631):386–389
16. Champagne FA, Weaver IC, Diorio J, Dymov S, Szyf M, Meaney MJ (2006) Maternal care associated with methylation of the estrogen receptor-alpha1b promoter and estrogen receptor-alpha expression in the medial preoptic area of female offspring. Endocrinology 147(6):2909–2915
17. Chen ZY, Bath K, McEwen B, Hempstead B, Lee F (2008) Impact of genetic variant BDNF (Val66Met) on brain structure and function. Novartis Found Symp 289:180–188, discussion 188–195
18. Cryan JF, Holmes A (2005) The ascent of mouse: advances in modeling human depression and anxiety. Nat Rev Drug Discov 4:775–790
19. Cryan JF, Slattery DA (2010) $GABA_B$ receptors and depression. Current status. Adv Pharmacol 58:427–451
20. Enhörning S, Bankir L, Bouby N, Struck J, Hedblad B, Persson M, Morgenthaler NG, Nilsson PM, Melander O (2012) Copeptin, a marker of vasopressin, in abdominal obesity, diabetes and microalbuminuria: the prospective Malmö Diet and Cancer Study cardiovascular cohort. Int J Obes (Lond). doi:10.1038/ijo.2012.88
21. Fernández-Guasti A, Fiedler JL, Herrera L, Handa RJ (2012) Sex, stress, and mood disorders: at the intersection of adrenal and gonadal hormones. Horm Metab Res 44:607–618. doi:10.1055/s-0032-1312592
22. Flak JN, Solomon MB, Jankord R, Krause EG, Herman JP (2012) Identification of chronic stress-activated regions reveals a potential recruited circuit in rat brain. Eur J Neurosci 36:2547–2555. doi:10.1111/j.1460-9568.2012.08161.x
23. Frahm KA, Schow MJ, Tobet SA (2012) The vasculature within the paraventricular nucleus of the hypothalamus in mice varies as a function of development, subnuclear location, and GABA signaling. Horm Metab Res 44:619–624. doi:10.1055/s-0032-1304624
24. Gao SF, Bao AM (2011) Corticotropin-releasing hormone, glutamate, and γ-aminobutyric acid in depression. Neuroscientist 17:124–144
25. Glassman AH, Shapiro PA (1998) Depression and the course of coronary artery disease. Am J Psychiatry 155:4–11
26. Goldstein JM (2006) Sex, hormones, and affective arousal dysfunction in schizophrenia. Horm Behav 50:612–622
27. Goldstein JM, Cherkerzian S, Buka S, Fitzmaurice G, Susser E, Hornig M, Gillman M, Factor-Litvak P, Sloan RP (2011) Sex-specific impact of maternal–fetal risk factors on depression and cardiovascular risk 40 years later. J Develop Origins Health Dis 2:353–364
28. Goldstein JM (2011b) Fetal programming of sex differences in stress response circuitry, endocrine and ANS deficits in adulthood: implications for understanding sex differences in comorbidity of depression and CVD risk. Presentation, 50th Annual Meeting, "Hot Topics" for American College of Neuropsychopharmacology (ACNP), Hawaii
29. Goldstein JM, Jerram M, Abbs B, Whitfield-Gabrieli S, Makris N (2010) Sex differences in stress response circuitry activation dependent on female hormonal cycle. J Neurosci 30:431–438

30. Goldstein JM, Jerram M, Poldrack R, Kennedy DN, Seidman LJ, Makris N (2005) Hormonal cycle modulates arousal circuitry in women using fMRI. J Neurosci 25:9309–9316
31. Goldstein JM, Seidman LJ, Makris N, Ahern T, O'Brien LM, Caviness VS, Kennedy DN, Faraone SV, Tsuang MT (2007) Hypothalamic abnormalities in schizophrenia: sex effects and genetic vulnerability. Biol Psychiatry 61:935–945
32. Granziera C, Hadjikhani N, Arzy S, Seeck M, Meuli R, Krueger G (2011) In vivo magnetic resonance imaging of the structural core of the Papez circuit in humans. Neuroreport 22:227–231. doi:10.1097/WNR.0b013e328344f75f
33. Gutkowska J, Jankowski M (2012) Oxytocin revisited: its role in cardiovascular regulation. J Neuroendocrinol 24:599–608. doi:10.1111/j.1365-2826.2011.02235.x
34. Gyekis JP, Yu W, Dong S, Wang H, Qian J, Kota P, Yang J (2013) No association of genetic variants in BDNF with major depression: a meta- and gene-based analysis. Am J Med Genet B Neuropsychiatr Genet 162:61–70. doi:10.1002/ajmg.b.32122
35. Harris A, Seckl J (2011) Glucocorticoids, prenatal stress and the programming of disease. Horm Behav 59:279–289. doi:10.1016/j.yhbeh.2010.06.007
36. Heo M, Pietrobelli A, Fontaine KR, Sirey JA, Faith MS (2006) Depressive mood and obesity in US adults: comparison and moderation by sex, age, and race. Int J Obes 30:513–519
37. Herman JP, Flak J, Jankord R (2008) Chronic stress plasticity in the hypothalamic paraventricular nucleus. Prog Brain Res 170:353–364. doi:10.1016/S0079-6123(08)00429-9
38. Herman JP, Ostrander MM, Mueller NK, Figueiredo H (2005) Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog Neuropsychopharmacol Biol Psychiatry 29(8):1201–1213
39. Herman JP, Seroogy K (2006) Hypothalamic–pituitary–adrenal axis, glucocorticoids, and neurologic disease. Neurol Clin 24:461–481
40. Holsen LM, Lawson EA, Ko E, Blum J, Makris N, Fazeli PK, Klibanksi A, Goldstein JM (2012) Food motivation circuitry hypoactivation related to hedonic and non-hedonic aspects of hunger and satiety in women with active and weight-restored anorexia nervosa. J Psychiatry Neurosci 37:322–332
41. Holsen LM, Spaeth SB, Lee J-H, Ogden LA, Klibanski A, Whitfield-Gabrieli S, Goldstein JM (2011) Stress response circuitry hypoactivation related to hormonal dysfunction in women with major depression. J Affect Dis 131:379–387
42. Holsen LM, Lee J-H, Spaeth SB, Ogden LA, Klibanski A, Whitfield-Gabrieli S, Sloan RP, Goldstein JM (2012) Brain hypoactivation, autonomic nervous system dysregulation, and gonadal hormones in depression: a preliminary study. Neurosci Lett 514:57–61
43. Hossain A, Hajman K, Charitidi K, Erhardt S, Zimmermann U, Knipper M, Canlon B (2008) Prenatal dexamethasone impairs behavior and the activation of the BDNF exon IV promoter in the paraventricular nucleus in adult offspring. Endocrinology 149:6356–6365. doi:10.1210/en.2008-0388
44. Insel TR, Cuthbert BN, Garvey MA, Heinssen RK, Pine DS, Quinn KJ, Sanislow CA, Wang PS (2010) Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 167:748–751
45. Jankord R, Herman JP (2008) Limbic regulation of hypothalamo-pituitary-adrenocortical function during acute and chronic stress. Ann NY Acad Sci 1148:64–73. doi:10.1196/annals.1410.012
46. Jeanneteau FD, Lambert WM, Ismaili N, Bath KG, Lee FS, Garabedian MJ, Chao MV (2012) BDNF and glucocorticoids regulate corticotrophin-releasing hormone (CRH) homeostasis in the hypothalamus. Proc Natl Acad Sci USA 109:1305–1310. doi:10.1073/pnas.1114122109
47. Jiang X, Xu K, Hoberman J, Tian F, Marko AJ, Waheed JF, Harris CR, Marini AM, Enoch MA, Lipsky RH (2005) BDNF variation and mood disorders: a novel functional promoter polymorphism and Val66Met are associated with anxiety but have opposing effects. Neuropsychopharmacology 30:1353–1361
48. Jones DJ, Bromberger JT, Sutton-Tyrrell K, Matthews KA (2003) Lifetime history of depression and carotid atherosclerosis in middle-aged women. Arch Gen Psychiatry 60:153–160
49. Kang H-J, Kim J-M, Stewart R, Kim S-Y, Bae K-Y, Kim S-W, Shin I-S, Shin M-G, Yoon J-S (2013) Association of SLC6A4 methylation with early adversity, characteristics and outcomes in depression. Prog Neuropsychopharmacol Biol Psychiatry. doi:10.1016/j.pnpbp.2013.01.006
50. Kawachi I, Sparrow D, Vokonas PS, Weiss ST (1994) Symptoms of anxiety and risk of coronary heart disease. The normative aging study. Circulation 90:2225–2229
51. Kendler KS, Gatz M, Gardner CO, Pedersen NL (2006) A Swedish national twin study of lifetime major depression. Am J Psychiatry 163:109–114
52. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS (2003) The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 289:3095–3105
53. Koutcherov Y, Mai JK, Ashwell KW, Paxinos G (2000) Organization of the human paraventricular hypothalamic nucleus. J Comp Neurol 423:299–318
54. Landa MS, Schuman ML, Burgueno A, Alvarez AL, Garcia SI, Pirola CJ (2007) SiRNA-mediated silencing of the diencephalic thyrotropin-releasing hormone precursor gene decreases the arterial blood pressure in the obese agouti mice. Front Biosci 12:3431–3435
55. Lauder JM (1993) Neurotransmitters as growth regulatory signals: role of receptors and second messengers. TINS 16:233–240
56. Lawson EA, Holsen LM, Santin M, Meenaghan E, Eddy KT, Becker AE, Herzog DB, Goldstein JM, Klibanski A (2012) Oxytocin secretion is associated with severity of disordered eating psychopathology and insular cortex hypoactivation in anorexia nervosa. J Clin Endocrinol Metab 97:E1898–E1908. doi:10.1210/jc.2012-1702
57. Levy BH, Tasker JG (2012) Synaptic regulation of the hypothalamic–pituitary–adrenal axis and its modulation by glucocorticoids and stress. Front Cell Neurosci 6:24. doi:10.3389/fncel.2012.00024
58. Li DP, Pan HL (2007) Role of gamma-aminobutyric acid $(GABA)_A$ and $GABA_B$ receptors in paraventricular nucleus in control of sympathetic vasomotor tone in hypertension. J Pharmacol Exp Ther 320:615–626
59. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, Ferguson TB, Ford E, Furie K, Gillespie C, Go A, Greenlund K, Haase N, Hailpern S, Ho PM, Howard V, Kissela B, Kittner S, Lackland D, Lisabeth L, Marelli A, McDermott MM, Meigs J, Mozaffarian D, Mussolino M, Nichol G, Roger VL, Rosamond W, Sacco R, Sorlie P, Thom T, Wasserthiel-Smoller S, Wong ND, Wylie-Rosett J (2010) Heart disease and stroke statistics—2010 update: a report from the American Heart Association. Circulation 121:e46–e215
60. Luscher B, Shen Q, Sahir N (2011) The GABAergic deficit hypothesis of major depressive disorder. Mol Psychiatry 16:383–406
61. Maggio N, Segal M (2009) Differential corticosteroid modulation of inhibitory synaptic currents in the dorsal and ventral hippocampus. J Neurosci 29:2857–2866. doi:10.1523/JNEUROSCI.4399-08.2009
62. Makris N, Swaab DF, van der Kouwe A, Abbs B, Boriel D, Handa R, Tobet S, Goldstein JM (2013) Volumetric parcellation methodology of the human hypothalamus in neuroimaging: normative data and sex differences. NeuroImage 69:1–10
63. McEachin RC, Sannareddy KS, Cavalcoli JD, Karnovsky A, Vink JM, Sartor MA (2012) Convergence of genetic influences in comorbidity. BMC Bioinformatics 13(Suppl 2):S8. doi:10.1186/1471-2105-13-S2-S8

64. McClellan KM, Calver AR, Tobet SA (2008) $GABA_B$ receptors role in cell migration and positioning within the ventromedial nucleus of the hypothalamus. Neuroscience 151:1119–1131. doi:10.1016/j.neuroscience.2007.11.048
65. McClellan KM, Stratton MS, Tobet SA (2010) Roles for gamma-aminobutyric acid in the development of the paraventricular nucleus of the hypothalamus. J Comp Neurol 518:2710–2728. doi:10.1002/cne.22360
66. Menéndez A, Alvarez-Uria M (1987) The development of vascularization in the postnatal rat paraventricular nucleus: a morphometric analysis. J Hirnforsch 28:325–329
67. Moller-Leimkuhler AM (2007) Gender differences in cardiovascular disease and comorbid depression. Dialogues Clin Neurosci 9:71–83
68. Murray CJ, Lopez AD (1997) Mortality by cause for eight regions of the world: global burden of disease study. Lancet 349:1269–1276
69. Musselman DL, Evans DL, Nemeroff CB (1998) The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry 55:580–592
70. Neumann ID, Landgraf R (2012) Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. Trends Neurosci 35:649–659
71. Papez JW (1937) A proposed mechanism of emotion. Arch Neur Psych 38:725–743
72. Perello M, Cakir I, Cyr NE, Romero A, Stuart RC, Chiappini F, Hollenberg AN, Nillni EA (2010) Maintenance of the thyroid axis during diet-induced obesity in rodents is controlled at the central level. Am J Physiol Endocrinol Metab 299:E976–E989. doi:10.1152/ajpendo.00448.201
73. Petropoulos S, Gibb W, Matthews SG (2010) Developmental expression of multidrug resistance phosphoglycoprotein (P-gp) in the mouse fetal brain and glucocorticoid regulation. Brain Res 1357:9–18
74. Rozanski A, Blumenthal JA, Kaplan J (1999) Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 99:2192–2217
75. Rutledge T, Reis SE, Olson MB, Owens J, Kelsey SF, Pepine CJ, Mankad S, Rogers WJ, Merz CN, Sopko G, Cornell CE, Sharaf B, Matthews KA, Vaccarino V (2006) Depression symptom severity and reported treatment history in the prediction of cardiac risk in women with suspected myocardial ischemia: the NHLBI-sponsored WISE study. Arch Gen Psychiatry 63:874–880
76. Scherrer JF, Xian H, Bucholz KK, Eisen SA, Lyons MJ, Goldberg J, Tsuang M, True WR (2003) A twin study of depression symptoms, hypertension, and heart disease in middle-aged men. Psychosom Med 65:548–557
77. Seckl JR (2001) Glucocorticoid programming of the fetus; adult phenotypes and molecular mechanisms. Mol Cell Endocrinol 185:61–71
78. Selye H (1970) The evolution of the stress concept. Stress and cardiovascular disease. Am J Cardiol 26:289–299
79. Sheline YI, Barch DM, Donnelly JM et al (2001) Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry 50:651–658
80. Simerly RB, Chang C, Muramatsu M, Swanson LW (1990) Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: an in situ hybridization study. J Comp Neurol 294(1):76–95
81. Solomon MB, Herman JP (2009) Sex differences in psychopathology: of gonads, adrenals and mental illness. Physiol Behav 97:250–258. doi:10.1016/j.physbeh.2009.02.033
82. Surguladze S, Brammer MJ, Keedwell P, Giampietro V, Young AW, Travis MJ, Williams SC, Phillips ML (2005) A differential pattern of neural response toward sad versus happy facial expressions in major depressive disorder. Biol Psychiatry 57:201–209
83. Suzuki S, Handa RJ (2004) Regulation of estrogen receptor-beta expression in the female rat hypothalamus: differential effects of dexamethasone and estradiol. Endocrinolog 145(8):3658–3670
84. Suzuki S, Handa RJ (2005) Estrogen receptor-beta, but not estrogen receptor-alpha, is expressed in prolactin neurons of the female rat paraventricular and supraoptic nuclei: comparison with other neuropeptides. J Comp Neurol 484(1):28–42
85. Swanson LW, Sawchenko PE (1983) Hypothalamic integration: organization of the paraventricular and supraoptic nuclei. Annu Rev Neurosci 6:269–324
86. Szabo S, Tache Y, Somogyi A (2012) The legacy of Hans Selye and the origins of stress research: a retrospective 75 years after his landmark brief "letter" to the editor of nature. Stress 15:472–478. doi:10.3109/10253890.2012.710919
87. Szczepanska-Sadowska E, Cudnoch-Jedrzejewska A, Ufnal M, Zera T (2010) Brain and cardiovascular diseases: common neurogenic background of cardiovascular, metabolic and inflammatory diseases. J Physiol Pharmacol 61:509–521
88. Tasker JG, Herman JP (2011) Mechanisms of rapid glucocorticoid feedback inhibition of the hypothalamic–pituitary–adrenal axis. Stress 14:398–406. doi:10.3109/10253890.2011.586446
89. Tobe I, Ishida Y, Tanaka M, Endoh H, Fujioka T, Nakamura S (2005) Effects of repeated maternal stress on FOS expression in the hypothalamic paraventricular nucleus of fetal rats. Neurosci 134(2):387–395
90. Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ (2004) Global burden of depressive disorders in the year 2000. Br J Psychiatry 184:386–392
91. Vaccarino V, McClure C, Johnson BD, Sheps DS, Bittner V, Rutledge T, Shaw LJ, Sopko G, Olson MB, Krantz DS, Parashar S, Marroquin OC, Merz CN (2008) Depression, the metabolic syndrome and cardiovascular risk. Psychosom Med 70:40–48
92. van den Pol AN (1982) The magnocellular and parvocellular paraventricular nucleus of rat: intrinsic organization. J Comp Neurol 206:317–345
93. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Charma S, Seckl JR, Dymov S, Szyf M, Meaney MJ (2004) Epigenetic programming by maternal behavior. Nat Neurosci 7(8):847–854
94. Welberg LA, Seckl JR (2001) Prenatal stress, glucocorticoids and the programming of the brain. J Neuroendocrinol 13:113–128
95. Whitnall MH (1990) Subpopulations of corticotropin-releasing hormone neuroseretory cells distinguished by the presence or absence of vasopressing: confirmation of multiple corticotropin-releasing hormone antisera. Neuroscience 36(1):201–205
96. Wilson AC, Clemente L, Liu T, Bowen RL, Meethal SV, Atwood CS (2008) Reproductive hormones regulate the selective permeability of the blood–brain barrier. Biochim Biophys Acta 1782:401–407
97. Wu Z, Xu Y, Zhu Y, Sutton AK, Zhao R, Lowell BB, Olson DP, Tong Q (2012) An obligate role of oxytocin neurons in diet induced energy expenditure. PLoS One 7(9):e45167. doi:10.1371/journal.pone.0045167
98. Yi SS, Kim HJ, Do SG, Lee YB, Ahn HJ, Hwang IK, Yoon YS (2012) Arginine vasopressin (AVP) expressional changes in the hypothalamic paraventricular and supraoptic nuclei of stroke-prone spontaneously hypertensive rats. Anat Cell Biol 45:114–120. doi:10.5115/acb.2012.45.2.114
99. Zacchigna S, Lambrechts D, Carmeliet P (2008) Neurovascular signalling defects in neurodegeneration. Nat Rev Neurosci 9:169–181. doi:10.1038/nrn2336
100. Zeng H, Schimpf BA, Rohde AD, Pavlova MN, Gragerov A, Bergmann JE (2007) Thyrotropin-releasing hormone receptor 1-deficient mice display increased depression and anxiety-like behavior. Mol Endocrinol 21(11):2795–2804
101. Zuloaga DG, Carbone DL, Quihuis A, Hiroi R, Chong DL, Handa RJ (2012) Perinatal dexamethasone-induced alterations in apoptosis within the hippocampus and paraventricular nucleus of the hypothalamus are influenced by age and sex. J Neurosci Res 90:1403–1412. doi:10.1002/jnr.23026